Original Article

Effects of 5α-reductase inhibitor therapy with dutasteride on bone metabolism in patients with benign prostatic hyperplasia

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ABSTRACT

Objectives: The aim of this study was to investigate the effect of dutasteride on bone metabolism in patients with benign prostate hyperplasia (BPH).
Design: Prospective study
Setting: Sakarya University Sakarya Training and Research Hospital
Subjects: Fifty patients were administered 0.5 mg dutasteride daily for treatment of BPH.
Interventions: All patients were evaluated prior and six months after the treatment for bone metabolism.
Main outcome measure: Standard parameters of bone metabolism and serum osteoprotogerin (OPG) levels, which is an important regulator for bone metabolism, were evaluated.
Results: Seven of the 50 patients were lost to follow up and the remaining 43 patients were included in the study. Mean age of patients was 60.3±5.5 (range: 48-74) years. Dutasteride significantly increased serum testosterone and estradiol levels compared to pretreatment values. Mean OPG level increased from 198.3±40.5 pg/ml to 240±90.1 pg/ml (*P*=.019). Except T score of femur neck, there was an increase of T-Z scores in the lumbar spine and in the femur neck (*P* >.05). There was an increase in bone mineral density levels of the body, but only the increase in L4 vertebral value was statistically significant (*P* <.008). The treatment with dutasteride also caused significant decrease in prostate specific antigen levels and prostate volume as expected.
Conclusions: It seems that, in addition to the benefits on prostatism symptoms, the short-term results of 5ARI on bone metabolism are promising.

KEY WORDS: Osteoclasts, osteopenia, osteoprotogerin

INTRODUCTION

More than 90% of testosterone is converted to dihydrotestosterone (DHT), the most potent androgen in prostate, irreversibly. 5α-reductase converts testosterone to DHT, which starts during intrauterine development, leading to differentiating of prostate. There are 2 isozymes of 5α-reductase in humans. Type 1 enzyme is mainly seen in the skin, adult scalp and liver, but detected with lesser degrees in the prostate. Type 2 isozyme, which is the dominant isoform, is seen in the prostate[1,2].

Dutasteride is a 5α-reductase inhibitor and inhibits both isozymes of 5α-reductase (types 1 and 2). Continuous administration of dutasteride decreases the serum DHT concentration to approximately 95% and prostate DHT concentration to 85-90%[3]. Blocking conversion of the testosterone results in an increase in testosterone level[4]. It is also well known that the increase of testosterone may cause an increase of the serum estradiol (E2) level, due to effect of an aromatase enzyme which converts testosterone to E2[5]. Low serum androgen level is related with an increased risk

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of osteoporosis and also fracture. It was demonstrated in the literature that the levels of bioavailable and free fractions of testosterone and E2 were positively associated with calcaneal quantitative ultrasound parameters, and that testosterone increases the bone mineral density (BMD)[6,7].

5 ARIs have been used in men for the treatment of benign prostatic hyperplasia (BPH) for a long time. Since BPH is a disease of the elderly men in population who are also prone to osteoporosis, we believe that it is also important to demonstrate whether dutasteride has any effect on bone metabolism in addition to BPH symptoms. In the present study, we aimed to investigate the effect of dutasteride, a 5 ARI, on bone metabolism in elderly men with BPH.

SUBJECTS AND METHODS

After having obtained approval of the Institutional Ethics Committee, we performed a prospective analysis of 50 patients administered with 0.5 mg dutasteride daily for treatment of BPH. All patients were evaluated prior and six months after the treatment for bone metabolism and also for bladder outlet obstruction symptoms.

Table 1: Effect of dutasteride on serum hormones

Variable	Before treatment (Average ± SD)	After treatment (Average ± SD)	*P*-value
Total testosterone (ng/ml)	5.4±1.9	7.0±2.7	<.001*
Estradiol (pg/ml)	30±10.1	35±14	.011*
LH (mmol/ml)	4.6±1.9	5.3±2.9	.060#
FSH (mmol/ml)	6.1±3.1	6.4±3.5	.230*
SHBG (mmol/l)	45±25	48.4±26.9	.744*
OPG (mmol/ml)	198.3±40.5	240±90.1	.019*
fTest (pg/ml)	7.05±3.2	6.41±2.44	.068*

OPG: osteoprotogerin; LH: luteinizing hormone; FSH: follicle-stimulating hormone; SHBG: sex hormone-binding globulin; *Wilcoxon Signed Ranks Test; #Paired T test.

Patients with bone metabolism disorders like multiple myeloma, endocrinological disease that could affect the results of blood samples, or who were administered any drugs which could affect the results such as androgen replacement therapy were excluded from the study.

After having a signed informed consent, patient's body mass index, prostate size measurements and uroflowmetric evaluation were recorded prior and six months after the treatment. BMD at the lumbar spine (L1-L4) and femur neck were measured in all patients, and TZ scores were measured by using whole-body dual-energy X-ray absorptiometry. Blood samples were analyzed for hemogram and biochemistry parameters with testosterone, E2, luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin, dehydroepiandrosterone sulfate, vitamin D, parathormone, bone alkaline phosphatase and osteoprotegerin (OPG) prior and six months after the treatment. Serum lipid profile including total cholesterol, triglycerides, high density lipoprotein and low-density lipoprotein were also analyzed. Hormone measurements were all analysed on the same assay to reduce variability.

Table 2: Effect of dutasteride on lumbar and femur T and Z scores.

Variable	Before treatment (Average ± SD)	After treatment (Average ± SD)	*P*-value
Lumbar T score	-0.944±1.33	-0.862±1.43	.269#
Lumbar Z score	-0.262±1.30	-0.227±1.50	.724#
Femur T score	-0.607±1.10	-0.748±0.83	.431*
Femur Z score	0.355±1.07	-0.241±0.76	.308*

*Wilcoxon Signed Ranks Test; #Paired T test

All statistical analyses were performed on SPSS (Statistical Package for the Social Science, Chicago, USA) version 20. Data were expressed as mean ± SD. The normal distribution of variables was determined by the Shapiro-Wilk test. A paired t-test is used to compare pre- and post-treatment observations on the same subjects when the differences of mean were normally distributed. Wilcoxon signed ranks test was used when the population cannot be assumed to be normally distributed. For all comparisons, P <.05 was considered significant.

RESULTS

Seven of the 50 patients were lost to follow up and the remaining 43 patients were included in the study. Mean age of patients was 60.3±5.5 (range: 48-74) years. Dutasteride significantly increased serum testosterone and E2 levels compared to pretreatment values. Total testosterone and E2 values increased from 5.4±1.9 ng/ml to 7.0±2.7 ng/ml (P <.001) and from 30±10.1 pg/ml to 35±14pg/ml (P=.011), respectively. However, there was no effect of the treatment on serum levels of luteinizing hormone, follicle-stimulating hormone or sex hormone-binding globulin. We also found that the dutasteride treatment increased OPG levels, which results in osteoblastic activity. Mean OPG level

Table 3: Effect of dutasteride on lumbar vertebral BMD scores

Variable	Before treatment (Average ± SD)	After treatment (Average ± SD)	*P*-value
BMD L1	0.877±0.154	0.895±0.155	.228#
BMD L2	0.956±0.156	0.977±0.172	.209#
BMD L3	0.996±0.183	1.012±0.163	.148#
BMD L4	1.018±0.182	1.057±0.189	.008#
BMD total	0.978±0.151	0.992±0.160	.065#

BMD: bone mineral density; #Paired T test

increased from 198.3±40.5 pg/ml to 240±90.1 pg/ml, which was statistically significant (*P* = .019) (Table 1). Except T score of femur neck, we demonstrated that there was an increase of T-Z scores in the lumbar spine and in the femur neck, but the change between baseline and month 6 of treatment was not statistically significant (*P* >.05) (Table 2). In addition, we detected an increase in BMD levels of the body, but only the increase in L4 vertebral value was statistically significant (*P* <.008) (Table 3).

Table 4: Effect of dutasteride on lipid profile and body image

Variable	Before treatment (Average ± SD)	After treatment (Average ± SD)	*P*-value
Total cholesterol (mg/dl)	188±30.4	202±37	<.001*
LDL cholesterol (mg/dl)	114±23	129±32	<.001*
HDL cholesterol (mg/dl)	40.9±10.3	44.1±9.5	<.001*
Triglyceride (mg/dl)	138.9±84.6	140.6±71.8	.836‡
Weight (kg)	83.44±5.5	85.58±13	<.001*
BMI (kg/m^2)	28.05±3.7	29.1±3.9	<.001*
Waist circumference (cm)	105.6±10.7	111±9.2	<.001*

LDL: low density lipoprotein; HDL: high density lipoprotein; BMI: body mass index; *Wilcoxon Signed Ranks Test; ‡Paired T test

At the end of 6-month administration of the treatment, a statistically significant increase of total cholesterol, low-density lipoprotein cholesterol and also high-density lipoprotein cholesterol was detected (*P* <.001). However, the increase in triglyceride was not statistically significant (*P* = .836). In addition, an increase of body mass index, weight and waist circumference was also detected (*P* <.001) (Table 4).

Table 5: Effects of dutasteride on urologic parameters

Variable	Before treatment (Average ± SD)	After treatment (Average ± SD)	*P*-value
Prostate volume (cc)	53±20.6	35±17.2	<.001‡
Uroflowmetry data			
Qmax (ml/sn)	11±2.9	16.1±4.7	<.001‡
Average flow rate (ml/sn)	5.7±2.0	7.5±1.7	< 001‡
Voiding volume (ml)	265±82.7	256±106	.508‡
Post voiding residue (ml)	107±37.3	38±29.7	<.001‡
Sum of IPSS	17.4±5.1	8.8±5.1	<.001‡

IPSS: International Prostate Symptom Score; ‡Paired T test

The treatment with dutasteride also caused 50% decrease in prostate specific antigen levels at the end of the six months. Mean prostate volume decreased from 53±20.6 gr to 35±17.2 gr (*P* <.001). International prostate symptom score and uroflowmetric parameters including Qmax, Qaverage and post voiding residual volume were significantly improved with the treatment of dutasteride (*P* <.001) (Table 5).

DISCUSSION

The effect of androgens on bone metabolism has been investigated in several studies in the literature. While E2 is positively associated with bone maturation and BMD, testosterone is associated with bone size in adolescents[8]. However, in men over the age of 40 years, testosterone level drops with an average decrease of 1-2% per year. Low serum testosterone is associated with osteopenia in elderly men and there is an increased incidence of osteoporosis, as well as increased falls and fractures, resulting in increased mortality[7,9-11]. The results of androgen suppression therapies in men with prostate cancer have also reported how important testosterone is for bone metabolism. According to Chernichenko *et al*'s study, the drop of testosterone to castration level due to androgen suppression therapies was strongly associated with the decrease in BMD. They found out a decrease in BMD in 78.6% of the patients administered with androgen suppression therapies[12]. It has been shown in several studies that the administration of testosterone results in an increase in the level of BMD by suppressing bone resorption[6,7]. In addition to the direct effect of testosterone, the conversion to E2 by the aromatase enzyme also has an important effect on bone metabolism. The protective effect of E2 from osteopenia is as important as testosterones[9,10].

The E2 receptors are detected more on osteoblasts than on osteoclasts. Here, E2 regulates and increases the amount of growth hormone, insulin growth factor binding protein-4 in osteoblastic cells. It also increases the transforming growth factor-β, which inhibits osteoclastic bone activity[13]. In addition, it has been reported that E2 has an effect on bone metabolism by inhibiting osteoclast formation and resorption, just like testosterone[13,14].

5alpha-reductase inhibitor increases the testosterone and E2 levels by blocking the conversion of testosterone to DHT. When we analyzed the literature, the first study about the effects of 5alpha-reductase inhibitor on bone metabolism was published by Amory *et al* in 2008[2]. They found out that dutasteride and finasteride did not have a significant impact on BMD and markers of bone metabolism after one year of treatment. In 2014, Mačukat *et al* evaluated dutasteride and finasteride by comparing with a control group[15]. They found out that total testosterone and E2 levels were higher in the dutasteride group and that dutasteride group had significantly higher BMD and mean T and Z scores at femoral neck than control group. Recently, Wada *et al* investigated the effect of dutasteride on bone metabolism[16] by evaluating the BMD in the lumbar and femur neck. Although they did not find a significant increase in testosterone level, they detected

an increase of BMD in lumbar and femur neck in patients with increased testosterone. They evaluated only 17 patients, and it seems that the low number of the patients was the main limitation of their study. In these previous studies, none of the authors evaluated the OPG, which is an important regulator for bone. OPG was used for evaluating bone metabolism in our study for the first time.

In the present study, testosterone and E2 levels were significantly increased after treatment with dutasteride for a six-month period. The increase in the androgen levels resulted in an improvement of the bone metabolism markers. Mean OPG level, which is an important bone metabolism regulator, was significantly increased after the dutasteride administration. OPG protein, which is one of the members of tumor necrosis factor receptor families, and which is produced by osteoblastic cells, inhibits the osteoclastic activity by binding and inhibiting the receptor activator of nuclear factor kappa-B ligand[13]. It has been well known that E2 and testosterone both enhance the OPG levels so that they can be called as protective factors for bone[13,17,18]. We believe that the increase in testosterone and E2 after dutasteride is an important factor that increased OPG level in the early period of the treatment.

An increased BMD level was detected in all measurements and in total, but only the increase in L4 vertebral value was statistically significant. Except for the T score of femur neck, there was an increase of T-Z scores in the lumbar spine and in the femur neck, but the change between baseline and month 6 of treatment was not statistically significant. It may be that long-term results of the therapy would be necessary to evaluate BMD due to slow turnover of bone tissue.

In addition to bone metabolism, dutasteride improved the prostatism symptoms and uroflowmetric parameters significantly, as expected. Post voiding residual volume amount, prostate volume and prostate specific antigen levels decreased significantly six months after the treatment, as reported in the literature[19].

The present study shows that increased androgens with six-month administration of dutasteride has significantly improved bone regulation by increasing OPG. In addition, due to slow turn-over of the bone tissue, it would be better to evaluate BMD after long term treatment. Although there is no cut-off value for evaluating the most suitable treatment period for drug studies, six months can be considered a short time to evaluate bone metabolism. This may be considered as a limitation of the study. Another limitation of the present study is that a control group was not used, although this is a prospective study. Despite the limitations, we believe that the results of this study are important since there are limited numbers of studies on this topic.

CONCLUSION

Treatment with dutasteride resulted in significant improvement of BMD and T-Z scores in the lumbar spine and in the femur neck. This is due to increased levels of testosterone, E2, as well as OPG which inhibits the osteoclastic activity. It seems that, in addition to benefits on prostatism symptoms, the short-term results of 5ARI on bone metabolism are promising.

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