Available online at www.sciencedirect.com
ScienceDirect
Clinical Biomechanics 23 (2008) 135–146
CLINICAL BIOMECHANICS
www.elsevier.com/locate/clinbiomech

Review

Mathematical relationships between bone density and mechanical properties: A literature review

Benedikt Helgason [a], Egon Perilli [b], Enrico Schileo [b], Fulvia Taddei [b,*], Sigurður Brynjólfsson [a], Marco Viceconti [b]

[a] University of Iceland, Department of Mechanical and Industrial Engineering, Reykjavík, Iceland
[b] Laboratorio di Tecnologia Medica, Istituti Ortopedici Rizzoli, Via di Barbiano 1/10, 40136 Bologna, Italy

Received 12 May 2006; accepted 31 August 2007

Abstract

Background. In many published studies, elastic properties of bone are correlated to the bone density, in order to derive an empirical elasticity–density relationship. The most common use of these relationships is the prediction of the bone local properties from medical imaging data in subject-specific numerical simulation studies. The proposed relationships are substantially different one from the other. It is unclear whether such differences in elasticity–density relationships can be entirely explained in terms of methodological discrepancies among studies.

Methods. All relevant literature was reviewed. Only elasticity–density relationships derived from similarly controlled experiments were included and properly normalized. The resulting relationships were grouped according to the most important methodological differences: type of end support during testing, specimen geometry, and anatomical sampling location.

Findings. Even after normalization with respect to strain rate and densitometric measurement unit, substantial inter-study differences do exist, and they can only be partially explained by the methodological differences between studies.

Interpretation. Some recommendations are made for the application of elasticity–density relationships to subject-specific finite element studies. The importance of defining a standardized mechanical testing methodology for bone specimens is stressed, and some guidelines that emerged from the literature are proposed. To identify density–elasticity relationships suitable for use in subject-specific FE studies, the development of a benchmark study is also proposed, where the elasticity–density relationship is taken as the variable under study, and a numerical model of known numerical accuracy predicts experimental strain measurements.

Keywords: Bone; Subject-specific finite element models; Mechanical properties; Constitutive law; Density; Elastic modulus

1. Introduction

Subject-specific finite element (FE) analysis of the skeleton, a very powerful tool for biomechanical research, is now being adopted in clinical applications (Taddei et al., 2003; Viceconti et al., 2005). The most common way of constructing the subject-specific FE models is by deriving information from X-ray computed tomography (CT) images. Information on the mechanical properties of bones can be derived from CT-data, using a mathematical relationship between the CT values and the mechanical properties of the bone (Keyak et al., 1990; Keaveny et al., 1993b; Merz et al., 1996; Zannoni et al., 1998; Taddei et al., 2004, 2007). The accurate determination of such a relationship is of great importance, and while the relationship between CT attenuation coefficients and ash density can be established with a direct calibration (McBroom et al., 1985; Ciarelli et al., 1991), the determination of a mathematical relationship between density and mechanical properties is more challenging.

A large number of mathematical relationships between densitometric measures and mechanical properties have

* Corresponding author.
E-mail address: taddei@tecno.ior.it (F. Taddei).

0268-0033/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.clinbiomech.2007.08.024

been introduced in the literature. Hereinafter the term *elasticity–density relationship* will be used for a mathematical relationship between a densitometric measure and Young's modulus. Many of the existing elasticity–density relationships have been adopted in the generation of subject-specific FE models (among those present in the current review: Carter and Hayes, 1977; Lotz et al., 1990; Snyder and Schneider, 1991; Linde et al., 1992; Dalstra et al., 1993; Keller, 1994; Keyak et al., 1994; Wirtz et al., 2000; Kaneko et al., 2004), in most cases with no explicit considerations on the suitability and accuracy of the chosen one. Reviewing elasticity–density relationships from 26 studies, Linde et al. (1992) found an almost tenfold inter-study difference in predicted Young's modulus for low-density cancellous bone. This large spread in the predicted Young's modulus can partially be explained by the complexity involved in the experimental techniques needed to measure the mechanical properties in a highly porous anisotropic material such as trabecular bone. Commonly, to determine the mechanical compressive properties, a trabecular bone specimen is cut out of a whole bone and loaded in a material testing machine. By recording the load–displacement curve, the stiffness can be calculated.

Over time, different testing set-ups were developed and applied, and it was found that different artefacts and source of errors can arise during a mechanical test. For all these methods, a key feature discussed in the literature is the measurement of the specimen deformation.

1.1. The platen-technique

Formerly, the *platen-technique* was the most used testing method. In the *platen-technique*, the bone specimen is placed between the two anvils of the material testing machine and then compressed. Strain measurements are obtained from the displacement of the two platens, usually directly recorded by the machine.

However, two major experimental problems with platen strain measurements were reported in the literature (Linde et al., 1992; Keaveny et al., 1997; Un et al., 2006): *machine compliance*, and *end-effects* (further divided in *structural end-effect* and *frictional end-effect*).

- *Machine compliance:* because of the small deformations of the bone specimen, deformations in the load cell and the test columns may result in an overestimation of strain (corresponding to an underestimation of stiffness), if the data are not corrected for the compliance of the testing device, which is not trivial to measure. This can have significant effects on the measured strain (Linde et al., 1992; Keaveny et al., 1993a).
- *Structural and frictional end-effects:* experimental artefacts (possibly acting in a combined way) that arise at the specimen–anvils interface, causing random and systematic errors (Odgaard and Linde, 1991; Keaveny et al., 1993a). The *structural end-effect* derives from the bending and sliding of trabeculae near the specimen–anvil interface, with relatively high axial deformations adjacent to the test platens, because the mutual support of the trabeculae is lessened near the cut surface of the specimen. This may lead to random uncertainties (Keaveny et al., 1997) and to a likely underestimation of the Young's modulus (Linde and Hvid, 1989; Linde et al., 1992; Keaveny et al., 1993a). The *frictional end-effect* is due to friction at the specimen–anvils interface. The central parts of the specimen are strained less than parts near the specimen–anvils interface, so a higher compressive force is needed to deform the specimen with respect to that expected from the application of Hooke's law (Linde and Hvid, 1989; Linde et al., 1992; Keaveny et al., 1993a). Thus, the friction likely results in an overestimation of Young's modulus.

1.2. The extensometer and the end-cap technique

To avoid the cited artefacts, other testing methods have been developed. To avoid machine compliance, an *extensometer* can be attached onto the specimen or to the anvils (Linde and Hvid, 1989; Linde et al., 1992; Keaveny et al., 1997). To avoid structural and frictional end-effects, the *end-cap technique* can be used, i.e. embedding the specimen ends in a layer of polymethylmethacrylate (Linde and Hvid, 1989; Keaveny et al., 1997; Odgaard, 1997).

In the *four-extensometer technique*, an extensometer is applied onto the centre of the specimen and rotated four times by 90° around the perimeter. The measurements are taken at each of the four positions of the extensometer. It is deemed an accurate modulus measurement, as it gives multiple direct strain measurements on bone away from end constraints (Keaveny et al., 1997). It was shown that an equivalent result in accuracy and even a better precision can be reached using a *single extensometer* attached to the specimen end-caps, as it is not wrapped around the inevitably rough surface of the bone specimen (Keaveny et al., 1997).

As a result, the platen-technique was found to systematically underestimate (from 20% to 40%) the elastic modulus with respect to the now considered more 'accurate' methods (Linde et al., 1992; Keaveny et al., 1997), relying on *optical methods* (Odgaard and Linde, 1991), *end-cap techniques*, *single extensometer* or *multiple extensometer techniques* (Keaveny et al., 1997).

1.3. Specimen size and geometry

Other extensively debated methodological features, that were found to affect the estimation of the elastic modulus, are the size and geometry of the bone specimens. The external size of the specimens should be greater than 4–5 mm (containing at least 5 trabeculae) to satisfy the continuum assumption (Harrigan et al., 1988). Concerning the geometry, cubic or cylindrical specimens have mainly been adopted. By eliminating frictional artefacts, the elastic modulus of a 1:1 cylinder was found to not differ significantly from a cube having the same side length as the cylinder diameter (Linde et al., 1992). However, structural artefacts were found to decrease with increasing specimen size and aspect ratio (length:width), suggesting a 2:1 cylindrical geometry as the most accurate (Linde et al., 1992). In addition, a cylinder with an aspect ratio of 2:1 gave even a better precision with respect to a cube (Linde et al., 1992; Keaveny et al., 1993b; Keaveny et al., 1997). On the other hand, cubic bone specimens are the most common choice when the orthogonal mechanical properties of cancellous bone are to be evaluated (Linde et al., 1992; Goulet et al., 1994).

In summary, the *end-cap technique* applied on a bone specimen of cylindrical geometry with a 2:1 length–diameter ratio has been presented as both an accurate and precise method to determine the mechanical properties of bone specimens (Keaveny et al., 1997; Guo, 2001). However, only few studies are available (mostly from the same research group, e.g. Keaveny et al., 1997 and Morgan et al., 2003), that followed this relatively recently introduced protocol. Moreover, it has been recently found that the elasticity–density relationships in trabecular bone are variable among anatomical sites (Keaveny et al., 1997; Morgan et al., 2003). This variation may contribute to the differences observed when comparing results from different studies.

The aim of the present review study is to investigate whether inter-study differences in elasticity–density relationships can be entirely explained in terms of methodological discrepancies or, on the contrary, if additional studies are required to confirm which of these relationships are reliable enough to be used in subject-specific FE studies. To try to answer this question the elasticity–density relationships proposed in the literature were reviewed by means of a comparison framework.

2. Methodology

Studies were included in this literature review according to the following criteria:

Only studies that explicitly proposed a mathematical relationship between density and Young's modulus, established empirically by correlating experimental measurements, were considered valid for this review.

Since the focus in this review is on modulus–density relationships that can be used in CT-based FE-modelling, those relationships that require the identification of additional information on bone architecture that cannot be derived from a conventional CT-scan, were excluded.

Animal studies were excluded from this review because of the differences in mechanical properties with respect to human bone, as manifest in Currey (2004), but mixed animal and human studies were included.

To exclude the effect of the measuring technique, only studies where the modulus of elasticity was measured by direct mechanical testing were included. Studies based on ultrasound or indentation methods were thus excluded.

Additionally, all those studies in which specimens were not tested fresh or fresh frozen and in wet conditions were excluded, since drying and other specimen preservation procedures are known to significantly alter tissue mechanical properties (Martin and Sharkey, 2001).

2.1. Picking criteria for studies reporting multiple elasticity–density relationships

In many of the cited studies multiple elasticity–density relationships are reported. These relationships are usually derived from sub-pooling of the data available according to specific factors, such as anatomical site or sampling direction, or they express the results of different regression procedures.

Some of these studies reported the elasticity–density relationships derived for each of the different anatomical sites, together with the pooled relationships. For those studies, only the relationships for different anatomical sites were included in the present review.

Since specimen sampling direction does greatly influence the results of mechanical testing due to the anisotropic nature of bone (Turner and Cowin, 1988; Ohman et al., 2007), in those studies for which the elasticity–density relationships were derived for multiple directions, only the relationship that resulted in the highest Young's modulus was included.

When multiple mathematical relationships were proposed for the same data in the same paper, only the relationship with the highest determination coefficient was considered.

One study (Ciarelli et al., 1991) was excluded from the review although it passed the exclusion criteria, because complete mathematical relationships were not presented for power regression, which in general had a higher determination coefficient with the experimental results than linear regression.

The synoptic table (Appendix A, Table A1) summarize all papers included in the review. For each cited study, the following information and parameters were reported: anatomical site, type of bone, densitometric measure, testing range, testing conditions, specimen dimensions, strain rate, number of samples tested, elasticity–density relationship and the corresponding determination coefficient.

2.2. Comparison criteria

Even with these exclusions, the studies to be reviewed presented major differences, which made any quantitative comparison difficult.

Two factors that prevented direct inter-study comparisons were identified: the use of different indicators for density measurements (Goulet et al., 1994; Keyak et al., 1994), and the loading rate at which the mechanical tests were performed.

Thus, the following normalization criteria were used to make inter-study comparisons possible:

Table 1
Conversion formulae between densities used in the present study

ρ_{app} (g/cm^3) $= \frac{\rho_{ash}}{0.55}$	From Keyak et al. (1994): ρ_{ash} (g/cm^3) $= 0.551\rho_{wet} - 0.00478$[a]
ρ_{app} (g/cm^3) $= \frac{\rho_{dry}}{0.92}$	From Keyak et al. (1994): ρ_{ash} (g/cm^3) $= 0.597\rho_{dry} - 0.00191$[a]
ρ_{app} (g/cm^3) $= \frac{BV}{TV}1.8$ (g/cm^3)	From Gibson (1985)[b]: $\frac{BV}{TV} = \frac{\text{apparent density}}{\text{real density}} = \frac{\text{apparent density}}{1.8\ (\text{g/cm}^3)}$

For the different terms for density please refer to Table A2, Appendix A.
[a] Intercept not significantly different from zero.
[b] Based on assumption that real density is equal to compact bone density, i.e. 1.8 g/cm^3 Carter and Hayes (1977).

– different terms for density were identified in accordance to Table A2, Appendix A (Galante et al., 1970; Sharp et al., 1990; Keyak et al., 1994). All density measures were transformed to apparent density using the normalization formulae reported by Keyak et al. (1994) (Table 1). Volume fraction was transformed to apparent density assuming compact bone density equal to 1.80 g/cm^3, as in Carter and Hayes (1977) and Gibson (1985);
– all the curves were normalized with respect to strain rate, as in Rice et al. (1988) and Linde et al. (1992), using the relationship reported by Carter and Hayes (1977):

$$E_{(\text{at } 0.01\ \text{s}^{-1})} = \left(\frac{0.01\ \text{s}^{-1}}{\dot{\varepsilon}_{\text{orig}}}\right)0.06\ E_{(\text{at } \dot{\varepsilon}_{\text{orig}})}$$

where $\dot{\varepsilon}_{\text{orig}}$ (s^{-1}) is the original strain rate used in each experiment. All relationships were normalized to a strain rate of 0.01 s^{-1}.

Despite these normalization procedures, results were still largely dispersed (Fig. 1). Since no other obvious normalization could be applied, the principal factors that may induce systematic differences in the outcome of mechanical testing were identified and used as criteria to compare the various studies:

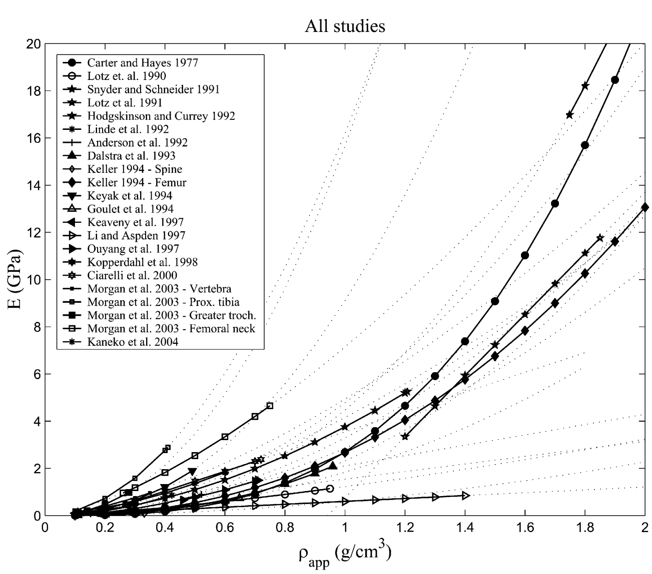

Fig. 1. Young's modulus vs. apparent wet density for all studies that passed the review criteria.

– the testing and measurement procedures cited in the introduction, i.e. specimen geometry (Linde et al., 1992; Keaveny et al., 1993b), specimen holders (Linde and Hvid, 1989; Keaveny et al., 1997) and measurement instrumentation;
– the anatomical site from which samples were retrieved (Morgan et al., 2003).

Consequently, data from all the reviewed studies were plotted separately, considering the following factors:

1. specimen boundary conditions: platen-technique vs. end-caps and other techniques;
2. specimen geometry: cube vs. cylinder;
3. anatomical site from which specimen were retrieved: femur, tibia, spine, and multiple sites. Data were separated down to the organ scale (e.g. data from different spine segments were put into the same 'spine' group), as this is the level at which a distinction between mechanical properties assignment can be easily performed when building a subject-specific FE model.

In the inter-study comparison of the present work, all the mathematical relationships included in the review were extrapolated over the whole density range commonly found in human bones (0–2 g/cm^3). This was done despite the fact that in many cases the elasticity–density relationships reported in the literature have been obtained from specimens that spanned a limited range of densities. The first reason for this choice is that none of the relationships has a clear indication on its range of validity, and the second reason is that only one relationship over the entire density range is commonly used when assigning material properties in a FE modelling procedure (Dalstra et al., 1995; Ota et al., 1999; Crawford et al., 2003; Barker et al., 2005; Bitsakos et al., 2005; Taddei et al., 2007). The relationships were plotted on the whole density range (0–2 g/cm^3), but to ensure graphs readability and to not overexpose the effects of the extrapolations performed, sub-plots in the 0–1 g/cm^3 range were included as Additional On-line Material. In all the plots, solid lines represent the actual experimental density range of the cited study, and dotted lines represent the extrapolation. Linde et al. (1992) did not report the density range of the tested specimens. In this case the solid line represents an interval of two standard deviations around the reported average value. Mathematical relationships based on volume fraction were only plotted up to an apparent density of

1.8 g/cm^3, which represents compact bone according to the definitions in Table A2 of the Appendix.

3. Results

3.1. General

A total of 18 studies and 22 elasticity–density relationships passed the review criteria (Table A1 of the Appendix): Carter and Hayes (1977), Lotz et al. (1990), Lotz et al. (1991), Snyder and Schneider (1991), Anderson et al. (1992), Hodgskinson and Currey (1992), Linde et al. (1992), Dalstra et al. (1993), Goulet et al. (1994), Keller (1994), Keyak et al. (1994), Keaveny et al. (1997), Li and Aspden (1997), Ouyang et al. (1997), Kopperdahl and Keaveny (1998), Ciarelli et al. (2000), Morgan et al. (2003), Kaneko et al. (2004).

A plot of all the normalized mathematical relationships that passed the review criteria is presented in Fig. 1.

It is evident that a large scatter exists in the reviewed elasticity–density relationships, even when disregarding the extrapolation.

3.2. Specimen boundary conditions

The first group represents mathematical relationships taken from studies where platen end-conditions were used (Fig. 2a) and the second group (Fig. 2b) represents all the other studies (end-caps, three-point bending) where end-effects were not likely to be present. A study where specimens were tested under confined compression (Carter and Hayes, 1977) was put into the 'platen' group, since end-effects were not prevented. Three-point bending tests (Lotz et al., 1991; Snyder and Schneider, 1991), numerically less

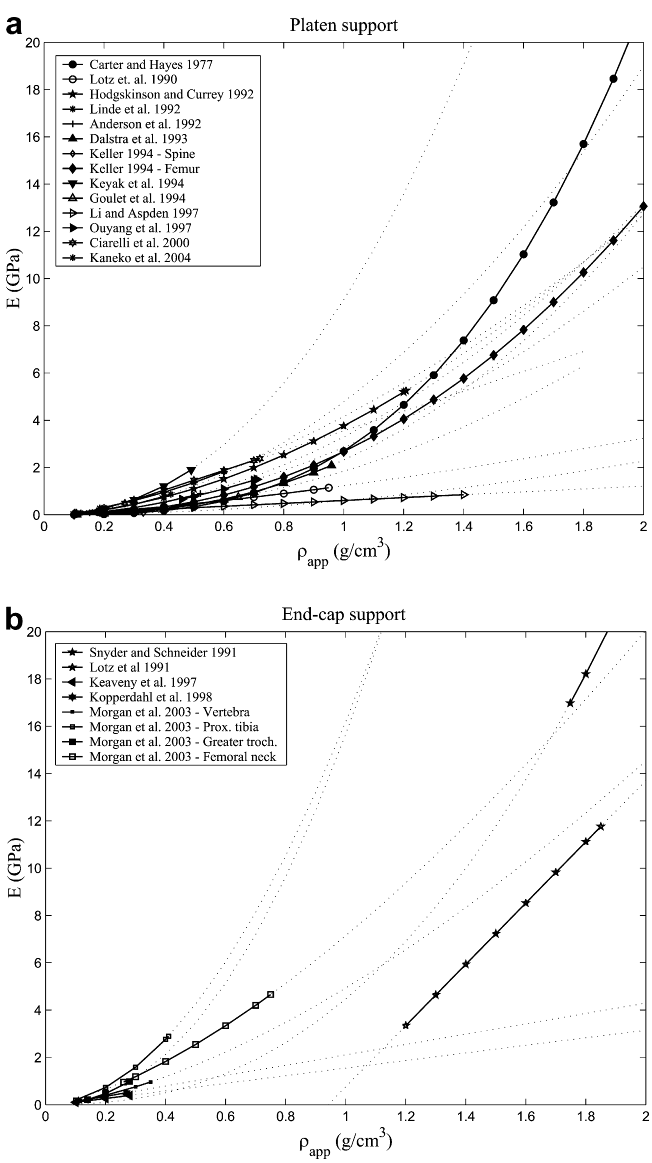

Fig. 2. Young's modulus vs. apparent wet density for studies where platen end-conditions (a) and end-cap conditions (b) were used.

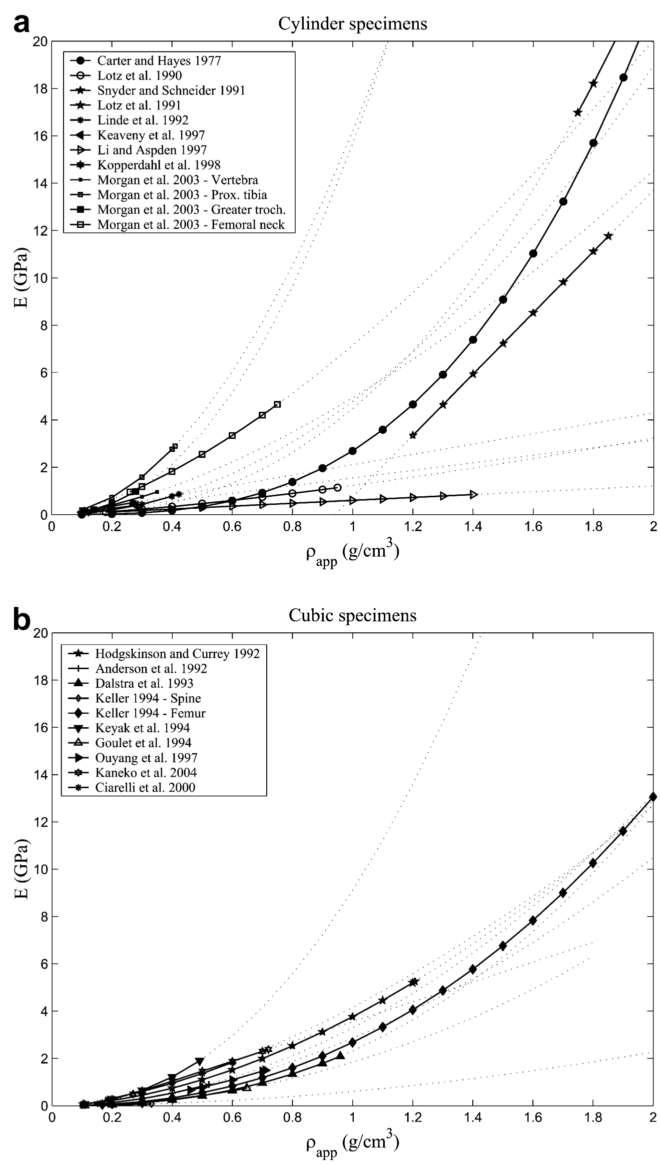

Fig. 3. Young's modulus vs. apparent wet density for studies where cylindrical (a) and cubic (b) specimens were tested.

relevant, were grouped with the 'end-caps' group, assuming that end-effects in these cases were low or negligible. All the relationships coming from Morgan et al. (2003) are listed with the end-caps group, even though 14 out of 142 specimens were tested between platens due to experimental difficulties. However, for these specimens the four-extensometer technique was used for strain measurement, which has been shown not to differ in accuracy from the end-cap technique (Keaveny et al., 1997).

3.3. Specimen geometry

The first group (Fig. 3a) represents mathematical relationships derived from studies where cylinder specimens were tested. This group also includes the mathematical relationship presented by Snyder and Schneider (1991) and Lotz et al. (1991), i.e., three-point bending tests, for which the specimen geometry was similar to a cylinder with a high aspect ratio. The second group (Fig. 3b) represents mathematical relationships where cubic specimens were tested.

3.4. Anatomic site

The first group (Fig. 4a) represents mathematical relationships derived from studies where femoral specimens were tested, the second group (Fig. 4b) relationships where tibial specimens were tested, the third group (Fig. 4c) relationships where spinal specimens were tested, and the fourth group (Fig. 4d) relationships obtained for specimens that were derived from multiple sites.

4. Discussion

The aim of this review study was to investigate whether inter-study differences in elasticity–density relationships

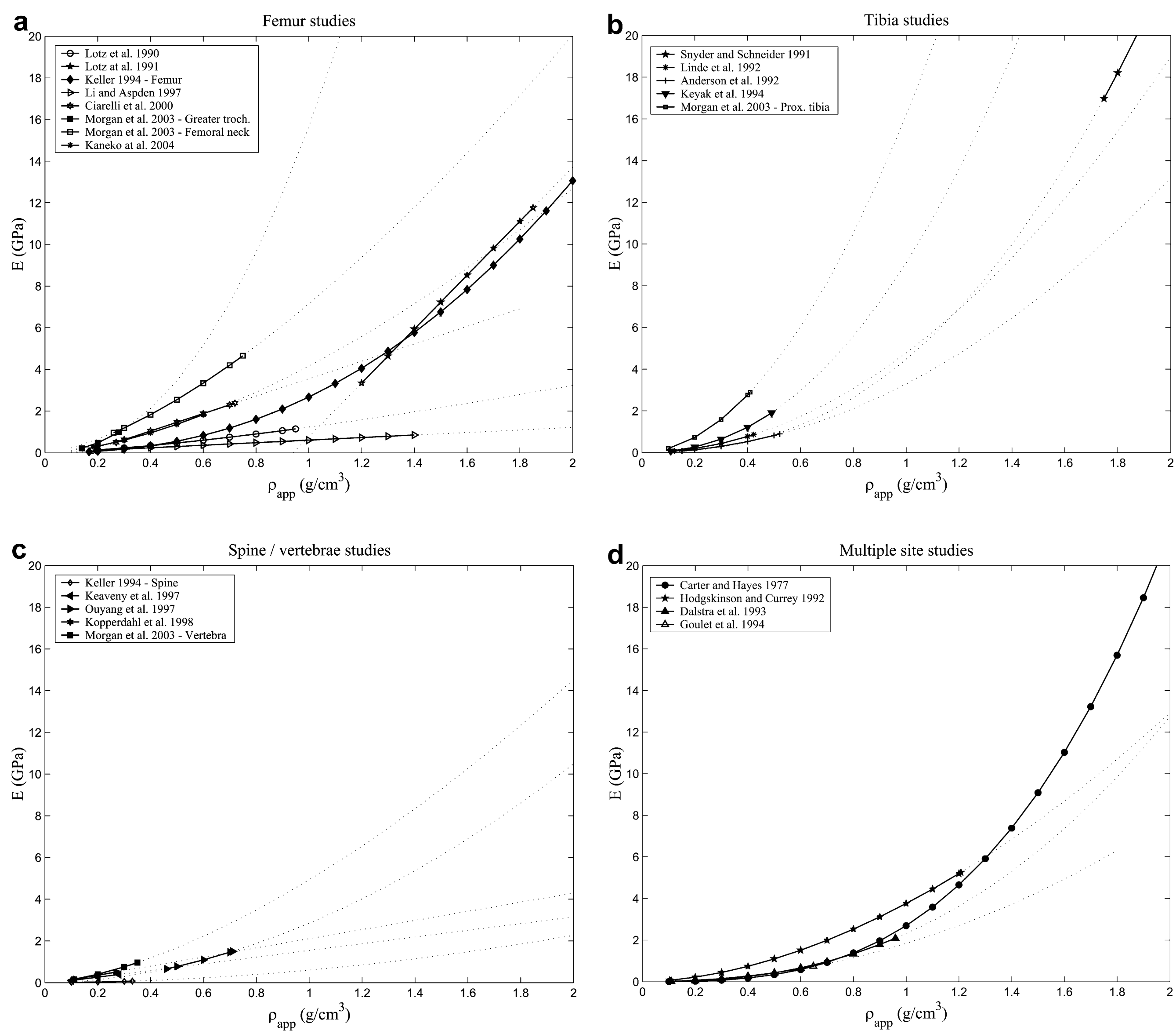

Fig. 4. Young's modulus vs. apparent wet density for studies where specimens from femoral (a), tibial (b), spine (c), or multiple sites (d) were tested.

could be entirely explained in terms of methodological discrepancies.

The available elasticity–density relationships derived from direct mechanical tests on fresh human bone specimens were selected, normalized according to density measurement unit and loading rate, and analysed either as a homogeneous group or grouped by the most important known factors of variability. The results show that a considerable scatter remains despite the grouping, and it is thus virtually impossible to draw definite conclusions. This could be due to an insufficient isolation of the factors of variability, because the methodological factors may act in a combined way, and thus mismatch their effects. A more conclusive evaluation of the variability due to the various experimental methods could be obtained by a systematic clustering of studies in a 2(specimen constraint) × 2(specimen geometry) × 4(anatomical site) matrix of methods, rather than pooling all methods and separating only one variable at a time, but this is not currently feasible due to the limited number of papers available. On the other hand, comparing the studies in pairs, it was possible to single out some of the effects described in the methodological literature, as explained below in the discussion of each of the variability factors.

In the present work, the elasticity–density relationships reported for the platen support fall within the scatter of the relationships of the end-cap support (Fig. 2). Thus, while it is well assessed that platen test underestimates stiffness compared to an end-cap test (Keaveny et al., 1997), such a conclusion cannot be directly drawn based on the present study alone. However, by including also anatomic site in the comparison, and by comparing the results on tibia specimens of Keyak et al. (1994) and Linde et al. (1992), who both used a platen test, to the results of Morgan et al. (2003), who used the end-cap technique, it can be seen that the platen test results yield lower stiffness (Fig. 4b). The same can be found for the studies on the human femoral neck, e.g. the studies of Lotz et al. (1990) (platen test, cylinder), and Morgan et al. (2003) (four-extensometer technique, i.e. end-cap test, cylinder), where the platen test yields an evident lower curve than the end-cap test (Fig. 4a).

The here reported elasticity–density relationships derived from cubic specimens data fall within the scatter of those derived from cylindrical specimens data (Fig. 3). It could thus be concluded that the cylindrical specimens produce more scattered relationships than cubic ones, which is in disagreement with the methodological studies of Linde et al. (1992) and Keaveny et al. (1993b). However, the reported relationships for the cylinders were obtained by different techniques (end-cap, platen, three-point bending), while the relationships for the cubic specimens were obtained only by platen tests. Consequently, the relationships reported for the cylinders had certainly one more factor contributing to scatter of data. Another contributor to the scatter of the relationships for the cylindrical specimens is, that these relationships were obtained from specimens having different size and aspect ratio. For example, it has been shown by Linde et al. (1992) that the elastic modulus increases with increasing specimen size and aspect ratio. This is supported by the fact that the softest relationships in this group are those reported by Li and Aspden (1997) and Lotz et al. (1990), which were obtained on cylinders having a low aspect ratio (inferior to 1:1) and using platen end-conditions. However, it is difficult to draw a direct general conclusion on the influence of specimen geometry based on the relationships presented in Fig. 3.

In the present work, the effect of anatomic site is also unclear (Fig. 4), because a high scatter remains present with the partial exception of vertebral bone specimens, as these appear to yield elasticity–density relationships 'softer' than those derived from long bone specimens. Morgan et al. (2003) investigated the effect of anatomical site using a protocol free from end-effects (cylinder 2:1, end-cap technique) and reporting specimen alignment. That study shows that the density–modulus curves vary significantly with anatomical site, as previously noted by Ciarelli et al. (1991) and Goulet et al. (1994). Therefore a growing consensus seems to exist in the literature on the effect of anatomical site on the elasticity–density relationships, that might be due to differences in trabecular architecture (Hildebrand et al., 1999) and tissue modulus (Hoffler et al., 2000). Those findings confirm the importance of choosing the density–elasticity relationships in FE subject-specific models depending also on the anatomical site.

Comparing our results to the literature is difficult because of the different methodology applied in the different review studies. In Rice et al. (1988) the original data were obtained and pooled from several studies, and statistical methods were used to derive elasticity–density relationships for different specimen orientation and tensile/compressive conditions. However, no comparison was made in that study between the experimentally derived laws reported in the reviewed studies, nor any discussion on the testing methods adopted. One of the principal results was that laws derived from trabecular bone specimens predicted very low elastic modulus values when extrapolated to density ranges typical of cortical bone, thus suggesting the unsuitability of an extrapolation like the one performed in the present work. However, this could be due, as discussed in that article, to the chemical composition and microstructural organisation of the bone, but maybe more considerably to the underestimation of trabecular Young's modulus: in fact, none of the experiments from which data were obtained used any device to reduce end artefacts, nor to precisely assess the trabecular alignment. In Wirtz et al. (2000) the literature was reviewed with respect to elasticity–density and strength–density of bone. Averaged elasticity–density relationships for cancellous bone ($E = 1.904\rho^{1.64}$) and cortical bone ($E = 2.065\rho^{3.09}$) were derived by combining information from the reviewed studies (specimens loaded in the axial direction). Unfortunately there is no mention of the methods that were used to select and combine information from the reviewed studies: it seems that some key-studies such as Keller (1994) and Keaveny et al. (1997) were missing from the review, and that the effects of methodological factors were neglected. Conversely, in Linde et al. (1992) a large spread in the predicted Young's modulus in low-density cancellous bone was pointed out; this is confirmed in the present study, even after accounting for methodological discrepancies.

A limitation of the present study is that several other factors, apart from those investigated here, may influence the experimental results obtained by mechanical testing. Inter-study differences in specimen preparation (i.e., cutting and milling), specimen aspect ratio, loading direction vs. dominant trabecular orientation, might to some extent contribute to the large differences observed among studies. In this review, we focused on those methodological differences that were mostly debated in the literature and are thus suspected to explain the largest inter-study differences. Actually, the direction of loading vs. dominant trabecular orientation is known to produce significant effects: a misalignment of 10° can produce an underestimation of 10% in elastic modulus, while for a misalignment of 20° an underestimation in the order of 30–40% can be expected (Turner and Cowin, 1988; Ohman et al., 2007). However, apart from the studies of Morgan and Keaveny (2001) and Morgan et al. (2003), the here reviewed studies reported the trabecular orientation only in a generic way, such as 'the specimens were oriented with their axes parallel to the long axes of the bone' (Carter and Hayes, 1977). This lead to an additional unknown scatter in the data: as discussed by Morgan et al. (2003), the anatomical axes can be misaligned with the principal material axes up to 40°. This misalignment can be quantified by calculating the mean intercept length ellipsoid (MIL) from micro-CT data, that was found closely aligned to the principal mechanical directions (Odgaard, 1997).

Given the focus of this review, some recommendations can be made for the application of elasticity–density relationships to subject-specific FE studies. The first recommendation is to consider experimental methodology issues when choosing an elasticity–density relationship; the second, to preferably use density–elasticity relationships derived from the same anatomical site on which the FE investigation is planned, provided they have been obtained with a well reported and accurate testing protocol. Although some experimental evidence exist (Issever et al., 2002) that even in the same anatomical site differences may be found between different locations, probably due to the different bone micro-architecture, still these differences are hard to capture in a continuum model of bone at the organ level, as the fabric tensor information cannot be derived from the currently available clinical CT technologies, which are not adequate to resolve trabecular bone (Müller et al., 1996; Mitton et al., 1998; Rüegsegger, 2001). As to the use of a single or multiple elasticity–density relationship over the entire range of densities, it is not clear if a single mathematical law can accurately relate density and elasticity over the full density range, mainly because none of the here reported studies has investigated the mechanical properties of both trabecular and cortical bone using a protocol aimed at minimizing experimental artefacts. The use of a single relationship can be proposed as a first attempt when modelling long bones, since trabecular bone can hardly be discriminated from cortical bone, starting from CT data. The adoption of a dedicated relationship for trabecular bone might apply to specific conditions, such as vertebral bone, where a clear border separates the low-density trabecular bone from the thin high density cortical shell, that will likely need a different modelling approach (e.g., using shell elements). Indeed, extrapolating the elasticity–density relationships derived on vertebral specimens, all showing very low density (Fig. 4c), to the high densities of cortical bone, might be misleading. Alternative approaches to the use of elasticity–density relationships might have to be considered, such as directly deriving the elastic modulus from CT Hounsfield Units (HU). However, a universally accepted calibration procedure, which ensures that the same HU value from two CT machines yields exactly the same coefficient of attenuation, does not exist. For this reason, a common procedure for the densitometric calibration of the CT machine is to use a bone-like hydroxy-apatite (HA) phantom. The debate on this issue is still open, but addressing it is out of the scope of this work.

In summary from this review it can be stated that a bias, related to the experimental methods used, is present. Because of this, all studies cannot be assumed equally valid and cannot be pooled together statistically, to derive an average elasticity–density relationship. In the authors' opinion, the roadmap to achieve accurate elasticity–density relationships could be twofold:

– it is evident, that we need to promote within the bone biomechanics community a methodological debate towards a consensus on sufficiently standardized testing procedures, as already mentioned by other authors (Linde et al., 1992; Keaveny et al., 1993b). We propose, that these future experimental studies should be conducted following the guidelines for accuracy and precision derived from the methodological literature, which are stated at the end of the Introduction section of the present work; i.e., using cylinders with 2:1 aspect ratio and at least 5 mm diameter (8 mm if possible), conducting strain measurements with one extensometer applied onto the specimen end-caps, or attached to the central part of the specimen, away from the end constraints, to reduce the end artefacts to a minimum (Keaveny et al., 1994; Guo, 2001). The angle (off-axis angle) between the loading direction and the main trabecular orientation should be reported, as suggested also by Morgan and Keaveny (2001), Wang et al. (2004) and Ohman et al. (2007). Also the recently investigated side-artefact may be taken into account, when calculating

Table A1
Modulus–density relationships in the cited studies

Study	Site	Type of bone	Densitometric measure	ρ-range (g/cm^3)	E (GPa)	Test condition	Geometry $B \times W \times L$ or $D \times L$ (mm)	Strain rate (s^{-1})	n	R^2
Carter and Hayes (1977)	Pooled	Cortical and trabecular	ρ_{app}	0.07–2.0	$E = 3.79\dot{\varepsilon}^{0.06}\rho_{app}^{3}$	Confined compression	20.6×5	0.001–10.0	124	NR
Lotz et al. (1990)	Human femoral neck	Trabecular	ρ_{app}	0.18–0.95[RFG]	$E = 1.310\rho_{app}^{1.40}$	Platen	9×5	0.03	49	0.91
Lotz et al. (1991)	Human femoral metaphysis	Cortical	ρ_{app}	1.20–1.85[RFG]	$E = -13.43 + 14.261\rho_{app}$	3-Point bending	$7 \times 5 \times 0.4$	0.05	123	0.67
Snyder and Schneider (1991)	Human tibial diaphysis	Cortical	ρ_{app}	1.748–1.952	$E = 3.891\rho_{app}^{2.39}$	3-Point bending	$2 \times 2 \times 40$	0.001	45	$r = 0.75$[a]
Hodgskinson and Currey (1992)	Pooled	Trabecular	ρ_{dry}	0.094–1.111	$E = 3.98\rho_{dry}^{1.78}$	Platen	NR	0.0011–0.0033	57	0.91
Linde et al. (1992)[b]	Human proximal tibia	Trabecular	ρ_{app}	0.273[c]	$E = 4.778\rho_{app}^{1.99}$	Platen	7.5×7.5	0.01	31	$r = 0.89$[a]
Anderson et al. (1992)	Human proximal tibia	Trabecular	ρ_{dry}	0.14–0.48[RFG]	$E = 3.890\rho_{dry}^{2.0}$	Platen	$10 \times 10 \times 20$	0.01	31	NR
Dalstra et al. (1993)	Human pelvis	Trabecular	ρ_{app}	0.109–0.959	$E = 2.0173\rho_{app}^{2.46}$	Platen	$6.5 \times 6.5 \times 6.5$	0.001	57	0.58
Keller (1994)	Human spine	Trabecular	ρ_{ash}	0.028–0.182	$E = 1.89\rho_{ash}^{1.92}$	Platen	$10 \times 10 \times 10$	0.01	199	0.702
Keller (1994)	Human femur	Cortical and trabecular	ρ_{ash}	0.092–1.221	$E = 10.5\rho_{ash}^{2.29}$	Platen	$8 \times 8 \times 8$	0.01	297	0.849
Keller (1994)	Pooled	Cortical and trabecular	ρ_{ash}	0.028–1.221	$E = 10.5\rho_{ash}^{2.57}$	Platen	$8 \times 8 \times 8$ $10 \times 10 \times 10$	0.01	496	0.965
Keyak et al. (1994)	Human proximal tibia	Trabecular	ρ_{ash}	0.06–0.27	$E = 33.9\rho_{ash}^{2.20}$	Platen	$15 \times 15 \times 15$	0.01	36	$r = 0.916$[a]
Goulet et al. (1994)	Pooled	Trabecular	BV/TV	0.06–0.36	$E = 6.310(\mathrm{BV/TV})^{2.10}$	Platen	$8 \times 8 \times 8$	0.01	104	0.88
Keaveny et al. (1997)	Human lumbar spine	Trabecular	ρ_{app}	0.09–0.28	$E = 1.540\rho_{app} - 0.058$	End-caps[d]	8×16	0.005	9	0.64
Li and Aspden (1997)	Human femoral head	Trabecular	ρ_{app}	0.14–1.4	$E = 0.573\rho_{app} - 0.0094$	Platen	9×7.7	0.0033	49	0.59
Ouyang et al. (1997)	Human vertebra	Trabecular	ρ_{app}	0.46–0.71	$E = 2.3828\dot{\varepsilon}^{0.07}\rho_{app}^{1.88}$	Platen	$10 \times 10 \times 24$	0.00001–0.001	36	NR
Kopperdahl and Keaveny (1998)	Human vertebra	Trabecular	ρ_{app}	0.11–0.27	$E = 2.1\rho_{app} - 0.08$	End-caps[d]	8×16	0.005	44	0.61
Ciarelli et al. (2000)	Human proximal femur	Trabecular	BV/TV	0.15–0.40[RFG]	$E = 7.541(\mathrm{BV/TV}) - 0.637$	Platen	$8 \times 8 \times 8$	0.01	32	0.88
Morgan et al. (2003)	Human vertebrae	Trabecular	ρ_{app}	0.11–0. 35	$E = 4.730\rho_{app}^{1.56}$	End-caps[d]	8×16	0.005	61	0.73
Morgan et al. (2003)	Human proximal tibia	Trabecular	ρ_{app}	0.09–0. 41	$E = 15.520\rho_{app}^{1.93}$	End-caps[d]	8×16	0.005	31	0.84
Morgan et al. (2003)	Greater trochanter	Trabecular	ρ_{app}	0.14–0. 28	$E = 15.010\rho_{app}^{2.18}$	End-caps[d]	8×16	0.005	23	0.82
Morgan et al. (2003)	Human femoral neck	Trabecular	ρ_{app}	0.26–0. 75	$E = 6.850\rho_{app}^{1.49}$	End-caps and platens[d,e]	8×16	0.005	27	0.85
Morgan et al. (2003)	Pooled	Trabecular	ρ_{app}	0.09–0. 75	$E = 8.920\rho_{app}^{1.83}$	End-caps and platens[d,e]	8×16	0.005	142	0.88
Kaneko et al. (2004)	Human distal femur	Trabecular	ρ_{ash}	0.102–0.331	$E = 10.88\rho_{ash}^{1.61}$	Platens	$15 \times 15 \times 15$	0.01	49	0.775

Young's modulus (E) in GPa and density in g/cm^3. NR = not reported. RGF = read from graph. R^2 = determination coefficient.

[a] Pearson correlation coefficient, as reported in the original work.

[b] Reported results are for cylindrical specimens with diameter of 7.5 mm and a height of 7.5 mm. These specimens gave the highest correlation. In addition, mineral oil was used to eliminate frictional effects on the specimen–anvils interface.

[c] Average value. Range not reported.

[d] The free length of the bone specimen between the end-caps was reported.

[e] Fourteen specimens were tested in compression with platen end-conditions due to experimental difficulties.

the elastic modulus (Un et al., 2006). This artefact consists in an underestimation of the measured elastic modulus of trabecular specimens with respect to the '*in situ*' behaviour, caused by peripheral trabeculae that lose their vertical load-bearing capacity due to interruption of connectivity (Un et al., 2006). Finally, it would be advisable to use a very large sample size to cope with the large inter-individual variability, and with the existence of many other (though perhaps minor) factors influencing the measurements. Should an adequate number of replication experiments be performed, then the scatter among relationships observed in the present study will likely be significantly reduced, and the sub-groupings to apply will be clearer than those reported here. The effect of the remaining variability of the density–elasticity law on the results of subject-specific FE models could then be explored on the modelling side, by using statistical FE approaches, that have already shown to be useful in identifying the most critical parameters of a FE modelling process or of a prosthesis design (Taddei et al., 2006; Viceconti et al., 2006).
– in parallel, we propose the setting up of indirect validation studies to find which elasticity–density relationships are the most accurate. One option is the development of a benchmark study, where the elasticity–density relationship is taken as the variable under study, and a numerical model of known numerical accuracy predicts experimental strain measurements.

Acknowledgements

The authors would like to thank Luigi Lena for the illustrations and Mauro Ansaloni for the technical support.

Appendix A

see Tables A1 and A2

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinbiomech.2007.08.024.

References

Anderson, M.J., Keyak, J.H., Skinner, H.B., 1992. Compressive mechanical properties of human cancellous bone after gamma irradiation. J. Bone Joint Surg. Am. 74, 747–752.
Barker, D.S., Netherway, D.J., Krishnan, J., Hearn, T.C., 2005. Validation of a finite element model of the human metacarpal. Med. Eng. Phys. 27, 103–113.
Bitsakos, C., Kerner, J., Fisher, I., Amis, A.A., 2005. The effect of muscle loading on the simulation of bone remodelling in the proximal femur. J. Biomech. 38, 133–139.
Carter, D.R., Hayes, W.C., 1977. The compressive behavior of bone as a two-phase porous structure. J. Bone Joint Surg. Am. 59, 954–962.
Ciarelli, M.J., Goldstein, S.A., Kuhn, J.L., Cody, D.D., Brown, M.B., 1991. Evaluation of orthogonal mechanical properties and density of human trabecular bone from the major metaphyseal regions with materials testing and computed tomography. J. Orthop. Res. 9, 674–682.
Ciarelli, T.E., Fyhrie, D.P., Schaffler, M.B., Goldstein, S.A., 2000. Variations in three-dimensional cancellous bone architecture of the proximal femur in female hip fractures and in controls. J. Bone Miner. Res. 15, 32–40.
Crawford, R.P., Cann, C.E., Keaveny, T.M., 2003. Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. Bone 33, 744–750.
Currey, J.D., 2004. Tensile yield in compact bone is determined by strain, post-yield behaviour by mineral content. J. Biomech. 37, 549–556.
Dalstra, M., Huiskes, R., Odgaard, A., van Erning, L., 1993. Mechanical and textural properties of pelvic trabecular bone. J. Biomech. 26, 523–535.
Dalstra, M., Huiskes, R., van Erning, L., 1995. Development and validation of a three-dimensional finite element model of the pelvic bone. J. Biomech. Eng. 117, 272–278.
Galante, J., Rostoker, W., Ray, R.D., 1970. Physical properties of trabecular bone. Calcif. Tissue Res. 5, 236–246.
Gibson, L.J., 1985. The mechanical behaviour of cancellous bone. J. Biomech. 18, 317–328.

Table A2
Definition of density

ρ_{real} (g/cm^3) = Real density = $\frac{\text{hydrated tissue mass}}{\text{bone tissue volume}}$	Galante et al. (1970)
ρ_{app} (g/cm^3) = Apparent density = $\frac{\text{hydrated tissue mass}}{\text{total specimen volume}}$	Galante et al. (1970)
ρ_{wet} (g/cm^3) = Apparent wet density = $\frac{\text{hydrated tissue mass}}{\text{total specimen volume}}$	Keyak et al. (1994)
ρ_{dry} (g/cm^3) = Apparent dry density = $\frac{\text{dry tissue mass}}{\text{total specimen volume}}$	Keller (1994), Keyak et al. (1994)
ρ_{ash} (g/cm^3) = Ash density = $\frac{\text{ash mass}}{\text{total specimen volume}}$	Galante et al. (1970)
ρ_{act} (g/cm^3) = Actual density = $\frac{\text{total specimen mass}}{\text{total specimen volume}}$	Sharp et al. (1990)
Porosity = $1 - \frac{\text{apparent density}}{\text{real density}}$	Sharp et al. (1990)
$\frac{BV}{TV}$ = Bone volume fraction = $\frac{\text{Bone tissue volume}}{\text{Total specimen volume}} = \frac{\text{apparent density}}{\text{real density}}$	Gibson (1985)

Total specimen mass: The specimen mass including marrow.
Hydrated tissue mass or wet tissue mass: The specimen mass weighted in air after defatting, rehydration and centrifuging on a blotting paper (Galante et al., 1970).
Dry tissue mass: The specimen mass weighted in air after defatting and drying at moderate temperatures (Keyak et al., 1994).
Ash mass: The specimen weight after defatting and heating in a furnace at a temperature of 500 °C or more for approximately 24 h (Galante et al., 1970).
Bone tissue volume: Volume of bone excluding pores (Galante et al., 1970).

Goulet, R.W., Goldstein, S.A., Ciarelli, M.J., Kuhn, J.L., Brown, M.B., Feldkamp, L.A., 1994. The relationship between the structural and orthogonal compressive properties of trabecular bone. J. Biomech. 27, 375–389.

Guo, X.E., 2001. Mechanical properties of cortical bone and cancellous bone tissue. In: Cowin, S. (Ed.), Bone Mechanics Handbook, Second ed. CRC Press, Boca Raton, USA, p. 10.01-23.

Harrigan, T.P., Jasty, M., Mann, R.W., Harris, W.H., 1988. Limitations of the continuum assumption in cancellous bone. J. Biomech. 21, 269–275.

Hildebrand, T., Laib, A., Muller, R., Dequeker, J., Ruegsegger, P., 1999. Direct three-dimensional morphometric analysis of human cancellous bone: microstructural data from spine, femur, iliac crest, and calcaneus. J. Bone Miner. Res. 14, 1167–1174.

Hodgskinson, R., Currey, J.D., 1992. Young's modulus, density and material properties in cancellous bone over a large density range. J. Mater. Sci.: Mater. Med. 3, 377–381.

Hoffler, C.E., Moore, K.E., Kozloff, K., Zysset, P.K., Brown, M.B., Goldstein, S.A., 2000. Heterogeneity of bone lamellar-level elastic moduli. Bone 26, 603–609.

Issever, A.S., Vieth, V., Lotter, A., Meier, N., Laib, A., Newitt, D., Majumdar, S., Link, T.M., 2002. Local differences in the trabecular bone structure of the proximal femur depicted with high-spatial-resolution MR imaging and multisection CT. Acad. Radiol. 9, 1395–1406.

Kaneko, T.S., Bell, J.S., Pejcic, M.R., Tehranzadeh, J., Keyak, J.H., 2004. Mechanical properties, density and quantitative CT scan data of trabecular bone with and without metastases. J. Biomech. 37, 523–530.

Keaveny, T.M., Borchers, R.E., Gibson, L.J., Hayes, W.C., 1993a. Theoretical analysis of the experimental artifact in trabecular bone compressive modulus. J. Biomech. 26, 599–607.

Keaveny, T.M., Borchers, R.E., Gibson, L.J., Hayes, W.C., 1993b. Trabecular bone modulus and strength can depend on specimen geometry. J. Biomech. 26, 991–1000.

Keaveny, T.M., Pinilla, T.P., Crawford, R.P., Kopperdahl, D.L., Lou, A., 1997. Systematic and random errors in compression testing of trabecular bone. J. Orthop. Res. 15, 101–110.

Keaveny, T.M., Wachtel, E.F., Ford, C.M., Hayes, W.C., 1994. Differences between the tensile and compressive strengths of bovine tibial trabecular bone depend on modulus. J. Biomech. 27, 1137–1146.

Keller, T.S., 1994. Predicting the compressive mechanical behavior of bone. J. Biomech. 27, 1159–1168.

Keyak, J.H., Meagher, J.M., Skinner, H.B., Mote Jr., C.D., 1990. Automated three-dimensional finite element modelling of bone: a new method. J. Biomed. Eng. 12, 389–397.

Keyak, J.H., Lee, I.Y., Skinner, H.B., 1994. Correlations between orthogonal mechanical properties and density of trabecular bone: use of different densitometric measures. J. Biomed. Mater. Res. 28, 1329–1336.

Kopperdahl, D.L., Keaveny, T.M., 1998. Yield strain behavior of trabecular bone. J. Biomech. 31, 601–608.

Li, B., Aspden, R.M., 1997. Composition and mechanical properties of cancellous bone from the femoral head of patients with osteoporosis or osteoarthritis. J. Bone Miner. Res. 12, 641–651.

Linde, F., Hvid, I., 1989. The effect of constraint on the mechanical behaviour of trabecular bone specimens. J. Biomech. 22, 485–490.

Linde, F., Hvid, I., Madsen, F., 1992. The effect of specimen geometry on the mechanical behaviour of trabecular bone specimens. J. Biomech. 25, 359–368.

Lotz, J.C., Gerhart, T.N., Hayes, W.C., 1990. Mechanical properties of trabecular bone from the proximal femur: a quantitative CT study. J. Comput. Assist. Tomogr. 14, 107–114.

Lotz, J.C., Gerhart, T.N., Hayes, W.C., 1991. Mechanical properties of metaphyseal bone in the proximal femur. J. Biomech. 24, 317–329.

Martin, R.B., Sharkey, N.A., 2001. Mechanical effects of postmortem changes, preservation, and allograft bone treatments, Second ed.. In: Cowin, S. (Ed.), . In: Bone Mechanics Handbook, vol. 20 CRC Press, Boca Raton, USA, pp. 1–24.

McBroom, R.J., Hayes, W.C., Edwards, W.T., Goldberg, R.P., White 3rd., A.A., 1985. Prediction of vertebral body compressive fracture using quantitative computed tomography. J. Bone Joint Surg. Am. 67, 1206–1214.

Merz, B., Niederer, P., Muller, R., Ruegsegger, P., 1996. Automated finite element analysis of excised human femora based on precision-QCT. J. Biomech. Eng. 118, 387–390.

Mitton, D., Cendre, E., Roux, J.P., Arlot, M.E., Peix, G., Rumelhart, C., Babot, D., Meunier, P.J., 1998. Mechanical properties of ewe vertebral cancellous bone compared with histomorphometry and high-resolution computed tomography parameters. Bone 22, 651–658.

Morgan, E.F., Keaveny, T.M., 2001. Dependence of yield strain of human trabecular bone on anatomic site. J. Biomech. 34, 569–577.

Morgan, E.F., Bayraktar, H.H., Keaveny, T.M., 2003. Trabecular bone modulus–density relationships depend on anatomic site. J. Biomech. 36, 897–904.

Müller, R., Koller, B., Hildebrand, T., Laib, A., Gianolini, S., Rüegsegger, P., 1996. Resolution dependency of microstructural properties of cancellous bone based on three-dimensional mu-tomography. Technol. Health Care 4, 113–119.

Odgaard, A., 1997. Three-dimensional methods for quantification of cancellous bone architecture. Bone 20, 315–328.

Odgaard, A., Linde, F., 1991. The underestimation of Young's modulus in compressive testing of cancellous bone specimens. J. Biomech. 24, 691–698.

Ohman, C., Baleani, M., Perilli, E., Dall'ara, E., Tassani, S., Baruffaldi, F., Viceconti, M., 2007. Mechanical testing of cancellous bone from the femoral head: experimental errors due to off-axis measurements. J. Biomech. 40, 2426–2433.

Ota, T., Yamamoto, I., Morita, R., 1999. Fracture simulation of the femoral bone using the finite-element method: how a fracture initiates and proceeds. J. Bone Miner. Metab. 17, 108–112.

Ouyang, J., Yang, G.T., Wu, W.Z., Zhu, Q.A., Zhong, S.Z., 1997. Biomechanical characteristics of human trabecular bone. Clin. Biomech. 12, 522–524.

Rice, J.C., Cowin, S.C., Bowman, J.A., 1988. On the dependence of the elasticity and strength of cancellous bone on apparent density. J. Biomech. 21, 155–168.

Rüegsegger, P., 2001. Imaging of bone structures. In: Cowin, S.C. (Ed.), Bone Mechanics Handbook, Second ed. CRC Press, Boca Raton, USA, p. 9.01-23.

Sharp, D.J., Tanner, K.E., Bonfield, W., 1990. Measurement of the density of trabecular bone. J. Biomech. 23, 853–857.

Snyder, S.M., Schneider, E., 1991. Estimation of mechanical properties of cortical bone by computed tomography. J. Orthop. Res. 9, 422–431.

Taddei, F., Viceconti, M., Manfrini, M., Toni, A., 2003. Mechanical strength of a femoral reconstruction in paediatric oncology: a finite element study. Proc. Inst. Mech. Eng. [H] 217, 111–119.

Taddei, F., Pancanti, A., Viceconti, M., 2004. An improved method for the automatic mapping of computed tomography numbers onto finite element models. Med. Eng. Phys. 26, 61–69.

Taddei, F., Martelli, S., Reggiani, B., Cristofolini, L., Viceconti, M., 2006. Finite-element modeling of bones from CT data: sensitivity to geometry and material uncertainties. IEEE Trans. Biomed. Eng. 53, 2194–2200.

Taddei, F., Schileo, E., Helgason, B., Cristofolini, L., Viceconti, M., 2007. The material mapping strategy influences the accuracy of CT-based finite element models of bones: an evaluation against experimental measurements. Med. Eng. Phys. 29, 973–979.

Turner, C.H., Cowin, S.C., 1988. Errors induced by off-axis measurement of the elastic properties of bone. J. Biomech. Eng. 110, 213–215.

Un, K., Bevill, G., Keaveny, T.M., 2006. The effects of side-artifacts on the elastic modulus of trabecular bone. J. Biomech. 39, 1955–1963.

Viceconti, M., Olsen, S., Nolte, L.P., Burton, K., 2005. Extracting clinically relevant data from finite element simulations. Clin. Biomech. 20, 451–454.

Viceconti, M., Brusi, G., Pancanti, A., Cristofolini, L., 2006. Primary stability of an anatomical cementless hip stem: a statistical analysis. J. Biomech. 39, 1169–1179.

Wang, X., Liu, X., Niebur, G.L., 2004. Preparation of on-axis cylindrical trabecular bone specimens using micro-CT imaging. J. Biomech. Eng. 126, 122–125.

Wirtz, D.C., Schiffers, N., Pandorf, T., Radermacher, K., Weichert, D., Forst, R., 2000. Critical evaluation of known bone material properties to realize anisotropic FE-simulation of the proximal femur. J. Biomech. 33, 1325–1330.

Zannoni, C., Mantovani, R., Viceconti, M., 1998. Material properties assignment to finite element models of bone structures: a new method. Med. Eng. Phys. 20, 735–740.