Subject-specific finite element models can accurately predict strain levels in long bones

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Abstract

The prediction of the stress-state and fracture risk induced in bones by various loading conditions in individual patients using subject-specific finite element models still represents a challenge in orthopaedic biomechanics. The accuracy of the strain predictions reported in the literature is variable and generally not satisfactory. The aim of the present study was to evaluate if a proper choice of the density–elasticity relationship can lead to accurate strain predictions in the frame of an automatic subject-specific model generation strategy. To this aim, a combined numerical–experimental study was performed comparing finite element predicted strains with strain-gauges measurements obtained on eight cadaver proximal femurs, each instrumented with 15 rosettes mostly concentrated in the bone metaphyses, tested non-destructively \textit{in vitro} under six different loading scenarios. Three different density–elasticity power relationships were selected from the literature and implemented in the finite element models derived from computed tomography data. The results of the present study confirm the great influence of the density–elasticity relationship used on the accuracy of numerical predictions. One of the tested constitutive laws provided a very good agreement ($R^2 = 0.91$, RMSE lower than 10\% of the maximum measured value) between numerical calculations and experimental measurements. The presented results show, in addition, that the adoption of a single density–elasticity relationship over the whole bone density range is adequate to obtain an accuracy that is already suitable for many applications.

Keywords: Subject-specific finite element modelling; Computed tomography; Automatic mesh generation; Experimental validation; Density–elasticity relationship

1. Introduction

Subject-specific finite element models of bones derived from computed tomography (CT) data are a promising tool to non-invasively assess the stress-state and fracture risk of bones in individual patients, but still represent a challenge. Their fields of application span from the design and optimisation of prosthetic devices, to the evaluation of skeletal reconstructions, or the definition of fracture risk for bone segments (Anderson et al., 2005; Barker et al., 2005; Bitsakos et al., 2005; Cody et al., 1999; Couteau et al., 2001; Crawford et al., 2003; Dalstra et al., 1995; Ford et al., 1996; Gardiner and Weiss, 2003; Gupta et al., 2004; Keyak et al., 1993; Keyak et al., 2005; Lotz et al., 1991; Maurel et al., 2005; Oden et al., 1999; Ota et al., 1999; Perillo-Marcone et al., 2004; Schmitz et al., 2004; Taddei et al., 2003; Taylor, 2006; Vazquez et al., 2003; Viceconti et al., 2004; Wagner et al., 2002; Weinans et al., 2000; Wong et al., 2005). A high level of automation is needed (Viceconti et al., 2004) and an evaluation of the obtainable numerical accuracy is mandatory (Viceconti et al., 2005) for the use of subject-specific FE models in the clinical practice. In particular a high accuracy in strain prediction is required to investigate bone limit conditions and eventually define fracture risk factors, given the growing consensus on the adoption of strain-based yield and failure criteria for bone tissue (Bayraktar et al.,...
A very limited number of studies have been dedicated to the systematic validation of subject-specific finite element models of bones against experimental measurements. A good accuracy ($R^2 > 0.8$) in the prediction of strain levels was reported only in three recent works (Anderson et al., 2005; Barker et al., 2005; Gupta et al., 2004) that present, however, a limited degree of generality and automation of the modelling procedures. All of them require high manual effort for tissue type distinction and rely on the assumption of a priori data for the mechanical properties of bone. To the authors’ knowledge the validation studies implementing general and automatic model generation procedures reported low correlations ($R^2 < 0.7$) between predicted and experimental strains (Keyak et al., 1993; Ota et al., 1999).

A very good accuracy ($R^2 > 0.9$) was reported in the prediction of stresses using an automated and general modelling procedure in Taddei et al. (2006a). However, when the same model was used to compare with the strain-gauges measurements, a lower degree of accuracy was found ($R^2 < 0.8$) (Taddei et al., 2006a). This might have been due to the density–Young’s modulus relationship adopted (Keller, 1994).

In fact, it has been demonstrated that the density–elasticity relationship influences subject-specific FE results (Weinans et al., 2000) but still a consensus on the constitutive law to be used has not been reached. This is indeed supported by the existence of a huge spread in the experimentally derived density–elasticity laws reported in the literature (Linde et al., 1992) and by the difficulty in judging which are the most accurate among them. In fact the experimental testing methods evolved through the last decade (Keaveny et al., 1997; Linde et al., 1992) and are still a matter of discussion (Un et al., 2006). To the authors’ knowledge only one study (Barker et al., 2005) investigated the influence of the density–elasticity law within a validation study. The resulting accuracy was dependent on the assignment of the material properties but no final conclusion can be derived from the presented results on the best law to adopt, since the predicted accuracy was highly dependent on the applied load case.

The aim of the present study is to verify which density–elasticity relationship, among three selected from the literature, leads to the most accurate strain predictions within an automated subject-specific finite element modelling strategy. To this aim, a combined numerical–experimental study was performed comparing FE predicted strains with strain-gauges measurements obtained on eight cadaver proximal femurs tested non-destructively in vitro under different loading scenarios.

### 2. Materials and methods

#### 2.1. Specimen details and diagnostic assessments

Four pairs of cadaver femurs, harvested fresh, (Table 1) were obtained (IAM Corporate, Jessup, PA, USA). They were preserved wrapped in a cloth soaked with physiological solution throughout all the experimental tests and kept frozen at $-25^\circ$C when not in use (Evans, 1973).

All the specimens were subjected to Dual energy X-ray Absorptiometry (DEXA) (Eclipse, Norland Co., Ft. Atkinson, WI, USA). All the femurs fell in the range from osteopenia to severe osteoporosis (AIM, 1991) (Table 1).

The specimens were CT-scanned (HiSpeed, GE Co., USA) immersed in water with peak voltage and tube current levels typical of clinical examinations (Table 2).

#### 2.2. Experimental tests

All the experimental procedures refer to validated methodologies described in Taddei et al. (2006a). Only the differences and improvements introduced in the present study are reported in detail.

#### 2.2.1. Specimen preparation

The femurs were prepared with a set of reference axes (Cristofolini, 1997; Ruff and Hayes, 1983). The femoral condyles were potted in a steel box with PMMA cement. Fifteen strain gauges were placed on each specimen, on the Anterior, Lateral, Posterior and Medial aspect of four levels located mostly in the metaphyseal and epiphyseal regions (Cristofolini et al., 1997) (Fig. 1).

The area for strain measurement was prepared using a validated procedure (Viceconti et al., 1992; Taddei et al., 2006a). Pre-wired stacked

### Table 1

**Detailed donor data and specimen information**

<table>
<thead>
<tr>
<th>Specimen #</th>
<th>Right/left</th>
<th>Sex</th>
<th>Cause of death</th>
<th>History of musculoskeletal diseases</th>
<th>Age at death</th>
<th>Donor height (cm)</th>
<th>Body weight (N)</th>
<th>DEXA assessment ($t$-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right</td>
<td>Male</td>
<td>Myocardial infarction</td>
<td>None</td>
<td>67</td>
<td>175</td>
<td>863</td>
<td>-3.21</td>
</tr>
<tr>
<td>2</td>
<td>Left</td>
<td>Male</td>
<td>Myocardial infarction</td>
<td>None</td>
<td>71</td>
<td>178</td>
<td>893</td>
<td>-1.87</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>Male</td>
<td>Myocardial infarction</td>
<td>None</td>
<td>82</td>
<td>175</td>
<td>765</td>
<td>-3.95</td>
</tr>
<tr>
<td>4</td>
<td>Left</td>
<td>Male</td>
<td>Myocardial infarction</td>
<td>None</td>
<td>73</td>
<td>175</td>
<td>716</td>
<td>-4.32</td>
</tr>
</tbody>
</table>

The DEXA results in terms of $t$-score, which is the number (and sign) of standard deviations from the mean reference for young and healthy people, are reported.
rosette strain gauges (KFG-3-120-D17-11L3M2S, Kyowa, Tokyo, Japan, 3 mm grid length) were used.

2.2.2. Loading scenarios

Six different loading conditions were tested that generate bending in different planes, axial loading, and torsion. Rather than replicating specific motor tasks it was decided to apply the resultant joint force at the extreme directions of the cone spanned by the hip joint reaction as recorded by Bergmann et al. (2001) for a wide range of motor tasks. Four extreme positions and a neutral vertical alignment were identified in the frontal and sagittal planes, as in Taddei et al. (2006a) (Fig. 2). A sixth testing scenario was added, tilting the specimens 8° in the frontal plane (LC6, Fig. 2). Preliminary FE analysis showed that this position, resembling the single stance phase of gait, mostly stresses the neck region with respect to the diaphyseal one (Cristofolini et al., 2006).

2.2.3. Load application and measurement protocol

To avoid bone damage, the maximum load applied was the 75% of the donor’s body weight (BW). The specimens were mounted on the 5 kN load cell of the material-testing machine (Mod. 8502, Instron, Canton, MA, USA). Cross-rails were used to avoid undesired horizontal force components.

The measurement protocol was similar to the one described in Cristofolini et al. (1997) and Taddei et al. (2006a) and permitted to quantify material linearity, viscoelastic phenomena and irreversible strains. The maximum and minimum principal strain values for the

Table 2

<table>
<thead>
<tr>
<th>Scanning mode</th>
<th>Helical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice thickness</td>
<td>1 mm from top to little trochanter</td>
</tr>
<tr>
<td>Pitch</td>
<td>1.3 from top to little trochanter</td>
</tr>
<tr>
<td>1.5 in the diaphysis</td>
<td></td>
</tr>
<tr>
<td>Reconstruction spacing</td>
<td>1.3 mm from top to little trochanter</td>
</tr>
<tr>
<td>5 mm in the diaphysis</td>
<td></td>
</tr>
<tr>
<td>Pixel dimension</td>
<td>0.59 mm</td>
</tr>
<tr>
<td>Tube current</td>
<td>160 mA</td>
</tr>
<tr>
<td>Voltage</td>
<td>120 kVP</td>
</tr>
</tbody>
</table>

Fig. 1. Sketch of the anterior and lateral aspect of an instrumented right femur: nominal rosette positions are shown, relatively to femoral biomechanical length and head diameter. The lateral side of the neck level was not instrumented as in this region the surface was too uneven. The distal pot is visible. In some cases the strain gauge location was slightly modified with respect to the nominal position, due to severe surface roughness or vessel insertions. A posterior view of an actual instrumented specimen is shown on the right.

Fig. 2. A visualisation of the different loading conditions applied. LC1 is the neutral vertical position, LC2 and LC3 identify the extreme positions in the frontal plane (3° and 24°), LC4 and LC5 the ones in the sagittal plane (−3° and 18°), LC6 the 8° loading in the frontal plane.
highest load collected from each rosette for each loading scenario (30 s after load application) were used for the validation of the numerical models for a total of 180 measurements for each femur.

### 2.3. Subject-specific finite element models

The generation of the FE-models from the CT data-set is based on the one described in detail by Taddei et al. (2006a). CT datasets were segmented (Amira 3.1.1, Mercury Computer Systems Inc., USA); NURBS models subsequently obtained (Geomagic Studio v. 7, Raindrop Geomagic, Inc., USA) and FE unstructured meshes (10-noded tetrahedra) automatically generated using an advancing-front algorithm (HyperMesh v. 7, Altair Engineering, Inc., USA) (Fig. 3). A node was placed at each strain gauge centre identified with a spatial registration procedure (see below). Each model was trimmed and constrained at the cement level. The average size of superficial elements was 3 mm on the diaphyses and 2 mm on the metaphyses. The eight FE models ranged from 104,020 to 124,592 nodes and from 69,272 to 80,508 elements.

Each CT dataset was calibrated using the European Spine Phantom (Kalender, 1992), assuming a linear relationship between Hounsfield Unit (HU) and bone ash density (Les et al., 1994). Inhomogeneous material properties were automatically mapped onto the FE models with the BoneMat_V3\(^{\text{r}}\) software (Taddei et al., 2004; Taddei et al., 2006b) (available at www.biomedtown.org) that calculates an average Young modulus (\(E\)) for each element of the mesh, firstly converting each HU value into \(E\) and then performing a numerical integration over the element’s volume. This procedure has shown to improve the FE predicted strain accuracy (Taddei et al., 2006b).

An extensive literature review of the different laws adopted in the subject-specific studies published so far, and of those directly derived from mechanical tests on human bone, was performed to identify three suitable relationships to be used over the whole bone densities range. The three density–elasticity relationships used to map the mechanical material properties onto the finite element models were (Fig. 4):

\[
E = 3.790\rho_{\text{ash}}^{0.39} \quad (\text{Carter and Hayes, 1977}),
\]

\[
E = 10.500\rho_{\text{app}}^{2.29} \quad (\text{Keller, 1994, femoral specimens}),
\]

\[
E = 6.950\rho_{\text{app}}^{1.49} \quad (\text{Morgan et al., 2003, femoral neck specimens}),
\]

where \(E\) is expressed in GPa, \(\rho_{\text{ash}}\) (ash density) and \(\rho_{\text{app}}\) (apparent density) in g/cm\(^3\). Ash density data obtained from the calibration had to be normalised to apparent density to apply Eqs. (1) and (3). The assumed \(\rho_{\text{ash}}/\rho_{\text{app}}\) ratio was 0.6, falling in the range 0.55–0.63 identified in the literature (Goulet et al., 1994; Keyak et al., 1994). The influence of strain rate was considered negligible as the tests were conducted in quasi-static conditions. A Poisson ratio of 0.3 was assumed in all cases (Wirtz et al., 2000).

Eq. (1) (Carter and Hayes, 1977), was chosen because it is the most referenced work in subject-specific FE studies (Bitsakos et al., 2005; Keyak et al., 1993; Ota et al., 1999; Perillo-Marcone et al., 2004; Taddei et al., 2004; Wagner et al., 2002; Weinans et al., 2000; Wong et al., 2005). Furthermore, the relationship is obtained by experimental data covering a full range of densities from trabecular to cortical bone. Eq. (2) (Keller, 1994), was chosen since it is the only other study in the literature whose experimental data cover the whole density range and was used in the previous validation study (Taddei et al., 2006a). The relationship relative to the femoral specimens was chosen among the different proposed, accordingly to Morgan et al. (2003) suggesting that anatomical site significantly influences the bone tissue properties and their relation with density. Eq. (3) (Morgan et al., 2003), was chosen because it was obtained with a very robust experimental protocol that minimises random errors.

The data directly referring to the femoral neck were chosen. Eq. (3) was chosen because it is the most referenced work in subject-specific FE studies (Bitsakos et al., 2005; Keyak et al., 1993; Ota et al., 1999; Perillo-Marcone et al., 2004; Taddei et al., 2004; Wagner et al., 2002; Weinans et al., 2000; Wong et al., 2005).

Fig. 3. A sample finite element model of the proximal femur where the registered strain gauges areas are shown in pink (left), and its section along the frontal plane.

Fig. 4. A plot of the Young's modulus as a function of apparent density for the three density–elasticity relationships selected, shown on a range of densities typical of human bones (Eq. (2) equation normalised).
extrapolated over the whole density range. Other relationships proposed in the literature showing very good correlations, such as Goulet et al. (1994) were not considered since they relate the elastic modulus to the ratio of bone tissue volume on total volume (BV/TV), hence they are not directly applicable to subject specific models derived from CT data.

2.4. Models spatial registration

The models were spatially registered, similarly to Taddei et al. (2006a), with the experimental laboratory reference system and the positions of some relevant points (gauges, constraint level, load application points) carefully replicated.

A digitiser (MicroScribe 3DX, Immersion Corporation, San Jose, CA, USA) with 0.2 mm resolution, and an iterative-closest-point algorithm (Besl and McKay, 1992) were used. The registration error ranged from 0.5 to 0.9 mm for the different femurs.

2.5. Determination of model accuracy

The strain rosettes provided the values of the two superficial principal strains. A procedure was developed to determine which FE-model principal strains should be compared to the experimental data, under the assumption of plane-stress state at the model surface.

The calculated principal strains at the surface nodes, corresponding to the sensing area of each strain gauge, were averaged and compared with the experimental measurements. No effect of the load case was observed on the difference between measured and FE predicted principal strains (factorial ANOVA, p-value > 0.9 for all femurs and models) for each specimen, thus all measurements from each femur were pooled together. In addition, the difference between measured and predicted principal strains did not vary between specimens (factorial ANOVA, p-value > 0.05). Hence the data of all models obtained by the same density-elasticity relationship were pooled. (Software used: SPSS, 14.0, v. 14.0.1, Chicago, IL, USA).

A linear regression between experimental and predicted strains was performed to quantify the prediction accuracy and the root mean square (RMS) error and the peak error were calculated.

3. Results

3.1. Experimental measurements

Strain measurements linearity was excellent for all grids and all load configurations on all specimens, with $R^2 \geq 0.95$ ($R^2 \geq 0.99$ in 98% of cases where $\epsilon \geq 50 \mu$). Residual strains were low (1–5% of the peak value 10 min after load removal). Thus a linear-elastic mechanical behaviour was assumed. Repeatability on the same specimen was satisfactory, in the order of few microstrains (1–6% of the measured magnitude for the largest principal strain).

3.2. Comparison between predicted and measured strains

The predicted principal strains correlated differently with the experimental values for the three elasticity–density relationships (Fig. 5). The local error metrics were also clearly different (Table 3). A detailed report of the validation parameters of each model is reported in Appendix. The highest correlation was found for models implementing Eq. (3) and the lowest for models implementing Eq. (1). The models implementing Eq. (3) constitutive equation provided results closest to the ideal values also in terms of slope and intercept value. A Student’s t-test was used to test the null hypothesis of regression slopes being equal to unity and intercept equal to zero. For models implementing Eq. (3) slope and intercept values were found to be not significantly different from unity and zero, respectively (significance level $\alpha = 0.001$). For the other two sets of models the slopes of the regression lines were significantly different from unity ($\alpha = 0.001$) and the intercepts significantly different from zero at a lower significance level ($\alpha = 0.05$) (Armitage and Berry, 1994).

Very low error values (RMSE < 10% of the highest measured strain) were found for the models implementing
Table 3
The validation parameter calculated on the pooled data, reported for the three different $E = f(r)$ functions implemented in the FE models

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</thead>
<tbody>
<tr>
<td>$R^2$</td>
<td>0.554</td>
<td>0.626</td>
<td>0.911</td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>1.434*</td>
<td>1.900*</td>
<td>1.005 NS</td>
<td></td>
</tr>
<tr>
<td>Intercept ($\mu$)</td>
<td>38*</td>
<td>40*</td>
<td>6 NS</td>
<td></td>
</tr>
<tr>
<td>RMSE ($\mu$)</td>
<td>486</td>
<td>616</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>RMSE% $^{b}$</td>
<td>42.27</td>
<td>53.52</td>
<td>9.78</td>
<td></td>
</tr>
<tr>
<td>Max err ($\mu$)</td>
<td>3119</td>
<td>4917</td>
<td>698</td>
<td></td>
</tr>
<tr>
<td>Max err% $^{b}$</td>
<td>271.02%</td>
<td>427.16%</td>
<td>60.61%</td>
<td></td>
</tr>
</tbody>
</table>

NS = not significantly different from 1 (slope) or 0 (intercept).
*Significantly different from 1 (slope) or 0 (intercept).
$^{b}$Percentage of the maximum measured strain.

Eq. (3). Errors were larger for the other two functions tested. Analogously, the peak error obtained using Eq. (3) was lower than the ones obtained with Eqs. (1) and (2), where the 100% of the highest measured strain was exceeded.

4. Discussion

The aim of the present study was to evaluate the influence of the density–elasticity relationship on the strain prediction accuracy of an automatic subject-specific finite element modelling strategy. A combined numerical–experimental study was performed on eight cadaver femurs. Three different density–elasticity power relationships were selected from a review of the literature and implemented in the subject-specific FE models derived from CT data. Strain-gauge measurements were taken in vitro under six different non-destructive loading scenarios, from 15 strain gauges mostly concentrated in the proximal part of the femur. To the authors’ knowledge no other comparable experimental–numerical study was conducted on such large a sample so far, both in terms of number of specimens and number of independent measurements to compare.

The main finding of the present work is that an excellent agreement was observed between numerical calculations and experimental measurements for one of the density–modulus relationships tested (Eq. (3), Morgan et al., 2003). The results obtained with this law neatly overcome those obtained with the other two functions. The experimental–numerical correlation was high for Eq. (3), while a consistent scatter exists for Eqs. (2) and (1). The slope of the regression line was statistically not significantly different from unity for Eq. (3), which therefore seems to well identify the global femoral bone stiffness under a variety of loading conditions. It was instead significantly higher than unity for Eqs. (1) and (2), indicating an overestimation of the predicted strains. The intercept of the regression line was also not significantly different from zero only for Eq. (3). However, the intercept value was very small for all laws, with respect to the range of strain measurements performed. The RMSE was very good when adopting Eq. (3), at least four-fold better than with the other two functions. The peak errors were quite variable between specimens and almost always occurred in areas with extremely localised features. In fact, the presence of peak errors was related to certain strain gauges, placed where surface irregularities were present, and not to the loading condition applied. Peak errors ranged from 25% to 67% when Eq. (3) was applied, but reached values well higher than 100% of the maximum measured strain for Eqs. (2) and (1). In summary, only the FE models mapped with Eq. (3) can be deemed structurally similar to the actual specimen, free of offset effects and with limited localised uncertainties.

The current results confirm the great influence of the density–elasticity relationship used on the outcome of subject-specific FE models of bones, coherently with Weinans et al. (2000). The present study shows a clear improvement of the predictions accuracy with respect to previous studies, although a systematic comparison with the results reported in the literature was not always possible. The only results comparable in terms of regression line parameters ($R^2 > 0.9$, slope and intercept not significantly different from one and zero, respectively) with those obtained in the present study using Eq. (3), are relative to the torsion load case of Barker et al. (2005). However, the accuracy reported in that study for the axial/bending load case was definitely lower ($R^2 = 0.71$) and their method was not fully automatic. All the published studies on the femur, showing a comparable degree of automation with the strategy here proposed, report a consistently lower accuracy. Keyak et al. (1993) reported a $R^2 = 0.59$, Ota et al. (1999) reported a $R^2 = 0.66$, Taddei et al. (2006b) reported a $R^2 = 0.79$, a slope of 1.7, a RMSE% of around 30%, and a peak error of 134%. The present study reveals a better accuracy in strains prediction also when compared to works in which specialised meshing and properties mapping strategies were used, such as Gupta et al. (2004) ($R^2 = 0.89$, but peak error > 200%), and
Anderson et al. (2005) \( (R^2 = 0.82) \). Other validation studies (Couteau et al., 2001; Maurel et al., 2005) did not report comprehensive error indicators and were therefore not directly comparable with the present work.

One of the hypotheses made in this study was the use of a single density–elasticity law over the whole range of densities. While Eqs. (1) and (2) were derived from tests on the entire density range, Eq. (3) was extrapolated. This may be considered a limitation of the present study. However, this extrapolation appears to be justified since the experimental data span a quite wide range of densities \((0.25–0.75 \text{ g cm}^{-3})\), and no limitation was posed by the authors to the generality of the testing approach. The very accurate strain predictions obtained with this law could be considered indirect evidence of the applicability of Eq. (3) to the whole density range.

All the femurs in the present study fell in the range from osteopenic to osteoporotic bones. However, this condition is particularly critical for modelling for the presence of structural discontinuities and extremely thin dense bone layers. The results thus indicate that the proposed procedure is a good candidate for the modelling of osteoporotic bones. In addition we can suppose that when modelling a normal femur the accuracy is not worsened.

In summary, it has been shown that a very good accuracy in the strains prediction is achievable with automatically generated subject specific finite element models from CT data. The presented results show, in addition, that the adoption of a single density–elasticity relationship over the whole bone density range is adequate to obtain a high accuracy. The very good results obtained may be ascribed to the coexistence of an accurate geometric reconstruction, an appropriate choice of the density–elasticity relationship, the use of an advanced algorithm for mapping the material properties onto the models, and an accurate replication of the boundary conditions. The present modelling procedure can be replicated for in vivo studies, where, however, the accurate identification of the real boundary conditions (e.g. the forces exerted by muscles, the ligaments constraints, and the joint reactions) is still a major scientific challenge.

Acknowledgements

The authors would like to thank Francesco Pallini for working in the experimental tests, Luigi Lena for the illustrations, Mauro Ansaloni for the technical support and Barbara Bordini for the help in the statistical analysis.

Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jbiomech.2007.02.010

References


