Fracture Risk of the Proximal Femur in Osteoporosis: A Closer Look at the Role of Geometry

Summary

Osteoporosis, the silent disease, is a metabolic disorder mainly affecting post-menopausal women which induces progressive loss and deterioration of the bone tissue. The bone gradually becomes more porous and fragile often without symptoms, until a fracture occurs. 200 million people are currently affected by this disorder globally, and due to the increased longevity of the population, especially in western countries, its incidence is expected to grow dramatically over the next 30 years. Osteoporosis clinical relevance lies in the fractures it causes: according to the World Health Organization, in 2010 3.5 million fractures were estimated to have occurred in European countries. Not only impressively high levels of morbidity and mortality are associated to these fractures, but there are also strong economic implications for the healthcare systems. Among osteoporotic fractures, hip fractures are considered to be particularly devastating because of the severe aftermaths they entail as well as the related costs. At present, the presence of osteoporosis is assessed based on the Bone Mineral Density (BMD) measurement using DXA, the standard imaging technology for diagnosis purposes. Comparing the patient-specific BMD value with that related to a standard young population, the T-score is computed, which represents the gold-standard for patients classification. Based on the T-score value, patients are indeed classified as healthy (T-score > -1), osteopenic ($-2.5 <$ T-score < -1) or osteoporotic (T-score < -2.5). However, T-score predictive weaknesses have increasingly been highlighted in literature. In particular, its poor sensitivity has been pointed out, given that almost half of the people suffering from an osteoporosis-related fracture would not be currently classified as at risk by the T-score.

Against this background, the main purpose of the work presented within this thesis was to investigate if the current gold-standard predictive performances in estimating the proximal femur fracture risk could be enhanced. Particular attention was paid to the proximal femur geometry, since geometry does represent a determinant of the resistance to loading of a structure. In this respect, Hip Structural Analysis (HSA) is a tool allowing the extraction of a number of geometric variables directly from the mineral mass information contained in DXA images. HSA variables are provided to clinicians together with the DXA related data, but do not actually find any practical application. To achieve the main objective of the study, a cohort of 28 post-menopausal was used, for whom DXA and CT images were available simultaneously. Unfortunately, no follow-up information was available for them, but two additional patients, fractured at the proximal femur within 1 year after the DXA exam, were included in the study although lacking the CT images.

In the first chapter, three-dimensional Finite Element (FE) analyses were built taking advantage of the available CT images. Indeed, they allowed the construction of realistic models combining the three-dimensional patient-specific anatomical features and heterogeneous material properties distribution. To investigate the patient-specific risk of proximal femur fracture, a sideways fall condition was simulated and two different fracture risk indices, the Risk Factor Index (RFI) and the Femoral Strength (FS) were extracted adopting principal strains-based failure criteria. Subsequently, a multivariate regression analysis was carried out in order to identify the optimal regression model for predicting the RFI and FS from the available HSA parameters. CT is not indeed routinely employed for osteoporotic patients and the 3D models development is therefore prevented. That is the main reason why HSA variables, clinically available, were included in the regression analysis, aiming to identify those most relevant with respect to estimated fracture predictors. The most meaningful HSA parameters turned out to be the buckling ratio at the neck and shaft together with the neck shaft angle. This outcome was consistent with the prevailing bending stress occurring, especially at the neck, during sideways falls and with the reduction in cortical stability which takes place with ageing, and is worsened by osteoporosis. Moreover, compared to the T-score, the two risk indices allowed to disclose distinct risk levels among

patients belonging to the same T-score range, with particular attention to the osteopenic one. From this perspective, the two additional fractured patients, osteopenic, were correctly predicted by the optimal regression models in the higher risk regions.

In the second chapter, two-dimensional FE analyses built on DXA images were performed in analogy with the CT-based ones of the previous chapter. Patient-specific proximal femur geometry and heterogeneous material properties based on the available pixel-by-pixel BMD maps were included in the analyses, although characterized by the projective nature of the DXA image. The purpose was to assess if DXA-based FE analyses, which would be clinically attainable because based on the standard imaging technique, could be considered comparable to the CT-based ones. Therefore, patient-specific 2D FE analyses reproducing a sideways fall were carried out for the 28 patients analogously to those performed in the previous chapter on the same patients. Equivalent fracture risk indices, RFI and FS, were computed (RFI_{2D} and FS_{2D}). Although a significant correlation was found between the 2D and 3D risk predictors, the correlation was modest, thus supporting the conclusion that CT- and DXA-based outcomes would not appear to be equivalent. However, the HSA variables identified as the most relevant to the two-dimensional fracture risk were the buckling ratio at the neck and shaft, cross-sectional moment of inertia and neck-shaft angle, not discordant to those relevant to the CT-based risk. Furthermore, compared to the T-score, RFI_{2D} and FS_{2D} highlighted as at higher risk the same patients the CT-based RFI and FS drew attention to. The fractured patients were correctly located in the high risk area by the FS_{2D}, only one by the RFI_{2D}.

In the third chapter, statistical shape and intensity models were built aiming to further investigate the role of geometry, BMD distribution and their interaction within the fracture risk determination. Principal Component Analysis (PCA) and Partial Least Square (PLS) algorithms were employed, aiming to identify not only the most meaningful modes of variations of the shape and BMD distribution, but also those most relevant with respect to the 3D-based Femoral Strength (FS). DXA-based shape and BMD data were used, with the purpose of accomplishing usable outcomes, able to be integrated in the current diagnostic framework. On the other hand, the FS extracted from the CT-based FE analyses was used as the reference response variable, judged more realistic and comprehensive. Statistical shape modelling allowed to capture global morphological features not limited to the HSA variables, which are discrete and often interrelated. In addition, the main intensity features could be gathered as a whole through statistical intensity modelling. Interestingly, significant correlations were identified between the main intensity and shape modes. The most meaningful BMD distribution features turned out to be able to explain most of the variance contained in the FS. However, when combined with shape features, the percentage of variance explained increased from 57.18% to 66.9%. Eventually, Canonical Correlation Analysis allowed to predict the changes in shape and BMD distribution occurring for decreasing FS values. In this respect, the main anatomical alterations interested an increase in the neck-shaft angle and a narrowing of the intertrochanter width.

In conclusion, this works represents an attempt to clarify the role of geometry within the osteoporotic fracture risk of the proximal femur. The HSA variables most relevant to the fracture risk were, except for the neck shaft angle, all intrinsically tightly related to the density distribution. This might appear an evidence of the fact that the use of HSA variables as risk predictors might be misleading in interpreting the role of geometry, since they are actually determined based on the mineral mass distribution enclosed in DXA images. From this perspective, statistical shape-intensity modelling highlighted this aspect, since most of the femoral strength variance was explained by the main BMD distribution features rather than by the anatomical ones. However, the inclusion of shape features did lead to an improvement, which might seem to witness a role of geometry. DXA-based FE analyses, combining the heterogeneous material properties extracted from the local BMD map with the patient-specific 2D femoral shape, did manage to better stratify osteopenic patients, although they may not be considered equivalent to CT-based FE analyses. Larger cohorts with available follow-up information will unquestionably help in gaining further insights in the synergistic role shape and BMD distribution play as proximal femur fracture risk determinants, but the results, with regard to the statistical shape-intensity modelling approaches especially, appear promising tools for accomplishing that ambition.