Epidemiology of osteoporotic fracture: looking to the future

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This paper reviews the recent literature on candidate genes, anthropometric and environmental factors, and the evolving area of intrauterine fetal programming with regard to the development of osteoporosis.

Osteoporosis is a major public health issue, with fragility fractures of the hip, vertebrae and distal radius being the most important consequences. These lead to increased morbidity, mortality, hospital care, and dependency. The risk factors for the development of fragility fractures are numerous and involve genetic and environmental influences, as well as an interaction between the two. In this review, the recent literature examining candidate genes, anthropometric and environmental factors, and the evolving area of intrauterine fetal programming, will be reviewed. The risk of sustaining an osteoporotic fracture is multifactorial in origin. Any bone will fracture if it is subjected to sufficient stress, and thus the threshold at which a bone fractures will depend on bone parameters (mineral density, matrix structure, turnover geometry) and also the nature of the force applied. Most osteoporotic hip and distal radial fractures occur as a result of falling from standing height or less, but only 1% of falls result in fracture. Clearly, the mechanics of falling play a part in this; falling onto the hip is more likely to cause a fracture than falling straight forward [1]. Most recent work has concentrated on factors affecting bone parameters, specifically bone mineral density (BMD), as this is the most powerful predictor of fracture. It is important, in the interpretation of studies using BMD, to remember that other factors are involved in actual fracture occurrence. This review will examine recent evidence relating to genetic predisposition, candidate genes, the evolving area of intrauterine fetal programming, environmental factors and the fascinating glimpses of interactions between genetic makeup and environmental influences.

Genetic studies

It is thought that genetic factors account for around 50% of the variance in BMD across populations. Bone mass at any time after development of peak bone mass is dependent on the peak bone mass achieved and the rate of loss after this. Inherited factors may differ in their effect on these two parameters. A study using the St Thomas’ UK Adult Twin Registry assessed the genetic proportion of total BMD variance before and after the menopause. Two thousand four hundred and ninety female twins were studied (360 monozygotic and 885 dizygotic pairs) and it was found that 88% of premenopausal and 77% of postmenopausal variance in lumbar spine BMD could be accounted for by genetic variance [2]. The total variance in BMD was greater postmenopausally, indicating a greater role for environmental factors after the menopause. This raises the possibility of significant menopause–gene interactions in determining osteoporosis. In contrast to these findings, a 25-yr prospective study of Finnish twins found that concordance for osteoporotic fracture was not significantly higher in monozygotic than dizygotic twins for females [9.5%, 95% confidence interval (CI) 5.3–15.5% vs 7.9%, 95% CI 5.2–11.4%]. The respective figures for males were 9.9% (95% CI 4.4–18.5%) and 2.3% (95% CI 0.6–5.7%) [3]. These results confirm the importance of environmental influences on the risk of actual fracture, especially in women, and also that using BMD as a surrogate outcome for osteoporosis may be misleading.

Specific candidate genes

There has been much work exploring possible candidate genes to explain the genetic variance of bone parameters. Most of these studies have examined the association between various polymorphisms of the vitamin D receptor (VDR), collagen 1 (COL1A1) and insulin-like growth factor-1 (IGF-1) genes. There is recent evidence concerning interleukin-6 (IL-6), transforming growth factor β1 (TGF-β1) and low-density lipoprotein receptor-related protein 5 (LRP5). Most studies have found a fairly small contribution from each gene, and results are conflicting.

Vitamin D receptor

Studies of BMD and vitamin D receptor (VDR) polymorphisms in type 2 diabetes [4], primary biliary cirrhosis [5] and coeliac disease [6] found no significant association with BMD. However the B-allele of the Bsm polymorphism of VDR was associated with lower BMD at the hip, with a tendency towards increased fractures [7]. In a cohort of 165 men and 126 women in whom birth records existed, VDR genotype was not associated with either birth weight, bone mineral density or bone loss at either femoral neck or lumbar spine. However, there was an interaction between spine BMD, VDR genotype and birth weight. Among individuals in the lowest third of birth weight, spine BMD was higher with the VDR BB genotype (P = 0.01) after adjusting for age, sex and adult weight. BMD was reduced (P = 0.04) in individuals with the same genotype in the highest third of birth weight [8]. Birth weight is a marker of nutrition in utero, and thus these results indicate interaction between intrauterine environment, genetic and environmental influences.

Collagen 1 α1

Type I collagen is an important protein constituent of bone matrix and thus is an attractive candidate. However, there was no association between polymorphisms at the Sp1 binding site of COL1A1 with BMD in an American sample of 38 monozygotic and 40 dizygotic premenopausal twins and 56 postmenopausal
women with idiopathic osteoporotic vertebral fractures [9]. In 185 healthy women, mean age 54.3 yr, carriage of the s allele of the COL1A1 gene was associated with a significant reduction in lumbar spine BMD (P = 0.02), an increased risk of fracture (P = 0.04), and an increase in urinary pyridinoline levels (P < 0.05) [10]. The Ss genotype was associated with a 6.7% lower cancellous bone density in 109 prepubertal girls [11]. The role of the s allele of the COL1A1 gene is further supported by evidence of its interaction with calcium intake. Brown et al. studied 45 dizygotic twin pairs and 29 nuclear families comprising 120 individuals together with 193 elderly postmenopausal women [12]. They found an association between the MscI polymorphism of COL1A1 and BMD, related to the level of calcium intake (P = 0.0006). In the lowest tertile of calcium intake carriers of the s allele lost more bone than SS homozygotes (P = 0.01) and this trend was reversed with the highest dietary intake (P = 0.003). A similar, but less marked genetic-environmental interaction was observed for the TaqI VDR polymorphisms.

**IGF-1, IL-6, TGF-β1, LRP5**

IGF-1 has marked effects on osteoblasts, and levels are influenced by growth hormone. Thus, it is an attractive candidate for a role in osteoporosis, but a study of 542 premenopausal sibling pairs (418 Caucasian and 124 African-American) found no association between various genetic loci and bone mineral density [13]. However, physiological studies of hypopituitary patients indicate that low levels of growth hormone per se increase the risk of osteoporotic fracture [14]. The prevalence of fractures was 2.66 times higher in hypopituitary patients compared with controls. Childhood-onset disease was associated with a lower fracture rate than adult-onset disease and subjects with isolated growth hormone deficiency had a fracture risk similar to those with multiple pituitary deficiencies. Hormone replacement with glucocorticoids, L-thyroxine and sex steroids did not affect risk.

IL-6 is a cytokine produced by bone cells and is involved in inflammation, and the European Vertebral Osteoporosis Study group found that serum levels of IL-6 predicted bone loss in postmenopausal women [15]. The CC IL-6 −174G → C polymorphism of IL-6 was associated with a reduced rate of bone resorption and less reduction in bone mass in older postmenopausal women [16]. Recent work has shown that allelic variation at the gene for TGF-β1 (an important regulatory cytokine active in bone matrix) may contribute to osteoporosis at the hip. The 4% decrease in hip BMD (P = 0.025) in homozygotes for the T-allele was found mainly in premenopausal women in this twin study, and therefore may indicate an effect on attainment of peak bone mass [17]. LRP5 is a developmental protein involved in the Wnt pathway, and loss-of-function mutations cause an inherited osteoporosis syndrome [18]. Recently, Boyden et al. [19] demonstrated a mutation in the LRP5 gene causing an inherited high bone density syndrome. It is possible that other mutations of this gene may have a more frequent but less dramatic role in the pathogenesis of osteoporosis.

Thus, the available evidence indicates that the contribution of any of these candidate genes to non-syndromic osteoporosis, in isolation, is at best modest, and that they may contribute even less to actual fracture risk. However, in the light of the above evidence for gene–environmental interaction, studies looking for a direct correlation between bone parameters and genetic polymorphisms may well miss a more complicated relationship.

**Intrauterine programming**

Until the last decade, work on osteoporosis had looked at the adult determinants of disease, such as smoking and hormone status. An alternative approach is to study the effect of the intrauterine environment and early life influences on later bone mass and risk of fracture. ‘Fetal programming’ is the term used to describe persisting changes in structure and function caused by environmental stimuli acting at critical periods during early development [20]. Rickets is an example of undernutrition at a critical stage of development leading to permanent skeletal changes. There is increasing evidence that the body’s ‘memories’ of early undernutrition, set by intrauterine fetal programming, influence the risk of osteoporosis in later life. In rats, a maternal low-protein diet leads to decreased lifespan of their offspring, which also have a significantly higher systolic blood pressure and a tendency to be smaller [21]. This contrasts with the well-documented association of postweaning dietary restriction with increased lifespan. In humans there is accumulating evidence for intrauterine programming. This is from epidemiological studies of adult cohorts where birth details are known, physiological evidence relating to candidate mechanisms (for example, vitamin D receptor polymorphisms), studies of maternal factors relating to the neonate and studies of the effect of childhood growth of risk of later fracture.

**Epidemiological evidence**

In a cohort of 143 men and women aged 70–75 yr, born and still living in Sheffield, UK, and in whom detailed birth records existed, there were significant (P < 0.01) positive associations between birth weight and adult whole body, lean and bone mass among men and women. There was also a significant positive correlation between birth weight and bone mineral content (BMC) at the lumbar spine and femoral neck (P < 0.03). The associations of whole body mineral content and lean mass with birth weight remained significant after adjusting for age, sex, adult height, smoking, alcohol consumption, dietary calcium intake and physical inactivity [22]. The association with BMC but not BMD may indicate that these parameters have different determinants.

**Physiological studies**

A study of 34 healthy men from the Hertfordshire (UK) cohort, measuring serum cortisol every 20 min for 24 h, showed a weak negative correlation between integrated cortisol level and BMD at the lumbar spine (r = −0.37, P < 0.05). Similar relationships were demonstrated at three of five proximal femoral sites [23]. There were also significant positive associations between trough cortisol level and rate of bone loss over the 4-yr follow-up period at the lumbar spine (r = 0.38, P < 0.05), femoral neck (r = 0.47, P < 0.001) and trochanteric region (r = 0.41, P = 0.02). The relationship between cortisol concentration and BMD did not remain after adjustment for body weight. However, the association with rate of bone loss did remain after adjustment for adiposity, cigarette smoking, alcohol consumption, dietary calcium intake and physical inactivity [22]. The association with BMC but not BMD may indicate that these parameters have different determinants.

**Foetal influences during pregnancy**

Parental birth weight, maternal smoking, body composition and activity during late pregnancy have all been demonstrated to effect neonatal bone mass [24]. In 145 infants born at term to women in Southampton, UK, the birth weights of both parents and the height of the father positively correlated with neonatal whole-body BMC, independent of the infants’ duration of gestation. Mothers who smoked during pregnancy had, on average, babies with a 7.1 g (11%) lower whole-body BMC than mothers who did not smoke (P = 0.005). They also had lower BMD. Smoking at the
time of the last menstrual period was not associated with lower BMC or BMD. Women who indulged in vigorous activity in late pregnancy, or had a faster walking pace, or had lower tripeps skin fold thickness (reflecting lower fat stores) tended to have babies with a lower BMC and BMD (P values for BMC: 0.05, 0.03, 0.02 respectively). These influences on skeletal weight and mineralization were independent of placental weight (a marker of the placental capacity to deliver nutrients to the growing foetus). These data therefore provide evidence that environmental modulation in utero, in combination with genetic factors, has an effect on neonatal bone parameters. The authors postulate that maternal thinness may reflect lower available nutrients for the fetus. The effect of exercise in the last trimester may be a simple competition for finite resources. Evidence regarding fracture risk comes from a unique Finnish cohort of men and women who were born, went to school, and still lived in Helsinki in 1971. After adjustment for age and sex, tall maternal height and slow rate of childhood growth were associated with increased risk of hip fracture in later life [25].

The hazard ratio for hip fracture for men and women born to mothers above 1.61 m compared with those below 1.54 m was 2.1 (95% CI 1.2–3.5). For those whose rate of childhood height gain was below the lowest quartile for the cohort, the hazard ratio for hip fracture was 1.9 (95% CI 1.1–3.2), compared with those above the highest quartile. These effects were independent of each other, and also of socioeconomic class.

Possible mechanisms of fetal programming

Neuroendocrine systems, including the pituitary/growth hormone axis, gonadal hormones and adrenal axis, are candidates for fetal programming. These might influence cell number, cell type and endocrine set points. In 93 neonates in Southampton, UK, umbilical cord serum IGF-1 concentration correlated positively with neonatal whole-body BMC (r = 0.30, P = 0.001), whole-body BMD (r = 0.30, P = 0.001), whole-body lean mass (r = 0.28, P = 0.003) and whole-body fat mass (r = 0.46, P < 0.001) [26]. Cord serum IGF-1 did not account for any of the previously shown effects of parental characteristics (such as height, weight and fat mass, but partially explaining the effect of smoking), suggesting that both IGF-1-dependent and -independent factors influence neonatal bone parameters. Data from the Hertfordshire (UK) cohort indicated an inverse correlation between weight at 1 yr and adult 1,25 dihydroxyvitamin D levels. There was a 19.1% reduction in vitamin D levels in the highest compared with the lowest tertile in weight at 1 yr. A similar association was found for free 1,25 dihydroxyvitamin D; these associations remained after adjustment for adult weight and serum albumin. The study by Dennison et al. [8], reported above, gives further support for the role of vitamin D, showing an association between birth weight and adult BMD, dependent on VDR genotype. These studies may provide part of the explanation for the effect of intrauterine environment on adult bone parameters; it can be hypothesized that low intrauterine calcium intake may lead to a programmed persistent up-regulation of the vitamin D system, presumably to scavenge all the available calcium.

Leptin is a peptide hormone encoded by the obese (ob) gene, and is a candidate for involvement in fetal programming. It is produced by adipocytes and seems to behave as a fat sensor, acting on the hypothalamus. There is recent evidence that adults who have a low birth weight have higher levels of leptin than would be expected from their level of adult obesity [27]. Data, again from the Hertfordshire cohort, showed a strong correlation between plasma leptin concentration and BMC (P < 0.001) [28]. However, the negative association with rate of bone loss was significant only at the femoral neck in women (P < 0.01) and all associations were explained by the association of leptin with adiposity.

**Table 1. Number of prevalent vertebral deformities and risk of subsequent vertebral fracture [29]**

<table>
<thead>
<tr>
<th>Number of deformities</th>
<th>Relative risk of subsequent vertebral fracture</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.2</td>
<td>2.1–4.8</td>
</tr>
<tr>
<td>2</td>
<td>9.8</td>
<td>6.1–15.8</td>
</tr>
<tr>
<td>≥3</td>
<td>23.3</td>
<td>15.3–35.4</td>
</tr>
</tbody>
</table>

**Table 2. Effect of position of height loss of prevalent vertebral deformity on risk of future vertebral fracture [29]**

<table>
<thead>
<tr>
<th>Position of height loss</th>
<th>Relative risk of subsequent vertebral fracture</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior/middle</td>
<td>5.9</td>
<td>4.1–8.6</td>
</tr>
<tr>
<td>Posterior/middle</td>
<td>1.6</td>
<td>0.8–3.2</td>
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**Lifestyle, anthropometric, and morphometric factors**

Work from several studies using data from European centres has explored the epidemiology of vertebral fractures. The European Prospective Osteoporosis/European Vertebral Osteoporosis Study Groups (EPOS/EVOS) recruited women aged 50–79 yr from population registers in 28 European centres. The effects of lifestyle, morphometric and hormonal factors on the incidence of vertebral fractures were studied over a mean follow-up period of 3.8 yr. The findings from several studies from these groups are summarized below.

After adjustment for age and centre, age at menarche ≥16 yr was associated with an increased risk of fracture (relative risk 1.6; 95% CI 1.0–2.4). There was a similar, but non-significant, association with non-use of hormone replacement therapy. Other lifestyle factors (including smoking, alcohol intake, milk consumption and physical activity) and other hormonal factors (such as use of the oral contraceptive pill) showed no significant associations.

BMD was not routinely assessed in this study.

Prevalent vertebral deformity strongly predicted incident hip fracture in women after adjusting for age [rate ratio (RR) 4.5; 95% CI 2.1–9.4], and more weakly predicted other limb fractures (RR 1.6; 95% CI 1.1–2.4), but not distal forearm fracture (RR 1.0; 95% CI 0.6–1.6). The predictive risk became stronger with the number of prevalent deformities and the rate ratio for 2 or more vertebral deformities and subsequent hip fracture was 7.2 (95% CI 3.0–17.3). In men there was a non-significant trend for prediction of hip fractures but no other association.

The shape of prevalent vertebral deformity was also shown to be an important predictor of future risk of vertebral fracture, with correlation between position of vertebral height loss (anterior, middle or posterior) and future risk. The risk also increased with the number of baseline deformities (Tables 1 and 2) [29]. Incident fracture was more likely to happen within three vertebrae of the number of prevalent deformities and the rate ratio for 2 or more vertebral deformities and subsequent hip fracture was 7.2 (95% CI 3.0–17.3). In men there was a non-significant trend for prediction of hip fractures but no other association.

In a large multicentre study of a different population, the relative risk of sustaining a fracture in the first year after baseline for those with one or more prevalent vertebral fractures was 5.1 (95% CI 3.1–8.4, P < 0.001), compared with those with no fracture at baseline [30]. Among those who developed an incident vertebral fracture, the incidence of subsequent vertebral fracture within 1 yr was 19.2% (95% CI 13.6–24.8%).
**Smoking**

Smoking has been shown to have an effect on bone density in women; a large study of 116,229 female nurses aged 34–59 yr at baseline and followed for 12 yr showed trends towards an increased risk of hip fracture in current smokers. The relative risk of hip fracture in current smokers was 1.3 (95% CI 1.0–1.7) compared with subjects who had never smoked. A benefit from stopping smoking was seen at 10 yr after cessation (relative risk 0.7; 95% CI 0.5–0.9) [31]. Smoking has been shown to affect the efficacy of hormone replacement therapy (HRT) and to lead to lower BMD and increased bone turnover. This was additive to the negative effect of low body mass, and smokers needed higher doses of oestra diol to achieve the equivalent improvement in bone loss [32]. This is unlikely to be the whole story however, as there is also evidence that the protective effect of HRT on hip fracture is greatest for women who have ever smoked, drink alcohol and take little exercise, independent of body mass index [33]. This probably reflects the higher risk of fracture in this group, and factors other than BMD in the determination of fracture risk. Data from the Raloxifene Efficacy Trial [34] indicated that the efficacy of raloxifene was unaffected by smoking. Those (postmenopausal) women who were current smokers had significantly lower baseline BMD at the femoral neck, and increased bone turnover markers. There was no difference in bone turnover at 6 months between smokers and non-smokers on raloxifene and there was no difference in the increase in BMD at the femoral neck or lumbar spine or in the reduction in vertebral fractures at 4 yr. Recent evidence suggests that, in men, current smoking increases bone resorption without increasing formation [35]. Past smokers had a lower BMD than those who had never smoked, but not increased resorption. Current smokers had an increased prevalence of vertebral deformity (13 vs 5%; P < 0.005). These associations were partly explained by lower levels of serum 25-hydroxy vitamin D, and secondary hyperparathyroidism in the smokers. The mechanism of the effect of smoking on bone turnover is becoming clearer. Cigarette smoke extract inhibited in vitro differentiation of human osteoprogenitor cells to osteoblast-like cells [36]. Assays of alkaline phosphatase activity and calcium incorporation into the cell layer gave similar results.

**Alcohol consumption**

Alcohol is likely to have a variable effect on the risk of fracture depending on consumption. Intuitively, even if it has a protective effect, increased fractures may be expected at high levels of intake, as a result of trauma. The evidence so far bears this out. In a study of 297 women who drank alcohol and 148 who did not, moderate alcohol consumption (>28.6 g/week) was significantly associated with a higher BMD at the lumbar spine and distal radius. Markers of bone turnover were also reduced in drinkers, as were levels of parathyroid hormone, suggesting that alcohol may reduce bone remodelling [37]. However, in a large study of 17,868 men and 13,917 women, pooling data from three population studies in Copenhagen, Denmark, from 1964 to 1992, alcohol intake above the current recommended allowance (1–27 drinks per week for men and 1–13 for women) was associated with increasing risk of hip fracture in a dose-dependent fashion [38]. Women showed a trend towards higher risk with 14–27 drinks per week. Drinking beer appeared to increase the risk of hip fracture compared with wine and spirits. This may be partly explained by differences in lifestyle associated with different drinking habits.

**Corticosteroids**

Corticosteroids are a major cause of secondary osteoporosis; indeed, at any one time corticosteroids are being used by 0.9% of the General Practice Research Database Population in the UK [39]. Initially, bone loss was thought to be an effect of long-term, high-dose treatment, but more recent evidence suggests that bone loss occurs early and with doses of less than 10 mg per day. The risk of fracture appears to be related to corticosteroids in a dose-dependent fashion (Table 3) [40]. It had been postulated that corticosteroids might alter the fracture threshold (that is, increase the magnitude of the negative correlation between BMD and fracture risk), but recent evidence does not support this view [41].

**Conclusions**

We are gradually coming closer to unravelling the causes of osteoporosis and many of the determinants of fracture risk. There is evidence for a significant genetic contribution interacting with environmental factors. This has been demonstrated in utero and in adulthood. There is mounting evidence for several candidate genes playing a role, including those for the vitamin D receptor, and for collagen Iα1. Lifestyle factors such as smoking and alcohol intake also contribute. One of the most intriguing findings is that environmental influences on the fetus appear to have an effect on adult skeletal status. Further work to elucidate these mechanisms, and thus potentially provide ways to reduce this devastating public health problem, is eagerly awaited.

The authors have declared no conflicts of interest.

**References**


