Bone and Muscle

RESEARCH ARTICLE

The Chapman Bone Algorithm: A Diagnostic Alternative for the Evaluation of Osteoporosis

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Abstract

Osteoporosis is the most common metabolic bone disease and goes largely undiagnosed throughout the world, due to the inaccessibility of DXA machines. Multivariate analyses of serum bone turnover markers were evaluated in 226 Orange County, California, residents with the intent to determine if serum osteocalcin and serum pyridinoline cross-links could be used to detect the onset of osteoporosis as effectively as a DXA scan. Descriptive analyses of the demographic and lab characteristics of the participants were performed through frequency, means and standard deviation estimations. We implemented logistic regression modeling to find the best classification algorithm for osteoporosis. All calculations and model building steps were carried out using R statistical language. Through these analyses, a mathematical algorithm with diagnostic potential was created. This algorithm showed a sensitivity of 1.0 and a specificity of 0.83, with an area under the Receiver Operating Characteristic curve of 0.93, thus demonstrating a high predictability for osteoporosis. Our intention is for this algorithm to be used to evaluate osteoporosis in locations where access to DXA scanning is scarce.

Introduction

Bone remodeling is a dynamic and life-long process that involves the resorption of mineralized bone by osteoclasts and the formation of bone matrix by osteoblasts [1]. Skeletal integrity is maintained through the systemic and local regulation of this bone remodeling process [2]. Among healthy adults, this process maintains parity between bone resorption and bone formation. Osteoporosis is caused by a disequilibrium of the bone remodeling process, leading to weak and porous bones [2]. Osteoporosis impedes an individual's life with a host of disorders and body changes that include, but are not limited to, intervertebral bone mass loss leading to reduced height, compromised posture, chronic pain, limited mobility and, most severely, bone fractures [3]. It is by far the most common metabolic bone disease, affecting over 200 million people worldwide and often has the secondary manifestation of being an economic burden on the individual and society [4]. Almost one quarter of osteoporosis diagnoses (44 million) come solely from the United States of America, a country that contributes to only 4.3% of the global population [5].

The most definitive method of diagnosing osteoporosis is through the use of Dual-energy X-ray Absorptiometry (DXA) [6]. Currently, DXA scanning is known as the gold standard for measuring bone mineral density (BMD), in which a low BMD is indicative of osteoporosis [7]. DXA findings are measured in mass per area (g/cm^3) and use the average of an individual's BMD from various body locations to generate a T-score and a Z-score [6]. Based on these statistical measures of variance from age-adjusted means, one can determine if they have normal bone density, below-normal bone density (a condition known as osteopenia) or are osteoporotic [7]. Without DXA scanning, individuals are unaware of this bone disease until they are faced with a fragility fracture [8]. The World Health Organization predicts that the number of osteoporotic fractures in men and women is certain to increase by more than 3-fold over the next fifty years [9]. There has been a definitive increase in awareness of the disease in developing countries, where accessibility to DXA scanning is limited. The most recent data portraying the global distribution of DXA machines highlights this inaccessibility: only 450 DXA machines in China, for a population of 1.3 billion (1 per 289,000) [10]. Only 34 machines exist in Indonesia, for a population of 237 million (1 per 7 million) and 161 machines in Chile, for a population of 17.62 million (1 per 109,000) [10]. The United States has approximately 35.8 DXA machines per million of the population (1 per 28,000), compared to a mere 2.3 machines per million of the population in Peru (1 per 435,000) [10]. These examples illustrate the inequity of DXA scanner distribution around the world, directly correlating to an inequity of osteoporosis diagnoses.

DXA scanning, while it is the current model for determining patient bone health, is a relatively new procedure, which

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began clinical use in the mid-1980's. The evolution of bone-scanning technology has significantly changed from early methods of X-ray detection (requiring 30% bone loss for visual recognition) to photon absorptiometry methods and finally to DXA technology, in which patient bone health can be recognized and classified for BMD as normal, osteoporotic, or osteopenic [11]. However, the fulcrum regarding the advances in technology, which have provided quick and accurate diagnoses for patient bone health, resides with the inaccessibility of this technology. Additionally, maintaining a DXA may be expensive. The latest DXA scanners, equipped with the World Health Organization Fracture Risk Assessment (FRAX) calculation tool, cost over $100,000 U.S. per machine, making them inaccessible to a majority of the global population [8]. As a result of the economic obstacles faced by developing nations, there is a need to establish an alternative form of diagnostic treatment for metabolic diseases, which may be found by examining specific bone turnover markers within the blood serum.

Bone Turnover Markers

A DXA scan measures and records the density of the bone, which is dependent upon the activity levels of osteoclasts and osteoblasts. Osteoclasts remove mineralized bone tissue, primarily protein and collagen, by secreting an acid containing specialized proteinases that degrade the organic matrix, which is re-circulated into the bloodstream [12]. Osteoblasts add protein and collagen back to bone to create the bone matrix [13,14]. The activity of these cells correlates to certain biochemical markers in the blood, known as bone turnover markers (BTMs) [15]. Therefore, the relative concentrations of BTMs may effectively contribute to the diagnosis of osteoporosis. Serum pyridinoline cross-links (s-PYD) and serum osteocalcin (s-OC) are known BTMs that correlate to osteoclast and osteoblast activity. They are among the least expensive assays to obtain, making them the most globally accessible. BTMs can be measured with specific blood assays through a simple blood draw [16].

DXA machine availability in developing countries is simply too scarce to provide adequate screening for bone health. The potential for diagnosing osteoporosis through a more simple blood draw and serum analysis, instead of through use of a DXA scan, provides important implications for the global community, especially in regions where DXA scanning is not available. Blood testing is already widely used around the world, relatively easy and does not require expensive on-site machinery. Blood samples could be sent to centralized medical laboratories for analysis and then these data could be relayed back to where it originated.

The purpose of this study was to determine the diagnostic potential of various BTMs—specifically serum OC and serum PYD—with the intention of creating a cost-effective and predictive algorithm for the diagnosis of osteoporosis.

Methods

Subject Enrollment

Over a three-year period, 555 subjects were recruited to participate in a study to determine the bone health of Orange County residents. Of these 555 subjects, data from 226 individuals were included in this study. This population represented individuals belonging to four self-described ethnic groups: Asian, African American, Caucasian and Hispanic. After the subjects were categorized by ethnicity and sex, they were then allocated to age divisions where potential changes in bone health were expected. An individual's bone health peaks around the age of 30 years [17]. After this age, the process of bone remodeling begins to favor resorption and bone mass gradually decreases [18]. Additionally, when women begin menopause at around the age of 50, their bone mass decreases at a much quicker rate than premenopausal declines [19-21].

Sample Demographics

The 226 subjects that met the inclusion criteria (no prior history of bone disorders, no bisphosphonates) for this study resided in Orange County, California. The majority were female (76.1%), older than 50 years of age (59.5%), with normal BMI values between 18.5 and 24.9 (57.5%). The average height and weights of the participants were 65.5 inches and 149.2 pounds with standard deviations of 3.5 inches and 31.2 pounds. Moreover, the average serum OC and serum PYD levels were 8.7 nmol/L and 6.6 nmol/L with standard deviations of 3.5 and 3.3. Slightly over half (55.3%) had healthy T-scores greater than or equal to -1, 41.6% had T-scores between -1 and -2.5 and 3.1% had scores below -2.5, reflecting the diagnosis of osteoporosis. Descriptive analysis of the sample demographics and lab characteristics are presented in Table 1.

Procedure and Tests Performed

Subjects were randomly recruited from the general Orange

Characteristic:	n(%):
1) **Age (years):**	
16-30	27 (11.9)
31-50	56 (24.8)
51-70	110 (48.7)
Greater than 70	24 (10.8)
2) **Sex**:	
Female	172 (76.1)
Male	54 (23.9)
3) **BMI**	
Less than 18.5	9 (4.0)
18.5-24.9	130 (57.5)
25-29.9	65 (28.8)
More than 30	22 (9.7)
4) **Height (inches)**	65.5 (3.5)
5) **Weight (pounds)**	149.2 (31.2)
6) **Serum OC (nmol/L)**	8.7 (3.5)
7) **Serum PYD (nmol/L)**	6.6 (3.3)
8) **T-score**	
-2.5 and below	7 (3.1)
-1 to -2.5	94 (41.6)
-1 and above	125 (55.3)

Table 1: Summary statistics of demographics and lab characteristics of the study participants (N=226).

County population after review and approval of the study protocol by the Chapman University Institutional Review Board. The subjects responded to advertisements in papers, flyers sent to athletic and religious organizations, posters presented in the windows of local stores, advertisements in newspapers, advertisements on various Internet websites and through direct contact. Demographic questions allowed the subjects to categorize themselves by ethnicity, sex and age. They also answered lifestyle questions, which were necessary to calculate the FRAX values [22]. After obtaining an informed consent, the subjects were sent to Marathon Medical Group clinic, heights and weights were measured, blood was drawn and DXA analyses were conducted. The DXA scan for each subject included analysis of the femoral neck, trochanter and the intertrochanteric regions of the femoral diaphysis, which taken together constituted the total hipbone mineral content. The anterio-posterior lumbar spine was also assessed. The DXA scans were performed using two effective energies of 38kW and 70kW. The BMD data obtained from the DXA reports were utilized to determine each individual's T-Score. By convention, a T-score of -1 or above is considered normal bone density, a score between -1.0 and -2.5 indicates an osteopenic state and a score of -2.5 or below is indicative of osteoporosis [23,24]. The blood samples taken at Marathon Medical Group clinic were sent to Quest Diagnostics and Chapman University for analysis of specific biomarkers.

Participants' body mass index (BMI) scores were also obtained. After the collection and organization of data, multivariate statistical analyses were performed.

Statistical Analysis

Demographic and lab characteristics of the study participants were analyzed through frequency, means and standard deviation estimations. We implemented logistic regression modeling to find the best classification algorithm for osteoporosis. All calculations and model building steps were carried out using R statistical language.

Results

Logistic regression modeling

We implemented exhaustive logistic regression modeling by comparing all possible univariate and multivariate models with and without interactions to identify the model with the best classification properties with respect to the presence and absence of osteoporosis given the collected set of covariates.

The best classification model that was created included main effects of serum OC with effect size of 0.39 and p-value of 0.001, serum PYD with effect size of -0.45 and p-value of 0.09 and age with effect size of 0.08 and p-value of 0.03. Inclusion of the marginally significant variable of serum PYD in the model was justified by the increase of the area under the Receiver Operating Characteristic (ROC) curve (from 0.89 to 0.93) and a decrease in the Akaike Information Criterion (AIC) statistic (from 54.15 to 52.41). Even though unimportant for the classification purposes of the model, the interpretation of the logistic regression coefficients shows that a one unit increase in the serum OC and serum PYD levels were associated with 47% increase and 37% decrease in the odds of osteoporosis respectively. Similarly, a one-year increase in age is associated with an 8% increase in the odds of osteoporosis. Detailed summary results from the best classification model that we identified are shown in Table 2 and Figure 1.

Classification of algorithm

The proposed classification algorithm that optimally assigns people to either the group with or without osteoporosis, given the values of serum OC, serum PYD and age is based on the model presented in Table 2. This model predicts log-odds of having osteoporosis and is given by:

$$Logit\left(\hat{p}(Y=1 \mid OC, PYD, Age)\right) = -9.20 + 0.39 * OC - 0.45 * PYD + 0.08 * \text{Age}$$

Equation 1

Similarly, the model predicted probability of having osteoporosis is:

$$\hat{p}(Y=1|OC, PYD, Age) = \frac{e^{-9.20+0.39*OC-0.45*PYD+0.08*Age}}{1+e^{-9.20+0.39*OC-0.45*PYD+0.08*Age}}$$

Equation 2

Variable	Estimate	Odd Ratio	SE	Z-value	P-value
Intercept	-9.20	-	2.69	-3.41	0.0006
Serum OC	0.39	1.47	0.12	3.19	0.001
Serum PYD	-0.45	0.63	0.27	-1.70	0.09
Age in years	0.08	1.08	0.03	2.22	0.03

Table 2: Summary results from the best classification logistic regression model.

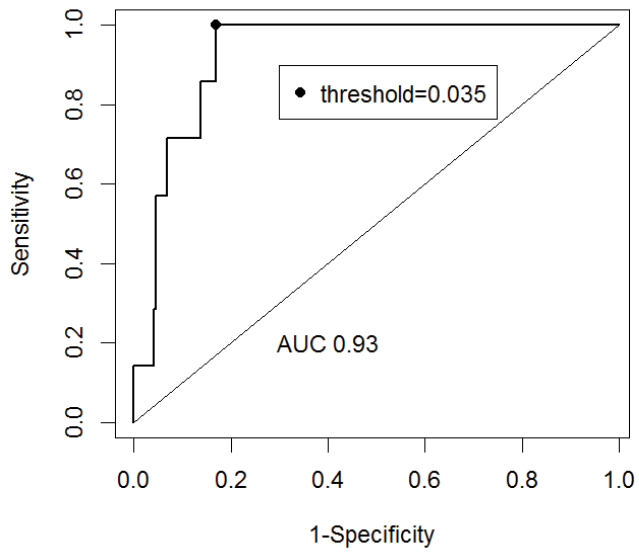

Figure 1: ROC Curve depicting the best classification model found through analysis of age, serum OC and serum PYD. An area under the curve (AUC) of 0.93 was calculated for this model. The AUC is arguably the best way to summarize the performance of a predictive model, of which an AUC close to 1 indicates a highly predictive model and a value at or below 0.5 indicates a model that is not predictive.

The values generated by Equation 2 are between 0 and 1 and subjects with high model predicted probabilities were assigned to the group with osteoporosis and the rest to the control group. The threshold that separated high and low predicted probabilities was chosen optimally so that there was simultaneously maximized sensitivity and specificity of the classification algorithm. The threshold that maximized the sum of the sensitivity and specificity was 0.035. It achieved sensitivity of 1.0 and specificity of 0.83 and it is denoted with a diamond on the ROC curve presented in Figure 1. Thus, the model predicted disease status $\hat{Y}$ given serum OC, serum PYD and age was assigned according to the following classification rule:

$$\hat{Y}|OC, PYD, Age = \begin{cases} 0, P(Y = 1|OC, PYD, Age) \leq 0.035, \\ 1, \mathrm{P(Y = 1|OC, PYD, Age)} > 0.035. \end{cases} \quad \text{Equation 3}$$

Discussion

Analysis of bone turnover markers indicative of bone formation and bone resorption proved to be encouraging in the creation of a diagnostic algorithm (Chapman Bone Algorithm) for the detection of osteoporosis. When analyzed with age, concentrations of serum OC and PYD had a direct correlation to a T-score of -2.5 or lower. Based on the significant outcome of the multivariate statistical analyses, as well as the extensively-studied physiology of the bone remodeling process, we believe that the variables of age, serum OC and serum PYD are sufficient in detecting osteoporosis. We initially expected that BMI would be a significant contributor to the Chapman Bone Algorithm (CBA). Women with low BMIs are characterized as having weaker bones that are more susceptible to fractures, while the bones of women with high BMIs must be proportionately stronger in order to support a greater body mass [25]. The analysis of BMI in this data set, however, was not statistically significant (P> 0.05). Knowing that osteoporosis affects females 4 times more than males, on cursory examination it might appear that biological sex was overlooked in the CBA [26,27]. While there is a high correlation between sex and bone-health predictors of age, OC and PYD, our statistical model examined direct predictors and not simply correlational relationships. For this reason, sex is not explicit in the Chapman Bone Algorithm.

In future studies, patient information will be collected using the same multivariate statistical analyses as described in this study on larger data sets containing a greater number of confirmed diagnoses of osteoporosis. Ultimately, the goal of these future studies will be to test the CBA's reliability on a larger data set. Additionally, the utilization of more variables or the testing of other bone turnover markers could contribute to a stronger predictive model.

Significance of the CBA

General implications of the CBA lie within the algorithm's nature for quick and cost-effective analysis of bone health, which can be of particular benefit in low socioeconomic conditions of developed nations or within developing communities. Disparities in healthcare access are evident in many global locations, even outside of prototypical Western cultures (e.g. United States of America), such as the existing disparity between countries like Israel and Egypt. Per the CIA World Factbook, Israel (7.80% GDP) ranks 60 spots higher in global rankings than Egypt (5.60%) in relative promotion, restoration and maintenance of health (indicated by health expenditures as a percentage of country GDP) [28]. Given this information, Israel would be an example of a non-Western nation with relatively high health standards and priority in comparison to neighboring Egypt. Israel is home to Holocaust survivors, who were typically malnourished at an early age, often a precursor for early onset osteoporosis [29]. Yet, impacts from malnutrition on bone health in Israel are less adverse due to higher healthcare priority and accessibility [29]. However, it is unlikely that similar testing practices would be conducted in countries with higher rates of early malnutrition and community-wide poverty, such as Africa and Southeast Asia [30].

Aside from being a chronic condition that affects those with low BMD, osteoporosis has also shown comorbid association with various other chronic health conditions, posing serious implications on the metabolic bone disease. In conjunction with HIV, however, limited research on its relationship with HIV has been conducted. The potential correlation between HIV prevalence and metabolic bone disease prevalence is largely unknown, but it may be due to the fact that areas with high HIV prevalence (e.g. Africa) also have limited resources for health screening [31]. Potential comorbid diseases with osteoporosis listed in the literature include ischemic cardiovascular disease (CVD) and HIV. Common factors between the CVD and osteoporosis are estrogen deprivation in women, smoking, low physical activity, or diabetes [32]. Due to the severity of these primitive potential relationships, establishing medical practices for determining early onset of osteoporosis, among other chronic metabolic conditions, is imperative to eliminating health disparities in regions with limited resources and lack of modern medical practice feasibility.

Although it may currently be the most common way to diagnose osteoporosis, DXA scanning is still largely inconvenient, inaccessible and requires expensive instrumentation worldwide. We are suggesting an alternative diagnosis for this bone disease, in which quantitative, statistically-significant risk factors are utilized in the CBA to determine an individual's bone health. We imagine the CBA to not only serve in the evaluation of osteoporosis but to also provide periodic evaluations to assess the efficacy of a treatment plan. Instead of relying on expensive DXA equipment, the Chapman Bone Algorithm utilizes easily obtained and commonly assayed biomarkers. We believe the CBA will have similar functionality to the American Heart Association's 10-year risk calculator for developing atherosclerotic cardiovascular disease; which indicates the likelihood of developing atherosclerosis [33]. It is

likely that the CBA will be an economical, effective and vastly more accessible diagnostic option for remote and developing populations and that healthcare providers around the world can use this algorithm with confidence.

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