Levels of Biochemical Bone Marker Procollagen Type I N-Propeptide (PINP) in Thai Women Aged 40-70 Years

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Objective: *To determine reference ranges for serum Procollagen type I N-propeptide (PINP), one of the bone formation markers, in Thai women aged 40-70 years old.*
Material and Method: *PINP was measured in fasting serum of 300 healthy Thai women who had never been diagnosed as osteoporosis. They were divided into 3 groups by age, 100 per each; the first were menstruating women aged 40-50 years, the second were 51-60 years old menopausal women, and the third were 61-70 year old postmenopausal women.*
Results: *The mean values of PINP with 95% confident interval in groups 1,2,3 were 42.67 (38.74, 46.59), 61.63 (55.94, 67.31) and 60.66 (55.35, 65.96) ng/ml respectively.*
Conclusion: *The present study showed PINP levels in Thai women in different age and menstrual status. The mean PINP in the postmenopausal group was higher than the premenopausal group, which confirmed postmenopausal women have more bone turnover rate.*

Keywords: *Procollagen type I N-propeptide, PINP, Menopause, Osteoporosis*

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Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue. It leads to bone fragility and increased susceptibility to fracture[1]. Fracture is followed by illness and disability, sometimes death, and uses up a huge medical expense[2]. This condition occurs in the aged population, of which the number is increasing; therefore, prevention and effective treatment are very important. Presently, since most treatment regimens for osteoporosis are expensive, the technique to evaluate an efficacy of such treatments is indicated. After initiating the treatment, however, it usually takes at least 1 to 2 years before bone mineral density (BMD) improvement can be detected. Repeated dual x-ray absorptiometry (DXA), which is currently counted as gold standard, has its limitation to monitor therapy efficacy because it does not identify all responders within the first year regardless of any types of treatment[3]. Therefore, a more effective and cheaper method with a rapid result is required. Recently, there have been many studies showing that the biochemical markers of bone turnover, both bone formation and bone resorption marker, are more sensitive for detecting abnormalities of bone turnover rate including osteoporosis[4-6]. The bone markers can be used to monitor the efficacy of treatment of osteoporosis and can identify effect of treatment within shorter period; between 3 and 6 months. However, the variability of bone turnover markers levels could occur as the result of uncontrollable factors such as age, gender, menopausal status, disease or recent fracture, or controllable factors such as circadian, menstrual or exercise effects[3]. Due to this variability, the interpretation of bone markers levels should be made carefully by using an appropriate reference range. Procollagen type I N propeptide (PINP) is a marker of early bone formation, generally appearing during osteoblast proliferation, and produced during the formation of type I collagen. Serum total Procollagen type I N propeptide (PINP) is most sensitive for follow-up after hormonal treatment[7] in menopausal women. At

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present, there is no data of the level of serum PINP in Thai elderly women, who commonly have osteoporosis and use hormonal therapy. Therefore, the present study was conducted to evaluate levels of serum PINP of Thai women in three separate reference ranges defined by age and menopausal status by cross-sectional study design.

Material and Method

Study population

The Thai healthy women aged between 40-70 years who live in Bangkok and Ratchaburi province were enrolled. To be selected, the women had to have no underlying disease related to hepatic disorder, chronic renal failure, diabetic mellitus, abnormality of bone metabolism, be free from cancer and have no history of fracture during the previous six months prior to the present study. Those who had received anti-resorptive treatments hormone replacement, selective estrogen receptor modulators and bisphosphonates, drugs that could affect bone turnover markers such as corticosteroid, anticonvulsant therapy and GnRH agonist were excluded. They were categorized by age and menstrual status into 3 groups; with one hundred persons each. The first group consisted of women between 40 and 50 years old who still had menstruation. The second and the third groups were composed of postmenopausal women aged 51-60 years and 61-70 years, respectively. All participants would be asked to give written informed consent before the recruitment. The present study protocol was approved by the ethics committee of Phramongkutklao Hospital.

Measurement of biochemical bone markers

The fasting for 8 hours; seven milliliters of fasting blood was collected between 8.00-10.00 am and measured for serum total Procollagen type I N propeptide (PINP). The PINP was measured by the electrochemiluminescence immunoassay (ECLIA) method following the direction of Elecsys PINP immunoassay (Roche Diagnostics, Switzerland). Both trimeric and monomeric structures of PINP, the substances secreted when type 1 collagen formation process occurred, were measured. The subjects were screened for liver enzymes, renal profile and fasting blood sugar to exclude any underlying diseases. If the screening test was abnormal, the subject would be excluded.

Statistic analysis

The data were evaluated using SPSS software version 12.0. Descriptive statistics was applied to describe the results of normal value with 95% confidence interval.

Results

The data was collected between April 2007 and August 2007. At first, there were 326 women included in the study after the blood test was done, 26 women were excluded due to 8 abnormal fasting blood glucose, 11 abnormal liver function test and 7 abnormal renal function. Finally, three hundred healthy women who lived in Bangkok and Ratchaburi were included in the present study, 100 for each group. In first group, premenopause women age between 40-50 years old. The mean age was 46.07 years old. The menopausal women aged 51-60 years were in the second group with mean age 54.92 years old. The last group was composed of 100 postmenopausal women aged 61-70 years with mean age 64.99 years old (Table 1).

The mean value of PINP of healthy premenopausal women in group 1 was 42.67 ng/ml (95% confidence interval = 38.74 to 46.59) (Fig. 1). The mean value of PINP of menopause women in group 2 and 3 were 61.63 ng/ml (95% confidence interval = 55.95 to 67.32) (Fig. 2) and 60.66 ng/ml (95% confidence interval = 55.35 to 65.97) (Fig. 3), respectively.

Discussion

Because DXA, the gold standard for evaluation efficacy of osteoporosis treatment, has limitation in follow up treatment, the measuring of bone turnover markers has increased a role due to the lower cost and

Table 1. Mean ages of subjects in each group

Group	Age	Status	Mean age	Mean total PINP
1	40-50 years	Premenopause	46.07 years	42.67 ng/ml
2	51-60 years	Menopause	54.92 years	61.63 ng/ml
3	61-70 years	Menopause	64.99 years	60.66 ng/ml

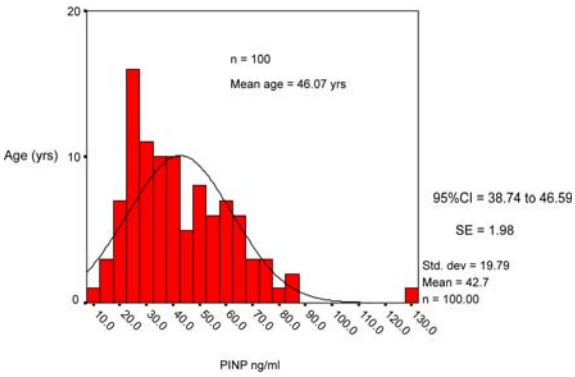

Fig. 1 Distribution of PINP of menstrual women aged 40-50 yrs

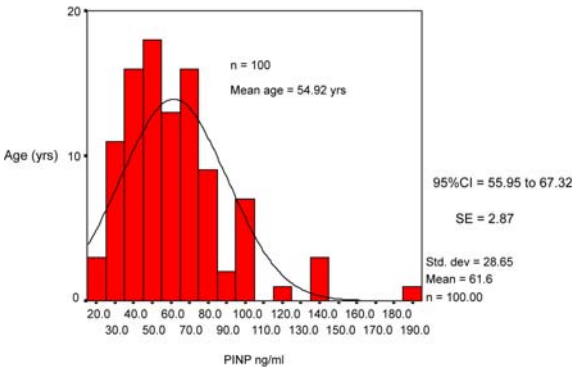

Fig. 2 Distribution of PINP of postmenopausal women aged 51-60 yrs

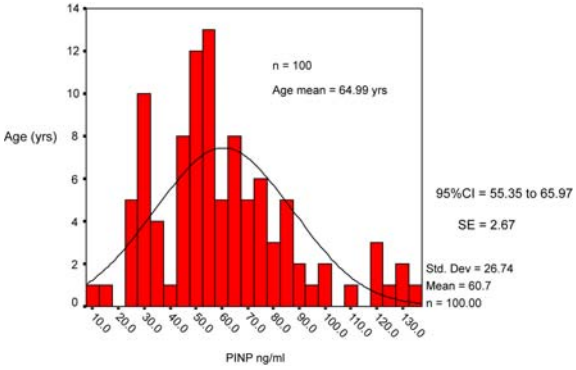

Fig. 3 Distribution of PINP of postmenopausal women aged 61-70 yrs

has the capability to detect bone change in shorter time after initiating treatment. From the previous study show that there is negative correlation between bone turnover marker, both bone formation and bone resorption marker, and rate of bone loss[8]. Among many bone formation markers presently used, serum total PINP is found to be the most sensitive marker for follow-up after hormonal treatment[7]. Serum total PINP is an appropriate test for monitoring treatment of osteoporosis with bone formation agent, including the new medication, parathyroid hormone (Teriparatide) and Strontium Ranelate. Since the level of total PINP could be affected by various factors, this bone formation marker should be used carefully by comparing its value to an appropriate reference range. The present study demonstrated values of total PINP in Thai women in three age groups: 40-50, 51-60 and 61-70 years old with different menopausal status.

In the premenopausal group, the mean value of this bone marker was similar to the previous study[9], which studied in Thai premenopausal women with average age 38.5 years old.

In postmenopausal women, the result of the present study shows the mean value of serum total PINP in the age group 51-60 years is higher than 61-70 years maybe because the women in early menopausal period had higher rate of bone loss than the later group[8,10] but non significance ($p > 0.05$). It maybe from effect of period after menopause that was not mentioned in the present study. In the present study, the level of serum total PINP in the menopausal group is higher than premenopausal group, it confirms that menopausal women had higher rate of bone turnover.

However, there are the limitations of the present study. Firstly, the demographic data was not recorded which can affect to the level of serum PINP, for example occupation and life style of subjects that effect to risk of osteoporosis and the duration after menopause to the time gotten blood test. Secondly, the small sample size may cause no statistical significance of PINP level between postmenopausal groups. Moreover, the other bone marker to confirm subjects' bone turnover rate or resorption wasn't measured due to limited budget so the authors could not correlate it with level of serum PINP. Lastly, the measurement of bone mineral density was not performed for confirmation of bone status. Further studies with controlled other risk factor of osteoporosis are needed. Currently, the usefulness of measuring bone turnover marker, include serum total PINP, is the assessment of the therapeutic effects, informing

patients of these changes may improve their compliance and reduce the number who drop out of therapy[11]. The bone formation markers can be used when using with the bone formation agents. On the other hand, the bone resorption markers can be used when using the bone resorption agents. The range of serum total PINP from the present study can reflect bone turnover rate of Thai premenopausal and postmenopausal women and may help to identify the patients with high level of bone turnover markers, but the data about correlation of this bone formation marker and bone mineral density is unknown.

Acknowledgments

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ระดับตัวชี้วัดทางชีวเคมีของกระดูก โปร์คอลลาเย็น ไทป หนึ่ง เอ็น โปร์เปปไทด์ ของสตรีไทยอายุระหว่าง 40-70 ปี

ปองรัก บุญญานุรักษ์, กิตติศักดิ์ วิลาวรรณ

***วัตถุประสงค์**: เพื่อตรวจหาระดับอ้างอิงของโปร์คอลลาเย็น ไทป หนึ่ง เอ็น โปร์เปปไทด์ หรือ พีวันเอ็นพี ซึ่งเป็นตัวชี้วัดการสร้างของกระดูกตัวหนึ่งของสตรีไทยอายุระหว่าง 40-70 ปี*

***วัสดุและวิธีการ**: สตรีไทยสุขภาพดีที่ไม่เคยได้รับการวินิจฉัยภาวะกระดูกพรุนมาก่อนจำนวน 300 คนจะได้รับการตรวจวัดระดับพีวันเอ็นพีในซีรัมขณะอยู่ในภาวะอดอาหาร โดยอาสาสมัครจะถูกแบ่งตามอายุเป็น 3 กลุ่ม กลุ่มละ 100 คน กลุ่มแรกประกอบด้วยสตรีวัยก่อนหมดประจำเดือนที่มีอายุระหว่าง 40-50 ปี กลุ่มที่สองประกอบด้วยสตรีวัยหมดประจำเดือนที่มีอายุ 51-60 ปีและกลุ่มที่สามประกอบด้วยสตรีวัยหมดประจำเดือนที่มีอายุ 61-70 ปี*

***ผลการศึกษา**: ค่าเฉลี่ยของระดับพีวันเอ็นพีในกลุ่มที่หนึ่งมีค่าเท่ากับ 42.7 นาโนกรัมต่อมิลลิลิตร ที่ระดับความเชื่อมั่นที่ 95 เปอร์เซ็นต์มีค่าเท่ากับ 38.74 ถึง 46.59 นาโนกรัมต่อมิลลิลิตร กลุ่มที่สองมีค่าเฉลี่ยเท่ากับ 61.6 นาโนกรัมต่อมิลลิลิตร ที่ระดับความเชื่อมั่นที่ 95 เปอร์เซ็นต์มีค่าเท่ากับ 55.95 ถึง 67.32 นาโนกรัมต่อมิลลิลิตร และกลุ่มที่สามมีค่าเฉลี่ยเท่ากับ 60.7 นาโนกรัมต่อมิลลิลิตร ที่ระดับความเชื่อมั่นที่ 95 เปอร์เซ็นต์มีค่าเท่ากับ 53.35 ถึง 65.97 นาโนกรัมต่อมิลลิลิตร*

***สรุป**: การศึกษานี้แสดงให้เห็นถึงระดับพีวันเอ็นพีของสตรีไทยในกลุ่มอายุและภาวะการมีประจำเดือนแตกต่างกัน ระดับพีวันเอ็นพีเฉลี่ยของสตรีวัยหมดประจำเดือนมีค่าสูงกว่าของสตรีวัยก่อนหมดประจำเดือน ซึ่งเป็นการยืนยันว่าสตรีวัยหมดประจำเดือนมีอัตราการเปลี่ยนแปลงของกระดูกมากกว่า*