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## NORMAL BONE DENSITY IN MALE PSEUDOHERMAPHRODITISM DUE TO 5 $\alpha$ - REDUCTASE 2 DEFICIENCY

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RHCFAP/3050

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COSTA EMF et al. - Normal bone density in male pseudohermaphroditism due to 5 $\alpha$ -reductase 2 deficiency. **Rev. Hosp. Clín. Fac. Med. S. Paulo** 56(5):139-142, 2001.

Bone is an androgen-dependent tissue, but it is not clear whether the androgen action in bone depends on testosterone or on dihydrotestosterone. Patients with 5 $\alpha$ -reductase 2 deficiency present normal levels of testosterone and low levels of dihydrotestosterone, providing an in vivo human model for the analysis of the effect of testosterone on bone.

**Objective:** To analyze bone mineral density in 4 adult patients with male pseudohermaphroditism due to 5 $\alpha$ -reductase 2 deficiency.

**Results:** Three patients presented normal bone mineral density of the lumbar column (L1-L4) and femur neck, and the other patient presented a slight osteopenia in the lumbar column.

**Conclusion:** Patients with dihydrotestosterone deficiency present normal bone mineral density, suggesting that dihydrotestosterone is not the main androgen acting in bone.

**DESCRIPTOR:** Bone mineral density. Male pseudohermaphroditism. 5 $\alpha$ -reductase type 2 deficiency.

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It has been well documented in the literature that gonadal steroids regulate normal bone metabolism and that inadequate estrogen concentrations in females and androgen concentrations in males cause osteoporosis<sup>1-4</sup>. In males, hypogonadism is the main risk factor for the development of osteoporosis<sup>2</sup>, and therapy with androgens increases bone mineral density<sup>5</sup>. In females, androgen therapy associated with estrogens has proven to be more effective in the prevention of post-menopausal bone loss in comparison to estrogen therapy alone<sup>6</sup>.

Up to the end of the 1980s, the mechanism of action of steroid hormones on bone was unknown, until Eriksen et al.<sup>7</sup> demonstrated the presence of estrogenic receptors in human osteoblasts, and Colvard et al.<sup>8</sup> identi-

fied androgenic receptors in these cells, thus demonstrating that both androgens and estrogens act by a direct mechanism through their respective receptors. Carani et al.<sup>9</sup>, studying a patient with aromatase deficiency, demonstrated that estrogen therapy had a greater positive effect over bone maturation and skeletal growth than testosterone therapy. These data suggest that estrogen has a crucial effect on skeletal maturation in males.

It is still unclear in literature, however, if the tropic effect of androgens on bone is mediated by testosterone or by its metabolite, dihydrotestosterone (DHT), or even if the androgenic ef-

fects require aromatization into estrogens with subsequent activation of the estrogenic receptor. Although it has been speculated that DHT is the active androgen in bone<sup>10</sup>, the effect of DHT deficiency on bone has not yet been demonstrated.

### PATIENTS AND METHODS

We performed bone densitometry in 4 male pseudohermaphrodites with 5 $\alpha$ -reductase 2 deficiency aged 25 to 40 years old. Diagnosis was confirmed through an elevated T/DHT ratio and the presence of mutations in the 5 $\alpha$ -reductase 2 gene<sup>11</sup>. Patients 1, 2, and 3, who are siblings, are compound heterozygous for the Q126R/N193S mutations. Patient 4 is homozygous for the R227\* mutation

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<sup>11</sup>. Basal TSH, free T4, PRL, LH, FSH, and cortisol were normal.

In order to increase penis size, patients were initially treated with 250 mg of mixed testosterone esters by intramuscular injections weekly from 2 to 8 months, and afterwards with 1.5 g of 2.5% DHT cream applied on the abdominal skin or thighs daily at night for 3 to 11 months. The chronological age at the time of treatment was 14 to 33 years old. Bone mineral density was measured through a dual energy x-ray bone densitometer (Hologic QDR 4500/A S/N – 45130) 7 to 9 years after completion of therapy. Bone mineral density values as determined by Hologic densitometry were compared with those of normal young men with the same weight and ethnic group.

## RESULTS

The T/DHT ratio varied from 37 to 46 (normal values=14±5.2), and the molecular study demonstrated the presence of mutations in the 5 $\alpha$ -reductase type 2 gene.

Three patients presented normal bone mineral density of the lumbar column (L1-L4) and femur neck, and patient 2 presented a slight osteopenia in the lumbar column (L1-L4) [Table 1].

## DISCUSSION

The effect of androgen on hair follicles, prostate, and seminal vesicles depends on the local conversion of testosterone into DHT. In contrast, the effects of androgen on muscle mass, spermatogenesis, and libido are maintained by testosterone only<sup>12</sup>. Even though bone is an androgen-dependent tissue, it is still unknown if 5 $\alpha$ -reductase type 2 activity is important for the androgenic action on bone cells. Previous studies demonstrated that the treatment of orchietomized rats with DHT stimulates the development of endochondral

bone<sup>13</sup> and attenuates bone loss after orchiectomy<sup>14</sup>; furthermore, both testosterone and DHT increase the transcription of  $\alpha_1(I)$ -procollagen mRNA in osteoblast-like osteosarcoma cells<sup>15</sup>.

On the other hand, Rosen et al.<sup>16</sup> demonstrated that rats treated with finasteride, which inhibits the action of 5 $\alpha$ -reductase 2, had normal bone density, concluding that DHT deficiency was not deleterious for bone. Elderly men with benign prostate hyperplasia treated with finasteride did not show any effect on bone density or on bone and mineral metabolism<sup>17</sup>. Human and rat bone have 5 $\alpha$ -reductase activity and can synthesize DHT *in vitro*<sup>10</sup>, but it is unclear which one of the two types of 5 $\alpha$ -reductase (type 1 or type 2) acts predominantly on bone.

We studied 4 male pseudohermaphrodites with 5 $\alpha$ -reductase 2 deficiency who were treated with DHT cream and testosterone esters for 3 to 11 months, 7 to 9 years before bone mass evaluation. One can speculate as to whether there was an effect of this short-period androgen therapy on the bone mass of our patients. However, our experience shows that this period of treatment is not enough to re-establish bone mass in men with hypogonadism. The same observation has been reported in men with isolated GnRH deficiency under gonadal steroid replacement therapy from 1 to 3 years whose bone density increased but failed to reach normal adult levels<sup>5</sup>. The importance of estrogen on bone maturation and mineralization has been recently demonstrated in 2 studies. Smith et al.<sup>18</sup> reported an individual

with estrogen-resistance syndrome who presented osteoporosis with increased bone resorption despite normal androgen concentrations. Another study demonstrated that the inhibition of androgen aromatization by vorozole (a non-steroid inhibitor of P450 aromatase) increases bone resorption, indicating the importance of estrogen on bone mineralization<sup>19</sup>.

Wiren et al.<sup>20</sup> demonstrated that there is an up-regulation of the androgen receptor to androgen action (testosterone and DHT) in osteoblasts, which might increase the responsiveness of these cells to androgens.

Our results suggest that 5 $\alpha$ -reductase 2 deficiency in humans does not have a significant effect on bone. Several assumptions can be made:

- 1) the enzyme involved in the 5 $\alpha$ -reduction in bone is 5 $\alpha$ -reductase 1, which is not responsible for male pseudohermaphroditism;
- 2) the small quantities of DHT produced by these patients might be enough to activate the androgenic receptor in bone cells;
- 3) testosterone, directly through the activation of its receptor, may be active in bone without converting into DHT;
- 4) testosterone is aromatized into estrogens that has a direct action on bone cells.

Further studies are required to determine the exact mechanism of androgen action in human bone. We conclude that patients with DHT deficiency present normal bone mineral density, suggesting that DHT is not the main androgen acting in bone.

**Table 1** - Bone mineral density (BMD) of the lumbar column (L1-L4) and femur neck in 4 male pseudohermaphrodites with 5 $\alpha$ -RD2 deficiency.

Patients	L1-L4		Femur Neck	
	BMD (g/cm <sup>2</sup> )	T score*	BMD (g/cm <sup>2</sup> )	T score*
1	1.141	+0.46	0.987	+0.07
2	0.920	-1.55	1.115	+1.24
3	0.990	-0.92	1.170	+1.74
4	1.014	-0.70	1.107	+1.16
Normal Lower Range	0.8	-1	0.6	

\*T score compared with the mean standard deviation for BMD of normal young adults.

## RESUMO

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COSTA EMF e col. - Pseudohermafroditas masculinos por deficiência de 5 $\alpha$ -redutase 2 apresentam densidade óssea normal. **Rev. Hosp. Clin. Fac. Med. S. Paulo** 56(5):139-142, 2001.

O tecido ósseo é um tecido andrógeno-dependente porém não está claro se a ação androgênica depende da testosterona ou da diidrotestosterona. Os pacientes portadores de deficiência

de 5 $\alpha$ -redutase tipo 2, constituem um modelo natural para avaliar o efeito isolado da testosterona sobre a massa óssea.

**Objetivo:** Avaliar a densidade mineral óssea em quatro pacientes adultos portadores de pseudohermafroditismo masculino por deficiência da 5 $\alpha$ -redutase tipo 2.

**Resultados:** Três pacientes apresentaram densidade mineral óssea normal na coluna lombar e fêmur e o

quarto paciente apresentou osteopenia leve em coluna lombar.

**Conclusão:** Pacientes com deficiência de diidrotestosterona apresentam densidade mineral óssea normal sugerindo que a diidrotestosterona não é o andrógeno que age sobre o osso.

**DESCRITORES:** Densidade mineral óssea. Pseudohermafroditismo masculino. Deficiência da 5 $\alpha$ -redutase tipo 2.

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Received for publication on January 15, 2001.