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Analysis of Bone Mineral Density and Polymorphism of Estrogen Receptor Gene in Patients with Precocious Puberty

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ESTROGEN plays an important role in bone maturation and bone mineralization during puberty [1]. We previously reported a dissociation between the degree of bone mineral density (BMD) gained and advanced bone age (BA) in girls with precocious puberty [2]. In the present study, we measured changes in BMD in precocious puberty during GnRH analog (GnRHa) therapy to assess the effect of estrogen on bone mineral status. And we also determined whether the estrogen receptor (ER) genotype is related to BMD gain during exposure to excess estrogen in patients.

Subjects and Methods

Patients

Eighteen girls with central precocious puberty aged 5–12 years (mean 8.97 ± 1.87 years) who had a history of breast development before the age of 8 were studied. One of the patients had been receiving treatment with GnRHa administered subcutaneously, three with GnRHa administered nasally, two with cyproterone acetate, and the remaining 12 patients were untreated. Nine cases (including 3 patients who had been receiving another treatment) started to receive GnRHa administration subcutaneously and 3 cases started to receive GnRHa administration nasally just after the first BMD analyses.

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Methods

Height and weight were measured, and sexual maturity was assessed by a single investigator using the criteria of Tanner. Bone age (BA) was analysed by the TW2 RUS method for Japanese. Sex steroids, insulin like growth factor-1 (IGF-1), and osteocalcin were measured with commercially available kits.

BMD (g/cm^2) was assessed at the baseline and 8–15 months after the initiation of GnRHa treatment by dual energy X-ray absorptiometry (Hologic QDR-2000), at the lumbar spine (L2–4).

ER genotype was analysed using polymorphism in intron1 by the polymerase chain reaction (PCR)-restriction fragment length polymorphisms (RFLP) method. After the amplification of genomic DNA by PCR, the PCR product was digested with restriction endonuclease (*PvuII*), and electrophorased in an agarose gel. The RFLP was coded either P (the absence of *PvuII* restriction site) or p (the presence of restriction site), and ER genotype was divided into 3 types (PP, Pp, pp).

Result

Before treatment, all of the patients except one had accelerated BA (BA/CA: 1.11–1.62), all had high serum estradiol, testosterone and IGF-1 concentrations (data not shown). The pubertal stage ranged from Tanner stage II to IV.

BMD values for the lumbar spine exceeded the normal mean for chronological age (CA) in 11 of the 18 patients, but BMD values adjusted for BA were lower than the normal mean except in 2 cases (Fig. 1). The second BMD measurment revealed normal BMD gain during treatment with GnRHa, although estrogen deprivation due to subcutaneous GnRHa administration caused a not significant decrease in the SD score of BMD compared to untreated or other therapy (subcutaneous GnRHa administration: -0.390 ± 0.240 SD, others: -0.045 ± 0.438 SD, $p=0.14$). ER gene polymorphism was not related to the BMD value at the baseline in the patients (data not shown).

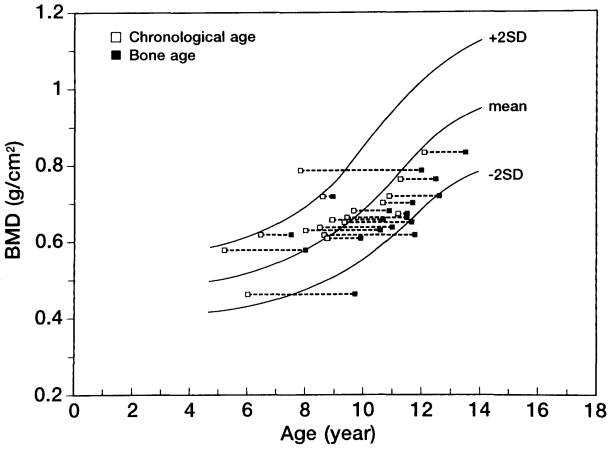

Fig. 1. Relationship between BMD values for the lumbar spine and chronological age (CA) or bone age (BA) in girls with precocious puberty. Clear squares (□) are plotted for CA, and solid squares (■) represent data adujusted for BA.

Discussion

There is abundant evidence to suggest that estrogen is essential for normal pubertal epiphyseal maturation and skeletal mineralization in both sexes [1]. Although one report has shown that estrogen deprivation due to GnRHa therapy in children with precocious puberty causes a significant decrease in BMD [3], Neely *et al.* reported that BMD gain in patients with precocious puberty was not affected by 2 years of GnRHa administration [4].

The present data showed that bone maturation was unlikely to be associated with BA-matched mineralization in untreated precocious puberty, and bone mineral accretion was not adversely affected by GnRHa treatment. Only a few studies on adult women have reported an association of BMD with polymorphism of the ER gene [5, 6], and further examination will be needed to determine whether the ER genotype affects bone mineral accretion during exposure to excess estrogen in patients.

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