THE COMBINATION OF BODY MASS INDEX AND AGE AS A NEW INDEX FOR IDENTIFYING OSTEOPOROSIS IN THAI POSTMENOPAUSAL WOMEN

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Health Development
Faculty of Medicine
Chulalongkorn University
Academic Year 2009

การใช้ดัชนีมวลกายร่วมกับอายุเป็นดัชนีใหม่ในการตรวจคัดกรองภาวะกระดูกพรุนในสตรีไทยวัยหมดระดู

นายชำนาญ แท่นประเสริฐกุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาการพัฒนาสุขภาพ
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2552

Thesis Title	THE COMBINATION OF BODY MASS INDEX AND AGE AS A NEW INDEX FOR IDENTIFYING OSTEOPOROSIS IN THAI POSTMENOPAUSAL WOMEN
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Field of Study	Health Development
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ชำนาญ แท่นประเสริฐกุล : การใช้ดัชนีมวลกายร่วมกับอายุเป็นดัชนีใหม่ในการตรวจคัดกรองภาวะกระดูกพรุนในสตรีไทยวัยหมดระดู (THE COMBINATION OF BODY MASS INDEX AND AGE AS A NEW INDEX FOR IDENTIFYING OSTEOPOROSIS IN THAI POSTMENOPAUSAL WOMEN)
อ. ที่ปรึกษาวิทยานิพนธ์หลัก : รศ.นพ.กระเษียร ปัญญาคำเลิศ, 41 หน้า

วัตถุประสงค์ : เพื่อประเมินคุณค่าของการใช้ดัชนีมวลกายร่วมกับอายุเป็นดัชนีใหม่ในการตรวจคัดกรองภาวะกระดูกพรุนในสตรีไทยวัยหมดระดู

รูปแบบการวิจัย : การวิจัยแบบ diagnostic study

วัสดุและวิธีการ : ได้รวบรวมข้อมูลการวัดค่ามวลกระดูกของสตรีไทยวัยหมดระดู อายุ 40- 80 ปี ซึ่งไม่มีโรคทางเมตาโบลิคของกระดูก ไม่พบโรคหรือมีการแพร่ลามของมะเร็งที่กระดูก และไม่ได้ใช้ยาที่มีผลต่อแคลเซียม หรือมวลกระดูก โดยมีค่าผลการตรวจมวลกระดูกในช่วง 1 มกราคม 2547 ถึง 31 ธันวาคม 2551 และมีข้อมูลของค่ามวลกระดูกครบที่ 3 ตำแหน่งได้แก่ lumbar spines , femoral neck และ intertrochanter ได้ข้อมูลครบถ้วนทั้งหมด 372 ราย การวินิจฉัยว่าเกิดภาวะกระดูกพรุนใช้ตามคำจำกัดความขององค์การอนามัยโลก นำข้อมูลที่ได้มาวิเคราะห์ผลทางสถิติ

ผลการศึกษา : พบความชุกของภาวะกระดูกพรุน ที่ตำแหน่ง lumbar spines , femoral neck และ intertrochanter ร้อยละ 8.1 , 20.2 และ 15.3 ตามลำดับ หากใช้ดัชนีใหม่ที่เกิดจากดัชนีมวลกายและอายุรวมกัน จะมีความไว (sensitivity) ร้อยละ 76.67 , 76 และ 77.19 ตามลำดับ เมื่อใช้ OSTA index โดยใช้จุดตัดที่ -1 จะมีความไว ร้อยละ 80 , 70.67 และ 70.17 ตามลำดับ แต่หากเปลี่ยนค่าจุดตัดเป็น 0 จะมีความไว ร้อยละ 90 , 85.33 และ 78.95 ตามลำดับ

สรุป : การใช้ดัชนีใหม่ที่เกิดจากดัชนีมวลกายและอายุ อาจเป็นทางเลือกหนึ่งในการตรวจคัดกรองหาภาวะกระดูกพรุนในสตรีไทยวัยหมดระดู และการเปลี่ยนค่าจุดตัดของ OSTA เป็น 0 จะช่วยเพิ่มความไวของการตรวจคัดกรองได้สูงขึ้นอย่างชัดเจน

สาขาวิชา.... การพัฒนาสุขภาพ.....ลายมือชื่อ.....

ปีการศึกษา.....2552.....ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

5175054830 : MAJOR HEALTH DEVELOPMENT

KEYWORDS : OSTEOPOROSIS / BMI / AGE / THAI

CHAMNAN TANPRASERTKUL : THE COMBINATION OF BODY MASS INDEX AND AGE AS A NEW INDEX FOR IDENTIFYING OSTEOPOROSIS IN THAI POSTMENOPAUSAL WOMEN

THESIS ADVISOR: ASSOC. PROF. KRASEAN PANYAKHAMLERD, M.D. 41 pp.

Objective: To evaluate the application of the combination of body mass index (BMI) and age as a new screening tool to identify osteoporosis in Thai postmenopausal women

Design: Diagnostic descriptive study

Material and Method : Bone mineral density (BMD) data of Thai postmenopausal women, age 40- 80 years old who attended the outpatient clinic, Thammasat university Hospital, Thailand, between January 2004 and December 2008 were enrolled. The participants with history of metabolic bone disease or use of drugs associated with secondary osteoporosis and/or history of treatment for osteoporosis were excluded. Each had BMD records of lumbar spines, femoral neck and intertrochanter. The data were completely collected in all 372 women.
A diagnosis of osteoporosis made according to WHO criteria.

Results: The prevalence of osteoporosis at lumbar spines, femoral neck and intertrochanter were 8.1 %, 20.2 % and 15.3 % respectively. The combination of BMI and age as the index to detect osteoporosis had a sensitivity at 76.67%, 76% and 77.19%, respectively. The OSTA index at the standard cut-off point of -1 had sensitivity at 80%, 70.67% and 70.17%, respectively. Raising the cut-off point to ≤ 0 would had a sensitivity at 90%, 85.33% and 78.95%, respectively.

Conclusion: The application of the combination of BMI and age as a screening tool is another option to identify osteoporosis in Thai postmenopausal women. Change the cut-off point of ≤ 0, OSTA index could improve the detection of osteoporosis at a very high level of the sensitivity.

Field of Study : Health Development Student's Signature .....

Academic Year : 2009 Advisor's Signature .....

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to my thesis advisor, Assoc. Prof. Krasean Panyakhamlerd for his invaluable help and constant encouragement throughout the course of this research. He also gave a good advice and had been a guidance of this thesis since the research had been started until completely finished .

I am grateful for all of staff at Thai CERTS consortium for their helpful in providing facilities and support for my thesis. In addition, I would like to special thank for Assoc. Prof. Paskorn Sritipsukko for his kindly suggestion and Assist. Prof. Junya Pattara-Archachai for her help in statistical analysis.

Finally, I most gratefully acknowledge my family and my colleges for all their support throughout the period of this research.

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CHAPTER I

INTRODUCTION

1.1 Background and Rationale

Osteoporosis is a common disease that is characterized by low bone mass with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fracture, particularly at the spine, hip, wrist, humerus, and pelvis [1]. The number of osteoporotic fractures is certain to increase in both men and women as a result of the aging population. The age- incidence increases exponentially with age, this burden occurs in many region of the world, including Asia resulting the greatest morbidity and mortality. Disabilities from osteoporotic fractures give rise to the highest direct costs for health services [2].

According to the report of a WHO Study Group meeting on Assessment of fracture risk and its application to screening for postmenopausal osteoporosis (2004), osteoporosis has been recognized as an established and well-defined disease that affects more than 75 million people in the United States, Europe and Japan[3,4] . Osteoporosis causes more than 8.9 million fractures annually worldwide, of which more than 4.5 million occur in the Americas and Europe. The lifetime risk for a wrist, hip or vertebral fracture has been estimated to be in the order of 30% to 40% in developed countries – in other words, very close to that for coronary heart disease. Osteoporosis is not only a major cause of fractures, it also ranks high among diseases that cause people to become bedridden with serious complications. These complications may be life threatening in elderly people. Osteoporotic fractures account for 2.8 million disability-adjusted life years (DALYs) annually in the United States and Europe, somewhat more than accounted for by hypertension and rheumatoid arthritis. Collectively, osteoporotic fractures account for approximately 1% of the DALYs attributable to non-communicable diseases [3].

In Thailand situation, Limpaphayom K, et al reported the prevalence of osteopenia and osteoporosis that the age-specific prevalence of osteoporosis among Thai women rose progressively with increasing age to more than 50% after the age of 70. The age-adjusted prevalence of osteoporosis also rose progressively. It was 19.8%, 13.6%, and 10% for lumbar spines, femoral neck, and intertrochanter respectively [5].

World Health Organization (WHO) established a classification of bone mineral density (BMD) according the standard deviation difference between a patient's BMD and that of a young-adult reference population. This value is now commonly expressed as a "T-score." A T-score that is equal to or less than -2.5 is consistent with a diagnosis of osteoporosis; a T-score between -1.0 and -2.5 is classified as low bone mass (osteopenia); and a T-score of -1.0 or higher is normal. The gold standard for measuring bone mineral density (BMD) is dual energy X-ray absorptiometry (DXA) [1, 6, 7]. The major disadvantages of DXA are that the machine is large, not portable and more expensive than most peripheral technologies. In clinical practice in Thailand, DXA is the technology used for diagnostic classification, however the normogram of BMD has not been standardized and applied to general practice. Moreover, there were estimated only 50 DXA machines all over the country. Most of them locate only in hospitals in Bangkok and large cities such as university hospitals.

Since the mid 1990s, a number of Clinical risk indexes (CRIs) are designed to assist clinicians in identifying women with low bone mass . Osteoporosis Self-assessment Tool for Asians (OSTA), one of CRIs which is wildly accepted index using chart or formula to predict low BMD simply on the basis of age and weight. It was firstly proposed by Koh LK, which had a sensitivity of 91% and specificity of 45% in identifying women of high risk when compared with final results of femoral neck BMD measurement in Asia women [8]. However, the performance of this index in Thai postmenopausal women had lower sensitivity than original report, especially in prediction of lumbar spine osteoporosis [9-11].

Low body mass index (BMI) is a well-documented risk factor for future fracture, largely independent of age and sex [12-16]. Meta -analysis study of 14 prospective

population-based cohorts demonstrated that the age-adjusted risk for any type of fracture increased significantly with lower BMI. The authors strongly recommended the use of this risk factor in case-finding strategies. Therefore, the objective of this study is to evaluate the application of the combination of BMI and age as the new index to identifying osteoporosis in Thai postmenopausal women.

1.2 Research question

Could the combination of BMI and age as a new index be the new screening tool for identifying osteoporosis in Thai postmenopausal women, with better diagnostic performances than the OSTA index?

1.3 Research objectives

- To develop a new index, the combination of BMI and age, as the screening tool for identifying osteoporosis in Thai postmenopausal women.
- To compare the diagnostic performances of a new index, the combination of BMI and age, with the OSTA index.

CHAPTER II

LITERATURE REVIEW

Osteoporosis has been defined as “a loss of bone mass and microarchitectural deterioration of the skeletal ton leading to increased risk of fracture” [17]. The majority of postmenopausal women with osteoporosis have bone loss related to estrogen deficiency and theirs advanced age. The initial evaluation includes a history to assess for clinical risk factors for fracture and to evaluate for other conditions that contribute to bone loss, a physical examination, and basic laboratory tests. There are many coexisting medical conditions that contribute to bone loss. Evaluation for alternative causes of bone loss to detect potentially reversible causes should be considered in those with abnormal initial findings. Early diagnosis and quantification of bone loss and fracture risk have become more important because of the availability of therapies that can slow or even reverse the progression of osteoporosis.

2.1 Clinical features

Osteoporosis has no clinical manifestations until there is a fracture. This illness is called the "silent disease” because it can appear without warning signs or symptoms. Many patients with bone pain or achy hips are unlikely to cause from bone loss until the fracture occurs.

Decreased bone strength is related to many factors other than bone mineral density, including rates of bone formation and resorption (turnover), bone geometry (size and shape of bone), and microarchitecture . Assessment of microarchitecture requires bone biopsy, which is not routinely used in clinical practice. Therefore, bone mineral density (BMD) assessment is the gold standard to diagnose osteoporosis.

2.2 Bone mineral density definition

The World Health Organization (WHO) established a classification of BMD according the standard deviation (SD) difference between a patient's BMD and that of a young-adult reference population (T-score) [6, 7]. A BMD T-score that is 2.5 standard deviations (SD) or more below the young-adult mean BMD is defined as osteoporosis, provided that other causes of low BMD have been ruled out (such as osteomalacia). A T-score that is 1 to 2.5 SD below the young-adult mean is termed osteopenia or low

bone mass. Normal bone density is defined as a value within one standard deviation of the mean value in the young adult reference population

2.3 Method of BMD measurement — Several different methods are available to measure bone density. Dual energy x-ray absorptiometry (DXA) gives an accurate and precise estimate of bone mineral density (BMD). Thus, in clinical practice DXA is the technology used for diagnostic classification.

Dual energy x-ray absorptiometry (DXA) is the most widely used method for measuring BMD because it gives very precise measurements at clinically relevant skeletal sites. The major disadvantages of DXA are that the machine is large (not portable) and expensive, and that it uses ionizing radiation. Although overall fracture risk can be predicted by measurement or estimation of BMD at many skeletal sites [18], the risk for fracture at a particular skeletal site is best estimated by measuring BMD at that skeletal site [19-20]. Since hip fracture is often associated with significant morbidity and mortality compared with other fractures, DXA of the hip is generally regarded as the best site for diagnosis of osteoporosis. In contrast, the lumbar spine is often considered the best skeletal site to monitor because it shows less variability and can detect responses to therapy earlier than hip BMD.

2.4 Review of related literatures

In 2001 Limpaphayom K, et al [5] reported the descriptive study of 1,935 Thai women by using the Thai BMD reference. The age-specific prevalence of osteoporosis among Thai women rose progressively with increasing age to more than 50% after the age of 70. The age-adjusted prevalence of osteoporosis also rose progressively. It was 19.8%, 13.6%, and 10% for lumbar spines, femoral neck, and intertrochanter. The authors suggested that using a Western BMD reference resulted in a misleadingly high prevalence of osteoporosis in the population of Asian countries.

In 2001 Koh LK, et al [8] purposed the OSTA index. Using data from 860 postmenopausal Asian women in 8 countries and evaluated the ability of these risk factors to identify women with osteoporosis as defined by femoral neck BMD. A final tool based on only age and body weight. This risk index had a sensitivity of 91% and specificity of 45%, with an area under the curve of 0.79. The authors validated the index in Japanese women. With cut-off of -1, the sensitivity was 98% and specificity was

29%. In the low-risk group whom represented 25% of all women, BMD is probably unnecessary. Using the OSTA index as the risk categories for Asian women . The cut-off of more than –1 was considered as the low risk, cut-off of –4 to –1 was considered as the intermediate risk and cut-off of less than –4 was considered as the high risk. BMD measurement should be avoided in the low risk group , however in the high risk group , diagnostic BMD measurement is strongly recommended . For the intermediate risk group , the other clinical risk factors should be considered and the availability of equipment , the cost for investigation must also be weighted and analyzed.

In 2004 Pongchaiyakul C, et al [21] reported the modified OSTA index in Thai menopausal women, by adjusting for age and bodyweight. This score had higher of sensitivity and specificity than OSTA. The authors renamed this index as Khon Kaen Osteoporosis Study Scores (KKOS Score).

In 2004 Geater S, et al [9] validated the properties of OSTA index as a screening tool among 380 postmenopausal women in southern Thailand. 31% of the women were detected as having osteoporosis, comprising neck of the femur (12 %) and lumbar spines (31 %). OSTA index at the standard cut-off point of < -1 had a sensitivity and specificity of 0.93 (95% CI:0.82 - 0.99) and 0.61 (95% CI: 0.56-0.66) respectively for neck of the femur but only 0.80 (95% CI: 0.72-0.87) and 0.70 (95% CI: 0.64-0.75) respectively for lumbar spines. Raising the cut-off point to < 0 could reduced the high false negative rate in prediction of lumbar spine osteoporosis, the authors suggested the cut-off point of < 0 for the lumbar spines may be more appropriate.

In 2005 De Laet C, et al [12] reported the meta-analysis study from 14 prospective population-based cohorts . The age-adjusted risk for any type of fracture increased significantly with lower BMI. Overall, the risk ratio (RR) per unit higher BMI was 0.98 (95% CI, 0.97–0.99) for any fracture, 0.97 (95% CI, 0.96–0.98) for osteoporotic fracture and 0.93 (95% CI, 0.91–0.94) for hip fracture (all p <0.001). The gradient of fracture risk without adjustment for BMD was not linearly distributed across values for BMI. Instead, the contribution to fracture risk was much more marked at low values of BMI than at values above the median. This nonlinear relation of risk with BMI was most evident for hip fracture risk. When compared with a BMI of 25 kg/m^2, a BMI of 20 kg/m^2 was associated with a nearly twofold increase in risk ratio (RR=1.95; 95% CI, 1.71–2.22)

for hip fracture. In contrast, a BMI of 30 kg/m^2, when compared with a BMI of 25 kg/m^2, was associated with only a 17% reduction in hip fracture risk (RR=0.83; 95% CI, 0.69–0.99).The authors concluded that low BMI confers a risk of substantial importance for all fractures that is largely independent of age and sex and stated the significance of BMI as a risk factor in case-finding strategies.

In 2007 Jarupanich T [22] reported the descriptive study for the prevalence of osteoporosis of lumbar spines and femoral neck was significantly higher in the late group of menopause (> 5 years since menopause) than in the early group of menopause . Osteoporosis at the lumbar spine was present in 1% of pre-menopause, 5.7% in the early group of menopause, and 10% in the late group of menopause. While osteoporosis at the femoral neck was present in 0.1% of pre-menopause, 0% in the early group of menopause, and 0.6% in the late group of menopause. Low body mass index, non-hormone intake, early and late group of menopause were highly significant correlated with osteoporosis.

In 2007 Pongchaiyakul C, et al [23] reported the diagnostic performance of clinical risk indices combined with quantitative ultra-sound calcaneus measurement (QUS) for identifying osteoporosis in 300 Thai postmenopausal women. Using DXA as the gold standard, the sensitivity of QUS to identify osteoporosis was lower than the sensitivity of OSTA/KKOS (60 vs. 71/74%) but the specificity and PPV of QUS were higher than OSTA/KKOS. The sensitivity increased when using OSTA/KKOS combined with QUS to identify osteoporosis (87-89%) while the specificity, PPV and NPV were comparable with using clinical risk indices alone. The authors concluded that using the clinical risk indices combined with QUS could improve the accuracy of screening for osteoporosis.

CHAPTER III

RESEARCH METHODOLOGY

3.1. Research hypotheses

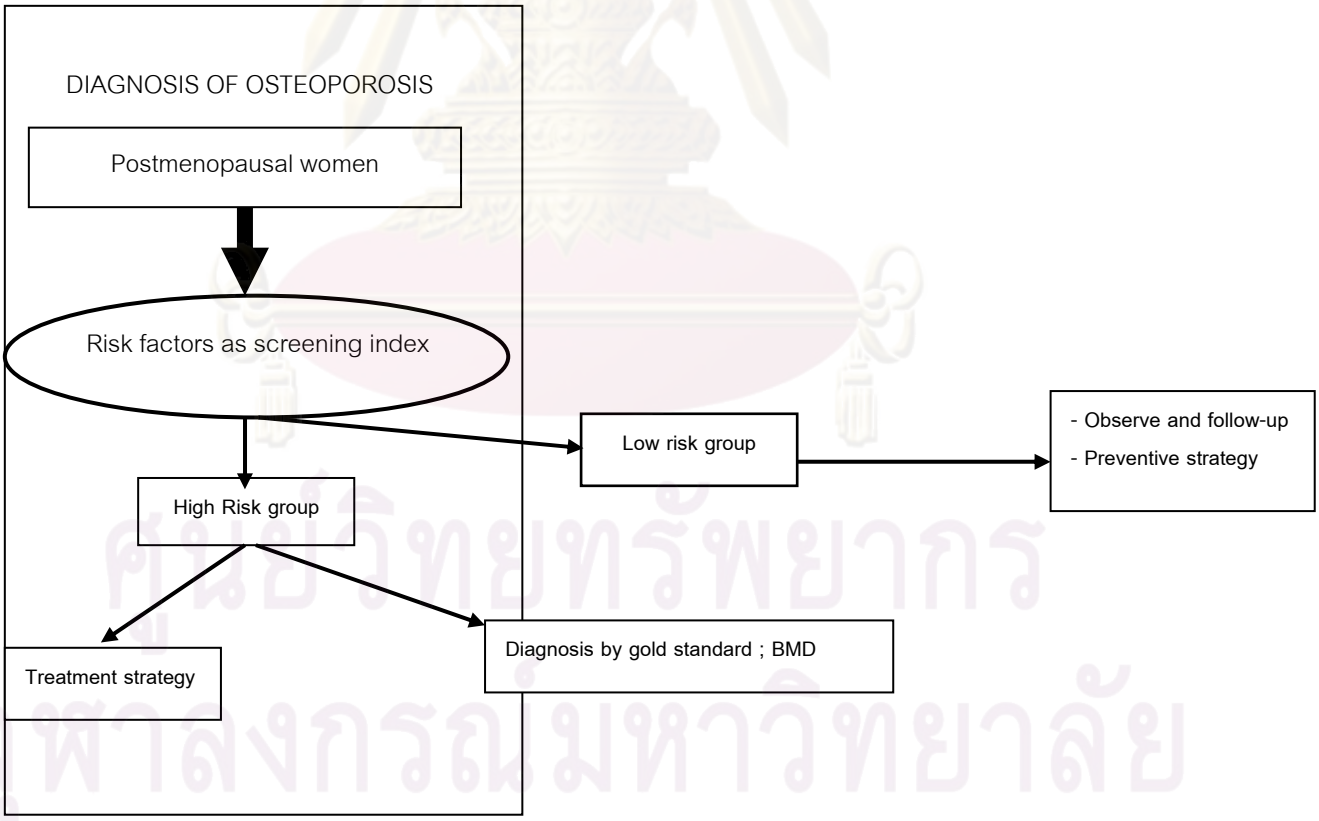
The combination of BMI and age as a new index could be the new screening tool for identifying osteoporosis in Thai postmenopausal women, with better diagnostic performances than the OSTA index.

Statistical Hypothesis

H_0: ROC AUC of new index = ROC AUC of OSTA index

H_1: ROC AUC of new index ≠ ROC AUC of OSTA index

3.2 Conceptual framework



3.3. Assumption

- Use OSTA index, base on data from different country, to evaluate risk of osteoporosis in Thai menopausal women might not had high sensitivity as the original study.
- BMI is one of the major factor affect risk of osteoporosis, using BMI in combination with age as the new index could increase sensitivity and accuracy of screening for osteoporosis in post menopausal women.

3.4 Key words

Osteoporosis, BMI, Age, Thai

3.5 Operational definition

Osteoporosis :	Bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) that are equal to or less than 0.682, 0.569 and 0.769 g/cm^2 at lumbar spines , femoral neck and intertrochanter , respectively [5].
Osteopenia :	Bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) that are between 0.682- 0.847, 0.569 - 0.716 and 0.769 - 0.940 g/cm^2 at lumbar spines , femoral neck and intertrochanter , respectively [5] .
OSTA index :	OSTA score = 0.2 [Body Weight (kg) – Age (years)]
BMI :	Body mass index calculated as bodyweight (kg) / Height (meter) ^{2}
Menopause :	The time when there has been no menstrual periods for 12 consecutive months and no other biological or physiological cause can be identified
Age (years) :	Patient's age at last birthday

3.6 Research design

A diagnostic descriptive study with retrospective data collection

3.7 Sample size calculation

Since the research objective includes determination of sensitivity of new index , the sample size is calculated based on confidence interval approach.

The sensitivity of the model from previous studies is used for sample size calculation. From the study of Koh LK, et al [8] the sensitivity of OSTA index was 91%. By using these values, the sample size is calculated.

$$n = \frac{Z^2_{\alpha/2}\, p\,(1-p)}{d^2}$$

Where p = Estimated sensitivity of the model

d = Margin of error in estimating p = .08

α = probability of type 1 error = 0.05 (two-tailed)

$Z_{0.025}$ = 1.96

For the sensitivity of the new index

$$n = \frac{(1.96)^2\,(0.91)\,(0.09)}{(0.08)^2}$$

$$= 49.16$$

Therefore, the number of women who have osteoporosis is at least 49.16. The estimation of total number of women is based on prevalence. Since the prevalence of osteoporosis at femoral neck in Thailand is 13.6% [5] , total number of patients should be:

$$n = \frac{49.16}{0.136}$$

$$= 361.47$$

Therefore, the minimum number of patients in the study is 362

3.8 Target population

Postmenopausal women , age 40- 80 years old .

Sample population

Postmenopausal women , age 40- 80 years old who attended department of Obstetrics - Gynecology and department of Radiology, Faculty of Medicine , Thammasat University during 10 January 2004 - 31 December 2008 and meet the following eligible criteria .

3.9 Inclusion criteria

- must be naturally postmenopausal at least 1 year since last menstruation , between the age 40 -80 years
- have the records of bone DEXA scan reported as T-score at lumbar spines , femoral neck and intertrochanter

Exclusion criteria

- a history or evidence of metabolic bone disorders (other than postmenopausal bone loss)
- presence of cancer(s) with known metastasis to bone
- menopause before the age of 40 years
- have at least one ovary removed
- a history of taking medications affecting calcium and bone metabolism, such as steroids, thyroid hormone, bisphosphonates, fluoride or calcitonin at least 6 months before measurement of BMD.

3.10 Data collection

The Constructed case record form was generated for each patient to keep the clinical data, with these following data.

1. Demographic data : age, height ,weight

2. Bone mineral density (g/cm^2) at lumbar spines , femoral neck and intertrochanter measured by DXA using a Hologic discovery (Hologic , MA, USA) densitometer.

DXA measures bone mineral content (BMC, in grams) and bone area (BA, in square centimeters), then calculates "areal" BMD in g/cm^2 by dividing BMC by BA. T-score, the value used for diagnosis of osteoporosis, is calculated by subtracting the mean BMD of a young-adult reference population from the patient's BMD and dividing by the standard deviation (SD) of young-adult population. Z-score, used to compare the patient's BMD to a population of peers, is calculated by subtracting the mean BMD of an age, ethnicity, and sex-matched reference population from the patient's BMD and dividing by the SD of the reference population.

Height and weight were measured on the same day of bone mineral density measurement , and recorded as centimeters and kilograms respectively.

3.11 Data and statistic analysis

Descriptive statistics was used to describe study subjects' characteristics. The analysis was performed to identify the relationship of characteristics; BMI, age of women with osteoporosis, defined by BMD reference values for lumbar spines , femoral neck and intertrochanter were equal to or less than 0.682, 0.569 and 0.769 g/cm^2 , respectively[5]. Multivariate logistic regression model was constructed as the osteoporotic case was a dependent variable, then the regression coefficients for each variable was calculated and converted to the simplified formula as the new index.

A receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was also inspected to evaluate the most optimal cut- off value. The optimal cut-off point was selected base on ROC curve analysis. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated on the 2 x 2 table of the collected data. The concordance between the new index and the actual BMD-based classification (by DXA) were summarized by a 2x2 table, to calculate the concordance, sensitivity, specificity, positive predictive value (PPV) and negative

predictive value (NPV) . Sensitivity was defined as the proportion of osteoporotic individuals who are identified as “high risk” by the new index and BMD or T-score < -2.5 SD. Specificity was the proportion of non-osteoporosis individuals who were identified by the new index as “low risk” and BMD or T-score > -2.5 SD. PPV was the probability that an individual with a “high risk” by new index and BMD or T-score < -2.5 SD indeed had osteoporosis. NPV was the probability that an individual with a “low risk” by new index and BMD or T-score > -2.5 SD indeed had non-osteoporosis. The association between osteoporosis defined by DXA (outcome) and (predictor) was assessed, in which the odds ratio (OR) and 95% confidence interval (CI) was presented. In addition, areas under the ROC curve (AUC) with 95% confidence intervals (CI) was calculated for OSTA index, to compare with the new index. The statistical significance of differences between each AUC was also determined. P value of less than .05 was considered statistically significant.

3.12 Ethical consideration

The study was conducted in gynecologic clinic and radiologic clinic, Thammasat University Hospital . The protocol was reviewed by the ethics committee of Faculty of Medicine, Thammasat University and Thammasat University Hospital.

The investigator was kept the confidentiality on the subject’s information. The data was analyzed and reported in general. For the purpose of confidentiality, research information was accessible only to the authorized persons who involved in this study . The subjects information was recorded as necessary and enough for the result analysis of this study. There was no records of the subjects’ names or other identifying information (such as patient number or hospital number) in the content case record form. However, for the purpose of maintaining a link between the data and the subjects’ identities throughout study, the investigators coded data with a unique study code and kept the master list in a secured location separate from the data. The investigators destroyed identifiers or master list as soon as the data had been final analyzed.

3.13 Limitation

This study had some limitations to the generalizability and quality of data. The studied population had baseline demographic characteristics different from the others . General application of the results had been restricted.

CHAPTER IV

RESULTS

4.1 PART 1 ; Patient Characteristics

Data were obtained for 372 women as shown in table 1 . Mean age was 59.99 years (SD 9.41, range 40 to 80 years), average bodyweight was 58.57 kg (SD 9.93, range 31 to 98 kg), mean height 153.02 cm (SD 5.93 , range 135 to 182 cm). In table 2, compared with the non-osteoporosis group, women with at least one of three osteoporotic sites had significantly higher mean age, lower mean bodyweight and lower mean height (p value for all comparisons < 0.001). They also had a significantly lower body mass index ($p = 0.003$).

Table 1 . Characteristics of the studied women

	n = 372 (mean $\pm$ SD)	Range (min – max)
Age (years)	59.99 $\pm$ 9.41	40-80
Bodyweight (kg)	58.51 $\pm$ 9.93	31-98
Height (cm)	153.02 $\pm$ 5.93	135-182
BMI (kg/m^2)	24.98 $\pm$ 3.97	14.47- 40.97
Age of menopause (years)	47.53 $\pm$ 5.90	41-62
BMD of lumbar spines (g/cm^2)	0.88 $\pm$ 0.15	0.34-1.41
BMD of femoral neck (g/cm^2)	0.65 $\pm$ 0.12	0.14-1.06
BMD of intertrochanter(g/cm^2)	0.91 $\pm$ 0.16	0.80-1.32

BMI, body mass index; BMD , bone mineral density

Table 2. Comparison of characteristics between non- osteoporotic women and those women who having at least one of osteoporotic sites

	Non-osteoporosis (n = 271)	Osteoporosis * (n = 101)	P value	Mean difference	95% CI
Age (years)	58.10±8.75	65.11±9.24	< 0.001	-7.01	(-9.05,-4.87)
Weight (kg)	60.13±9.92	54.13±8.60	< 0.001	6.00	(3.81 ,8.20)
Height (cm)	154.03±5.74	150.28±5.59	< 0.001	3.75	(2.44,5.06)
BMI (kg/m^2)	25.36±4.06	23.96±3.55	0.003	1.39	(1.04,1.83)
Age of menopause (years)	47.24±6.26	48.26±4.82	0.151	-1.03	(-2.43,0.38)

Data are mean ± SD

*based on at least one of osteoporotic sites

4.2 PART 2: The prevalence and characteristics of women who had osteoporosis

The figure 1-3 demonstrated the prevalence of women who had normal bone mass, osteopenia and osteoporosis at each site of bone measurement. When using the Thai BMD reference values , the prevalence of osteoporosis at lumbar spines, femoral neck and intertrochanter were 8.1 %, 20.2 % and 15.3 %, respectively. The prevalence of osteopenia at lumbar spines, femoral neck and intertrochanter were 32.3 %, 51.3 % and 43.5 %, respectively.

Figure 1. The comparison between the prevalence of women who had normal bone mass , osteopenia and osteoporosis at lumbar spines when using Thai BMD reference

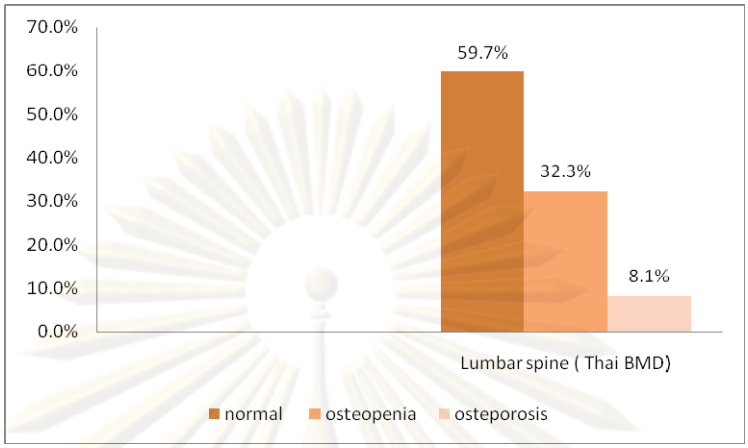


Figure 2. The comparison between the prevalence of women who had normal bone mass , osteopenia and osteoporosis at femoral neck when using Thai BMD reference

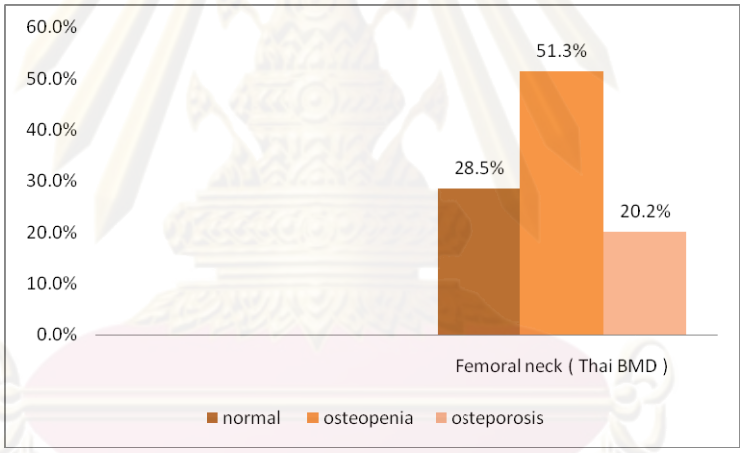


Figure 3. The comparison between the prevalence of women who had normal bone mass , osteopenia and osteoporosis at intertrochanter when using Thai BMD reference

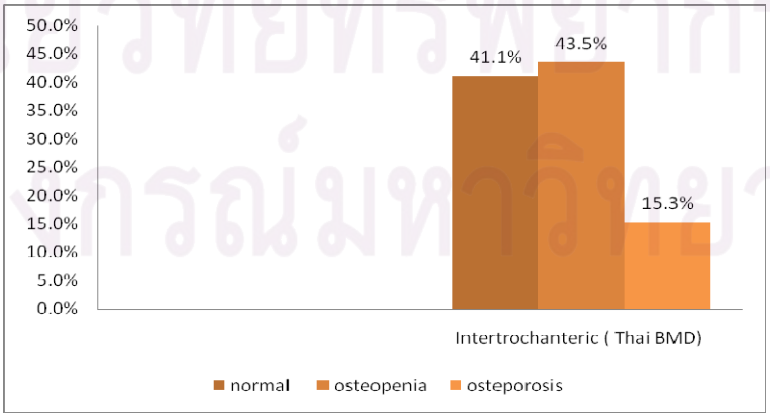


Table 3 . Characteristics of women who are having osteoporosis

	Lumbar spines	Femoral neck	Intertrochanter
Prevalence of osteoporosis	30 (8.1%)	75 (20.2%)	57 (15.3 %)
Age (years)	67.50±8.36	65.61±8.79	66.24±9.23
Bodyweight(kg)	52.33±9.46	52.99±8.07	53.47±8.77
Height (cm)	148.97±5.18	149.78±5.26	149.87±5.94
BMI (kg/m^2)	25.57±4.02	23.62±3.38	23.79±3.55
Bone mass density (g/cm^2)	0.59±.082	0.74± 0.13	0.74±.14
Age of menopause (years)	47.86±3.64	48.93±4.34	48.62±4.62

Data are mean± SD or n (%)

The prevalence of osteoporosis at lumbar spines , femoral neck and of femur were 8.1 %, 20.2 % and 15.3 % respectively . The baseline characteristics ; mean age ,bodyweight height and body mass index, of postmenopausal women who having osteoporosis at each site (lumbar spines, femoral neck, intertrochanter) were similar as demonstrated in table 3 .

4.3 PART 3 : The correlation of the BMD , T –score and other variables

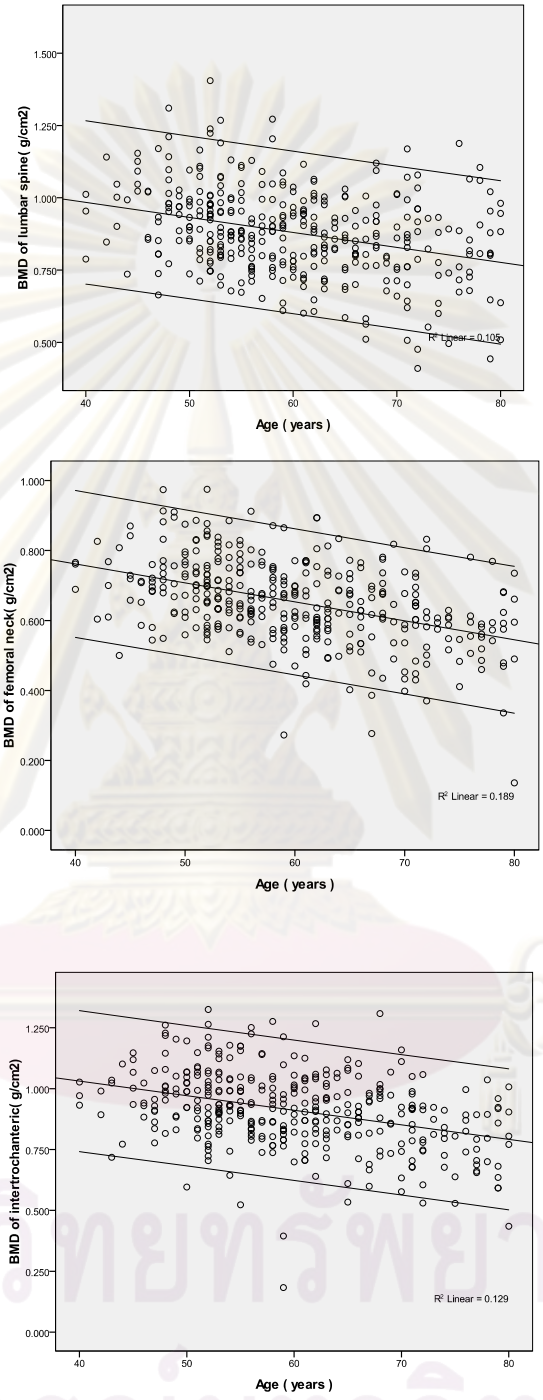


Figure 4. The scatter plots showed correlation between BMD of three measured sites and age .

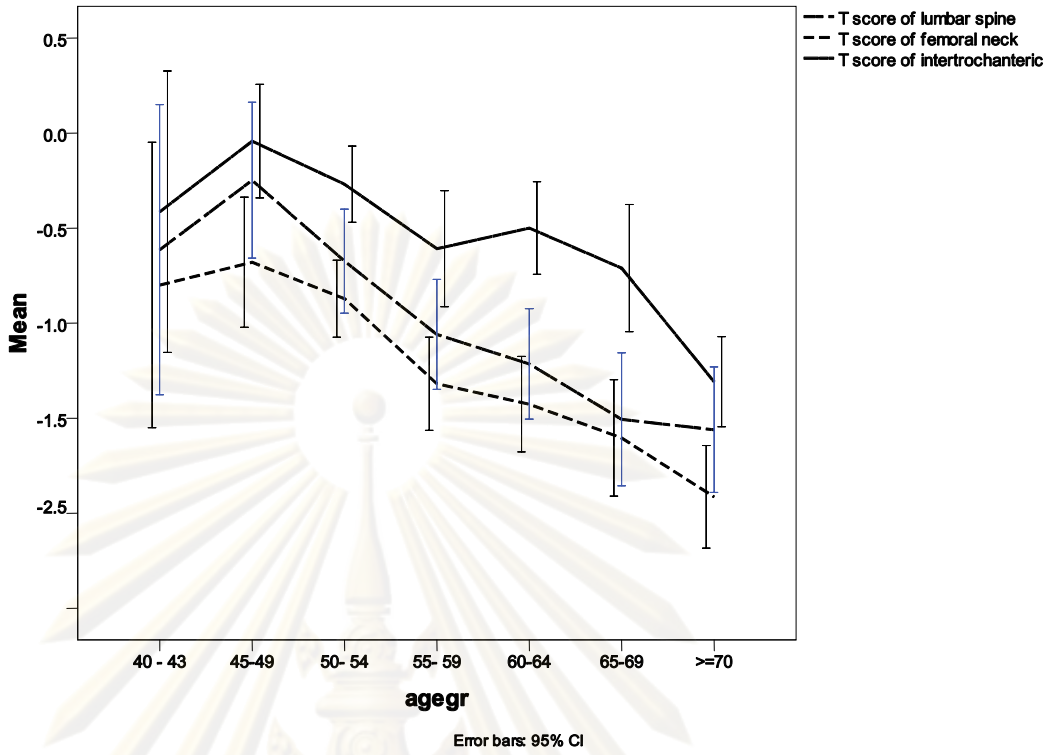


Figure 5. The correlation between mean T score with 95%CI of three measured sites and age group

Figure 4, 5 showed that BMD of all 3 sites were decreasing with advanced age of menopause. Mean T score with 95%CI were also decline as the more advanced age groups.

When OSTA index was calculated and categorized as the previous recommendation . The prevalence of osteoporosis at each measurement sites in OSTA risk categories showed in table 4 . In the low risk group , the prevalence were 2.6% , 9.5 %, 7.3 % and 14.7 % at lumbar spines , femoral neck , intertrochanter and one of three sites , respectively . The prevalence in high risk group were much ore higher than the others ; 25.7% , 54.3 %, 48.6 % and 68.6 % at lumbar spines , femoral neck , intertrochanter and one of three sites , respectively .

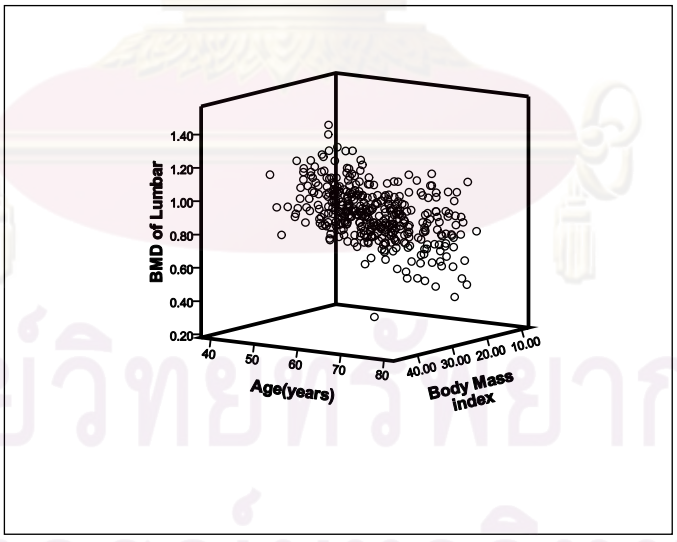
Table 4 . The prevalence of osteoporosis at each measurement sites in OSTA risk categories

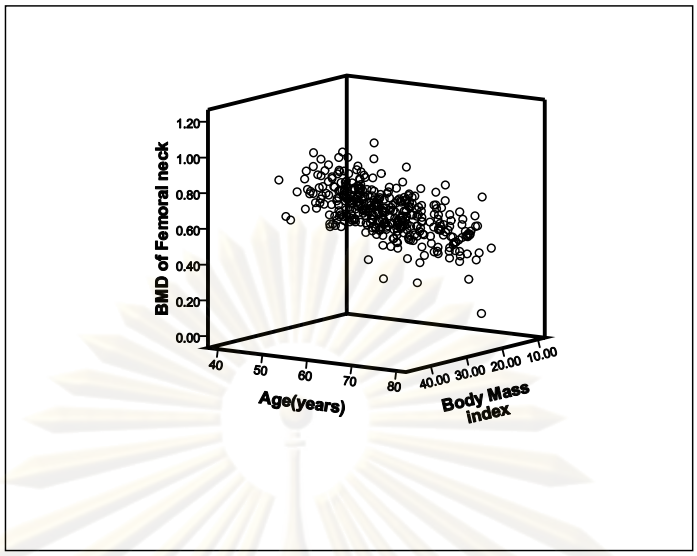
	Low risk	Intermediate risk	High risk
Lumbar spines	6	15	9
	2.6%	14%	25.7%
Femoral neck	22	34	19
	9.5%	31.8%	54.3%
Intertrochanter	17	23	17
	7.3%	21.5%	48.6%
One of 3 sites	34	43	24
	14.7%	40.2%	68.6%

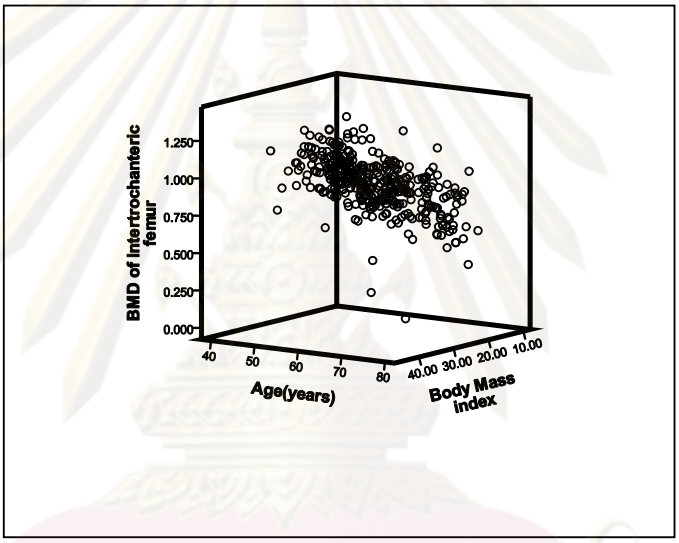
Data were expressed as number and percentage in each column

OSTA index >-1 is classified as having low risk of osteoporosis, -1 to -4 as intermediate risk and, <-4 as high risk.

Figure 6 . The correlation between BMD of three measured sites and age with BMI







The 3 -dimensions scatter plots of showed the similar patterns of correlation between BMD of three measured sites and age with BMI. The higher BMI was correlated with the grater BMD , also the more advanced of the age was correlated with the lesser BMD .

4.4 PART 4 : The statistically analysis model for the diagnostic performance of the new index and the OSTA index

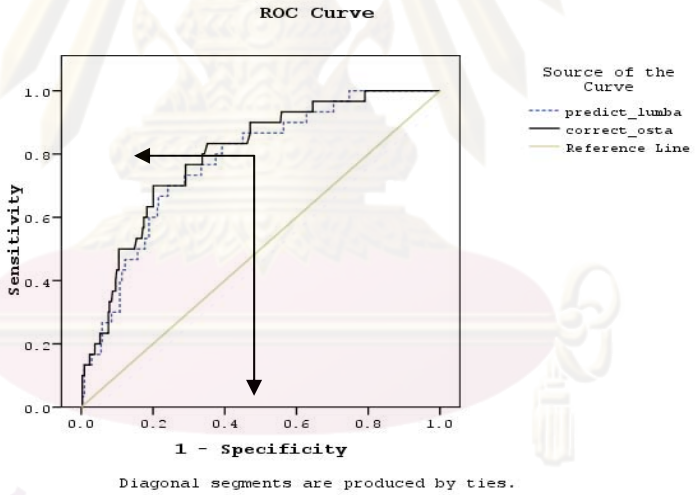
Figure 7. Logistic regression model for new index and the selected cut- off point for optimal diagnostic performances of the new index at lumbar spines

Variables in the Equation

		B	S.E.	p-value	Exp(B)	95.0% C.I.for EXP(B)	
						Lower	Upper
Step 1(a)	age	0.0996	0.0222	0.0000	1.1047	1.0578	1.1537
	BMI	-0.1459	0.0586	0.0128	0.8642	0.7704	0.9694
	Constant	-5.2084	1.8799	0.0056	0.0055		

Simplify and convert coefficients to the New index formula = 0.15* BMI – 0.1 AGE

AUC result Variable(s)	Area	Std. Error(a)	p-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
predict_lumba	0.775	0.040	0.000	0.696	0.855
correct_osta	0.796	0.039	0.000	0.719	0.872



Test Result Variable(s) at lumbar spines

predict_lumba			correct_osta		
Positive if Greater Than or Equal To(a)	Sensitivity	specification	Positive if Greater Than or Equal To(a)	Sensitivity	specification
1.51	0.97	0.26	-1.81	0.97	0.21
1.64	0.93	0.32	-0.28	0.90	0.44
1.86	0.90	0.40	0.12	0.87	0.53
2.38	0.80	0.61	1.01	0.80	0.66
2.45	0.77	0.63	1.15	0.77	0.66
2.59	0.77	0.67	1.47	0.70	0.71
2.66	0.73	0.71	2.28	0.67	0.80
2.70	0.70	0.73	2.57	0.60	0.82

The flow for searching the sensitivity and specificity of the new index was demonstrated in figure 7. First, the logistic regression model was constructed as the osteoporotic case was a dependent variable, then the regression coefficients for BMI and age variables were converted to the formula as the new index. Then the receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was inspected to evaluate the most optimal cut-off value. At lumbar spines, the cut-off point at 2.59 was selected with the sensitivity, specificity were 77% and 67% repectively , Moreover , The ROC curve was calculated for OSTA index, to compare with the new index. The recommended cut-off point at -1 was selected to get the sensitivity, specificity .

The results of coordinates of the ROC Curves and the cut- off point at 1.3 , 2.2 and 2.1 were selected for optimal diagnostic performances of the new index at femoral neck , intertrochanter and one of three sites respectively (Figure 8) .

Figure 8. The results of coordinates of the ROC Curves and the selected cut- off point for optimal diagnostic performances of the new index at femoral neck , intertrochanter and one of three sites

Coordinates of the ROC at femoral neck

Test Result Variable(s)

predict_FN			correct_osta		
Positive if Greater Than or Equal To(a)	Sensitivity	specification	Positive if Greater Than or Equal To(a)	Sensitivity	specification
0.739	0.920	0.351	-0.01	0.85	0.57
0.817	0.907	0.398	0.44	0.80	0.64
1.100	0.853	0.512	0.77	0.72	0.67
1.333	0.767	0.612	0.93	0.71	0.69
1.398	0.707	0.635	1.02	0.70	0.70
1.607	0.640	0.729	1.28	0.65	0.73
1.693	0.613	0.766	1.59	0.61	0.77

Coordinates of the ROC at intertrochanter

Test Result Variable(s)

predict_inter			correct_osta		
Positive if Greater Than or Equal To(a)	Sensitivity	specification	Positive if Greater Than or Equal To(a)	Sensitivity	specification
1.665	0.912	0.388	-0.730	0.912	0.401
1.999	0.860	0.549	-0.280	0.860	0.467
2.073	0.807	0.574	-0.090	0.807	0.524
2.210	0.772	0.615	0.150	0.754	0.555
2.305	0.667	0.653	1.030	0.702	0.678
2.428	0.649	0.697	1.330	0.667	0.719
2.473	0.614	0.732	1.620	0.614	0.757

Coordinates of the ROC of one of three sites

Test Result Variable(s)

predict_osc			correct_osta		
Positive if Greater Than or Equal To(a)	Sensitivity	specification	Positive if Greater Than or Equal To(a)	Sensitivity	specification
1.916	0.822	0.560	-0.030	0.802	0.586
2.081	0.752	0.634	0.440	0.752	0.663
2.187	0.703	0.674	0.730	0.703	0.700
2.303	0.653	0.707	1.190	0.663	0.720
2.437	0.604	0.766	1.390	0.604	0.777

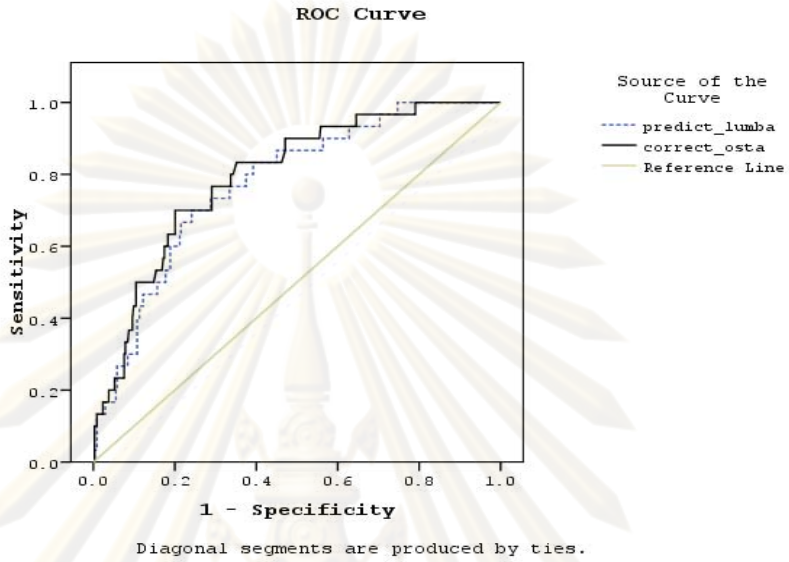
Table 5. Diagnostic performances of OSTA index and the new index for identifying osteoporosis in Thai menopausal women

	Lumbar spine	Femoral neck	Intertrochanter	At least one of osteoporotic sites
-OSTA at -1				
Sensitivity	80.00	70.67	70.17	66.33
Specificity	65.70	70.24	67.83	72.53
PPV	16.90	37.72	28.16	47.18
NPV	97.41	90.51	92.67	85.34
-OSTA at 0				
Sensitivity	90.00	85.33	78.95	79.20
Specificity	52.62	57.86	54.26	59.71
PPV	14.21	33.68	23.68	42.10
NPV	98.36	94.02	93.47	88.58
AUC	0.79(0.72-0.87)*	0.78(0.73-0.84)*	0.76(0.68-0.83)*	0.77(0.72-0.82)*
-New index				
Sensitivity	76.67	76.00	77.19	75.25
Specificity	66.57	61.20	61.52	63.37
PPV	16.67	32.94	26.50	43.18
NPV	97.03	91.04	93.75	87.37
AUC	0.78(0.69-0.85)*	0.76 (0.69-0.81)*	0.76(0.69-0.83)*	0.75(0.70-0.81)*

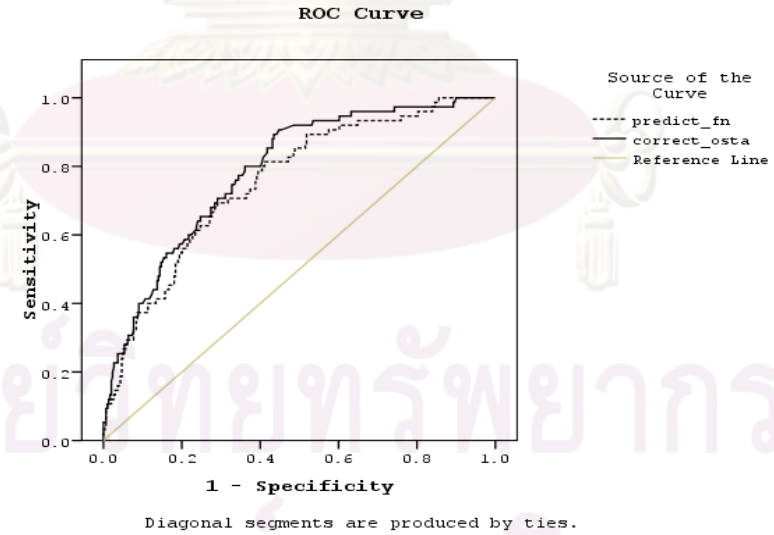
PPV; Positive predictive value , NPV ; Negative predictive value, AUC ; Area under curve

*(95% confidence interval)

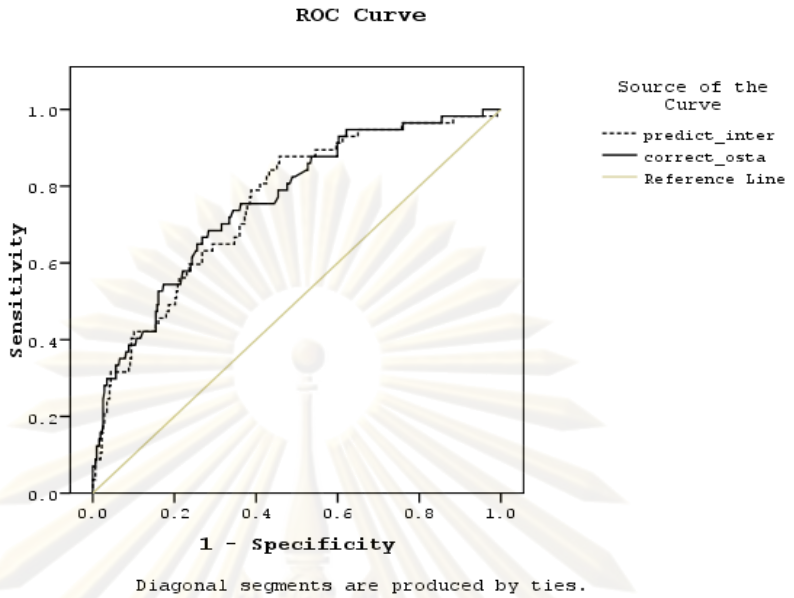
Figure 9 . Comparison of ROC curves between the OSTA index and the new index for identifying women who having osteoporosis



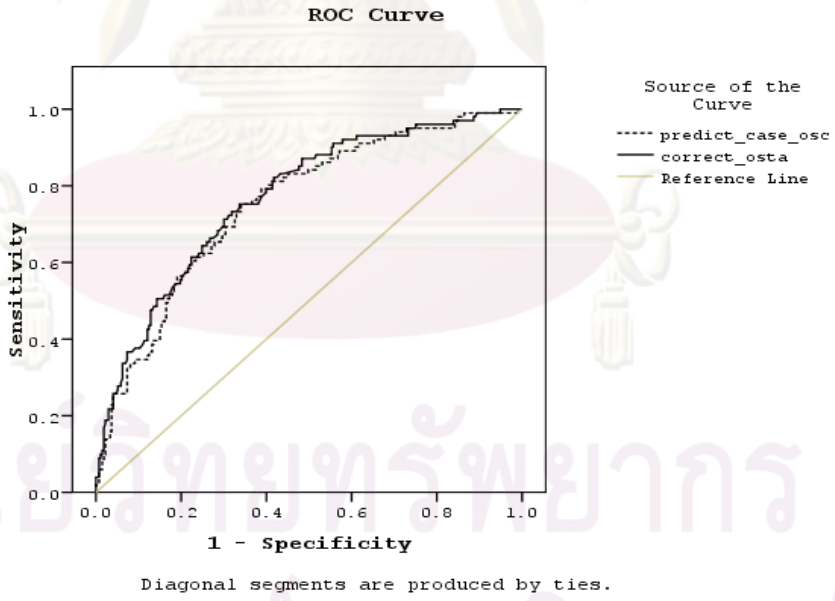
Lumbar spines



Femoral neck



Intertrochanter



At least one of 3 sites

Comparison of ROC curves between the OSTA index and the new index for identifying women who having osteoporosis was demonstrated in Figure 1 . AUC with 95% of confidence interval of all three osteoporotic sites, including osteoporosis at least one site were not different. In table 4, the diagnostic performances of OSTA index and the new index for identifying osteoporosis in Thai menopausal women were compared. The OSTA index , cut-off point at -1 , had a higher sensitivity (80 % vs. 76.67%) and specificity (65.70% vs. 66.57%) with AUC of 0.79 when compared with new index in detecting women with osteoporosis at lumbar spines . However, it had a lower sensitivity (70.67 % vs. 76% ,70.17% vs. 77.19%) in detecting women with osteoporosis at femoral neck and intertrochanter, respectively . With raising the cut-off point at 0, the OSTA index had a higher sensitivity at (90% vs. 76.67% , 85.33% vs. 76% and 78.95% vs. 77.19% at lumbar spines, femoral neck and intertrochanter, respectively compared with the new index .

CHAPTER V

SUMMARY, DISCUSSION, AND RECOMMENDATIONS

5.1 Summary of the study

The purpose of this study was to compare the combination of BMI and age as a new index with the OSTA index for identifying osteoporosis in Thai postmenopausal women. The diagnostic performances (e.g. sensitivity and specificity) and ROC with area under the curve of both index were determined .

Three hundred and seventy two Thai postmenopausal women with mean age was 59.99 years who had BMD records at outpatient clinic were recruited . Three skeletal sites ; lumbar spines , femoral neck and intertrochanter were measured .

Compared with the non-osteoporosis group, women with at least one of three osteoporotic sites had significantly higher mean age, lower mean bodyweight and lower mean height .They also had a significantly lower body mass index .

The prevalence of osteoporosis at lumbar spines , femoral neck and of femur were 8.1 %, 20.2 % and 15.3 % , respectively when using the Thai BMD reference values. However , when using T-score as the reference points, the prevalence of women who had osteoporosis were different ; 12.9%, 12.6%, 4.6 % at, respectively. The pattern of these discrepancies were also the same for the prevalence of osteopenia or normal bone mass.

The new index ; combination of BMI and age was calculated by coefficient of logistic regression model . For each measured site , ROC curve was created and the cut-off point was selected base on the most optimal diagnostic performances ,sensitivity and specificity . Also, ROC curves of OSTA index for each measured site were created and compared . Finally , AUC with 95% of confidence interval of all three osteoporotic sites , including osteoporosis at least one site were compared and the results were demonstrated.

5.2 Discussion

Although the treatment of osteoporosis is effective , screening for osteoporosis is essential because this silent disease is common and associated with high morbidity and mortality. Also , the healthcare cost of these burdens is great amount . Bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) is the most widely recognized as the standard predictor for fracture occurrence [1]. however examination DXA for in all postmenopausal women is not cost-effective. Because this instrument is not widely available in most developing countries including Thailand . Moreover, it was estimated that there have been only 50 DXA absorptiometer machines all over Thailand and most of them are limited to university or tertiary level hospitals [24].

It is very reasonable to use the clinical risk indices for identifying women with low BMD or high risk fracture individuals before sending them to test their BMD. OSTA index was formulated to predict BMD by using only age and bodyweight. Indeed, the two factors collectively account for 40 to 60 percent variance of BMD in the population[25-27]. In the present study, an another important clinical risk , BMI , was added into OSTA index to have the better diagnostic performances as the new index. Our findings revealed that using of the combination of age and BMI as the index for identifying osteoporosis in Thai postmenopausal women had high diagnostic performances as well as OSTA index . The original OSTA index , cut-off point at -1 , had a sensitivity of 91 % and specificity of 45% with AUC of 0.79 in detecting women with osteoporosis at femoral neck . The new index, compared to OSTA index , had higher sensitivity at femoral neck (76% vs. 70.67 %), intertrochanter (77.19% vs. 70.17%) but had lower sensitivity for lumbar spines (76.67 vs. 80%). Based on at least one of three osteoporotic sites, the new index has also higher sensitivity (75.25 vs. 66.33%). Therefore, this new index could be have a role in early detection and prevention of hip fracture more than vertebral fractures. Also, the new index could be useful to screen osteoporosis when there are suspected of any osteoporotic sites.

Despite the sensitivity of the new index is the most diagnostic performance that we have concerned, the positive predictive value (PPV) is another important indicator of

this new index. PPV would be much higher, particularly in the advanced age group such as 60- 80 years because of the high prevalence of osteoporosis of this age group. This is needed to explore and analyze in more details.

Raising the cut-off point to $\leq$ 0, OSTA index had a very high sensitivity and much more better diagnostic performances in all three osteoporotic sites ; 90%, 85.33% and 78.95% at lumbar spines , femoral neck and intertrochanter , respectively . These could increase negative predictive value and also reduce the high false negative rate in prediction of osteoporosis. Similar to Geater et al study [4] that the authors suggested the cut-off point of $\leq$ 0 for the lumbar spines may be more appropriate . It could be explained that the baseline characteristic of population and the prevalence of disease were different. Most of participants in the OSTA original report were Chinese whose baseline BMD were lower than our sample Thai population . The present study use Thai BMD reference values from Limpaphayom et al study [13] to diagnose osteoporosis, not T- score as the other studies because the most reference values in available DXA machines are Japanese or United states based data. Currently, the normogram of BMD has not been standardized and applied to general practice.

This study has several limitations. Firstly, the other clinical risks such as previous fragility fracture , current smoking , alcoholism , history of recurrent falls should also included and analyzed. These should have more accuracy to represent the BMD. Secondly , the precision and reliability of height measurement are the issues to concern , particularly in older postmenopausal women . Because the loss of height is well-known consequence of aging and development of spinal osteoporosis. Thirdly, the accuracy error of DXA in BMD measurement have ranged from 2-4 % .The precision depends on both machine, patient and operator –dependent factors. However, for well maintenance system, the machine error is small and long term precision is typical less than 1%. Lastly, this study is retrospective data collection, participants' data might be incomplete and have the information bias.

5.3 Conclusions

In conclusion this new index, compared to the OSTA at recommended cut-off point -1, is superior in ability of predictive osteoporotic sites at femoral neck and

intertrochanter but it is inferior at lumbar spines. Therefore, the application of the combination of BMI and age as a screening tool might be an another option to early detection and prevention of hip fracture in Thai postmenopausal women. Also, our data analysis strongly supported that changing the cut-off point of ≤ 0 , OSTA index could improve the detection of osteoporosis at very high level of the sensitivity .

5.4 Implications

Base on previous studies, BMI was demonstrated that it is the one of most important clinical risk factors that contribute to BMD . However, our analytic diagnostic model demonstrated that BMI combination with age was not superior to OSTA index for screening osteoporosis in Thai postmenopausal women particularly at lumbar spines . At hip; femoral neck and intertrochanter, the new combination index was higher sensitivity. This new index might be the screening tool for these skeletal areas but there is a necessary to simplify the formula for easiness of implication. In our study , OSTA index has high diagnostic performance but the cut –off point should be adjusted and tailored to each measured sites.

5.5 Suggestions for further studies

- Since there are no standardized normograms of the BMD for the Thai population, normograms is currently used as provided by the manufacturer of the DEXA scanner. Therefore, development of normograms of Thai BMD is urgent and it is needed to be established. This could be done as multicenter study to represent Thai baseline as much as possible.

- Bone mineral density (BMD) measurement by dual energy X-rays absorptiometry (DXA) is accepted as the gold standard predictor of osteoporosis fractures, however it is only a surrogate measurement of osteoporosis. The investigation for the most accuracy of diagnostic test is warranted.

- OSTA index is needed to validated to Thai population and the most optimal cut-off point of OSTA index for each skeletal site should be carefully determined.

- The other clinical risk factors such as previous fragility fracture, current smoking , alcoholism , risk of falls should be included and analyzed in the predictive model of osteoporosis. This could be a highly satisfactory screening index and represent more accuracy of BMD .

- The number and proportion of women with osteopenia are contribute at least one –third of all postmenopausal women . This group of patients, the precursor to osteoporosis should be more investigated and explored to have an appropriate diagnostic strategy.

- The study of cost – benefit analysis for this strategy is needed to be investigated . The final outcome or clinical endpoint, if possible should be osteoporotic fracture.

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APPENDICES

APPENDIX A

Case record form

Case number □□□

Date of measurement □□ / □□/ 25□□ HN. □□/ □□□□□

Part 1. Baseline characteristic information

Age □□ year Weight □□□.□ kg

Height □□□ cm. Parity □□

Age of menopause □□ year

Part 2 . BMD & T -score outcomes

		BMD (g/cm^2)	T-score
Lumbar spines	L1		
	L2		
	L3		
	L4		
	total		
Femoral neck			
Trochanteric			
Intertrochanter			
total			

Name of Recorder……..

Date of Recording ……□□ / □□/ 25□□

APPENDIX B

หนังสือรับรองอนุมัติของคณะอนุกรรมการการวิจัยในคน

คณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 คณะแพทยศาสตร์

.....

รหัสโครงการ MTU-P-2-56/52

ชื่อโครงการวิจัย การใช้ดัชนีมวลกายร่วมกับอายุเป็นดัชนีชนิดใหม่ในการตรวจคัดกรองหาภาวะกระดูกพรุนในสตรีไทยวัยหมดระดู

ชื่อผู้วิจัยหลัก ผู้ช่วยศาสตราจารย์ นายแพทย์ชำนาญ แท่นประเสริฐกุล

หน่วยงานที่รับผิดชอบ โครงการจัดตั้งภาควิชาสูติศาสตร์-นรีเวชวิทยา
คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์
โทรศัพท์ 02-926-9343 , 089-699-9240

เอกสารที่รับรอง

1. โครงการวิจัยฉบับลงวันที่ 31 สิงหาคม 2552

คณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 คณะแพทยศาสตร์ ได้พิจารณาอนุมัติด้านจริยธรรมการทำวิจัยในคนให้ดำเนินการวิจัยข้างต้นได้ ตามมติการพิจารณาโครงการวิจัยแบบ Expedited Review

ลงชื่อ ..... ลงชื่อ .....

(รองศาสตราจารย์ นายแพทย์ จักรชัย จิงธีรพานิช)
ประธานอนุกรรมการ

(ผู้ช่วยศาสตราจารย์ นายแพทย์ สุธน พรธีสาร)
อนุกรรมการและเลขานุการ

อนุมัติ ณ วันที่ 29 ตุลาคม 2552

VITAE

NAME : CHAMNAN TANPRASERTKUL, MD.

BIRTHDATE : October 17th, 1971

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CONTACT : Department of Obstetrics and Gynecology, Thammasat university,
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ACADEMIC ACHIEVEMENT :

1994	Doctor of medicine	Faculty of Medicine, Chulalongkorn University
2000	Certificate in Ob-Gyn Board	Faculty of Medicine, Chulalongkorn University
2002	Certificate in Family Medicine Board	Thai Royal College of Family Medicine
2004	Fellowship in Reproductive medicine	Baylor College of Medicine , Houston , Texas ,USA

RESEARCHES AND ARTICLES:

1. Use of Norplant implants in the immediate postpartum period among asymptomatic HIV-1-positive mothers. Taneepanichskul S, Tanprasertkul C. Contraception 2001 ;64:39-41.

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