COMPARATIVE ANALYSIS OF THE OSTEOPOROTIC BONE QUANTITATIVE PARAMETERS – COMPUTATIONAL BONE REMODELLING MODEL VS DUAL ENERGY X-RAY ABSORPTIOMETRY

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Abstract. With the aging of the population worldwide, osteoporosis is an increasingly serious public health problem. Therefore, this subject is under intensive research, with the last decade bringing great advances in the understanding of the bone remodelling process. Diagnosis of osteoporosis is based on the T-score calculated from bone mineral density (BMD) measurements by dual energy x-ray absorptiometry (DEXA). On the other hand, the development of computational models for bone remodelling provides a valuable tool for bone density analysis. This work presents a comparative analysis of the DEXA results from a Portuguese population, with the results obtained from a computational model of bone remodelling. This comparison was based on a quantitative and qualitative perspective. The results suggest a strong correlation between the biological parameter of the computational model $\kappa$ and the T-score of the exams in the femoral neck region of interest (ROI).

1. INTRODUCTION

Osteoporosis is a systemic skeletal disease characterised by a reduction of total bone mass, followed by the microarchitectural deterioration of bone structure. These factors lead to a state of enhanced bone fragility and hence susceptibility to fracture [1]. The demographical trends point to the aging of the population worldwide, with the number of hip fractures expected to rise from 1.7 million in 1990 to 6.3 million in 2050, even if the age-adjusted incidence rates for hip fractures remain constant which is not expected [2].

The bone remodelling process plays a key role in osteoporosis, with the net balance between bone resorption and bone formation settling the gain or loss of bone. The advances in the understanding of this process in the last decade lead to the development of new therapies acting primarily in the bone resorption process. Nevertheless osteoporosis is still a serious public health issue.

The diagnosis of osteoporosis is based on the T-score calculated from bone mineral density (BMD) measurements by dual energy x-ray absorptiometry (DEXA). This technology represents the gold standard for the diagnosis of osteoporosis. It provides a 2-D image of
proximal femur and its measurements of BMD correlates partially (R=0.6) with bone resistance to fracture. The bone resistance to fracture depends not only on the quantitative aspects of bone, like BMD, but also on the qualitative aspects of bone structure [3]. In fact, the measures of BMD do not explain totally fracture incidence, as over half of those who experience fragility fractures do not have a T-score value below the threshold proposed by the World Health Organization (WHO) to classify osteoporosis [4]. Therefore, the “bone quality” aspects like the bone microarchitecture, porosity or orientation of collagen fibres are under intense research.

On the other hand, the development of computational remodelling models provides another basis of discussion for the understanding of remodelling processes. The interpretation of Wolff’s postulates stated that (1) the trabecular bone self-reacts in function of the daily imposed mechanical stresses; (2) the trabecular bone structure is aligned accordingly to the principal strain directions (3) the bone behaviour can be modelled by mathematical laws.

These principles were used by several authors in their studies of bone remodelling behaviour, e.g [5]. These studies used design variables such as bone density or trabecular orientation evolving in function of some mechanical stimulus like strain energy density or strain. In the present work, the computational model used includes a biological parameter \( \kappa \) that influences the total bone mass. Therefore, this parameter can be interpreted as a biological cost for maintaining proper bone tissue. In that sense, it is clear that this biological cost depend on variables like age, sex or hormonal status. This work establish himself as the first approach to study a possible correlation between the T-score calculated on the basis of the BMD measure by DEXA and the biological parameter \( \kappa \) of the computational model. This approach is a contribution for a better understanding of bone redistribution in osteoporosis, establishing a mathematical relation between T-score and \( \kappa \). In addition, the computational model results were compared with clinical results to ascertain his predictive value.

2. METHODS

This section provides a detailed explanation of the methodology of comparison between the results from the computational model and the DEXA results.

2.1. Computational bone remodelling model

The bone remodelling model used in the present work [6] is an extension of a structural optimization model [7] to the study of trabecular bone adaptation. Assuming bone self-adapts in order to have the stiffest structure for the supported loads, this model combines a stiffness criterion with a biological cost parameter \( \kappa \) that control the total bone mass. Trabecular bone microstructure was modelled by the periodic repetition of a cubic cell with a prismatic hole of dimensions \( a_1, a_2 \) and \( a_3 \). The relative density, \( \mu \), depends on the local hole dimensions, in the form \( \mu = 1 - \frac{a_1}{a_2} \frac{a_3}{a_3} \). In this work, the relative density is the design variable and the strain field represents the mechanical stimulus. The bone remodelling law may be stated in a simplified form by equation 1:

\[
\frac{\partial \mu}{\partial t} = \sum_{i=1}^{P} \left[ \alpha^i \frac{\partial E_{ijkl}^H(\mu)}{\partial \mu} \epsilon_{ij}(u^*) \epsilon_{kl}(u^*) \right] - k
\]
This equation is derived for a multiple load formulation where a weighted set of $P$ loads characterizes the loading environment applied to bone, where $\alpha$ is the weight for each load, $\varepsilon_{ij}(u^r)$ is the strain field for the load case $r$ and $E_{ijkl}^H$ are the bone elastic properties obtained by the homogenization method [8]. It should be noted that the remodelling equilibrium ($\partial \mu / \partial t = 0$) corresponds to the stationarity condition of the optimization problem with respect to bone relative density $\mu$.

The model described above was applied to a three-dimensional model of proximal femur; the finite element mesh, generated by the interaction of a Fortran routine with ABAQUS, has 12408 8-node solid elements.

The three load cases used in this work [9] are summarized in table 1; the load cases 1 and 2 correspond to the movement of walking while load case 3 correspond to the movement of climbing stairs. For a more realistic approach to the physiological movements and loads that act on proximal femur daily the multiple load formulation was used with equal load weights ($\alpha_1 = \alpha_2 = \alpha_3 = 1/3$).

The problem was solved for 5 different values for the parameter $\kappa$ ($\kappa=0.01;0.05;0.1;0.25;0.5$). The values of relative density and volume for the 12408 elements were imported from ABAQUS to Microsoft Excel (ME), where the absolute densities were computed multiplying the relative densities by a multiplicative factor of 1.74. Therefore, the range of absolute densities obtained was 0.01-1.74 g/cm$^3$. The Young’s modulus was assumed to be 20GPa for dense compact bone.
Table 2.1 – Load cases applied to the proximal femur

<table>
<thead>
<tr>
<th>LOAD CASE</th>
<th>$F_x$ (N)</th>
<th>$F_y$ (N)</th>
<th>$F_z$ (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>768</td>
<td>726</td>
<td>1210</td>
</tr>
<tr>
<td></td>
<td>-224</td>
<td>-972</td>
<td>-2246</td>
</tr>
<tr>
<td>2</td>
<td>166</td>
<td>382</td>
<td>957</td>
</tr>
<tr>
<td></td>
<td>136</td>
<td>-680</td>
<td>-1692</td>
</tr>
<tr>
<td>3</td>
<td>383</td>
<td>669</td>
<td>547</td>
</tr>
<tr>
<td></td>
<td>457</td>
<td>-796</td>
<td>-1707</td>
</tr>
</tbody>
</table>

The next step was the selective choice of elements from the finite element mesh that represent the three most important regions of interest (ROI) from the clinic exam of DEXA: femoral neck, Ward’s triangle and trochanteric region (figure 2.2). As an example, figure 2.3 shows the set of elements that represent the femoral neck ROI.

The values of bone mineral content (BMC) were computed in ME for the whole set of elements, and sequentially for the elements composing the 3 ROI studied in this work, with the relation:

\[
BMC_e = BMD_e \times V_e \tag{2}
\]

with $V_e$ representing the volume of the element. These results were computed for the whole
range of values taken for parameter $\kappa$.

2.2 DEXA results

At this level, 160 Caucasian women DEXA exams were chosen from the database of the Rheumatology Department of Santa Maria Hospital, following the criterion of anatomical pattern of proximal femur. This criterion excluded exams showing a high level of femoral anatomical variation, that impairs the correct definition of the ROI by the software used in this analysis (enCORE2007®), and sequentially the correct measure of BMD and BMC. The values of height, weight, BMC and T-score for the 3 ROI in study were imported to ME, where the age, bone mass index (BMI) and the ratios femoral neck BMC/Ward BMC, trochanter BMC/femoral neck BMC, trochanter BMC/Ward BMC were computed using macros developed in Microsoft Visual Basic (MVB). A statistical study was undertaken to study the demographical characteristics and osteoporotic classification of the subset taken from the original database.

2.3 Comparative analysis of the clinical and computational results

This analysis was made regarding the differences between the outputs of the two methods in study. As so, the computational output provides relative densities and volumes for the whole set of elements, which are computed in the BMC and ratios referred in 2.2, for the 3 set of elements that represent the 3 ROI from the DEXA exam. On the other hand, the DEXA exam provides values of BMC, BMD and T-scores for the 3 ROI.

The two methods used in the present work differ in dimensional space, with DEXA representing the bone as a two-dimensional image and the computational model representing it as a three-dimensional body. This fact, do not allow the comparison between these methods to be made on a BMD basis, because DEXA measures it in $g/cm^2$ and not in $g/cm^3$ like the computational model. Therefore, only BMC and BMC ratios can be used in this comparison, as they relate to the bone itself in its three dimensions. The predictive value of the computational model to estimate BMC and BMC ratios of the 3 ROI was evaluated with a criterion of error of 10%, 15% and 20%, using macros that select and count the exams from the subset in study, whose values for BMC and BMC ratios are within this range. The criterions used in this study were: femoral neck BMC, region of Ward BMC, trochanter BMC, ratio femoral neck BMC/Ward BMC, ratio trochanter BMC/Ward BMC and ratio trochanter BMC/femoral neck BMC. An additional and more restrictive criterion – “ratios criterion” – was developed to complete this study. This criterion states that the 3 ratios must be concordant between the models under a 10% criterion of error. This analysis was done for the whole set of values taken for the parameter $\kappa$.

The methodology to study the possible correlation between $\kappa$ and T-score, was undertaken by plotting the values of T-score for the subset of exams with BMC values concordant with the computational model for the whole set of values used for the parameter $\kappa$. This analysis was done, using 3 criterions of comparison: femoral neck BMC, region of Ward BMC and trochanter BMC. Another methodology was developed for this study as the exams from women with less than 50 years and outside the BMC range of [20;30] (kg/m²) were excluded. This methodology was named “additional selection” and intended to exclude other contributions to the variation of T-score, than the variation of the parameter $\kappa$. The correlation was studied with linear and quadratic regression between the two sets of values for the whole set of criterions stated.
The qualitative approach used the visualization toolbox of ABAQUS that provide two-dimensional section views of the 3-D proximal femur model, enabling direct comparison between the two methods. This comparison was based on the mathematical relation obtained in the correlation study; using this relation, the T-scores were computed for $k=0.01; 0.05; 0.1; 0.25$. The goal is the qualitative validation of the mathematical relation obtained in this work, based on the analysis of the density profiles from the two methods for the pairs of values obtained (T-score/$k$).

3. RESULTS

The density profiles obtained from the computational model results reflect certain important morphological features of the proximal femur. In the diaphysis one obtains a hollow cylinder with high relative densities in the periphery representing cortical bone; this external layer of elements with maximum densities is not highly affected by changes in $k$. In turn, the epiphysis exhibits lower densities, corresponding essentially to trabecular bone; this anatomical region is very sensitive to changes in the parameter $k$.

Figures 3.1, 3.2 and 3.3 represent the quantitative comparison based on the methodologies described in 2.3, with $p$ representing the clinical exam percentage that mimics the computational model results for an error criterion of 10, 15 and 20%.

![Quantitative comparison of BMC from femoral neck](image)

Figure 3.1 – Quantitative comparison – femoral neck BMC criterion

The quantitative comparison based on the femoral neck BMC shows the highest concordance level (almost 80%) between the computational model results and the clinical DEXA results, as shown in figure 3.1. The results analysis based on the variation of the parameter $k$, shows higher concordance levels for the intermediate values of 0.05 and 0.1. For instance, this can reflect already a relationship between the parameter $k$ and the T-score of the population that was confirmed later in the correlation study. The figure 3.2 represents the quantitative comparison based on the ratio: femoral neck BMC/Ward BMC; the results also show high levels of concordance between the two methods studied in this work. For the 20% error criterion, the values of $p$ reach 90%, which highlights the predictive potential of the computational model in bone distribution simulation. The figure 3.3 summarizes quantitative
comparison for the 7 criterions described in 2.3, using a 20% error criterion and k=0.1.

Figure 3.2 – Quantitative comparison - ratio femoral neck BMC/ Ward BMC criterion

Figure 3.3 – Quantitative comparison by criterion (error=20%/k=0.1)

For k=0.1, the results highlight, in general, a good concordance, with the ratios femoral neck BMC/Ward BMC and trochanter BMC/femoral neck BMC showing the highest values for p (79 and 76% respectively); these results show the computational model potential in the simulation of the physiological event of bone remodelling.

The correlation study followed the methodology explained in 2.3; table 3.1 presents the obtained correlation coefficient values. From a biological point of view, the quadratic regression suits better the purpose of correlation study, as the T-score values tend to stabilize in a negative value due to the therapeutic interventions associated with extreme osteoporotic clinical cases. Accordingly, the highest correlation coefficients were obtained for this type of regression (Table 3.1).
The best results were obtained for the femoral neck ROI, using the additional selection criterion (R value = -0.8068); figure 3.4 illustrate the correlation study for this ROI, using quadratic and linear regression. In clinical practice, osteoporosis diagnosis is based on the T-score results from the femoral neck ROI as a result of its high precision and reproducibility in terms of DEXA results; this can be explained by its less subjective demarcation in DEXA global ROI. This fact was transposed to the computational model as its demarcation in the finite element mesh was objective and relatively easy. In addiction, the results obtained by the computational model in femoral neck ROI, do not depend on the way the loads are applied, since this region is far enough from loads application points. Together, this can explain the better correlation results obtained in the present work for the femoral neck ROI. On the other hand, the analysis of table 3.1 shows the failure of the additional selection criterion to improve the correlation coefficients using Ward and trochanter ROIs.

From the correlation results for femoral neck ROI one obtains the following mathematical relation:

\[ T - \text{score} = 24.086\kappa^2 - 16.601\kappa + 0.0553 \]  

Figure 3.4 – Linear and quadratic regression between parameter k and T-score for the femoral neck ROI (additional selection)
The figure 3.5 represents the qualitative comparison between the two methods analysed in this work, using (3) to compute T-score for $k=0.05$ and $k=0.25$; this figure confronts the computational model results, for these $k$ values, with clinical DEXA exams which T-score was computed by (3). For $k=0.05$ and $k=0.25$, one obtains T-score values of -0.7 and -2.6 respectively. These values are classified by the World Health Organization (WHO) as normal and osteoporotic. The chosen values of $k$ may represent the bone loss evolution that leads to osteoporosis; in this basis, the mathematical modelling of computational model parameter $k$ shows effectiveness as the computational model results mimic the bone loss associated with the transition from a normal to an osteoporotic state in the DEXA results. This bone loss begins in Ward’s triangle ROI and expands to the whole global ROI with the thinning of cortical bone peripheral layer as shown in figure 3.5. The qualitative analysis based on (3) evidences a strong concordance in density profiles between the computational model results and clinical DEXA results, which validates the predictive potential of the former in the simulation of bone remodelling processes.

![Figure 3.5 – Qualitative analysis – (up) $k=0.05$/T-score= -0.7 (below) $k=0.25$/T-score= -2.6](image)

5. CONCLUSIONS

With the aging of the population worldwide, osteoporosis is an increasingly serious public health problem. Therefore, this subject is under intensive research, with computational models assuming an important role as a valuable analysis tool of bone remodelling processes.

This work presents a comparative analysis of the DEXA clinical results from a Portuguese population, with the results obtained from a computational model of bone remodelling. This comparison was based on a quantitative and qualitative perspective. The quantitative comparison goal was the validation of computational model predictive value to mimic the physiological bone density profiles.

This work also presents, a correlation study between the T-score calculated based on the BMD measure by DEXA and the biological parameter $k$ of the computational model. The goal is the characterization of the biological component of the computational model that may lead to the understanding of population variational behaviour relative to distribution patterns.
of BMC and incidence of fractures.

The quantitative analysis results highlight the predictive potential of the computational model in bone distribution simulation, with concordance values near or above 50% for all criterions. These results validate the computational model as a valuable tool of analysis in the bone remodeling field. The correlation study between T-score and model parameter k was proposed as the first approach on the mathematical modelling of k. The results showed a strong correlation for these two variables, with the best results obtained for the femoral neck ROI with quadratic regression using the additional selection criterion (R= - 0.8068). From this case one deduces a mathematical relation that relates k with T-score; this relation was qualitatively tested for the whole set of k values used in this work, illustrating the osteoporotic bone loss evolution. The results showed evidences of a strong concordance in density profiles between the computational model results and clinical DEXA results, which validates the predictive potential of the computational model, in the simulation of bone remodelling processes, and the mathematical relation effectiveness. Taken together, the results obtained in the present work provided a contribution to the understanding and characterization of the biological component of the computational model. Further studies are necessary for the long-term objective of computational models integration in osteoporosis clinical diagnosis.

REFERENCES


