AGE-RELATED BONE LOSS AND FRACTURE RISK: A STOCHASTIC MODEL†

A. HORSMAN and D. H. MARSHALL

MRC Mineral Metabolism Unit
The General Infirmary, Leeds
Leeds LS1 3EX, United Kingdom

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Abstract—A stochastic model of age-related bone loss capable of predicting age-specific incidence of fractures has been implemented by Monte Carlo simulation. Each simulation involves ageing a large cohort of individuals from 20 to 100 years. Every individual is randomly allocated a particular amount of bone as a young adult, an age of onset of bone loss, and parameter values which determine the subsequent loss. Fracture risk is assumed to be zero when the amount of bone is above a global threshold level, increasing progressively as the amount of bone falls below the threshold. From the individual fracture risks, a fracture subpopulation is identified and age-specific incidence evaluated numerically. By adjusting the model parameters, predicted and observed incidence of femoral neck fractures can be closely matched in both sexes using a linear function to describe age-related bone loss. For the fracture of the distal radius, a close match can be achieved in females using an exponential function to describe the bone loss phase; in males, the incidence is independent of age and trauma, rather than the amount of bone in the forearm, appears to be the main determinant of fracture risk.

INTRODUCTION

The age-specific incidence of fractures of the proximal femur doubles every 5 years after age 60 (Fig. 1); by age 80, about 1% of females and about 0.5% of males fracture each year (Baker[1], Gallagher et al.[2], Knowelden et al.[3]). One factor responsible for these fractures is declining bone mass at the fracture site (Dalen et al.[4], Horsman et al.[5]), which decreases at 0.5–1.0% per annum in females and less rapidly in males (Dalen and Jacobson[6]). The loss occurs by cortical thinning (Harty[7]) and resorption of the structural arches of trabeculae in the medullary cavity (Singh et al.[8]).

Other common fractures have similarly been attributed to age-related bone loss (Buhr and Cooke[9], Lamke et al.[10]), in particular fracture of the distal radius (Colles' fracture) (Knowelden et al.[3], Owen et al.[11]). However, the age-specific incidence of that fracture rises rapidly in women after age 50, reaching a constant level of about 0.5% per annum by age 70 (Fig. 2). In women therefore, the incidence patterns of fractures of the proximal femur and distal radius are different. They are also different in men; whereas the incidence of femoral fracture increases rapidly with age, the incidence of Colles' fracture is constant, remaining at about the level observed in younger men. In young adults, the incidence is comparable in both sexes.

The problem of constructing a conceptual framework to describe in semiquantitative terms the association between bone measurements and fracture risk was first approached by Newton-John and Morgan in 1968[12, 13]. They presented a model capable of predicting from the distribution of the amount of bone the proportion of the total population at any age at risk of fracture (Fig. 3). A “fracture threshold” was defined as the amount of bone

† Computer diskette available.
above which the risk of fracture is zero, and below which the risk is constant. Fracture cases are randomly selected from the members of the population below the fracture threshold; in that subpopulation, the fracture risk for an individual was assumed to be independent of that individual's amount of bone. With suitable choices of fracture threshold, the Newton-John and Morgan model is capable of predicting the age-related changes in the incidence of fractures of the proximal femur and distal radius in women but not in men.

In this paper we present a stochastic model of age-related bone loss and fractures. Our approach enables characteristics of populations in which the amount of bone in the young adult, the age of onset of bone loss and the subsequent bone loss all vary between individuals to be evaluated. Fracture risk (per unit time) is calculated for each individual.
increasing as the difference between the fracture threshold and amount of bone increases. Fracture cases are identified and the age-specific incidence predicted for both fracture types.

**THE MODEL**

(a) *General considerations*

The term "amount of bone" is used only as a label for the dependent variable which we regard as a local property of the fracture site. In defining the model, we do not stipulate which physical property "amount of bone" represents. (See Discussion section.) Age-related bone loss in the individual is represented by a function which is either linear or exponential. Two different functions are used to model observations of the proximal femur and distal radius primarily because the age-specific incidence curves for the two fractures have different forms. (See Figs. 1 and 2.)

(b) *Definitions of the model parameters*

These definitions can be split into two parts: first, those parameters which determine the age-related changes in the amount of bone in individuals and second, those parameters which determine fracture risk in relation to the amount of bone. All the parameters are independent and each is normally distributed about a mean value.

The following parameters come into the first category and are illustrated in Fig. 4(a)-(c).

(i) \( M_i \) is the amount of bone in the \( i \)th young adult and \( M \) is the population mean. Young adults are taken to be over 20 years old and it is assumed that their skeleton is in dynamic equilibrium (zero bone balance). [See Fig. 4(a).]

(ii) \( s_M \) is the standard deviation about \( M \).

(iii) \( A_i \) is the age at which bone loss starts in an individual and \( A \) is the population mean.

(iv) \( s_A \) is the standard deviation about \( A \).

When modelling observations of the proximal femur, the bone loss is assumed to be linear. [See Fig. 4(b).] In that case:

(v) \( R_i \) is the rate of decrease of the amount of bone in an individual who is older than \( A_i \). \( R \) is the population mean rate of decrease.

(vi) \( s_R \) is the standard deviation about \( R \).

When modelling observations of the distal radius, the bone loss is assumed to be exponential. [See Fig. 4(c).] In that case:

(vii) \( M'_i \) is the amount of bone which the \( i \)th individual would approach asymptotically if age increased indefinitely. \( M' \) is the population mean asymptote.

(viii) \( s_{M'} \) is the standard deviation about \( M' \).

(ix) \( T_i \) is the time constant of the exponential decrease in the amount of bone in an individual. \( T \) is the population mean.

(x) \( s_T \) is the standard deviation about \( T \).

We denote the amount of bone at age \( a \) for the \( i \)th individual as \( M_i(a) \):

- for \( a < A_i \), we have
  \[ M_i(a) = M \]

- and for \( a \geq A_i \), we have either
  \[ M_i(a) = M_i - R_i(a - A_i) \] (proximal femur)
Fig. 4(a). Definition of model parameters for the equilibrium phase, in which the skeleton of young adults is assumed to be in balance.

Fig. 4(b). Definition of model parameters for the bone loss phase, in which the rate of bone loss in any one individual is assumed to be constant (linear model).

Fig. 4(c). Definition of model parameters for the bone loss phase, in which the decrease in the amount of bone in any one individual is described by an exponential.

Fig. 4(d). Illustration of how fracture risk is calculated. While the amount of bone in the individual is greater than the fracture threshold, the risk is zero. Otherwise the risk (per unit time) is assumed to be proportional to the difference shown.

or

\[ M_i(a) = M_i' + (M_i' - M_i') \cdot \exp[-\ln(2) \cdot (a - A_i)/T_i] \quad \text{(distal radius).} \]

The following parameters determine the fracture risk in relation to the amount of bone (see Fig. 4(d):

(i) \( M^* \) is the “fracture threshold” common to all members of the population; it is the amount of bone above which the probability of fracture is zero. When an individual’s amount of bone is below \( M^* \), the fracture risk is nonzero, increasing as the amount of bone decreases as defined below.

(ii) \( K \) is a constant (the “fracture probability constant”) common to all members of the population which determines the risk of fracture given the amount of bone. For the \( i \)th individual, the risk that a fracture will occur in a given small age
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interval $\Delta a$ at age $a$ is assumed to be

$$K \cdot \{M^* - M_{\Delta}(a)\} \cdot \Delta a.$$  

**MONTE CARLO SIMULATIONS**

The simulations were carried out on an Amdahl V7 computer using a program written in Algol. At the start of each simulation, the global model parameters (section (b) above) were specified together with the number of individuals (typically 30,000–100,000). Values of the model parameters used in specific simulations are given later. The width of intervals into which the total age range was to be divided for the purpose of evaluating the fracture incidence as a function of age was also specified. In each simulation, fracture cases in a large cohort of individuals ageing progressively from 20 to 100 years were identified as described below.

Individual random values of each parameter were sampled from gaussian distributions using a standard algorithm. Using the individual values of $M_i$, $A_i$ and $R_i$, or $M_i^* \text{ and } T_i$, every member of the cohort was traced over the 80 year span. There were three types of case to consider:

(i) The individual never had an amount of bone less than the fracture threshold. In such cases the risk of fracture is always zero.

(ii) The individual started as a young adult with an amount of bone in excess of the fracture threshold and at some particular age $Z_i$ crossed the fracture threshold. In such cases the fracture risk (per unit time) is zero before $Z_i$ and thereafter is proportional to $M^* - M_{\Delta}(a)$.

(iii) The individual started as a young adult with an amount of bone below the fracture threshold. Such cases are always at risk, and from age 20 onwards the fracture risk (per unit time) is proportional to $M^* - M_{\Delta}(a)$.

The simulation program first classified every individual into one of these three categories and in cases like (ii) and (iii) tested for fracture when $M^* - M_{\Delta}(a)$ became positive. The fracture risk (per unit time) (i.e. $K \cdot \{M^* - M_{\Delta}(a)\}$) was computed at given intervals (5 years) and compared with a number selected from a uniform random distribution ranging from 0 to 1. If the risk exceeded the random number then that individual was classified as having had a fracture at that age. (For any given value of risk, this technique when applied to a large number of subjects produces the required proportion of fracture and nonfracture cases.) Fracture cases were not removed from the cohort after the first fracture, nor were cases with more than one fracture separately identified. Counts of the number of fractures in the specified age intervals were accumulated and used to derive the age-specific incidence.

**SPECIFIC MODELS OF BONE LOSS AND FRACTURE**

(1) *Fracture of the proximal femur*

The observation that the age-specific incidence of femoral fracture increases continuously with age in both sexes (Fig. 1) indicates that the proportion of the surviving population at risk also increases continuously, assuming that factors responsible for the fracture other than the amount of bone do not change with age. If that is so, a function which contains only a linear term may be sufficient to describe the bone loss phase. We therefore started by carrying out a simulation of the female population using the following values for the parameters:

$$M = 70, \quad s_M = 7, \quad A = 50, \quad s_A = 3, \quad R = 0.5, \quad s_R = 0.05.$$
The absolute value of $M$ is arbitrarily chosen, but once fixed sets the scale for $s_M$. $R$ and $s_R$. $s_M$ was chosen so that the coefficient of variation of the amount of bone in young adults ($s_M/M \times 100\%$) was 10%. $A$ is the mean age of onset of bone loss and was taken to be the same as the mean age of menopause (Jaszmann[14]); $s_A$ was obtained from the same source. The mean rate of loss, $R$, was chosen such that $R$ expressed as a percentage of the mean young adult amount of bone was between 0.5 and 1.0% per annum (Dalen and Jacobson[6]). The true variability in the rate of bone loss between individuals is not known at present: rather than set $s_R$ to zero, the value 0.05 was arbitrarily chosen so that the effect of this dispersion on the variance of the amount of bone in the elderly could be examined.

The above parameters determine the way in which the amount of bone changes with age in individual women, and the simulation allows the mean amount of bone and its standard deviation to be computed in relation to age. The results are shown at 5-year intervals in Fig. 5 for a simulation involving 75 000 subjects. The gradual rather than sudden change in mean slope around age 50 is due to the dispersion in $A$. There is a slight increase in the variance in the amount of bone with age due to the dispersion in $R$, but this is not marked.

Evaluations of fracture risk and subsequent prediction of the age-specific incidence of fractures require two more parameters to be specified, $M^*$ (the fracture threshold) and $K$ (the fracture probability constant). Because few femoral neck fractures occur in young adults, we initially chose $M^* = M - 2s_M = 56$. No experimental data are available which allow $K$ to be estimated. An approximate value of $K$ (0.002) was therefore determined by trial and error so that the model generated realistic figures for the age-specific incidence of fractures at age 80. A large series of simulations was then carried out to find a set of values of all the parameters which produced a close fit to the Leeds data on femur fracture incidence in females. The upper curve in Fig. 6 was the closest match to the female data. The parameters values are given in the inset table: the fracture threshold was 2.5 SD below the mean $M(\bar{Q})$, with $K = 0.0015$.

Although the values of the parameters leading to the upper curve in Fig. 6 were specifically chosen to model bone loss in a female population, the previous trials suggested that it might be possible to match observations of femur fracture incidence in males by leaving all parameter values except $M$ and its standard deviation unchanged. increasing

![Fig. 5. Results of a Monte Carlo simulation of a cohort of 75 000 women ageing from 20 to 100 (linear bone loss model). Values of the model parameters are given in the table (inset).](image-url)
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Fig. 6. Model predictions of age-specific incidence of femur fractures compared with Leeds data. Values of the model parameters are given in the table (inset). With the exception of \( M \) and its standard deviation, values of all parameters were common to the two simulations generating the male and female curves.

Those by about 10%. Real data on males are shown in the same figure and they are in fact consistent with the predictions based on \( M = 77 \) (lower curve). Differences in the age of onset of bone loss or rate of bone loss between the sexes are therefore not essential to explain the difference between the age-specific incidences of fracture in men and women, as has often been suggested (Nordin[15], Nordin et al.[16]).

The results shown in Fig. 6 do not imply, however, that differences between the sexes in the other variables either do not occur in reality or cannot explain equally well the sex difference in the observed fracture incidence. For example, using common values of all parameters (as above, with \( M = 70 \)) except the age of onset of bone loss (\( A \)), it is possible to match the observed fracture incidence in both sexes provided \( A \) is larger in males by about 10 years. Clearly there are infinitely many alternative sets of parameter values in which more than one value differs between the sexes which can match observations of fracture incidence in men and women. Which of these alternatives corresponds to reality must depend on observations of the amount of bone at the fracture site; the simulations serve to demonstrate the wide spectrum of possibilities, even within the constraints of the linear model, which are compatible with observations of femur fracture incidence.

(2) Fracture of the distal radius

The observation that the age-specific incidence of fracture of the distal radius in women rises rapidly between age 50 and 70 then tends to remain at a constant level (Fig. 2) suggests that the proportion of survivors at risk of fracture (i.e. the population at risk) does not increase in size after 70, provided factors responsible for the fracture other than the amount of bone do not change with age. If individual age-related bone loss is described by an exponential function with a decay time constant of about 15 years or less, the model can be made to generate a population at risk which reaches a limiting size. This choice of function is not arbitrary: it is known that in individual women bone loss from the distal radius tends to slow down later in life (Smith et al.[17]) and cross-sectional bone measurements have previously been fitted by exponential functions (Khairi and Johnston[18]).
We therefore carried out a trial simulation of the ageing female population using the following values for the parameters:

\[ M = 70, \quad s_m = 7, \quad A = 50, \quad s_A = 3, \quad M' = 45, \quad s_{M'} = 7, \quad T = 15, \quad s_T = 1.5. \]

The values of \( M, s_M, A, \) and \( s_A \) were chosen as before. \( M' \) was chosen on the basis that the overall decrease \( M - M' \) should be about 0.35\( M \) (the amount of bone decreases by about 35% throughout life). \( s_{M'} \) was chosen such that the variance of the amount of bone in the elderly would be comparable with the variance in the young. \( T \) was chosen so that the majority of the decrease in the amount of bone occurred within 20 years of \( A \) and \( s_T \) was arbitrarily set to 0.1\( T \). The results of a simulation of 75 000 subjects using these values for the parameters are shown in Fig. 7. Means and standard deviations of the amount of bone are shown at 5-year intervals.
As for the femur fracture, a large series of simulations was carried out to find a set of values of all the parameters which produced a close fit to the Leeds data on Colles' fracture incidence in females. The upper curve in Fig. 8 was the closest match achieved to the female data. The parameter values are given in the inset table; the fracture threshold was only 0.5 SD below the mean $M(\bar{\epsilon})$, with a relatively low value of $K (0.0002)$.

The male incidence data are virtually independent of age, and it cannot therefore be expected that the model will provide an accurate prediction over the whole age span. The lower curve in Fig. 8 is the predicted age-specific incidence when $M$ and $M'$ and their standard deviations are increased by 40%, based on observations of the relative bone mineral content of the distal radius in males and females (Johnston et al.[19]). The other parameter values were not changed. The mismatch between predictions and observations can be explained if it is postulated that in males, when falls occur they are of such severity that irrespective of the amount of bone, they usually lead to a Colles' fracture.

**DISCUSSION**

The stochastic model of age-related bone loss and osteoporosis described above is new in several respects. Every individual in the population examined has unique characteristics: for example the amount of bone as a young adult, the age of onset of bone loss and subsequent rate of loss are all specific to the individual. The population means and standard deviations of the model parameters must be supplied, but thereafter the simulation program chooses the particular values of each variable for each individual. Because individual characteristics are known, it is possible to predict the individual risk of fracture. The prediction is based on a hypothetical underlying relationship between the amount of bone at any particular time and the instantaneous risk of fracture at that time.

Given the number of parameters in the model and the choice of linear or exponential functions to describe the bone loss phase, it is to be expected that by manipulating the fracture threshold and fracture probability constant a reasonable fit to observed age-specific incidence curves will be achieved. This flexibility can be regarded as a limitation inasmuch as there is no unique set of values for the parameters which can be determined from the observations of fracture incidence. Another problem is that arbitrary values have to be allocated to certain parameters, such as the variability in the rate of loss. However, all the parameters are necessary to describe the equilibrium and bone loss phases of individuals at two different skeletal sites whether their values are known yet or not. For example, Newton-John and Morgan assumed that the rate of decrease in the amount of bone did not vary between individuals, arguing that such variability would necessarily produce an increase in variance of the amount of bone with age (Morgan and Newton-John[12], Newton-John and Morgan[13]). Although this is true, our simulations of linear bone loss with a variability of 10% (1SD) in rate between individuals revealed that the standard deviation increased by a factor of only 1.1, comparing young women with women aged 80. Such an increase would not be detected except in very large-scale cross-sectional studies, and a nonzero dispersion in the individual rates of loss is not inconsistent with the majority of published sets of cross-sectional data.

The relationship between the amount of bone and fracture risk could take any form. In the absence of experimental evidence for a particular functional relationship, we have chosen a simple form which extends the "fracture threshold" concept of Newton-John and Morgan. The risk is taken to be zero when the amount of bone is above the fracture threshold; when it is below the threshold, the risk (per unit time) is assumed to be proportional to the difference between the fracture threshold and the amount of bone. Although it is difficult to envisage how the validity of this assumption could be tested, it is more satisfactory than the assumption that a discontinuity in risk occurs at the fracture
threshold. The maximum longitudinal load which a bone can withstand is a continuously increasing function of its bone mineral mass per unit length (Currey and Horsman[20, Dalen et al.[4], Horsman and Currey[21]) and, when loaded longitudinally, the bone fractures if this load is exceeded. The particular values of load in a potential fracture incident, such as a fall with the arm outstretched in the case of the Colles' fracture, will depend in part on the response of the person falling. For example the energy which has to be dissipated (mainly the standing potential energy) may be absorbed slowly through muscular action or abruptly if the person breaks the fall on the hand with the arm straightened. Thus whatever the amount of bone might be, and whatever the circumstances of the fall, there must be a probability distribution associated with the incident which describes the fracture risk, and the amplitude of that distribution will increase as the amount of bone decreases. Our model as presented in this paper effectively combines that probability distribution with others which describe the varying circumstances of the falls and the probability of falling, and we have assumed that the combined distribution is independent of age. Although the only age-dependent factor which has been separated out is the amount of bone, in principle there is no reason why the approach cannot be extended to take account of other age-related factors provided appropriate data are available.

The model is useful in providing a conceptual framework for the interpretation of age-related changes in quantitative bone measurements and fracture epidemiology. Since osteoporosis has been previously been "defined" in terms of bone measurements and/or fractures (Morgan[22], Nordin[15, Nordin et al.[16]), the model is also a means of predicting the differences one might expect to observe between osteoporotic and nonosteoporotic groups given any particular definition. For example, it is to be expected that fracture cases will tend to have faster rates of bone loss and/or lower amounts of bone as young adults since both factors reduce the age at which the individuals cross the fracture threshold. This expectation has been confirmed by the model but the results indicate that the search for one measurement which might enable individuals to be classified as either osteoporotic or not is probably futile. If osteoporotic subjects are so-called because they have fractures, many can be expected to have amounts of bone in the normal range for their age, having had normal bones as young adults and normal rates of bone loss. If osteoporotic subjects are defined in terms of particular bone measurements (including rates of loss), many osteoporotics will not fracture. It is inherent in the stochastic nature of age-related bone loss and fractures that categorization of individuals other than by the fracture event itself is not meaningful.

More positively, our approach does suggest a means by which fracture risk might be predicted in an individual provided sufficient is known about the particular variables which determine the risk and provided appropriate measurements are available on the individual. As far as the choice of measurements is concerned, it is clear from the attempts to match predictions of the model with observed fracture incidence that the measure of the amount of bone which predicts fracture risk might have a higher mean value in men than in women. Although this may appear an obvious conclusion, in general the tendency has been to quantify "osteoporosis" in terms of bulk densities of bones (or their equivalents) in the measurement region (e.g. the fractional volume of a biopsy plug occupied by bone tissue and the mass per unit volume of bone mineral) (Horsman and Leach[23], Nordin et al.[16]). These quantities usually have closely comparable mean values in the two sexes (although there are exceptions) (Horsman[24]). Other properties, such as the bone mass per unit length, differ between the sexes, with higher values in males (Johnston et al.[19]). Thus it would seem that in quantifying osteoporosis in terms of bulk densities, the expected association between osteoporosis and fracture risk has been inadvertently weakened. The argument that variability in bone mass per unit length measurements associated with differences in bone size should be removed for no other reason than to generate a new measure with reduced dispersion clearly leads to conceptual difficulties.
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The implication of our approach is that osteoporosis is quantifiable as a set of probabilities, the instantaneous fracture probabilities at the sites particularly susceptible to a large increase in risk with advancing age. The derivation of these probabilities involves measurements at the fracture sites themselves. The probabilities are not independent because correlations exist between bone mass measurements at different sites in the skeleton (Horsman et al.[25], Ingalls[26]) and it is possible to envisage that the probabilities might be combined to estimate the risk that a fracture of unspecified type will occur. This single risk estimator would be the unifying link between the measurements and the clinical diagnosis of osteoporosis through a history of atraumatic fractures.

REFERENCES