DXAGE: a new method for age at death estimation based on femoral bone mineral density and artificial neural networks

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ABSTRACT

Age at death estimation in adult skeletons is hampered, among others, by the unremarkable correlation of bone estimators with chronological age, implementation of inappropriate statistical techniques, observer error and skeletal incompleteness or destruction. Therefore, it is beneficial to consider alternative methods to assess age at death in adult skeletons. The decrease of bone mineral density with age was explored to generate a method to assess age at death in human remains. A connectionist computational approach, artificial neural networks, was employed to model femur densitometry data gathered in 100 female individuals from the Coimbra Identified Skeletal Collection. Bone mineral density declines consistently with age and the method performs appropriately, with mean absolute differences between known and predicted age ranging from 9.19 to 13.49 years. The proposed method – DXAGE – was implemented online to streamline age estimation. This preliminary study highlights the value of densitometry to assess age at death in human remains.

Keywords

Forensic science; biological profile; BMD; DXA; machine learning; forensic anthropology

Introduction

The accurate estimation of age at death in human skeletal remains is a major requirement for establishing a biological profile and for individual identification and endures as a major challenge in forensic anthropology (1–3). There are several methods available based on macroscopic observation of degenerative skeletal features (4–12). However, these tend to have lower reproducibility because of the subjective nature of user-observation (2,11,13–17). The effectiveness of these methods is thus deeply influenced by observer experience and the archetypal nature of the observed features in comparison to the published standards and guidelines. Institutions and researchers have been recommending more stringent, objective and quantitative procedures for age at death analyses (18). As such, methods that are dependent on features extracted without observer intervention should be developed and established in the forensic anthropology toolkit.

The decline of bone mass with increasing age has been established for a long time (19–21). Age influences bone health with direct and indirect effects on bone mass, and mechanisms of age-related bone loss include remodelling imbalances, the decrease in the intestinal production of 1,25-$(OH)_2D_3$, secondary hyperparathyroidism, and the accumulation of damage in osseous tissue and reduction of viable osteocytes (22–24). Although there are regional, ethnic and individual (e.g., body mass) variations, the reduction of bone mineral density (BMD) – as measured through bone densitometry of the femur – with age is a universal phenomenon, most notably in women (e.g. 25–36). Therefore, it can be considered as a relevant biological indicator for age at death estimation (37). In accordance to this hypothesis, Fernández Castillo and López Ruiz (38) created an aging technique supported by densitometric measurements and conventional least squares regression. BMD is instrumentally determined and obtained through bone densitometry (DXA), thus reducing observer bias in data acquisition.

Artificial neural networks (ANN) were used to model data obtained from DXA to estimate

age at death in adult skeletal individuals. ANN are a biological inspired computational technique for unsupervised and supervised learning, that attempt to mimic the interconnected structure of the human brain (39). Our specific objectives were to explore the association of BMD decline with age and to create an accurate method to estimate age at death in human remains based on BMD features. The development of an online application in order to facilitate age at death estimation constituted a subsidiary goal.

Materials and Methods

The training sample consisted of 100 femora of female individuals with ages at death ranging from 21 to 95 years, belonging to the ‘‘Coimbra Identified Skeletal Collection’’ (CISC). These individuals were buried in shallow graves of the *Cemitério da Conchada* (Coimbra) for at least five years – after that the bodies were commonly exhumed (40). Only femora devoid of gross diagenetic alterations and significant pathological conditions (e.g., hip fracture) were included in the sample. A sizeable number of femora (N=48) were radiographed (exposure time of mAseg 80-50, exposure of Kv 30-35 and focal distance of 1.0 m) to assess soil erosion – results showed that soil erosion (macroscopical destruction of trabecular or endocortical bone caused by soil) was insignificant or null. Bone densitometry evaluation was performed with a Hologic QDR 4500C Elite densitometer (published formulae should be used to convert the BMD measured on any other model for a given manufacturer, e.g., Lunar or Nordland (41)) by a medical imaging technologist. Femora were placed on low-density cardboard recipients, on top of 10 cm of rice, in anteroposterior position and with the diaphysis parallel to the scanner’s central axis (42). In order to increase reproducibility, the femora were internally rotated ~35º (43). For the purposes of bone densitometry, the proximal femur is divided in different regions of interest (ROI): femoral neck, trochanter, intertrochanteric region, Ward’s area and total hip (Figure 1). Bone area (cm^2), bone mineral content (BMC, g) and bone mineral density (BMD, g/cm^2) were semi-automatically

identified in the ROI of the proximal femur (if necessary the technologist delivers minoradjustments) and then were automatically extracted by the densitometer software. For this study only three variables that represent BMD were selected: BMD Total, BMD Ward and BMD Neck. Thirty femora were scanned twofold to establish the repeatability of the DXA scans and intraobserver error was evaluated with the relative technical error of measurement (rTEM) (44). rTEM was 0.86%, a very low value, indicating a precise placing of the femur in the densitometer.

To model the BMD variables into predictors of age at death, we used a modified *General Regression Neural Network* (45,46). It is an ANN that attempts to mimic the associative memory and encompasses four different layers: input, pattern, summation, and output (Figure 2). The *input* layer matches the BMD vector to estimate age. In the *pattern* layer, the input is compared to other examples kept on the network's memory. Each example (pattern) in the network is used as an artificial neuron, whose activation relies upon a radial basis function. The *summation* and *output* layers allow the attainment of a regression surface and an estimate of the variable to predict – age – through a weighted arithmetic mean of the examples previously stored in memory.

Weights or ponderation factors are given by the activation values of the radial basis function associated with each artificial neuron. Given a matrix or vector of predictors *X*, and a response variable *Y*, the estimation of the network *Y(X)'* can be mathematically defined as:

$$Y(X)' = \frac{\sum_{i=1}^{n} Y^i e^{-\frac{D_i^2}{2\sigma^2}}}{\sum_{i=1}^{n} e^{-\frac{D_i^2}{2\sigma^2}}}$$

here D_i^2 is the distance, typically Euclidean, between the vector of the input layer and the i^{th} example pre-stored in the memory of the pattern layer, whereas σ^2 is a smoothing parameter that regulates estimated density and controls the volume of information neighboring each artificial neuron.

The major advantage in this type of network architecture is its fast training. It takes only one step, given that σ^2 is the only parameter to be optimized. The optimization process consists on finding the σ^2 that minimizes, for example, the mean absolute error. In this study, the training of different ANN models was performed with Brent's algorithm, combined with a cross-validation scheme ($K = n - 1$).

In the forensic sciences, the probabilistic estimation of age at death has acquired special relevance, because it is important to quantify and visualize the uncertainty associated with each estimation (3,11). The ANN used in this study was modified in order to estimate all *a posteriori* distribution, and not just the conditional mean. From a probabilistic point of view, age at death estimation can be defined as:

$$f(y|x) = \frac{f(x|y)f(y)}{f(x)} = \frac{f(x|y)f(y)}{\int_a^b f(x|y)f(y)dy}$$

In order to obtain *f(y|x)*, the third and fourth layer of the ANN need to be modified in such a way that allows for the estimation of *f(x|y)*. A Gaussian kernel function is used to calculate *f(x|y)*, weighted by activation values of the radial basis function. The final estimation of age at death is obtained by the quantile estimation associated to the normalized *a posteriori* distribution.

Neural network training was performed following the original implementation by Specht (45) and the modification just described. For the latter, a uniform prior distribution over age at death was assumed. Such prior is more likely to result in higher estimate error but the proposed models are thus less sensitive to the age structure of the studied sample. The proposed modification to the original ANN algorithm also allows to compute additional error metrics such as predictive interval mean width and coverage.

Results

BMD Total shows a moderate and negative linear correlation with age at death (Pearson's $r = -0.696$; $p < 0.001$), while both BMD at the neck (Pearson's $r = -0.747$; $p < 0.001$) and BMD at the Ward's area (Pearson's $r = -0.761$; $p < 0.001$) show a strong, negative, association with age at death (Figure 3). Relative variation of BMD between the younger (20 – 29 years) and the oldest age classes (80+ years) is impressive, fluctuating between 39.4% (BMD Total) and 57.0% (BMD Ward). Results by age class are summarized in Table 1.

Using the non-probabilistic ANN, as described by Specht (45), the mean absolute difference between real and estimated age ranged from 9.19 to 12.03 years depending on the variables used through modelling. Variance explained by the ANN models extended from 46.4 to 69.1%. Among the three variables, BMD Total was the least efficient for age estimation, when isolated. The measurements in the neck area were the most useful, in particular the measurement associated to Ward's area. Interestingly, a model containing only the neck and Ward variables had a slightly better performance than a model based on all features (Table 2).

Probabilistic ANN resulted in slightly higher estimation errors, 10.07 – 13.49 (MAE, Table 2) but allowed to compute heteroscedastic predictive intervals. Predictive interval mean width ranged from 42.26 to 55.00 years. Coverage, the amount of cases that are correct given the estimated predictive intervals, varied from 94% to 97%. All values reported in Table 3 are based on an alpha value of 0.05.

This computational approach was implemented as an online web application – DXAGE, available at http://osteomics.com/DXAGE – that allows an interactive use of the new aging technique (Figure 4). DXAGE gives the most likely estimate for age and also a credible interval with the minimum and maximum ages estimated. Since all BMD features are highly correlated amongst them, using contradicting numeric values will not match any expected pattern, both biologically and database-wise. Thus, DXAGE will not be able to create a predictive or a graphical

output if the inputs provided by users are inconsistent. It is also possible to exclude any of the variables from the model when deemed appropriate. It is important to note that, for now, DXAGE is limited to females of European origin.

Discussion

This exploratory analysis, that focused in a sample of women of European ancestry, conveys the potential relevance of BMD decline to the estimation of age at death in human remains (38,42). BMD at different ROI shows a sharp decline with age at death, a pattern observed in both epidemiological (25–36,47–53) and anthropological research (38,42,54–56). BMD has a multifactorial etiology and, like most skeletal indicators of age in adults, varies between individuals and between populations, reflecting the complexity of the senescence process (57). In general, circa 60% of the variation in skeletal age indicators is related with *features other than age* (58): compare it with the percent variance of BMD Ward that is explained by age at death (57.8%). Considering that population and individual factors influence skeletal remodelling and biological age, it is advisable to employ an eclectic range of indicators of age to assess age at death (1,59). DXAGE seems to predict age at death as well as, most classical techniques for age estimation in human skeletal remains (2,14,60–63) – standing as a valuable alternative to include in the forensic anthropologist toolkit. This is especially relevant if other highly accurate methods cannot be performed (e.g. 64–66).

The differences in the performance of the original ANN algorithm and the modification proposed are due the prior over age at death assumed in each approach. A standard regression approach assumes the distribution of the training set as the implicit distribution of data, while blending ANNs with Bayesian prediction allows to perform age estimation with any given prior over age at death. A uniform prior was selected, because it represents the less biased approach and avoids projecting the age distribution of the studied sample on new cases.

The femur is the strongest bone in the human skeleton and it is frequently well preserved

in forensic contexts (67). It is also highly dimorphic and useful for sex estimation of unknown skeletal remains (68). An important advantage of this method is the possibility to apply it to incomplete and fragmentary human remains, particularly when primary regions for aging skeletal remains, such as the *os coxae*, are missing or damaged (15,59). Moreover, research in forensic anthropology often includes cadaveric remains with soft tissues. Thus, medical imaging techniques, such as DXA or X-ray computed tomography, are valuable to assess age at death in individuals not entirely skeletonized in which skeletal preparation is not practical, or culturally reasonable (38,69–75). DXA has been uncommonly exploited in forensic anthropology; nonetheless, it can be used, not only to estimate age at death, but also to assess sex (76–79). Ancestry estimation with the proximal femur has also been attempted but results are inconclusive (61,62). Accordingly, a single femur can add valuable data to the establishment of a biological profile.

DXA measurements are precise and reproducible, but can be affected by taphonomic processes (e.g., microstructural or chemical alterations of bone) in forensic and, especially, in archaeological skeletal material (80). As such, the possible influence of diagenesis on DXA readings should always be evaluated. There are evidences implying that, even in bones with some form of diagenetic change, bone mineral content is marginally altered (81,82). Recently, Spinek et al. (83) conducted a Fourier transform infrared spectrometry analysis in femora from various archaeological sites and chronologies (including a Neolithic sample [4600 – 4000 BCE]) that indicated a good state of preservation, with no diagenetic alterations. A set of direct - macroscopical analysis, absence of soil erosion on plain radiographs and microradiography (84) – and indirect - the pattern of bone loss is epidemiologically expected (42) – evidences suggest that the sample from the CISC is also in good state of preservation.

Modelling data through the adapted ANN presents definite advantages. In particular, the output emerges as the *a posteriori* distribution, allowing to visualize the uncertainty associated with each estimate. Presenting age at death as a probability density typifies the complete range

of possible ages (57). We introduce this feature to others through DXAGE, an online web application, allowing researchers and students to interactively apply and test the new method. Previous studies (85,86) have proven the value of artificial neural networks in age estimation. However, such studies failed to provide an easy interface to apply those models in real cases. As a decision support system, DXAGE is rather simple to use, continuing a recent trend that employs online applications to simplify different forensic goals (e.g. 87–89), thus enabling the models hereby presented to be applicable and usable by others.

Conclusions

The estimation of age at death is a crucial research topic in forensic anthropology and the development of reliable methods for age at death estimation from different skeletal regions increases the probability of identifying anonymous skeletal remains. Our results have highlighted the potential of DXA scans and data modelling through ANN to achieve accurate predictions of age at death in adult human remains, in a straightforward online interface that we hope will increase the applicability of our method. These preliminary models present some limitations, namely the inclusion in the training sample of females of European ancestry only, and must be expanded to include males and individuals from independent skeletal reference collections.

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Table 1. Average values of BMD (Total, Neck, and Ward) in the different age classes.

		Mean	**SD**	**N**
BMD Total	20-29	0.924	0.11	15
	30-49	0.913	0.10	14
	40-49	0.834	0.14	14
	50-59	0.781	0.12	14
	60-69	0.746	0.12	14
	70-79	0.716	0.10	14
	80+	0.560	0.10	15
BMD Neck	20-29	0.820	0.12	15
	30-49	0.836	0.11	14
	40-49	0.732	0.13	14
	50-59	0.674	0.10	14
	60-69	0.611	0.11	14
	70-79	0.609	0.08	14
	80+	0.474	0.07	15
BMD Ward	20-29	0.745	0.21	15
	30-49	0.731	0.13	14
	40-49	0.589	0.13	14
	50-59	0.491	0.13	14
	60-69	0.429	0.13	14
	70-79	0.397	0.07	14
	80+	0.320	0.07	15

SD: standard deviation; **N**: number of individuals.

Table 2. Statistical metrics for seven different non-probabilistic ANN models used to estimate age at death through BMD.

	MAE	RMAE	MAPE	RMSE	RRMSE	RSQ	ARSQ
BMD Total	12.025	0.673	27.376	15.091	0.732	0.464	0.459
BMD Neck	10.751	0.601	24.273	13.402	0.650	0.578	0.573
BMD Ward	9.592	0.537	21.260	12.042	0.584	0.659	0.655
BMD Total, Neck	11.350	0.635	26.026	14.017	0.680	0.538	0.528
BMD Total, Ward	9.382	0.525	20.498	11.906	0.577	0.667	0.660
BMD Neck, Ward	9.190	0.514	20.026	11.462	0.556	0.691	0.685
BMD Total, Neck, Ward	9.508	0.532	21.114	12.031	0.584	0.660	0.649

MAE, mean absolute error; **RMAE**, relative mean absolute error; **MAPE**, mean absolute percent error; **RMSE**, root of mean square error; **RRMSE**, relative root of mean square error; **RSQ**, coefficient of determination (R^2); **ARSQ**, pseudo coefficient of determination (adjusted R^2).

Table 3. Models using the modified ANN, allowing the calculation of the predicted interval mean width and the coverage. All results here were obtained using an alpha value of 0.05 and a uniform prior.

	MAE	**RMAE**	**MAPE**	**RMSE**	**RRMSE**	**RSQ**	**ARSQ**	**PIMW**	**%C**
BMD Total	13.49	0.76	27.91	16.84	0.82	0.33	0.33	55.00	0.97
BMD Neck	11.86	0.66	25.27	14.56	0.71	0.50	0.50	49.23	0.95
BMD Ward	10.25	0.57	22.01	12.61	0.61	0.63	0.62	48.44	0.96
BMD Total, Neck	12.88	0.72	28.37	16.45	0.80	0.36	0.35	52.84	0.96
BMD Total, Ward	10.07	0.56	21.24	12.77	0.62	0.62	0.61	45.85	0.95
BMD Neck, Ward	10.12	0.57	20.88	12.54	0.61	0.63	0.62	42.26	0.94
BMD Total, Neck, Ward	10.76	0.60	22.94	13.38	0.65	0.58	0.56	44.15	0.95

MAE, mean absolute error; **RMAE**, relative mean absolute error; **MAPE**, mean absolute percent error; **RMSE**, root of mean square error; **RRMSE**, relative root of mean square error; **RSQ**, coefficient of determination (R^2); **ARSQ**, pseudo coefficient of determination (adjusted R^2); **PIMW**, predicted interval mean width; **%C**, coverage.