Bone Mineral Density and Body Composition in Thai Precocious Puberty Girls Treated with GnRH Agonist

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Treatment of true Precocious Puberty (PP) with GnRH agonist can improve final adult height by suppressing gonadotropin and sex hormone levels that delays the fusion of long bone epiphyseal growth plates. However, deprivation of estrogen may affect the acquisition of peak bone mass, especially in individuals with low calcium intake. Ten Thai girls with idiopathic true PP were evaluated for Bone Mineral Density (BMD) and body composition by DXA scanner (Hologic, Inc) before and after GnRH agonist therapy for 1 year. During treatment, all children were allowed to consume a normal diet without extra calcium supplementation. In addition, serum calcium, phosphate, alkaline phosphatase and osteocalcin were also measured. The results showed that GnRH agonist could improve predicted adult height from 149.4 5.4 to 153.6 6.8 cm ($p < 0.001$). Serum osteocalcin, representing the bone marker formation, decreased from 184.2 66.7 to 108.6 35.3 ng/mL ($p = 0.012$) However, the treatment had no negative effects on BMD lumbar spine and total BMD but increased percentage of fat mass from 25.7 5.2 to 31.6 5.5%. ($p = 0.007$). In conclusion, treatment with GnRH agonist in Thai girls with true PP for 1 year can improve PAH without negative effects on BMD but a longer period of treatment needs to be studied.

Keywords: *True precocious puberty, GnRH agonist, Bone mineral density, Body composition*

J Med Assoc Thai 2006; 89 (8): 1194-8
Full text. e-Journal: *http://www.medassocthai.org/journal*

Puberty is a crucial period to achieve the adequate peak bone mass. Precocious Puberty (PP) treatment with GnRH agonist inhibits the hypothalamo-pituiatry-gonadal hormone secretion and eventually deprives estrogen. This may affect the acquisition of peak bone mass. Nutritional intake is one factor influencing bone mass. People from Western countries consume a diet containing high calcium such as milk and cheese. Nevertheless, the reports on the impact of GnRH agonist on BMD from these countries showed various results. Such reports from Asian countries whose people consume less calcium are so limited. Therefore, the aim of this study was to evaluate the Bone Mineral Density (BMD), body composition and bone marker in Thai PP girls treated with GnRH agonist.

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Material and Method

Ten Thai girls, who had been diagnosed as having idiopathic true PP and treated with GnRH agonist for 1 year, were enrolled in the present study. Treatment with GnRH agonist 3.75 mg intramascular was given to all PP girls every 4 weeks for a period of 1 year. During the period of treatment, all patients were advised to consume their usual diet without extra calcium or vitamin tablets. Auxological data including height and weight and pubertal staging were recorded before and after the treatment. BMD of Lumbar Spine (LS), Total Body (TB) and body composition was measured by dual energy x-ray absorptiometry (DEXA), Hologic, Inc. Blood samples were obtained for the assessment of Calcium (Ca), Phosphate (P), alkaline phosphatase and osteocalcin as bone marker formation before and after the treatment. Serum FSH, LH, estradiol levels were measured at 0, 6, 12 months to

monitor adequate gonadotrophin suppression. Bone age was assessed by the Greulich and Pyle method and subsequently, the Predicted Adult Height (PAH) was calculated by the method of Bayley&Pinneau. Mean, standard deviation and paired T test were used to describe and compare the data before and after treatment and the significance level was set at $p \leq 0.05$. The present study was approved by the Ethic Committee of Faculty of Medicine, Chulalongkorn University.

Results

Ten girls with idiopathic true PP, who had a mean Chronological Age (CA) of 8.5 ± 0.2 years, had had history of breast development before 8 years of age with increased height velocity. Three of them (30%) had already had menstruation before seeking medical treatment. A mean for breast Tanner stage was 3.2 ± 0.4 and pubic hair Tanner stage was 1.1 ± 0.3. All of them had Bone Age (BA) advancement that made a BA/CA ratio of 1.3 ± 0.08. The PAH, before treatment, was 149.4 ± 5.4 cm. During treatment with GnRH agonist 3.75 mg intramuscular monthly, no girls developed any complications related to the treatment except for some vaginal bleeding, a normal flare-up phase of therapy.

Bone age and PAH

GnRH agonist could slow down the bone age advancement by decreasing the BA/CA ratio from 1.3 ± 0.08 to 1.18 ± 0.09 (p 0.005). Therefore, PAH was improved from 149.4 ± 5.4 to 153.6 ± 6.8 cm (p 0.007).

Serum LH, FSH, estradiol

Serum level of LH, FSH and estradiol at 0, 6, 12 months during treatment is shown in Fig. 1 and 2. GnRH agonist could suppress LH by 6 months with marginal significance. However, serum FSH and estradiol levels were significantly suppressed by 6 and 12 months.

Biochemistry, bone markers, BMD and body composition (Table 1)

Serum Ca, P and AP were not significantly changed during treatment. However, serum osteocalcin representing bone marker formation was significantly decreased. After treatment, BMD lumbar spine and total BMD were not decreased. In contrast, percentage of fat increased significantly from 25.7 ± 5.2 to 31.7 ± 5.5 (p 0.007).

Discussion

A decrease in BMD during GnRH agonist therapy has been observed in women with endometriosis and in men with benign prostatic hyperplasia[1]. In children with true precocious puberty, BMD was reported to be increased for chronological age but normal for bone age[2-4] There are many factors affecting mineralization of the skeletal and BMD such as ethnic, nutrition, physical activity, sex hormone, growth hormone and IGF-I. Defect of bone mineralization has been observed in patients with estrogen receptor defect, untreated constitutional delayed growth and puberty, menopausal women, GH deficient patients[5-7]. Treatment with GnRH agonist in true PP girls can arrest the progression of secondary sexual characteristics and advancement of bone maturation and, eventually improve final adult height. However, this treatment can deprive the estrogen level similar to that in menopausal stage and may affect the acquisition of bone mass. The changes of BMD during GnRH agonist have been reported with various results. Antoniazzi F et al reported this unwanted effect could be prevented by giving Ca supplementation in conjunction with GnRH agonist therapy[8]. Ca intake in a normal growing girl may not result in maximal mineral retention during pubertal growth as reported by Abrams SA et al[9]. Therefore, Ca intake should be encouraged during this period. Dietary Ca intake in Asian countries may be lower than

Table 1. Biochemitry, BMD and percent fat mass before and after one year application of GnRH agonist

	Before treatment	1 year after treatment	
Serum calcium (mg/dL)	9.8 ± 0.4	9.8 ± 0.4	NS
Serum phosphate (mg/dL)	5.1 ± 0.4	4.8 ± 0.4	NS
Serum AP (U/L)	271.4 ± 61.4	221.3 ± 37.1	NS
Serum osteocalcin (ng/mL)	184.2 ± 66.7	108.6 ± 35.3	p = 0.012
BMD lumbar (gm/m^2)	0.6142 ± 0.1072	0.6422 ± 0.1057	p = 0.019
Total BMD (gm/m^2)	0.8062 ± 0.0694	0.8268 ± 0.0719	p = 0.013
% fat	25.7 ± 5.2	31.7 ± 5.5	p = 0.007

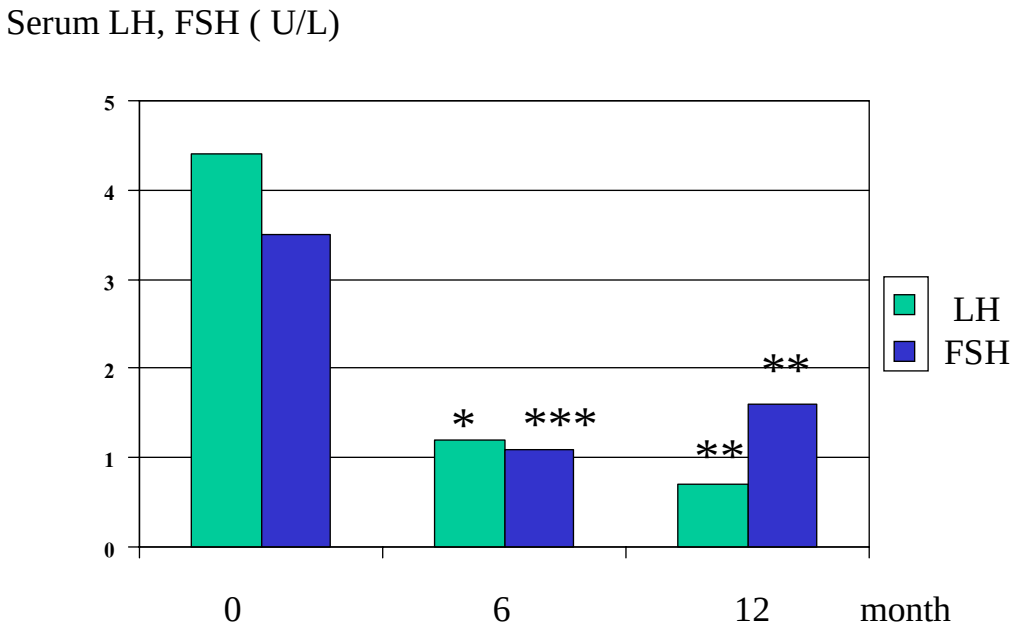

Fig. 1 Serum LH, FSH during GnRH agonist at 0,6,12 months
* p 0.05, ** p0.01, *** p 0.005 compared with baseline

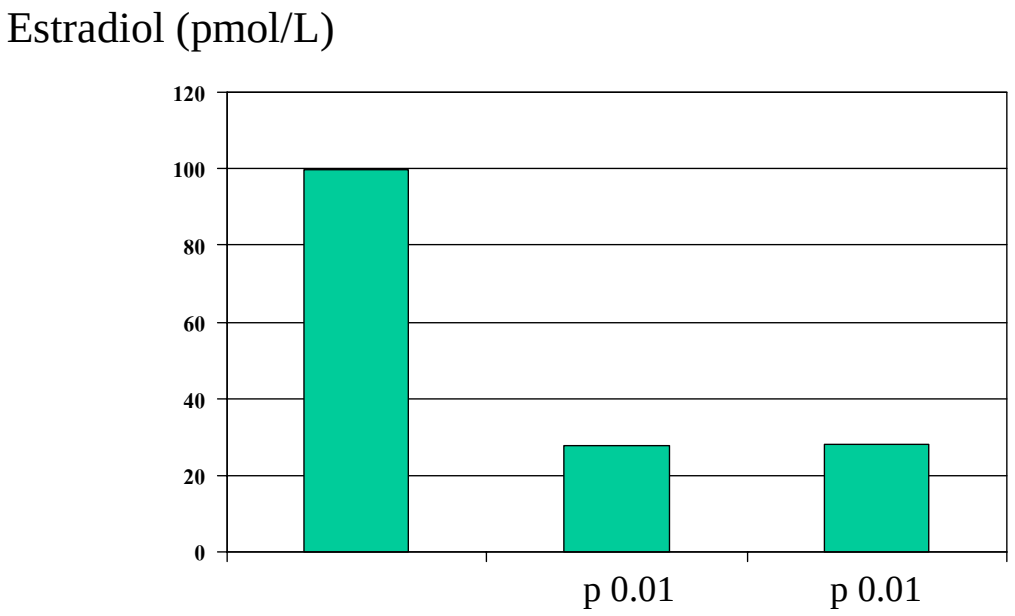

Fig. 2 Serum estradiol during GnRH agonist at 0, 6, 12 months

that in Western countries probably due to the different ingredients used for cooking and the habit of milk intake. The results from the present study showed that, even in Thai girls who normally consume a low Ca diet, treatment with GnRH agonist for 1 year could suppress estradiol level but had no negative effect on BMD with slightly positive effect on total BMD. This result was similar to other previous studies in Western countries

where the people consume a higher Ca diet than in Asian countries[4,10,11]. Therefore, extra Ca supplementation may not be necessary for children treated with GnRH agonist. However, long term follow up when these children reach their final height should be reevaluated. Heger S et al studied the long-term outcome in young women who had been treated with GnRH agonist for 4 years and reached their final heights and found no negative effects on BMD and reproductive function but improved height outcome[11].

One-year period of the present study may be too short to evaluate the changes in BMD although the estrogen levels had already been suppressed 6 months after treatment. In addition, there is no normal value of BMD for Thai children. Previous studies showed the disturbance of both bone formation and bone resorption with this therapy[4,10,12]. Serum osteocalcin representing bone formation was also suppressed one year after the treatment, similar to other studies[8,13]. However, the changes of bone marker were normalized two years after cessation of therapy. Obesity is commonly found with PP girls but not aggravated by GnRH agonist. Although the percentage of body fat increased during treatment, it returned to normal within one year after cessation of treatment[8]. From a prospective multicentric study looking at the long-term outcome after GnRH agonist, they found that there was no negative effect on BMD, BMI, body proportion and reproductive function at 5.7 years after stopping treatment[11]. While an increased percentage of body fat has been reported in this study as well as in previous studies, a long-term outcome should be observed.

In conclusion, treatment with GnRH agonist in Thai girls with PP can improve PAH but has no negative effect on BMD. However, treatment can decrease bone turnover and increase fat accumulation. Therefore, the present study demonstrated a beneficial effect of GnRH agonist for 1 year of therapy in Thai girl with PP but a longer period of treatment should be reevaluated.

Acknowledgement

This study was supported by Ratchadapisek Sompoch Fund, Faculty of Medicine, Chulalongkorn university.

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การศึกษาความหนาแน่นของมวลกระดูกและส่วนประกอบของร่างกายในเด็กผู้หญิงไทยที่เป็นสาวก่อนวัยอันควรและได้รับการรักษาด้วย GnRH agonist

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การรักษาเด็กที่เป็นสาวก่อนวัยอันควรชนิด true precocious puberty ด้วยยา GnRH agonist สามารถทำให้ความสูงสุดท้ายเมื่อเป็นผู้ใหญ่ดีขึ้น ยาดังกล่าวออกฤทธิ์โดยการยับยั้งการหลั่งฮอร์โมน gonadotropin และ estrogen มีผลทำให้การเชื่อมกันของ epiphyseal plate ช้าลง แต่การรักษาดังกล่าวอาจมีผลต่อความหนาแน่นของมวลกระดูกโดยเฉพาะในเด็กที่รับประทานแคลเซียมน้อย ผู้วิจัยได้ทำการศึกษาในเด็กผู้หญิงไทยที่เป็นสาวก่อนวัยอันควรและได้รับการรักษาด้วย GnRH agonist เป็นระยะเวลา 1 ปี ระหว่างที่ผู้ป่วยได้รับการรักษาด้วยวิธีดังกล่าวผู้ป่วยจะได้รับประทานอาหารปกติโดยไม่ได้ยาเม็ดแคลเซียมเสริม ผลจากการวิจัยพบว่า การรักษาด้วยวิธีดังกล่าวสามารถเพิ่มความสูงที่คาดว่าจะได้จาก 149.4 $\pm$ 5.4 เป็น 153.6 $\pm$ 6.8 เซนติเมตร ($p < 0.001$) ระดับ serum osteocalcin ซึ่งบอกถึงกระบวนการสร้างของกระดูกลดลงจาก 184.2 $\pm$ 66.7 เป็น108.6 $\pm$ 35.3 นาโนกรัมต่อ มิลลิลิตร ($p = 0.012$) การรักษาไม่ทำให้ความหนาแน่นของมวลกระดูกลดลงแต่พบว่า จำนวนไขมันสะสมเพิ่มขึ้นจากร้อยละ 25.7 $\pm$ 5.2 เป็น ร้อยละ 31.6 $\pm$ 5.5 . ($p =0.007$). กล่าวโดยสรุปพบว่า การรักษาดังกล่าวเป็นระยะเวลา 1 ปี สามารถเพิ่มความสูงแต่ไม่ทำให้ความหนาแน่นของมวลกระดูกลดลง อย่างไรก็ตามควรมีการติดตามในระยะยาวต่อไป