Prediction of Low Bone Mineral Density in Postmenopausal Women by Artificial Neural Network Model Compared to Logistic Regression Model†

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Abstract

Measuring bone mineral density (BMD) is currently the best modality to diagnose osteoporosis and predict future fractures. The use of risk factors to predict BMD and fracture risk has been considered to be inadequate for precise diagnostic purpose, but it may be helpful as a screening tool to determine who actually needs BMD assessment. Recently, artificial neural network (ANN), a nonlinear computational model, has been used in clinical diagnosis and classification. In the present study, we evaluated the risk factors associated with low BMD in Thai postmenopausal women and assessed the prediction of low BMD using an ANN model compared to a logistic regression model. The subjects consisted of 129 Thai postmenopausal women divided into 2 groups, 100 subjects in the training set and the remaining 29 subjects in the validation set. The subjects were classified as having either low BMD or normal BMD by using BMD value 1 SD lower than the mean value of young adults as the cutoff point. Decreased body weight, decreased hip circumference and increased years since menopause were found to be associated with low BMD at the lumbar spine by logistic regression. For the femoral neck, increased age and decreased urinary calcium were associated with low BMD. The models had a sensitivity of 85.0 per cent, a specificity of 11.1 per cent and an accuracy of 62.0 per cent for the diagnosis of low BMD at the lumbar spine when tested in the validation group. For the femoral neck, the sensitivity, specificity and accuracy were 90.5 per cent, 12.5 per cent, and 69.0 per cent, respectively. Models based on ANN correctly classified 65.5 per cent of the subjects in the validation group according to BMD at the lumbar spine with a sensitivity of 80.0 per cent and a specificity of 33.3 per cent while it correctly classified 58.6 per cent of the subjects at the femoral neck with a sensitivity of 76.2 per cent and a specificity of 12.5 per cent. There was no significant difference in terms of accuracy, sensitivity and specificity in the prediction of low BMD at the lumbar spine or the femoral neck between ANN model and logistic regression model. We concluded that ANN does not perform better than convention statistical methods in the prediction of low BMD. The less than perfect performance of the prediction rules used in the prediction of low BMD may be due to the lack of adequate association between the commonly used risk factors and BMD rather than the nature of the computational models.

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Osteoporotic fracture is a major health problem in many geographic areas. It has been estimated that osteoporotic fractures not only impair the quality of life of the affected person but also impose an enormous economic cost[1]. Bone mass is a major determinant of bone strength accounting for 75-85 per cent of the variance in the strength of bone[2]. It is generally accepted that measuring bone mineral density (BMD), which indirectly reflects bone mass, by various methods can predict future fracture risks[3]. Although BMD measurement is an excellent method to estimate bone mass and predict fracture risks, instruments for measuring BMD are costly and not widely available at present in some areas.

Risk factors for low bone mass have been studied in a number of studies[4-6]. At best, the combination of these factors can classify patients correctly according to their bone mass status in only 60-70 per cent. Thus it is generally held that risk-factors analysis is not an adequate means to substitute BMD measurement. However, unnecessary bone mass measurements may be reduced by stratifying patients according to their risk factors before sending for a BMD assessment. Almost all the studies concerning risk factors for osteoporosis were done in Caucasians. It is unclear whether the risk factors for osteoporosis and their inadequate ability to predict bone mass will be the same in other populations with different genetic makeup, calcium intake, lifestyle and sunlight exposure.

Conventional statistical methods such as linear regression and logistic regression have generally been used for the identification of risk factors for osteoporosis. Recently, artificial neural network (ANN)[7], has been used in clinical diagnosis and classification. ANN is a computational system composed of a large number of simple units that process information in parallel. In some instances, ANN was demonstrated to be more accurate than the prediction rules obtained by conventional statistical methods, which may be due to the nonlinear nature of ANN model. The finding that risk-factor analysis for osteoporosis using traditional methods is not accurate enough for the prediction of low bone mass may be accounted for by the inadequate degree of correlation between risk factors and bone mass or possibly by the inappropriate use of the linear model in the analysis of nonlinear problem. If the latter were the case, using ANN in the prediction of low bone mass may yield more accurate results.

In the present study we investigated the risk factors associated with low bone mass in the Thai population, the accuracy of these risk factors in the prediction of low bone mass and the performance of ANN compared to logistic regression model in the classification of subjects according to bone mass status.

MATERIAL AND METHOD

The subjects were recruited as part of a study of BMD in Thai women. All subjects gave informed consent to the study and the study was approved by the ethical committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University. One hundred and twenty nine ambulatory postmenopausal women aged up to 80 years in Bangkok were recruited by direct contact or placing an advertisement. All subjects were apparently healthy and were not taking medications known to influence calcium homeostasis.

Daily calcium intake was determined by a 3-day dietary record in each subject. Subjects were instructed how to keep an accurate 3-day food record. All food items and portions were recorded in the record form for 3 days. Food brand names, methods of food preparation and recipes for any mixed dish eaten during the record period were also included. At the end of the 3-day recording period, they were asked to return the record form for verification of completeness and accuracy by an experienced dietitian at our institute. The subjects were asked to provide additional information about any unclear food item. The computation of calcium intake and nutrient data was done by using the computerized food composition analysis package, "Nutritionist III", modified for Thai foods by the Institute of Nutrition, Mahidol University, Thailand.

BMD was measured by dual-energy X-ray absorptiometry (DEXA) (Lunar DPX-L, Lunar Corp., Wisconsin). Daily calibration and quality control were done regularly according to the manufacturer's recommendation. The *in vitro* precision using the spine phantom provided by the manufacturer was 0.6 per cent. *In vivo* coefficients of variation for anteroposterior spine and femoral neck measurements were 2.0 per cent and 2.2 per cent, respectively. BMD at anteroposterior L2-L4 and femoral neck were measured in each subject.

Data were expressed as mean±SD. Statistical analyses were performed by SPSS 6.0 (SPSS Inc., Illinois). Differences in variables were determined by Student's *t* test. The correlations between variables and bone mass status were determined by stepwise logistic regression. Feed-forward back-propagation ANN models were built and trained by using a commercial software (Brainmaker, California Scientific Software, California). Two ANN models were constructed for the classification at the lumbar spine and the femoral neck. Both ANN models consisted of 4 layers; 1 input layer with 18 nodes, 2 hidden layers with 18 nodes each, and 1 output layer with 1 node. Each node in the input layer corresponded to each variable used in the training of the ANN. Supervised training of the ANN was done by presenting data from each subject in the training set to the ANN iteratively. This caused changes in the connection weights among nodes in the ANN so that the output pattern from the ANN best matches the actual bone mass status. Evaluation of the performance of the logistic regression models and the ANN models were done by cross validation in a separate validation group. Sensitivity, specificity and accuracy of the prediction were compared by Mann-Whitney U test.

RESULTS

Subjects were classified as having normal or low bone mass using BMD value at 1 SD below the mean value of young adults as the cutoff point. There was no significant difference in BMD, clinical, anthropometric and biochemical variables between the training group and the validation group as shown in Table 1. Table 2 shows the result from univariate analysis. Of all 18 variables entered for analysis, 8 variables turned out to be significantly different between the normal and the low bone mass groups at the spine. For bone mass at the femoral neck, univariate analysis revealed that 3 out of 18 factors, i.e. age, years since menopause and urinary calcium excretion, were different in the two groups (Table 3).

Factors shown to be significantly different by univariate analysis were then analyzed by multivariate methods. Using stepwise multiple logistic regression, decreased body weight, increased years since menopause and increased hip circumference were shown to be associated with low bone mass at anteroposterior lumbar spine (Table 4A); while increased age and decreased 24-hour urinary calcium excretion were associated with low bone mass at the femoral neck (Table 4B) .The model

Table 1. Comparison of clinical, anthropometric and biochemical variables between the training group and the validation group.

	Training group (n =100)	Validation group (n = 29)	P
Lumbar spine BMD (g/cm^2)	0.92±0.23	0.90±0.24	NS
Femoral neck BMD (g/cm^2)	0.70±0.16	0.70±0.18	NS
Age (years)	64.0±7.4	61.8±8.1	NS
Body weight (kg)	57.1±8.9	55.5±8.1	NS
Height (cm)	153.30±5.7	153.0±4.9	NS
Age at menarche (years)	12.2±2.6	12.8±0.7	NS
Years since menopause (years)	13.7±10.3	12.8±7.9	NS
Alkaline phosphatase (U/L)	22.2±7.8	21.3±6.9	NS
Arm span (cm)	156.3±6.2	156.9±5.3	NS
Hip circumference (cm)	95.2±7.2	94.7±5.4	NS
Waist circumference (cm)	82.8±8.3	81.6±6.6	NS
Triceps skinfold (mm)	17.0±3.1	17.4±2.9	NS
Dietary calcium (mg/day)	343.1±173.1	351.3±200.3	NS
Serum creatinine (mg/dL)	0.7±0.3	0.7±0.1	NS
Serum calcium (mg/dL)	9.6±1.2	9.6±0.8	NS
Serum phosphorus (mg/dL)	3.4±0.9	3.4±0.6	NS
Serum protein (g/L)	71.0±8.0	72.4±3.1	NS
Serum albumin (g/L)	46.4±6.2	48.2±3.1	NS
Urinary calcium (mg/day)	234.8±131.7	213.3±119.2	NS
Urinary creatinine (mg/day)	827.3±239.1	829.5±416.2	NS

Table 2. Comparison of clinical, anthropometric and biochemical variables between the low BMD group and the normal BMD group at the lumbar spine by univariate analysis.

	Low BMD (n =72)	Normal BMD (n = 28)	P
Age (years)	63.0±8.1	58.8±6.1	< 0.05
Body weight (kg)	54.6±8.2	63.8±7.4	< 0.001
Height (cm)	152.3±5.7	155.7±5.0	< 0.01
Age at menarche (years)	12.6±1.7	12.6±0.6	NS
Years since menopause (years)	15.5±11.3	9.0±6.0	< 0.001
Arm span (cm)	155.5±6.5	158.2±5.1	NS
Hip circumference (cm)	93.7±7.2	98.8±5.9	< 0.01
Waist circumference (cm)	81.3±8.1	86.5±7.8	< 0.01
Triceps skinfold (mm)	16.6±3.3	17.9±2.1	NS
Dietary calcium (mg/day)	349.0±179.1	328.4±159.7	NS
Serum calcium (mg/dL)	9.2±1.6	9.6±6.8	NS
Serum creatinine (mg/dL)	0.7±0.3	0.7±0.1	NS
Serum phosphorus (mg/dL)	3.4±0.9	3.4±4.7	NS
Serum protein (g/L)	70.4±9.3	72.5±2.6	NS
Serum albumin (g/L)	45.6±7.0	48.3±2.7	< 0.01
Alkaline phosphatase (U/L)	20.0±7.0	21.3±7.9	NS
Urinary calcium (mg/day)	237.4±142.5	228.3±102.3	NS
Urinary creatinine (mg/day)	781.2±256.7	941.0±135.9	< 0.01

Table 3. Comparison of anthropometric and biochemical variables between the low BMD group and the normal BMD group at the femoral neck by univariate analysis.

	Low BMD (n= 66)	Normal BMD (n = 34)	P
Age (years)	64.3±7.9	57.8±5.9	< 0.001
Body weight (kg)	56.3±9.2	59.0±8.3	NS
Height (cm)	153.5±5.8	153.0±5.7	NS
Age at menarche (years)	12.5±1.7	12.7±0.7	NS
Years since menopause (years)	16.2±10.9	9.9±7.6	< 0.001
Arm span (cm)	156.6±6.2	155.6±6.3	NS
Hip circumference (cm)	94.3±7.5	96.7±6.3	NS
Waist circumference (cm)	82.6±8.4	83.2±8.2	NS
Triceps skinfold (mm)	16.8±3.2	17.3±2.8	NS
Dietary calcium (mg/day)	346.5±171.1	336.6±179.2	NS
Serum creatinine (mg/dL)	0.7±0.3	0.7±0.1	NS
Serum calcium (mg/dL)	9.6±1.6	9.6±1.2	NS
Serum phosphorus (mg/dL)	3.4±0.6	3.4±0.6	NS
Serum protein (g/L)	70.6±9.7	71.7±3.1	NS
Serum albumin (g/L)	46.0±7.3	47.2±3.2	NS
Alkaline phosphatase (U/L)	21.2±7.5	20.8±8.6	NS
Urinary calcium (mg/day)	201.3±120.0	279.1±151.2	< 0.01
Urinary creatinine (mg/day)	806.3±240.5	866.3±234.9	NS

Table 4A. Factors associated with low BMD at the lumbar spine identified by logistic regression.

Variable	Odds ratio	95% confidence interval
Body weight (per kg)	0.76	0.65-0.88
Hip circumference (per cm)	1.19	1.01-1.41
Years since menopause (per year)	1.10	1.01-1.41

Table 4B. Factors associated with low bone mass at the femoral neck identified by logistic regression.

Variable	Odds ratio	95% confidence interval
Age (per year)	1.16	1.07- 1.26
Urinary calcium (per 50 mg/day)	0.80	0.66-0.96

Table 5A. Sensitivity, specificity and accuracy of the prediction of low BMD at the lumbar spine from the ANN model and the logistic regression model. There was no difference in sensitivity, specificity or accuracy between the two models.

	ANN model (%)	Logistic regression model (%)	P
Sensitivity	80.0	85.0	NS
Specificity	33.3	11.1	NS
Accuracy	65.5	62.0	NS

Table 5B. Sensitity, specificity and accuracy of the prediction of low BMD at the femoral neck from the ANN model and the logistic regression model. There was no difference in sensitivity, specificity or accuracy between the two models.

	ANN model (%)	Logistic regression model (%)	P
Sensitivity	76.2	90.5	NS
Specificity	12.5	12.5	NS
Accuracy	58.6	69.0	NS

can correctly classify the subjects according to their bone mass status in 81.4 per cent of the subjects with a sensitivity of 88.4 per cent and a specificity of 64.3 per cent for spinal BMD and correctly classify 67.0 per cent of the subjects for femoral neck BMD with a sensitivity of 82.5 per cent and a specificity of 38.2 per cent. When the models were tested in a separate group of 29 subjects, the model could correctly classify 62.0 per cent of the subjects with a sensitivity of 85.0 per cent and a specificity of 11.1 per cent at the spine while it could correctly classify 68.9 per cent of the subjects with a sensitivity of 90.5 and a specificity of 12.5 per cent at the femoral neck.

Eighteen variables from the same 100 patients which have been used in the univariate analysis were used to train ANN models to predict osteopenia. The trained ANN can correctly predict osteopenia at the lumbar spine in 65.5 per cent of subjects, with a sensitivity of 80 per cent and a specificity of 33.3 per cent in the validation group (Table 5A). Compared to the results from logistic regression, there was no significant difference in sensitivity, specificity or accuracy. For the femoral neck, the trained ANN had an accuracy of 58.6 per cent with a sensitivity of 76.2 per cent and a specificity of 12.5 per cent in the validation groups (Table 5B). Similar to the results at the lumbar spine, the predictions from the ANN model were not significantly different from those of the logistic regression model.

DISCUSSION

The prediction of bone mass based on the analysis of risk factors has been shown to be inaccurate for general use[8]. There are relatively few studies which considered the prediction of fractures based on risk factors[9,10]. Nevertheless, findings generally suggested that considering risk factors for the prediction of fractures is more inaccurate than the prediction of bone mass although adding related risk factors to BMD permits better prediction than considering BMD alone[11]. However, the assessment of risk factors for low bone mass or osteoporotic fractures in clinical practice is still worthwhile since it may identify people with potentially modifiable factors to ameliorate the process. Risk factors identified among studies vary. There are certain factors such as age, low body weight and years since menopause which are suggested by most of the studies to be associated with low bone

mass[4,12,13] while certain factors were identified as significant in only a few studies. The reasons for this variation is unclear but may be related to the differences in study design, genetic makeup, life style, nutrition and degree of sunlight exposure of the studied population. There are relatively few studies which compared the risk factors at the axial and the appendicular skeletal sites. However, risk factors for different skeletal sites may be different since bone at different sites contain different proportions of trabecular and cortical bone which are metabolically different. In the present study, increased years since menopause, decreased body weight and increased hip circumference were associated with low bone mass at lumbar spine, a site rich in trabecular bone; while greater age and lower daily urinary excretion of calcium were related to low bone mass at the femoral neck, a site mixed between trabecular and cortical bone. It is conceivable that years since menopause was associated with low trabecular bone mass since estrogen deficiency affects trabecular bone predominantly[14]. On the other hand, chronological age but not years since menopause was related to low bone mass at the femoral neck. This may be due to the propensity of cortical bone to be affected by parathyroid hormone[15] which increases with advancing age[16].

Much of the variance in bone mass cannot be explained by risk factors[13]. This was supported in the present study in which the accuracy, sensitivity and specificity for the prediction of low bone mass in the validation groups were 62 per cent, 85 per cent and 11.1 per cent, respectively at the lumbar spine and were 68.9 per cent, 90.5 per cent and 12.5 per cent, respectively at the femoral neck. It is of note that when tested both in the group of subjects from which the model was derived and in another separate group of subjects, analysis of risk factors using logistic linear regression yielded a decent sensitivity in the 80-90 per cent range. However, the specificity was rather low and the model misclassified a large proportion of subjects without osteopenia. This suggests that, at least in our population, although risk-factor analysis may not be accurate enough to precisely classify patients in terms of bone mass, it may be useful in the initial screening of osteopenia because of the high sensitivity. In areas where bone densitometer is not readily available, stratifying patients according to risk factors may help decide which individual really needs bone mineral density measurement.

ANN has gained more utilization in clinical diagnosis and classification recently. Compared to conventional statistical methods such as multiple linear regression or logistic regression, ANN has been found to be superior or comparable in terms of accuracy of the classifications[17-20]. The reason for the superiority may be due to the fact that most biological systems are nonlinear in nature. Although linear transformation of nonlinear systems by logarithmic modelling techniques before conventional statistical analysis may improve the classification, it may not be able to adequately represent complex relationships among variables of interest besides those of logarithmic in nature. Being based on a nonlinear model, ANN can be more appropriate in certain situations[21]. However, one of the drawbacks of ANN is its inability to discriminate the relative importance of the risk factors used in the model due to the black box nature of ANN, although there was attempt to gain more understanding of the contribution of each factor by differential network analysis[22]. Being able to factor complex interactions among variables may also help to improve classification accuracy of ANN. There are certain factors which may influence the accuracy of ANN model in classification problems. Apart from the training set being representative of the actual problem, the intrinsic relationship of the outcome of interest and its associated factors is also important. In the situations where there is less than adequate causal or associative relationships between risk factors and the outcome of interest, the accuracy of the classification derived from the prediction models will not be good enough regardless of the computational models used. In the present study, the accuracy of the prediction using various parameters from ANN model was not superior to that of logistic regression. This may suggest that the inability of risk-factor analysis based on conventional statistical methods to accurately predict bone mass may be less likely to be due to the inappropriateness of the computational model used. The lack of adequate intrinsic association between the commonly used risk factors and bone mass may be more important.

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รายงานการวิจัยเรื่องการทำนายภาวะความหนาแน่นของกระดูกต่ำในสตรีวัยหมดประจำเดือนเปรียบเทียบวิธี Artificial neural network และ Logistic regression

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การวัดความหนาแน่นของกระดูกเป็นวิธีที่แม่นยำที่สุดในการวินิจฉัยโรคกระดูกพรุนและทำนายความเสี่ยงต่อการการกระดูกหัก แต่เครื่องวัดความหนาแน่นของกระดูกยังมีไม่แพร่หลายในประเทศไทย ผู้ดำเนินการวิจัยได้ทำการหาปัจจัยเสี่ยงทางคลีนิกเพื่อทำนายภาวะความหนาแน่นกระดูกต่ำในสตรีไทยวัยหมดประจำเดือน นอกจากนี้ ได้ศึกษาว่าการใช้ neural network ซึ่งเป็นวิธีการสร้างแบบจำลองแบบ nonlinear ว่าจะสามารถทำนายภาวะความหนาแน่นกระดูกต่ำได้ดีกว่าวิธี logistic regression ซึ่งเป็นวิธีที่ใช้โดยทั่วไปหรือไม่

ผลการวิจัยพบว่าปัจจัยเสี่ยงสำหรับภาวะความหนาแน่นของกระดูกบริเวณกระดูกสันหลังต่ำในหญิงไทยวัยหมดประจำเดือนได้แก่ น้ำหนักตัวน้อย เส้นรอบวงสะโพกน้อย และระยะเวลาหลังหมดประจำเดือนนาน ส่วนที่บริเวณ femoral neck ปัจจัยเสี่ยงสำหรับความหนาแน่นของกระดูกต่ำได้แก่ อายุที่มากขึ้น และปริมาณ calcium ในปัสสาวะที่มากขึ้น วิธี logistic regression สามารถทำนายภาวะความหนาแน่นกระดูกต่ำได้ถูกต้องร้อยละ 62-69 ในขณะที่วิธี neural network สามารถทำนายได้ถูกต้องร้อยละ 58.6-65.5 ทั้ง 2 วิธีนี้ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติทั้งในด้านความถูกต้อง, sensitivity และ specificity

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