Research Paper

Evaluation of the structural quality of bone in a case of progressive osteoporosis complicating a Complex Regional Pain Syndrome (CRPS) of the upper limb

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Abstract

Densitometry is considered to be the gold standard in bone quality assessment. However, since its introduction, the medical community has been aware that mineral density is only one of the factors that influence the bone risk of fracture, which also depends on the bone’s trabecular arrangement and, in particular, on the trabecular architecture’s load bearing capabilities. At the University of Trieste, in recent years, a test has been developed that simulates the application of compressive loads on trabecular architecture’s reconstructions extracted from digital radiographs. In this work, the test is described, and the results obtained by applying the appraisal in a particular case of severe osteoporosis of the hand, complicating a Complex Regional Pain Syndrome (CRPS) type II, are presented. The test was able to quantify the pathological alterations of bone micro-architecture by means of a Structural Index (SI), which was absolutely significant and relevant to the clinical situation. Important research and clinical opportunities of application of the test include accurate evaluation of osteoporotic bone diseases, careful clinical follow-up and monitoring of responses to therapeutic approaches, and, prospectively, reliable quantification of biological damage (forensic field).

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1 Introduction

According to the National Institutes of Health (NIH) definition, osteoporosis is a disease in which the bones become weak and are more likely to break (National Institutes of Health, 2011). The Dual Energy X-ray Absorptiometry (DEXA) is currently the golden standard for measuring bone density (BMD) and the diagnosis is made based on the number (T-score) of standard deviations below the young Caucasian female adult mean BMD (World Health Organization Scientific Group, 2008). However, even though a low value of bone mineral density is considered to increase the fracture risk, the majority of fractures take place in postmenopausal women and elderly men at moderate risk (Pasco et al., 2006; Siris et al., 2004; Sornay-Rendu et al., 2005; Szulc et al., 2005).

Abbreviations: CRPS, Complex Regional Pain Syndrome; BMD, bone mineral density; CF, content factor; CM, Cell Method; \( E^* \), apparent elastic modulus; ROI, region of interest; SI, Structural Index

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The medical community has long been aware that there are two factors that increase bone weakness: bone mineralization loss and micro-architectural deterioration (Consensus Development Conference, 1993). In effect, without prejudice to the importance of the contribution to bone resistance provided by mineralization, it is well known that the ability of bone to resist the applied loads also depends on the structural architecture of the trabeculae, an aspect which the techniques currently available are not able to take into account (Liu et al., 2009; Yeni et al., 2009; Haiat et al., 2009).

Estimating the bone density alone is not, therefore, a parameter sufficient for a complete evaluation of the load bearing capability of the bone, and, for a better quantitative understanding of bone quality, also the spatial arrangement of the trabecular tissue should be taken into consideration.

An example is given to emphasize this point. Fig. 1 shows two portions of micro-CT slices from a pig humerus, in which the trabecular phase has been meshed with triangular cells. The bone fraction BF in both images is the same by simulating a compression test along the long side of the phase in the two images, the stress distributions obtained under the trabecular tissue has been meshed with triangular cells. two portions of micro-CT slices from a pig humerus, in which the elastic properties of cancellous bone, but also its mechanical strength (Kleerekoper et al., 1985; Uchiyama et al., 1999).

Different Von Mises stress distribution (MPa) computed by simulation of the top slice is only 25.9% of the bottom one. The images were obtained by phase-contrast micro-CT at the Elettra synchrotron radiation facility in Trieste, with a resolution of 14 μm. It must be noted that they represent two particular portions from two different slices (not projected images) and cannot be used alone to assess the bone tissue fraction in the bone.

In general, the trabecular arrangement influences not only the elastic properties of cancellous bone, but also its mechanical strength (Kleerekoper et al., 1985; Uchiyama et al., 1999). In effect, the mechanical properties of bone are regulated by the composition and by the structural organization at the micro- and nano-scale (Zysset et al., 1999). Also, the failure mechanisms in trabecular bone are related to the tissue composition and the microstructure (Morgan, 2008), but, in this case, the non-linearity of the load-deformation curve must be taken into account (Linde, 1994). Both elastic modulus and ultimate strength of cortical and cancellous bone decrease in humans with increasing age (Boukeïn et al., 2008) and, even if a direct relation has not been established, inferences can be drawn between the failure and the elastic properties of trabecular bone (Brear et al., 1988) that can be very useful for the purpose of bone quality ranking.

Micro-numerical models applied to 3D micro-CT or micro-MRI reconstructions, based on finite elements or alternative methods, have been developed to compute the elastic properties of trabecular structures (Cosmi et al., 2009; Niebur et al., 2000; Viceconti et al., 2004, Zysset, 2003) and to perform strength predictions by incorporating the post-yield behavior of the trabecular bone tissue (Verhulp et al., 2008). Nevertheless, a widespread clinical application of 3D methods seems unlikely in the near future, given the examination costs and computational requirements. These considerations led us to investigate whether the information contained in a 2D digital radiographic image can contribute, along with the methods already in use, to give a clinical indication, namely a ranking, of the bone structure’s load bearing capabilities.

The approach followed in this work focuses on the characterization of the bone structure by numerical simulation, obtained from conventional radiographic images of suitable anatomical districts. In a few seconds, the test can quantify the possible pathological alterations of bone micro-architecture by means of a Structural Index (SI), which is calculated from the elastic response of the reconstructed structure and the normalized sum of gray tones, indicative of the mineralization in the region under examination (Cosmi, 2008).

For the assessment of bone quality ranking in age-related osteoporosis, after the first tests on a small number of subjects (Cosmi and Dreossi, 2007a), a wider clinical validation has been recently conducted (Cosmi et al., 2011). The very positive results obtained in these studies, the low cost of the examination and the wide availability of the necessary equipment, make the proposed method a highly promising tool, able to equip the physician with a simple, inexpensive and readily available complementary technique, useful for providing information on the patient’s bone tissue quality, thus completing the data supplied by the methods currently in use, for a more accurate assessment and also for screening purposes.

In this paper we present the results obtained by applying the test to a particular case of rapidly progressing, limb-confined osteoporosis, which occurred in a case of Complex Regional Pain Syndrome (CRPS) of the arm.

We chose this particular (and rare) case of CRPS-linked, severe osteoporosis, since, among other bone diseases, this unique clinical situation provides all the elements necessary for proving the validity of the proposed computational method for a wide range of research and clinical applications in osteoporotic pathologies (see below).
In most cases, CRPS syndrome is a limb-confined chronic and progressive disease (de Mos et al., 2007). Formerly known as “reflex sympathetic dystrophy” (RSD) and “causal-gia” (now classified as CRPS type I and CRPS type II, respectively) (Stanton-Hicks et al., 1995), this syndrome, which involves both the central and peripheral nervous systems, is a highly heterogeneous pathological condition, whose clinical diagnosis is still underestimated and pathophysiology poorly understood (de Mos et al., 2008; Marinus et al., 2011). Often arising after triggering events (e.g. traumatic lesions, fractures or elective surgery of the limbs) (>90% of cases) (de Mos et al., 2007), this severe and painful disease is associated with a particularly poor quality of life and large health-care and societal costs (Goebel, 2011). Due to the complexity of the disorder, and to the lack of scientifically validated studies, the correct diagnosis of CRPS syndrome is often delayed (even for years after the disease onset), and the treatment, which is multidisciplinary and very complex, is not yet standardized (Harden et al., 2013).

Besides intense pain, the heterogeneous clinical expression of long-standing CRPS is characterized by multiple system dysfunctions, which may include, in combination with sensory abnormalities, autonomic disturbances of vasomotor origin, trophic skin and muscle changes, also a rapidly progressive demineralization of the bones (“patchy osteoporosis”) (Park, 2012). Since bone loss in CRPS occurs regionally, with prevalent loss of the trabecular bone and marked bone demineralization predominant at the epiphyseal regions (Doury, 1988), and the recovery of lost mineral bone is very slow (even several years) – thus predisposing the patient to future fractures after minor injuries (Sarangi et al., 1993) – the severe clinical case of CRPS object of our study appeared particularly suitable for our investigation purpose.

The results obtained show how the developed tool may be able to open important prospective applications for the study of bone pathologies (namely osteoporotic ones), not only in regards to the assessment of the illness course and the efficacy of potential therapies, but also with the aim to clarify the pathophysiological aspects of those diseases. Moreover, interesting possibilities of application exist also in the medical forensic field, where this new method can help the physician in the quantification of the biological damage.

2. Materials and methods

2.1. Image elaboration and structural analysis

As already mentioned in the Introduction, the test simulates compression tests on a structure obtained by processing radiographic images, allowing for a quantitative assessment of trabecular bone quality, which can be usefully employed in clinical practice.

The structural numerical model is based on the Cell Method, a recently introduced discrete method (Tonti, 2001), which is particularly interesting from the point of view of calculation time and memory requirements, without compromising the accuracy of the results.

Without going into the details of the formulation, which can be found in the relevant literature mentioned in Section 2.1 here below, suffice it to say that the application of this method is particularly appropriate in the presence of heterogeneities. In effect, the Cell Method is based on a direct discrete formulation of field laws, so that the characteristic dimension of the mesh can be of the same order of magnitude as that of the heterogeneities, without any constraints imposed by mathematical differentiability.

The details of the Cell Method formulation for elastostatics and elastodynamics are discussed in detail in Cosmi (2001, 2005) and Tonti and Zarantonello (2009, 2010). The method has already been successfully applied for the estimation of the elastic properties of sintered materials, short fiber reinforced polyamide composites, and for the analysis of three-dimensional models of the structure of the trabecular bone (Cosmi, 2011a, b, c, 2004, 2003; Cosmi and Dreossi, 2007b; Cosmi and Di Marino, 2001; Taddei et al., 2008). The website http://discretephysics.dic.units.it/ also collects work on the Cell Method by several authors.

The anatomical regions chosen as the most appropriate for the analyses are the first phalanx of the second, third and fourth finger (proximal epiphyses). In these anatomic regions, in fact, it is possible to identify the outline of the trabecular structure even in a plain radiograph, since the pattern develops in layers with a certain regularity, despite the irregularities of the bone shape.

The operator interface with the radiographic image of the hand, a zoom of the second finger proximal epiphysis, and the region of interest, ROI, selected for the structural analysis, is shown in Fig. 2. The size of the ROI can be adjusted by the operator in each finger, so that it covers the largest possible square trabecular region within the cortical boundaries.

The structure used for the numerical analysis is obtained from the digital X-ray image through a number of steps:

1. A nonlinear sub-threshold erosion filter is applied to the ROI image in order to remove the smaller elements, not connected with the tissue. Each pixel of the selected image has a gray tone value between 0 and 255, Fig. 3(a).
2. A grid of nodes is laid on the image, Fig. 3(b). The same initial spacing has been used throughout this work. The nodes are then automatically connected to form a mesh of triangular cells, with larger cells over regions with same gray level. Consequently, the number of cells can change with the ROI structure. In this work, the number of cells in the simulations ranged roughly from 3200 to 3500, depending on the bone dimensions and the local pattern.
3. The elastic modulus of each cell is scaled between 0 and 1000 MPa on the basis of the average gray level in 7 points of the cell (barycenter, vertexes and sides middle points). A linear elastic constitutive law has been assumed, with a Poisson’s ratio of 0.3. The cells with average gray level zero do not have mechanical characteristics. Fig. 3(c) graphically depicts the elastic modulus distribution in the cells.

By means of the described procedure, the image has been transformed into a structural model suitable for simulating the application of compressive loads along the orthogonal axes. The average value of the apparent elastic moduli in the two directions, \( E^* \), can be then computed. The sum of the
Gray tone values in the ROI, normalized to 100, is the CF and provides an indication of the local level of mineralization, somehow related to the matter content in the ROI (Cosmi, 2008).

These two values are then combined in a Structure Index, SI. In order to explain the meaning of SI, it can be useful to point out that the simulation results in terms of apparent elastic modulus incorporate both aspects of bone strength: the matter content and its architectural organization. Since the purpose of the proposed approach is to highlight the contribution to bone quality of the structural arrangement, as a complement to the well-established bone mineral density measurements, the SI has been introduced with the aim of removing the effect linked to the mineralization level from the apparent elastic moduli in the ROI. The mathematical expression for computing the Structure Index is as follows:

\[ SI = a_1 \frac{b_1 E^* - b_2 \text{CF}}{C_0} \]

where \( a_1 \) is a normalization factor computed from the radiographic acquisition parameters, and \( b_1 \) and \( b_2 \) are positive constants. The complied code running in the IDL Virtual Machine platform (http://www.exelisvis.com/ accessed January 28, 2013) gives the results in less than 1 min on a normal personal computer, including both image processing and numerical model solution.
In application to the evaluation of the risk of fracture in osteopenic and osteoporotic patients, the first trials performed are described in Cosmi and Dreossi (2007a) and Cosmi et al. (2011). These studies confirmed that Structural Index is able to separate the clinically positive subjects from the healthy ones, despite a possible information loss due to the use of planar radiographic images.

This last aspect is detailed in Section 4, where it is shown that, even if a 2D image based simulation cannot offer an accurate prediction for the 3D structure mechanical properties, the SI can still provide an accurate tool for bone quality ranking, being able to preserve, and even amplify, the differences among trabecular patterns detected in appropriate anatomical regions.

2.2. Application of the method in a case of Complex Regional Pain Syndrome of the upper limb

The object of the present study is a case of Complex Regional Pain Syndrome (CRPS), type II (ICD-10 GM 2010, G56.4) (Albazaz et al., 2008), which was diagnosed in a woman of 50 years, following a lacerated major blunt trauma of the right hand, with partial nerve injury (second finger) and fracture of the proximal epiphysis of the first phalanx of the third finger. The diagnosis was performed according to the Budapest criteria endorsed by the International Association for the Study of Pain (Budapest/IASP CRPS criteria), recently validated for clinical and research use (Harden et al., 2013).

The case was particularly interesting, as complicated by severe osteoporosis, which, during the six months following the trauma, extended in a distal to proximal direction, affecting, progressively, all the bone structures of the hand, radius and ulna, mostly involving, as typically occurs in this particular syndrome, the trabecular bone of the epiphyseal portions of the interested bones (Doury, 1988).

Fig. 4 shows a detail of the specific alterations observed under X-rays in the case object of study, exhibiting the typical “patchy” osteoporosis pattern, with a predominant involvement of the trabecular bone of the epiphyses.

3. Results

As already discussed in Section 2, the software computes:

1. the average value of the apparent elastic moduli along the axes of the structure obtained from the ROI image elaboration, $E^*$,

2. the CF, that gives an indication of the local level of mineralization, and combines these values in a SI.

In a first series of evaluations, the data were obtained from the radiographs of the right hand, carried out during the usual clinical examination procedures provided in these cases, i.e. immediately following the trauma, and after 2 and 5 months from the onset of the syndrome. In particular, the radiography performed at the time of the trauma corresponds to a situation of healthy trabecular structure, not yet altered by the CPRS-induced abnormalities. The damage induced by the osteoporotic disorder, however, is well detectable in the successive radiographs. An interesting visual comparison is shown in Fig. 5, where the trabecular region in the proximal epiphyses of the first phalanx (middle finger) is depicted. The progressive damage to the trabecular structure (bone resorption) appears to be easily observable, but cannot be quantified by the visual examination of the radiographs alone.

In this particular case of CRPS, that involved all the structures of the hand, it was possible to perform a more specific assessment of the clinical situation by following into the detail the time evolution of each finger. For a quantitative assessment of the overall situation of the bone’s features, the values of the Structural Index (SI), of the apparent elastic modulus ($E^*$), and of the content factor (CF) were computed in each finger (thumb excluded). Given the non-optimal image resolution, the average of three tests was always considered in each finger. The results are shown in Fig. 6.

The SI, as well as being able to quantify the bone’s damage and of following its evolution over time, appears to be more sensitive to the alterations of the bone structure rather than the average modulus of elasticity and the parameters related to mineralization. For example, the percentage of change between the initial (healthy) situation and the condition found after 5 months for SI is 48%, while it is 27% for $E^*$, and only 20% if CF is considered. These indications reflect those obtained from the analysis of the simplified models discussed in Section 4. It is noteworthy the strict correspondence found between the time-course of SI values (whole hand and single fingers) and the corresponding clinical situation (i.e. severity of pain, local swelling, trophic condition, articular mobility). Images of the affected hand after 2 (a) and 5 (b) months from the onset of the syndrome are shown in Fig. 7. Consequently, $E^*$ and CF were not considered in the successive clinical assessments, and only SI, the parameter with the greatest ability to discriminate differences, was recorded.

Given the encouraging results obtained, in the following radiologic controls it was decided to acquire higher resolution radiographs by a digital mammograph, with an appropriate setting of the parameters and the adoption of a RH-RH filter, similarly to that described in Cosmi and Dreossi (2007a). In this case, since no reference data were available for the right hand in good physical shape (before or immediately after the trauma), the left hand not affected by the CRPS syndrome was used as internal healthy control, in order to assess the characteristic values of an unaltered trabecular structure. The images of the trabecular region analyzed offer again an interesting visual comparison, and allow to appreciate the
improvement in the definition of the trabecular structure obtained by the mammograph (Fig. 8).

The numerical results are shown in Table 1. By 8 months after the disease onset, a significant recovery of the bone quality was evident, and, specifically, it was noteworthy at the level of the third and the fourth fingers, which, in the analyzed region, showed SI values similar to those observed in the corresponding regions of healthy left hand’s fingers. Interestingly, when each single finger was considered, a close correlation between the estimated recovery of bone loss and the objective osteo-articular
Fig. 7 – Representative photographs of the CRPS-affected hand, taken after 2 (a), 5 (b), 8 (c and c₁) and 12 (d and d₁) months following the onset of the disease. It is possible to appreciate the clinical evolution of the syndrome. In particular, (c₁) and (d₁) refer to soft tissues appearance and articular mobility after 8 (c) and 12 (d) months after the beginning of the disease.
improvement of function (motility) and soft tissues’ trophy was observed, thus confirming the potential clinical value of the adopted method for a correct estimation of the severity and course of CRPS-linked osteoporotic bone diseases.

Pictures of the CRPS-affected hand taken 8 (c and c1) and 12 (d and d1) months after the onset of the syndrome are shown in Fig. 7. In particular, in Fig. 7 (c1) and (d1), which refer to soft tissues appearance and articular mobility after 8 (c) and 12 (d) months from the onset of the disease, it is possible to appreciate the parallel between bone quality (expressed by the value of the calculated SI) (Fig. 6 and Table 1) and the clinical situation.

4. Discussion

In this work we decided to use planar radiographies to investigate the mechanical properties of the bone during the course of a severe CRPS-induced “patchy osteoporosis” of the upper limb. The proposed method is based on the in silico mechanical characterization of bone trabecular structures obtained by conventional radiographic images.

In our study, information from the measurement of bone densitometry obtained by conventional Dual Energy X-ray Absorptiometry (DEXA) scans used for the analysis of generalized age-related osteoporosis was not employed for crossed assessments with the SI. Provided that our main objective was not to compare the accuracy of the results obtained with our method with those from DEXA scans (or from other imaging techniques, that, except for radionuclide bone imaging, are not clinically accepted for providing objective and relatively specific evidence of CRPS disease), the internal controls provided by the Rx images taken from the right hand immediately after the trauma and from the healthy left hand, the information obtained from the CF (that gives an indication of the local level of bone mineralization), and the typical images obtained

<table>
<thead>
<tr>
<th>SI</th>
<th>First finger</th>
<th>Second finger</th>
<th>Third finger</th>
<th>Fourth finger</th>
<th>Hand average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hand</td>
<td>314</td>
<td>163</td>
<td>160</td>
<td>179</td>
<td>204</td>
</tr>
<tr>
<td>8 months</td>
<td>86</td>
<td>106</td>
<td>122</td>
<td>144</td>
<td>115</td>
</tr>
<tr>
<td>12 months</td>
<td>105</td>
<td>127</td>
<td>161</td>
<td>176</td>
<td>142</td>
</tr>
</tbody>
</table>

Table 1 — Values of SI in each finger, and average values in the healthy left hand and in the CRPS-affected right hand thumb excluded after 8 and 12 months from the disease’s onset. SI values were computed from mammographic images.
from three-phase radionuclide bone scans, used for confirming the diagnosis of CRPS-related bone alterations (Mackinnon and Holder, 1984) (data not shown), made unnecessary to perform other tests such as DEXA.

By definition, it is not possible to resolve a 3D structure by a single radiographic image. An example is here discussed to show that, even if a 2D image-based simulation cannot provide an accurate prediction for the 3D structure mechanical properties, the SI can still provide an accurate tool for bone quality ranking, being able to preserve, and even to amplify, the differences among trabecular patterns in the particular anatomical region used for the analysis.

Quite obviously, since this study regards a living patient, it was not possible to conduct any direct mechanical tests. More pointedly, the Structural Index could be, in theory, obtained from cadaver’s hand bones, which could be tested for mechanical-property data, such as elastic modulus or bone strength, and if this possibility arises, the authors fully intend to follow this path. Nevertheless, since the mechanical properties of a composite material strictly depend on its structure and composition, even if the direct mechanical test could be performed on a cadaver’s hand bones, the results obtained could obviously differ from those of a living, blood-perfused bone.

In principle, a 3D trabecular architecture can be reconstructed by CT scans and successively imported in a numerical model, e.g. based on the Finite Element Method, to calculate its apparent elastic properties. Unfortunately, in the case of the present study a comparison between data obtained from 3D direct numerical models and from planar radiographic images in the same anatomical region was not possible, since 3D scans at the level of resolution required for this purpose were not available at the facility where this study was conducted.

To overcome this limitations, we considered a very simplified, out-of-scale model of the three-dimensional trabecular structure in the examined region (the proximal epiphyses of the first phalanx of the second, third and fourth finger), which, as already mentioned, develops in a planar, regular fashion, very different from the complex 3D micro-architecture, as found, for example, in the femoral neck or in the calcaneus. The simplified model consists of two orthogonal square-section rods, lying in the xy plane and joined by a frame (see 3D_A, Fig. 9 top left). Frame side size is 11 mm, bar thickness in the xy plane is 3 mm, and 1 mm along z. The bars are separated along the z-axis, and the distance between the two orthogonal rods is 1 mm. In an X-ray image (X-ray path following z-axis), the structure appears with areas of increased absorption at the greatest thickness, as in the model 2D_A shown in Fig. 9 (bottom left). In a similar manner, it is possible to obtain the out-of-scale models of an altered trabecular structure (as occurs, for example, during osteoporosis) by changing the rods thickness in the yx plane. The frame side size in the corresponding 3D_B (Fig. 9 top center) and 2D_B (Fig. 9 bottom center) models is the same, but the rod thickness in the xy plane is now changed to 1 mm. A third structure is obtained by changing the frame side size to 7 mm and by keeping the trabecular thickness value 1 mm in the yx plane. The corresponding 3D_C and 2D_C models are shown in Fig. 9 top right and Fig. 9 bottom right, respectively.

In the three-dimensional models, an arbitrary value of $E=1000$ MPa is assumed as the elastic modulus of the bars. In the planar models, by proceeding in a manner similar to the calculations described in the previous Section 2.1, a value of $E=1000$ MPa is assumed for the bars elastic modulus, except in the central area, where the difference in X-ray absorption can

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Fig. 9 – 3D_A and 2D_A, respectively, 3D and 2D models of simplified, out-of-scale-trabecular structure in the examined anatomical region; 3D_B and 2D_B, 3D_C and 2D_C, analogous models of two differently altered structures (higher absorption areas are shown darker for clarity of representation).
be taken into account by posing $E = 2000$ MPa, and in the frame, where for the same reason $E = 3000$ MPa.

Compression tests along the x and y-axes can be simulated, and the apparent elastic moduli $E^*$ of the six models can be evaluated, together with the $CF$ defined in Section 2.1 and the $SI$ of the 2D models (the index is only defined for plane structures).

Obviously, since a 2D simulation cannot accurately predict the behavior of a 3D structure, the apparent elastic moduli and the content factor in the 2D_A, 2D_B, and 2D_C models are quite different from those computed for the corresponding 3D_A, 3D_B, and 3D_C models, as expected, but the ratio between the apparent elastic moduli in the 2D and in the 3D structures is approximately the same (and equal to 3) for all the structures A, B and C. Nevertheless, it must be pointed out that, for this application, the most important element to be conserved in the 3D to 2D simplification is the ability to discriminate between the structures, rather than the exact value of the considered parameter, i.e. the apparent elastic moduli or the content factor.

A simple indicator of the changes between the two structures is represented by the ratio between the parameters computed for the different structures, as summarized in Table 2. It can be appreciated that the 3D and the 2D results are practically equivalent for the purpose of structure ranking, since there is no difference between the ratios computed in the 2D and in the 3D structures. It can be therefore affirmed that, in this regard, the 2D and 3D models are equivalent.

If the discriminatory power of parameters such as content factor ($CF$) and apparent elastic modulus ($E^*$) are considered, the $CF$ ratio, linked to the differences in mineralization, has a discriminatory capability that is comparable to that of the 2D elastic moduli in the case of the structures A and B, and a little smaller than the $E^*$ ratio in all the other cases, that is the 2D models of structures A and C and all the 3D models. But, if for the planar models the Structural Index ($SI$) ratio is considered instead of the elastic moduli, it can be seen that $SI$ is able to amplify the differences among the structures with respect to the other parameters. In the present case of very simplified bone architectures, this amplification effect is small, but it becomes more relevant when more dense patterns, in which the trabeculae are regularly organized, are considered, like in the proximal side of the first phalanges of hand fingers, used for the clinical evaluation of the bone structures. This is a definitely positive effect for the purposes of clinical classification.

Therefore, from the methodological point of view, it can be concluded that the planar model obtained from a digital radiography with the procedure described in Section 2.1, appears to be able to give results that can be useful for classifying the quality of bone for the purpose of a research application or a clinical evaluation, even if it is not possible to use a 2D model for predicting the exact value of the elastic modulus of the 3D bone structure.

### Table 2 - Ratios of the apparent elastic moduli $E^*$, $CF$ and $SI$ computed for the different structures.

<table>
<thead>
<tr>
<th></th>
<th>$E/A^*$</th>
<th>$E/B^*$</th>
<th>$CF_A/CF_B$</th>
<th>$CF_C/CF_B$</th>
<th>$SI_A/SI_B$</th>
<th>$SI_C/SI_B$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D</td>
<td>1.4</td>
<td>1.6</td>
<td>1.3</td>
<td>1.5</td>
<td>1.5</td>
<td>1.7</td>
</tr>
<tr>
<td>2D</td>
<td>1.3</td>
<td>1.6</td>
<td>1.3</td>
<td>1.5</td>
<td>1.5</td>
<td>1.7</td>
</tr>
</tbody>
</table>

5. Conclusions

The present paper illustrates the results derived from the analysis of a particular case of rapidly progressing, severe osteoporosis of the upper limb, associated with a Complex Regional Pain Syndrome (CRPS) type II, and obtained by applying a new computational method, developed in order to permit to “classify” bone’s quality in osteoporotic syndromes.

Based on the Cell Method, the approach followed in this work focuses on the characterization of bone strength, obtained by numerical simulations of load application to a numerical structure derived from a conventional (2D) digital radiographic image of the hand. The proposed test can quantify the pathological alterations of bone micro-architecture by means of a Structural Index ($SI$), which is calculated from the elastic response of the reconstructed structure and the normalized sum of gray tones, indicative of the mineralization in the region of interest. In the particular (and not frequent) CRPS case chosen for our study, the calculated Structural Index was absolutely significant and relevant to the clinical situation.

The test, originally developed as a complementary tool for the evaluation of the risk of fracture in osteopenic and osteoporotic patients, is very fast (the result is given within 1 min), can be performed at low cost, and can be easily executed and implemented within a traditional unit of Radiology, since it requires only a conventional 2D digital radiograph of the hand.

The results obtained in the present study demonstrate, in their complex, as the developed method may have wide and important prospects of application in the medical context, that include, besides specific research objective directed to add new insight into the pathogenesis of complex bone alterations (such as CRPS-linked osteoporosis is), also the possibility of a more accurate clinical evaluation of the degree and course of osteoporotic bone diseases, a careful monitoring of their responses to specific therapeutic approaches (e.g. functional, pharmacologic or other interventional procedures), and, prospectively, a more precise and reliable quantification of the biological damage (forensic field).

### Acknowledgments

This study has been performed on a CRPS patient followed by the clinical team of the “Casa di Cura San Francesco” (Bergamo, Italy). The authors are particularly thankful to Dr. D. Malgrati for his generous enthusiasm and motivation, which made possible the realization of this work, to Dr. G. Ronzoni, for providing the X-ray images used in this study, and to Mr. R. Pozzon, for his expert technical assistance in their acquisition. Ing. S. Scozese’s contribution to the simulations of the simplified model of the
trabecular structure is also acknowledged. G.M. is particularly grateful to Mr. P. Panichi, whose professional competence, human sensibility and insight permitted to achieve the clinical results shown in this study. The authors are also indebted to Dr. N. Steinberg, Dr. J. Boniotti and Dr. M. Attanasio for their constant encouragement and assistance all during the preparation of this paper. This work was supported by local funds of the University of Trieste (to F.C.) and of the University of Brescia (to G.M.).

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