Published in final edited form as:
Osteoporos Int. 2010 November ; 21(11): 1881–1888. doi:10.1007/s00198-009-1160-2.

Does Using Lower Limit of Normal Normative Values Enhance the Ability of a Single Bone Mineral Density Measure to Predict Fractures?

QING WU, MD, ScD[1], **JEANETTE H. MAGNUS, MD, PhD**[2], **JANET C. RICE, PhD**[3], and **JOHN J. LEFANTE, PhD**[3]

[1]Biostatistics, Mayo Clinic, 13400 East Shea Blvd, Scottsdale, AZ 85259

[2]School of Medicine, Suite 2300 1440 Canal Street, New Orleans, LA 70112

[3]Department of Biostatistics, Tulane University School of Public Health and Tropical Medicine, Suite 2100 1440 Canal Street, New Orleans, LA 70112

Abstract

Introduction—In order to circumvent the inconsistencies and limitations with using the T-score when defining osteoporosis we propose using 95% Lower Limit of Normal (LLN) values derived from centered polynomial models using the NHANES III BMD measures. The main aim of this study was to compare the two methods in prediction of fracture and agreement in osteoporosis classification using cohort data.

Methods—We compared the fracture prediction ability of the two methods using a single BMD measurement in 4,948 white women aged 67–74 years in the SOF employing kappa statistics, sensitivity and specificity.

Results—The T-score provided inconsistent osteoporosis classification (46.6%) across the five hip regions of interest (ROIs) and this was significantly ($p<0.0001$) reduced when using the LLN method (36.5%). Kappa statistics of incident fracture during 12 years of follow up related to the prevalence of osteoporosis at baseline was significantly improved using the LLN method compared to using T-score. Sensitivity and specificity for fracture based on a single BMD measurement of different hip ROIs were more consistent using the LLN method.

Conclusion—The LLN method provides a more consistent and efficient method for osteoporosis fracture prediction than the T-score in 67–74 years old white women.

Keywords

Bone Density; classification; osteoporosis; diagnosis; LLN; T-score

Introduction

Bone mineral density (BMD) has been recognized as the best predictor of a future osteoporotic fracture [1]. The original WHO classification system using T-score as a method to define osteoporosis, was devised as a public health tool for evaluating the prevalence of osteoporosis in populations of postmenopausal women, was initially not intended to be used

Reprints: Qing Wu, MD, ScD, Mayo Clinic, 13400 East Shea Boulevard, Scottsdale, AZ 85259 (wu.qing@mayo.edu).

Conflicts of interest:
All authors have no conflicts of interest.

to make clinical treatment decisions [2, 3]; however, in the absence of a better diagnostic tool, it has been widely used clinically to classify individual patients [4].

Several studies have questioned the efficiency of the T-score in clinic practice [5–11]. In recognizing BMD as most important component when defining osteoporosis, we attempted to seek a better method to interpret BMD in term of osteoporosis and fracture risk. Our previous study explored the best statistical model to derive normative BMD values at various hip ROIs using the data from a “bone healthy” population in NHANES III, and we proposed the 95% lower limited of normal (LLN) method derived from the best centered polynomial model as a new osteoporosis diagnosis method [12]. The aim of the current study was to investigate the magnitude of discordance in the prediction of osteoporosis fracture in white women using a single BMD measure by applying these two diagnostic approaches to a prospective cohort from the Study of Osteoporotic Fracture (SOF) study. We also examined whether combining BMD values derived from different hip ROIs could increase the prediction power of a single DXA BMD measure of future fractures in a screening setting.

Materials and Methods

The Third National Health and Nutrition Examination Survey (NHANES III)

NHANES III include a representative sample of the civilian, non-institutionalized US population collected by the National Center for Health Statistics and Centers for Disease Control and Prevention between 1988 and 1994. The plan of operation and sampling scheme are described in detail elsewhere [13]. The BMD measurements of the total region, femoral neck, trochanter, intertrochanter, and Ward’s triangle, were made by dual-energy X-ray absorptiometry (DXA) using Hologic QDR 1000 densitometers (Hologic, Waltham, Mass, USA). All of these hip regions of interest (ROI) have been used in the present study. BMD from other regions are not available in NHANES III. Subjects who reported smoking fewer than 100 cigarettes in their lifetime were classified as non-smokers; otherwise, subjects were classified as smokers. Physical inactivity was defined as no leisure-time physical activity during the month prior to the survey. Subjects were regarded as physically inactive if they had not participated in any activities the prior month.

Only “bone healthy” white women in NHANES III were included in this study to develop the best model to predict normative BMD and to derive the LLN model. Subjects not considered as “bone healthy” were excluded; if they had conditions affecting bone metabolism, such as rheumatoid arthritis, osteoporosis, osteoporotic fracture, thyroid disease, diabetes, cancer, kidney diseases, ovaries removed or menopause before age 40. Also excluded were subjects who had been receiving estrogens, insulin or diabetes or osteoporosis medication. Subjects under 20 years of age were excluded because BMD measurements were not available. Considering that the mean life expectancy of white females is 81 years in the USA [14], subjects over 74 years of age were excluded to omit “supernormal” elderly survivors. To ensure sufficient sample size, smoker and persons with sedentary life styles were not excluded, but smoking and physical inactivity were adjusted in the models.

Study of Osteoporotic Fractures (SOF)

The SOF data up to 7th clinic visit were employed to have sufficient power to compare the ability of predicting fracture between the LLN and the-score. Sampling procedure, inclusion and exclusion criteria, data collection procedures are referenced elsewhere [15, 16]. Only the BMD measurements (g/cm^2) of total hip and its sub-regions (the femoral neck, intertrochanteric region, trochanter, and the Ward’s triangle) were used in this study. DXA

BMD measurements from the 2nd SOF clinic visit are used as baseline for the data analysis presented in the current study since single photon absorptiometry were used at the first visit [16]. The method for identifying fractures in SOF has been described in detail elsewhere [15]. In the current study, fractures that occurred because of major trauma such as motor vehicle accidents were excluded, all other non-vertebral fractures occurring after the 2nd clinic visit were included. Non-smokers were defined as the same as in NHANES III. Sedentary life style was defined as no physical activities or sports during the past 12 months.

Statistics

Modeling in NHANES III—Separate models were developed for each hip ROIs. For all models body weight was selected instead of height or body mass index (BMI) during the variable selection process. The appropriate formulas of the normative regression models were developed using traditional statistical model selection techniques based on partial F-tests. The interaction term of age and body weight, the quadratic term of age, and the cubic term of age were added in turn and tested until no further significant polynomial terms were accepted in the model. Various powers of body weight were not included in the model, because partial *F*-tests for these terms indicated that they were not significant.

STATA 10 (College Station, TX) was used to take into account the sampling weight and design effects of the NHANES III data. Residual diagnostic plots were developed to check model assumptions. Centered predictors were used as a special solution addressing multicollinearity problems in polynomial regression models. The Variance Inflation Factor (VIF) measures the impact of collinearity among the variables in a regression model. In this study, a VIF <10 was considered to be acceptable.

BMD Normative Value and LLN method—The Normative BMD values were derived from the best model in non smokers and physical active subjects. One-sided lower 95% prediction intervals from the best model in non smokers and physical active subjects were considered as the threshold of low BMD, and were used to determine Lower Limits of Normal (LLN) of BMD for intervention threshold of osteoporosis. Plots of residuals versus age were employed to check homogeneity of variance for residuals in the model. Logarithmic transformations were used to stabilize the variance when necessary. The equation to calculate LLN is: *LLN=predicted value-1.645*standard error.* The trends of normative value (or LLN) versus age (or weight) were explored by setting body weight (or age) at different fixed levels.

Analysis of SOF data—We used the WHO criteria as well as the LLN method to classify the white women in the SOF study as osteoporotic or non osteoporotic according to the DXA BMD taken at their 2nd clinical visit. With the T-score method, using the WHO criteria and the reference BMD values presented by Looker et al [17] from the NHANES study, women were classified as having osteoporosis if the T-score was less than -2.5. The young adult mean reference BMD values in Ward's triangle were not available in the Looker et al study, so it was calculated using the method described in their original study. The mean and standard deviation of reference Ward's triangle BMD values in white women (20–29 years old) in NHANES III are 0.734 and 0.117 (g/cm^2), respectively. Using the LLN method, women were classified as osteoporosis if her BMD was below the corresponding age and weight adjusted LLN value.

Mean and standard deviation were used to describe the distribution of BMD in the SOF study population. Pearson's correlation coefficients were used to evaluate the association of BMD values from the different hip ROIs. Kappa statistics were used to study the agreement

between the later fracture occurrence in this cohort and the classification of osteoporosis at the 2nd visit by the T-score and the LLN methods.

SAS 9.0 (SAS Institute, Cary, NC, USA) was employed to conduct the data analysis for the SOF data. The statistical significance level was set at 0.05 throughout the study.

Results

Modeling in white women aged 20–74 years in NHANES III

The best model derived from “bone healthy” white women age 20–74 years in NHANES is age centered polynomial model for all five hip ROIs studied. Plots of residuals versus age show homogeneity of variance for residuals in each model (data are not shown). Multicollinearity problems between age and its quadratic term were presented in polynomial models yielding VIFs much larger than 10, however, these multicollinearity problems were greatly reduced using centering methods resulting in final VIFs below 10. The coefficients of the best models identified in white women aged 20–74 years in NHANES III are summarized in table 1.

BMD Normative Value and LLN value

Using the best models identified in this study and by setting body weight at the mean level of white women for each age category, normative BMDs at various hip ROIs were plotted against age (figure 1A). Different patterns of hip ROI BMDs versus age indicate different BMD declining patterns with age for each ROI at the hip. As shown in figure 1B, there is a significant decline in the normative BMD and the corresponding LLN value with age for body weight, here illustrated with weight set at 60, 80 and 100kg. Figure 1C demonstrates that the normative BMD of femur neck and the respective LLN increase with increasing weight in white women when age is set at 20, 40 and 60 years. These data demonstrate that normative BMD and LLN values are determined by both age and weight. This highlights the importance that two women would need the same age and weight to have the same BMD cut point for an osteoporosis diagnosis. Tables and formulas providing the normative BMD and corresponding LLN that we proposed as a new diagnostic BMD cut-point can be developed for each ROI for osteoporosis diagnostics.

BMD measurements in SOF study

A total of 4,948 white women in the SOF study were between 67 and 74 years of age at the 2nd visit. Mean BMD values with corresponding standard deviation are shown in the first row of table 2. Correlation coefficients between BMD parameters measured at different hip ROIs are shown in the second row of table 2. The correlation coefficients ranged from 0.764 between the trochanter ROI BMD and the femur neck BMD to 0.984 between the intertrochanter ROI BMD and total region BMD, which shows strong correlation between the BMD mean values of different hip ROIs.

Classification of osteoporosis

As shown in figure 2, using the T-score method, the prevalence of osteoporosis varied in this study population from 12.4% (total hip BMD) to 52.0% (Ward’s triangle BMD). However, using the LLN method, the prevalence of osteoporosis at different ROIs is less variable, between 27.7% (total region) and 33.4% (Ward’s triangle). The overall incidence of non-spinal non-traumatic osteoporosis fracture during the 12 years of follow-up in this population was 30.2%. This is more consistent with the predictions of the DXA BMD value using the LLN method than the T-scores (Figure 2). As shown in figure 3, using the LLN method, the percentage of women consistently classified by all five measurement sites is 63.6%: 48.6% were classified as normal and 14.9% classified as osteoporotic; however if

using the WHO criteria, only 53.4% of women were consistently classified by all five measurement sites: 47.4% were classified as normal and mere 6.0% classified as osteoporotic.

Fracture outcome versus diagnostic classification

Another important aspect is whether a diagnostic method reflects future patient prognosis. Kappa statistics between incident fracture and earlier osteoporosis classification by T-score and LLN methods, and correspond 95% CIs are shown in the third row of table 2. The kappa statistics between fracture and diagnosis of osteoporosis using the LLN method are statistically significantly higher than those using the WHO criteria. The 95% CIs do not overlap, except for the Ward's triangle, for which the kappa statistics are similar.

Figure 2 demonstrates that the percentage of fractures during the follow-up is more consistent with the diagnostic classification obtained by the LLN method than with the WHO criteria in this study population. Figure 4 compares the sensitivity, specificity, and the positive and negative predictive values for any future osteoporotic hip and/or spine fracture for each measurement by the two classification methods. Sensitivities, specificities and negative predictive values of the various hip ROIs are more consistent across the ROIs when using the LLN method compared to the WHO t-score.

The relative risk for fracture in women with low BMD compared to all the non-osteoporotic women in the current study vary from 1.52 (femur neck) to 1.68 (total region), according to WHO diagnostic methods. When using the LLN method, the relative risk is more consistent, ranging from 1.52 (Ward's triangle) to 1.56 (total region) (data not shown). The LLN method improves agreement in classification of osteoporosis and provides homogeneity of sensitivity.

Combination of measurements on diagnosis

Both methods provide some inconsistency in patient classification; however the results using the LLN method are more constant with future fracture. Table 3 shows the relative risk of osteoporotic fracture as a function of the number of osteoporotic ROI sites identified in one hip scan, in reference to women without any osteoporotic BMD values. The risk of fracture increased with the number of osteoporotic skeletal sites at the hip using both the WHO criteria and the LLN method (Armitage trend test, $p<0.001$). This suggests that a total assessment of all hip ROIs from a single hip DXA BMD measure improve the evaluation of the prognosis of a patient.

Discussion

This study demonstrates that a BMD defined osteoporosis cut off value obtained by a single BMD measurement using the LLN method provides better prediction of a future fracture than the WHO T-score in a white postmenopausal 67–74 years old female population. The LLN method has better agreement between the classification of the initial BMD level and the incidence of fracture than the WHO criteria for all the hip BMD ROIs except for Ward's triangle. This study also shows that the LLN method improves the diagnostic consistency compared to the WHO T-score method in white women after age 65 years. Several other studies have addressed the concerns related to diagnostic inconsistency when using the WHO classification, particularly in the age group currently assessed [18–22]. The variable use of normative populations to calculate the young adult BMD mean are a source of inconsistencies in classification based on T-scores [21, 23, 24] and The International Committee for Standards in Bone Measurement has recommended the adoption of hip BMD

NIH-PA Author Manuscript

NIH-PA Author Manuscript

measurements from young subjects from NHANES III [16, 25], as the global standardized reference population for white women.

Some studies have argued that a replacement of the T-score −2.5 criterion by more precise cutoff levels could remedy the inconsistent diagnosis obtained by the WHO criteria [26, 27]. Given very inconsistent prevalence (figure 2) and sensitivity (figure 4) in different ROIs when using the WHO criteria, a single cut-off value of T-score is apparently no suitable. To avoid the variation problem of the T-score on different ROIs, the International Society for Clinical Densitometry guidelines recommended [27–29] excluding Ward's triangle. However, our study demonstrates that a BMD measurement in Ward's triangle has similar diagnostic value as other hip ROIs when appropriate statistical models are used.

Risk-based diagnostic criteria developed by Lu et al have been demonstrated to be more consistent than the WHO criteria [30]. However, they used the same data to build and to evaluate the model, which could introduce some biases in favor of their model. Although they used a 10-fold cross-prediction method in order to reduce bias, potential bias could not be eliminated. Their model can only be used for white women over the age of 65. We used cross-sectional data from NHANES III to identify the best models and then derived the LLN values, which may be applied to all gender-, race- specific populations (20–74 years for the white women and age between 20–65 years for men and other race ethnic groups) [12]. The presented evaluation of the LLN method using the SOF data has shown that this method offers a more consistent diagnosis and greater accuracy in prediction of future fracture in 65–74 years old white women. Further longitudinal studies from other gender, race and age populations are warranted to fully evaluate the LLN method vs. T-score in classification of osteoporosis followed by a single BMD measurement. Consistent with an earlier study [30], combining the results of BMD assessments at more than one hip ROI significantly increases prediction of fracture risk, the relative risk increases with the number of ROIs with lower BMD.

According to osteoporosis definition [31], both bone mass (measured by BMD) and bone quality are major components. The reason that T-score could not well explained fracture risk because partial risk was captured by bone quality. There are no satisfactory clinical tools available to assess bone quality independently of bone density. LLN method used defined bone-healthy populations of various gender, race and age as reference group (with lowest fracture risk). In the reference groups, bone quality may be somehow different due to genetic variation. To be eligible to enter the defined bone healthy population, people who has lower bone quality have to have higher BMD, on the other hand, people who has higher bone quality can enter this reference group with relative lower BMD. Therefore, LLN method, developed from the best statistical model from the reference populations could capture partial risk that belong to bone quality, by adjusting BMD reference value in the bone healthy population.

For any given T-score, it has been reported that different age has different fracture risk; the elderly has much higher risk than the young [32], which indicated an optimal interpretation of BMD (in term of fracture risk) should incorporate age. On the other hand, different body weight may need different BMD to support, therefore, including age and its quadratic term (when significant) in the model, as well as body weight, are beneficial when develop a method to classify osteoporosis basing on a single BMD measurement and might overcome the limitations of the T-score.

In recognizing the limitation of T-score, recently WHO developed FRAX models, which used multiple risk factors, includes T-score to predict absolute risk of fragile fracture [33]. Assessment of fracture risk should encompass all aspects of risk and the intervention should

not be guided solely by BMD. Giving the fact that LLN method is better than T-score to interpret BMD in term of fracture risk, using LLN instead of T-score may enhance FRAX model performance.

In conclusion, our study presents the development of a new osteoporosis prediction model using a national representative population and evaluates and compares the diagnostic classification impact of the new model to the established WHO criteria. Using the SOF cohort data providing 12 years of incidence fractures, we demonstrated that the LLN method is more consistent and efficient for osteoporosis diagnosis in white postmenopausal women. Unlike the lack of generalization of the T-score method to nonwhite populations, the best statistical model and the corresponding LLN diagnosis tool could be developed from various race/ethnicity and gender populations and could be used to diagnosis osteoporosis in these populations. Longitudinal studies are required to fully evaluate and compare the ability of the LLN methods with the T-score method in predicting future fractures in men and women of different race/ethnicity.

Acknowledgments

The Study of Osteoporotic Fractures (SOF) is supported by National Institutes of Health funding. The National Institute on Aging (NIA) provides support under the following grant numbers: AG05407, AR35582, AG05394, AR35584, AR35583, R01 AG005407, R01 AG027576-22, 2 R01 AG005394-22A1, and 2 R01 AG027574-22A1. We thank Li-Yung Lui at San Francisco Coordinating Center for her assistance with the SOF data. These analyses were done independently of the SOF study, and therefore should not be interpreted as representing the views of the SOF investigator group.

References

1. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996; 312:1254–1259. [PubMed: 8634613]
2. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis Technique report series. Vol. No. 843. WHO; Geneva, Switzerland: 1994.
3. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: Scientific review. JAMA. 2002; 288:1889–1897. [PubMed: 12377088]
4. Lewiecki, Michael E. Mike's Manual 6th New Mexico. Clinical Research & osteoporosis Center, Inc; Albuquerque, NM, USA: 2003.
5. Greenspan SL, Maitland-Ramsey L, Myers E. Classification of osteoporosis in the elderly is dependent on site-specific analysis. Calcif Tissue Int. 1996; 58:409–414. [PubMed: 8661481]
6. Faulkner KG, von Stetten E, Miller P. Discordance in patient classification using T-scores. J Clin Densitom. 1999; 2:343–350. [PubMed: 10548828]
7. Faulkner KG. Bone densitometry: Choosing the proper skeletal site to measure. J Clin Densitom. 1998; 1:279–285. [PubMed: 15304900]
8. Pocock NA, Sambrook PN, Nguyen T, Kelly P, Freund J, Eisman JA. Assessment of spinal and femoral bone density by dual X-ray absorptiometry: comparison of lunar and hologic instruments. J Bone Miner Res. 1992; 7:1081–1084. [PubMed: 1414500]
9. Faulkner KG, Roberts LA, McClung MR. Discrepancies in normative data between Lunar and Hologic DXA systems. Osteoporos Int. 1996; 6:432–436. [PubMed: 9116387]
10. Lofman O, Larsson L, Toss G. Bone Bone mineral density in diagnosis of osteoporosis: reference population, definition of peak bone mass, and measured site determine prevalence. J Clin Densitom. 2000; 3:177–186. [PubMed: 10871911]
11. Lewiecki EM, Kendler DL, Kiebzak GM, Schmeer P, Prince RL, El-Hajj Fuleihan G, Hans D. Special report on the official positions of the International Society for Clinical Densitometry. Osteoporos Int. 2004; 15:779–784. [PubMed: 15278247]

12. [Accessed January 15, 2009] American Statistical Association JSM online program. Available at: http://www.amstat.org/meetings/jsm/2007/onlineprogram/index.cfm?fuseaction=abstract_details&abstractid=309589
13. National Center for Health Statistics. DHHS publication no (PHS) 94–1308 NCHS. Vol. 1. Hyattsville, Maryland: 1994. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–1994 Vital Health Stat.
14. Kung, HC.; Hoyert, DL.; Xu, JQ.; Murphy, SL. National vital statistics reports. Vol. 56. Hyattsville MD: National Center for Health Statistics; 2008. Deaths: Final data for 2005.
15. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995; 332:767–773. [PubMed: 7862179]
16. Steiger P, Cummings SR, Black DM, Spencer NE, Genant HK. Age-related decrements in bone mineral density in women over 65. J Bone Miner Res. 1992; 7:625–632. [PubMed: 1414480]
17. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Johnston CC Jr, Lindsay R. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int. 1998; 8:468–489. [PubMed: 9850356]
18. Faulkner KG, von Stetten E, Steiger P, Miller P. Discrepancies in osteoporosis prevalence at different skeletal sites: Impact on the WHO criteria. Bone. 1998; 12:S198.
19. Grampp S, Genant HK, Mathur A, Lang P, Jergas M, Takada M, Glüer CC, Lu Y, Chavez M. Comparisons of non-invasive bone mineral measurements in assessing age-related loss, fracture discrimination, and diagnostic classification. J Bone Miner Res. 1997; 12:697–711. [PubMed: 9144335]
20. Davis JW, Ross PD, Wasnich RD. Evidence for both generalized and regional low bone mass among elderly women. J Bone Miner Res. 1994; 9:305–309. [PubMed: 8191922]
21. Greenspan SL, Maitland-Ramsey L, Myers E. Classification of osteoporosis in the elderly is dependent on site-specific analysis. Calcif Tissue Int. 1996; 58:409–414. [PubMed: 8661481]
22. Genant H, Lu Y, Mathur A, Fuerst T, Cummings S. Classification based on DXA measurements for assessing the risk of hip fractures. J Bone Miner Res. 1996; 11:S120.
23. Genant H, Lu Y, Mathur A, Fuerst T, Zhao S, Cummings S. Diverse diagnostic armamentarium in bone mass measures: Opportunities and dilemmas. Osteoporos Int. 1997; 7:258.
24. Mazess RB, Barden HS. T-scores differ among skeletal sites. Calcif Tissue Int. 1999; 64:S104.
25. Hanson J. Standardization of femur. BMD J Bone Miner Res. 1997; 12:1316–1317. (Letter).
26. Lofman O, Larsson L, Toss G. Bone mineral density instead of T-score? J Clin Densitom. 2001; 4:75–77.
27. Leib, ES.; Binkley, N.; Bilezikian, JP.; Kendler, DL.; Lewiecki, EM.; Petak, SM. J Rheumatol; Position Development Conference of the International Society for Clinical Densitometry; Vancouver, BC. July 15–17, 2005; 2006. p. 2319-2321.
28. Hans D, Downs R, Duboeuf JF, Greenspan S, Jankowski L, Kiebzak G, Petak S. Skeletal Sites for Osteoporosis Diagnosis: The 2005 ISCD Official Positions. J Clin Densitom. 2005; 9:15–21. [PubMed: 16731427]
29. Binkley N, Bilezikian J, Kendler D, Leib E, Lewiecki E, Petak S. Official Positions of the International Society for Clinical Densitometry and Executive Summary of the 2005 Position Development Conference. J Clin Densitom. 2005; 9:4–14. [PubMed: 16731426]
30. Lu Y, Genant HK, Shepherd J, Zhao S, Mathur A, Fuerst TP, Cummings SR. Classification of osteoporosis based on bone mineral densities. J Bone Miner Res. 2001; 16:901–910. [PubMed: 11341335]
31. Consensus development conference: diagnosis, prophylaxis and treatment of osteoporosis. Am J Med. 1993; 94:646–650. [PubMed: 8506892]
32. Hui SL, Slemenda CW, Johnston CC. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest. 1988; 81:1804–1809. [PubMed: 3384952]
33. Kanis J, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporosis Int. 2005; 16:581–89.

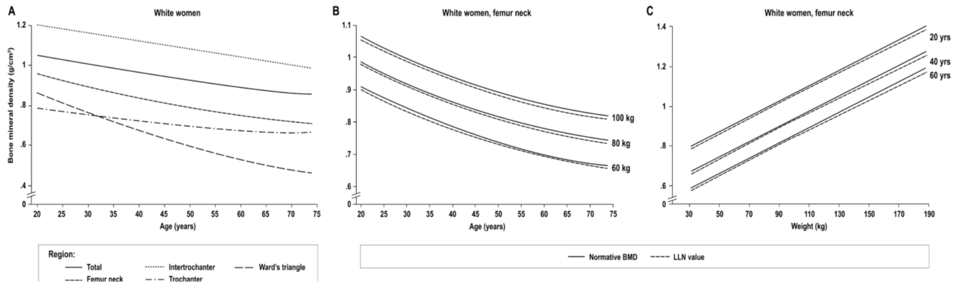

Figure 1.
Plots of normative BMD and LLN values for hip ROIs versus age or weight, derived from the best models identified using BMD measures of 20–74 years old bone healthy white women in the NHANES III study.

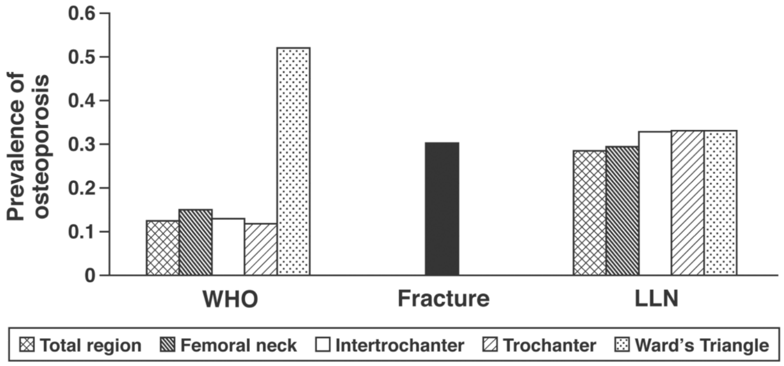

Figure 2.
Prevalence of osteoporosis as identified by T-score and the LLN method in 4,948 white women aged 67~74 years at the second visit in the SOF study, and the incidence of fracture during the 12 years follow-up.

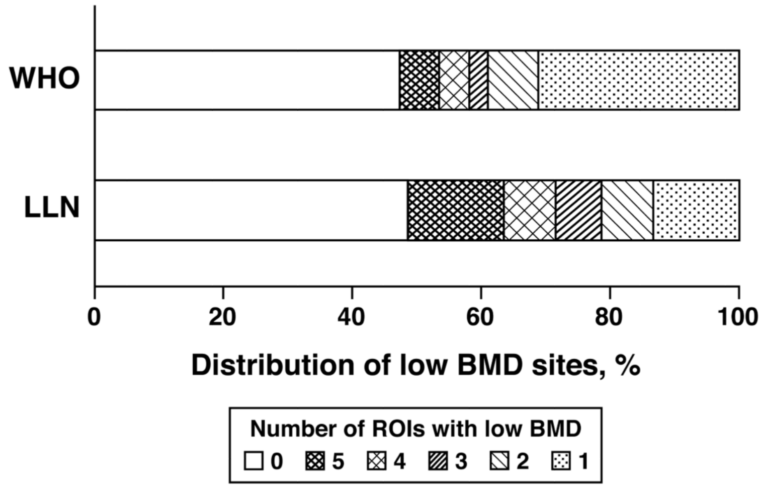

Figure 3.
Distribution of the number of osteoporotic Region of Interest (ROI) hip sites identified by T-score and the LLN method among 4,948 white women aged 67 – 74 years in the SOF study.

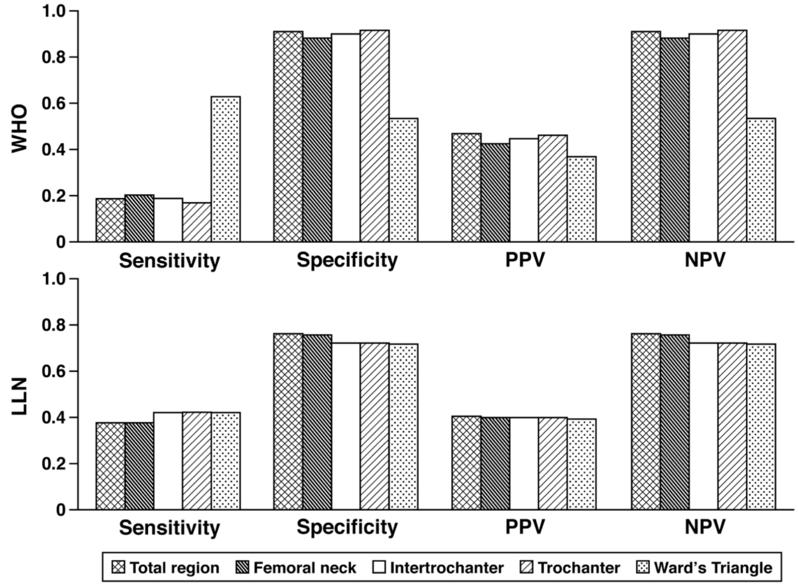

Figure 4.
Sensitivity, specificity, PPV (positive predictive values) and NPV (negative predictive value) for osteoporosis fracture by hip Region of Interest (ROI) sites using T-score and the LLN method in 4,948 white women aged 67–74 years in the SOF study.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Age centered polynomial regression models for five hip BMD ROI sites in “bone healthy” white women aged 20–74 years in NHANES III (1988–1994).

ROIs	Constant	Weight	Physical inactivity	Smoking	Age	Age^2	R^2
Total hip	0.6475	0.0043	−0.0458	−0.0133	−0.0036	−0.00008	0.395
Femur neck	0.5914	0.0034	−0.0385	−0.0067	−0.0048	−0.00004	0.373
Intertrochant	0.7450	0.0053	−0.0527	−0.0155	−0.0034	−0.00011	0.384
Trochanter	0.5214	0.0026	−0.0364	−0.0085	−0.0028	−0.00006	0.309
Ward’s triangle	0.5085	0.0028	−0.0436	−0.0150	−0.0074	−0.00003	0.413

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 2

Mean bone mineral density (BMD) (g/cm2) value and Standard deviation, correlation coefficients* between five hip ROI BMD measurements, and kappa statistics between fracture and classification of osteoporosis using WHO T-score criteria and the LLN method of 4948 white women aged 67–76 years in the SOF study.

		Total region	**Femur neck**	**Intertrochanter**	**Trochanter**	**Ward's triangle**
SOF data at 2nd visit	Mean (g/cm2)	0.778	0.666	0.909	0.572	0.445
	SD	0.130	0.110	0.159	0.102	0.111
Correlation coefficient between BMD mean values at 2nd visit in SOF*	Total region		0.863	0.984	0.900	0.837
	Femur neck			0.826	0.764	0.868
	Intertrochanter				0.841	0.809
	Trochanter					0.768
Kappa statistics for fracture in SOF **	WHO criteria (95% CI)	10.28 (7.87, 12.69)	9.40 (6.86, 11.93)	9.67 (7.23, 12.12)	9.47 (7.10, 11.84)	15.96 (13.32, 18.60)
	LLN method (95% CI)	15.87 (12.96, 18.77)	15.07 (12.14, 18.00)	15.82 (12.89, 18.76)	15.52 (12.58, 18.46)	16.45 (13.51, 19.38)

* $p<0.0001$ for all correlations

** The kappa statistics of classification of osteoporosis diagnosis by BMD measure at visit 2 and fracture occurring after this visit for all hip ROIs.

Table 3

Relative osteoporotic fracture risk as a function of number of osteoporotic sites in total hip and its sub-regions (the femoral neck, intertrochanteric region, and trochanter) defined by the T-score and the LLN method

Method	No. of osteoporotic site	Prevalence	Relative risk	Trend test	
				χ^2	p-value
WHO	1	31.2	1.16(1.11, 1.21)	5.68	<0.0001
	2	7.8	1.19(1.10, 1.29)		
	3	2.9	1.33(1.15, 1.54)		
	4	4.7	1.43(1.27, 1.62)		
	5	6.0	1.49(1.33,1.67)		
LLN	1	13.5	1.05(1.00, 1.50)	5.64	<0.0001
	2	7.9	1.13(1.05, 1.23)		
	3	7.2	1.22(1.12, 1.34)		
	4	7.9	1.22(1.12, 1.32)		
	5	14.9	1.40(1.30. 1.50)		