Predictions of Age-specific Hip Fracture Incidence in Elderly British Women based on a Virtual Population Model

Li, Q.[1,2], Prabhu H.R., S.[1,2], Altai, Z.[1,2], Qasim, M.[1,2], Paggiosi, M.A.[1,3], McCloskey, E.V.[1,3], Eastell, R.[1,3], Viceconti, M.[1,2,4,5], Bhattacharya, P.[1,2]

[1]Insigneo Institute for *in silico* Medicine, The University of Sheffield, Sheffield, U.K.

[2]Department of Mechanical Engineering, The University of Sheffield, Sheffield, U.K.

[3]Academic Unit of Bone Metabolism, University of Sheffield, Sheffield, U.K.

[4]Department of Industrial Engineering, Alma Mater Studiorum - University of Bologna, Italy

[5]Laboratorio di Tecnologia Medica, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

1. Introduction

Clinical trials are expensive, and the risks posed to the participants are not fully known. Yet, participant numbers in clinical trials are often too small to conclude a statistically significant positive effect of the proposed intervention. A case in point are interventions targeting the reduction of hip fracture risk due to ageing in women. The socioeconomic relevance of this condition is well-known: for women over the age of 50, the remaining lifetime risk of suffering a hip fracture is equivalent to that of breast cancer; the cost of treating fragility fractures at the hip is over £2 billion annually in the UK. Yet, hip fracture incidence in the general population is very small (32 fractures per 10,000 person-years in British women over 50 [1]). This impedes reaching a statistically significant conclusion in a clinical trial with fracture as endpoint. *In silico* clinical trials (ISCTs) have been proposed as a computational tool to alleviate such challenges. Here, virtual patients are recruited in the trial increase the confidence in the study result. A virtual patient is a digitised data-set comprising biomedical information relevant to the disease/condition and treatment in question. An ISCT simulates a standard trial by subjecting virtual patients to untreated and treated conditions, where each condition is expressed by a mathematical model. Therefore, two ingredients are indispensable in any ISCT, irrespective of the intervention: a virtual patient definition and a mathematical model for the untreated condition.

In this study, we focus on absolute risk of current hip fracture due to age in elderly British women as the untreated condition. A recent study [2] – revisited briefly below – determined a minimal data-set that can describe a virtual patient when considering this untreated condition. The present study focuses on the remaining key ingredient, i.e. the untreated condition model for the effect of ageing on these virtual patients. The aim of this study is to validate the predictions of the untreated condition model against epidemiological data in the literature, as a first-step towards realising an ISCT for interventions to reduce risk of fragility hip fractures.

2. Methods

Recently, a multiscale model [2] was shown to be able to classify current hip fracture status in a post-menopausal cohort of British women who were referred to secondary osteoporosis care in the UK (henceforth, Sheffield cohort; $n = 49$ hip fracture patients and $n = 49$ age-, weight- and height-paired control subjects) with 77.6% specificity and 81.6% sensitivity. This model accounted for patient-specific determinants from the whole-body scale – specifically, body mass (m) and body height (H) – and from the organ scale – specifically, proximal femur geometry and the

volumetric bone mineral density (vBMD) distribution within it. Whole-body scale determinants (characteristics of fall frequency and kinematics) were assumed identical across all subjects. The model predicted the quantity ARF0, defined as the absolute risk of hip fracture over a period less than a year, such that age-related changes could be neglected. Thus, henceforth a virtual patient for the untreated condition considered here is characterised by the above determinants (both patient-specific and non-patient-specific).

The untreated condition model aims to create a virtual patient population by considering how virtual patient characteristics change between age-groups. However, not all changes need to be captured. The strength of the proximal femur depends on its geometry and the distribution of volumetric bone mineral density (vBMD) within it. As the elderly are skeletally mature, and because 84% of the variation in ARF0 in the Sheffield cohort was explained by the variation in bone strength alone [2], in this first-order untreated condition model, it is assumed that the distributions of bone geometry and fall frequency and kinematics are identical between any two of the 5-year age-groups: 55–59, 60–64, ..., 75–79. The main approach to developing the untreated condition model is that the distribution of ARF0 varies between age groups due to variation in the distributions in bone strength. This is based on the observation that bone is lost during ageing, as characterised by decrease in average femoral neck areal bone mineral density (FN-aBMD) across age-groups [3]. The untreated condition model predicts how ARF0 distributions vary between age-groups based on epidemiologically-observed variations in FN-aBMD distributions. The model implementation is described below.

A unit change in FN-aBMD changes vBMD by an amount M^0 that is assumed to be a universal constant and is determined as follows. Clinical computed-tomography (CT) scans of the hip taken from the Sheffield cohort subjects are segmented to obtain the proximal femur region, which is then discretised into a finite-element (FE) tetrahedral mesh with element-wise vBMD (obtained by mapping the mesh to the CT image). Ninety-two of the (native) FE meshes are morphed to a template mesh (the remaining 6 could not be morphed) such that all morphed meshes had identical number of elements and at anatomically similar locations. A non-linear least-squares procedure that minimises the difference $\max_{e^*}\left|D_s^{e^*} - \langle D_s^{e^*}\rangle_s - M^0(d_s - \langle d_s\rangle_s)\right|$ is used to determine M^0. Here, D and d denote vBMD and FN-aBMD respectively, indices e^* and s (s = 1...92) identify a specific morphed mesh element and a specific subject respectively, the operators $\langle\cdot\rangle_s$ and $\max_{e^*}|\cdot|$ denote an average taken over all subjects and the maximum absolute value taken over all morphed mesh elements respectively.

For each of the 5-year age-groups above, 31×N virtual subjects are defined (N = 10000) as follows. N samples of the triplet (m, H and d) are drawn and each triplet is associated to the 31 proximal femur geometries of the control subjects in the Sheffield cohort. The distributions of m and H are assumed to be correlated and the distributions of d and proximal femur geometries are assumed to be independent with respect to all other variables; m, H and d are assumed to be normally distributed and the 49 proximal femur geometries are assumed to represent the distribution of proximal femur geometries in the general British elderly female population. Mean and standard deviation (SD) of m and H are based on age-specific data [3] but the covariance is considered age-group independent [4]. Age-group-specific mean and SD of d are taken from the OPUS study [3]. To complete the definition of a virtual subject the vBMD distribution within the

proximal femur geometry needs to be specified, which is straightforward given M and the FN-aBMD of the Sheffield cohort subject. As this requires substantial computational effort in executing FE simulations for all virtual subjects, the following approach is instead taken. Here, it is assumed that a unit change in FN-aBMD changes bone strength under side-fall configuration by an amount $k_s^{\alpha',\beta'}$, which for a given combination of loading orientation and proximal femur geometry, is a universal constant. The angles of hip abduction (α') and internal hip rotation (β') specify the loading orientation (see [2] for details) and the label s identifies the proximal femur geometry of a Sheffield cohort control subject. We obtain $k_s^{\alpha',\beta'} = \left(S_{s'}^{\alpha',\beta'} - S_s^{\alpha',\beta'}\right)/(d_{s'} - d_s)$ by determining the orientation- and femur geometry-specific bone strength $S_{s'}^{\alpha',\beta'}$ for only one virtual subject s' with geometry identical to s (discretised identically to the native FE mesh of s) and with $d_{s'}$ sufficiently different from d_s. With $k_s^{\alpha',\beta'}$ known, $S_{s'}^{\alpha',\beta'}$ for any arbitrary virtual subject is known without needing any further FE analysis. In order to ensure repeatability of determining $k_s^{\alpha',\beta'}$, we set $d_{s'} = \bar{d}_j$ where is $\bar{d}_j$ is the mean FN-aBMD of either 55–59 or 75–79 age-group in the OPUS study, whichever is father from d_s.

3. Results and Discussion

The rate of change in vBMD with respect to FN-aBMD was found to be M = 0.391 cm^{-1}. The residual of the non-linear least squares error was found to be 0.092 g/cm^3 and quantifies the error in predicting vBMD due to its assumed linear relationship with FN-aBMD. Considering that the average vBMD across all elements and subjects is 0.2607 g/cm^3, the linear relationship is associated with an error of 35.3% on average. The rather large error is clearly a limitation of the assumption that bone loss is homogeneous, which is known to be higher in trabecular bone relative to cortical bone. When considered over all orientations and geometries, the median rate of change of bone strength with respect to FN-aBMD was found to be 44.9 N/(10 mg/cm^2). Considered across all geometries, the median rate of change ranged from 34.8–59.5 N/(10 mg/cm^2), while considered across all orientations, the median rate of change ranged from 26.7–58.1 N/(10 mg/cm^2) – revealing a stronger sensitivity to impact orientation than to bone geometry. It must be noted that this result is potentially affected by the ranges of impact orientations and femoral geometries considered here. In the previous study, it was found that the threshold value of ARF0=37.4% resulted in the most optimal stratification between fracture and non-fracture subjects. Figure 1 compares fracture incidence predictions based on this threshold against epidemiological data [1].

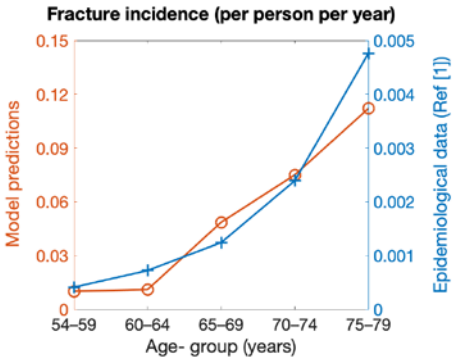

Figure 1 Comparison of model prediction and epidemiological observation of hip fracture in elderly British women. Note the difference in scale between the left and right vertical axes.

The untreated condition model predicts similar trends in age-specific hip fracture incidences, however with magnitudes ~30 times higher than those observed epidemiologically. The

discrepancies arise from the following assumptions: (i) postural attenuation of impact (accounted for in the ARF0 model) remains constant between age-groups (potentially overestimating fall severity in the younger elderly), (ii) bone geometry in the Sheffield cohort is representative of its distribution in the general population, (iii) fall rate data is reliable and (iv) bone loss is spatially homogeneous. The first three are due to paucity of biomedical input data that feeds the model and are major research questions in themselves. The last assumption can be removed by developing a law for bone loss based on tissue type and is currently under progress.

The model validation strategy is to test predictions against epidemiological data. i.e. by comparing predictions against parts of the population (e.g. different age bands). The advantage is that sufficient epidemiological data regarding fracture incidence is available. The disadvantage is that we test whether fracture incidence is matched, not whether a specific subject suffers a fracture. However, imagine that we compartmentalise the same population in different ways by age bands, by sex, by geographical regions, etc. If the model predictions are satisfactory for each method of compartmentalisation, then one can argue that the model will also satisfactorily predict fracture risk by combining the compartmentalisations. This would imply that model prediction is satisfactory in a specific age-band, for a specific sex, for a specific region, etc. As we increase the number of ways the population is compartmentalised, and in turn validate the model, we narrow down the number of subjects that meet the conditions when all compartments are combined, thus achieving subject-specific validation in the limit.

4. Conclusions

An untreated condition model was developed with the aim of predicting age-specific hip fracture incidence in British women. Several lacunae in the quantitative characterisation of ageing need to be met in order to realise an accurate ISCT for fragility hip fractures.

This study was partially supported by the UK Engineering and Physical Sciences Research Council through the MultiSim Project (EP/K03877X/1).

References

1. Curtis EM, van der Velde R, Moon RJ, et al. Epidemiology of fractures in the United Kingdom 1988-2012: Variation with age, sex, geography, ethnicity and socioeconomic status. Bone. 2016;87:19–26. doi:10.1016/j.bone.2016.03.006
2. Bhattacharya P, Altai Z, Qasim M, et al. A multiscale model to predict current absolute risk of femoral fracture in a postmenopausal population. Biomech Model Mechanobiol. 2019;18(2):301–318. doi:10.1007/s10237-018-1081-0
3. Paggiosi MA, Glueer CC, Roux C. et al. International variation in proximal femur bone mineral density. Osteoporos Int. 2011;22:721–729. doi:10.1007/s00198-010-1336-9
4. Wells JCK, Treleaven P, Cole TJ. BMI compared with 3-dimensional body shape: the UK National Sizing Survey. Am J Clin Nutr. 2007;85:419–425. doi:10.1093/ajcn/85.2.419
5. Gale CR, Cooper C, Sayer AA. Prevalence and risk factors for falls in older men and women: The English Longitudinal Study of Ageing. Age Ageing. 2016;45:789–794. doi:10.1093/ageing/afw129