.Coll. Antropol. **38** (2014) 3: 835–839
Original scientific paper

The Effect of 5α-reductase Inhibition with Finasteride and Dutasteride on Bone Mineral Density in Older Men with Benign Prostatic Hyperplasia

Indira Radin Mačukat[1], Josip Španjol[2], Željka Crnčević Orlić[3], Marta Žuvić Butorac[1], Marin Marinović[4] and Dora Fučkar Ćupić[5]

[1] University of Rijeka, School of Medicine, Department of Anesthesiology, Rijeka, Croatia
[2] University of Rijeka, School of Medicine, Department of Urology, Rijeka, Croatia
[3] University of Rijeka, School of Medicine, Department of Endocrinology, Rijeka, Croatia
[4] University of Rijeka, School of Medicine, Department of Surgery, Rijeka, Croatia
[5] University of Rijeka, School of Medicine, Department of Pathology, Rijeka, Croatia

A B S T R A C T

Testosterone is converted to dihyrotestosterone by two isoenzymes of 5α-reductase. Finasteride and dutasteride are 5α-reductase inhibitors commonly used in the treatment of benign prostatic hyperplasia. We compared indices of bone mineral density in 50 men treated with finasteride, 50 men treated with dutasteride and 50 men as control. Bone mineral density of spine and hip were measured using dual energy X-ray absorptiometry. Bone formation was assessed by measuring serum osteocalcin and bone resorption by measuring serum C-terminal telopeptide of collagen type 1. In addition serum total testosteron and estradiol were determined. The dutasteride group had significantly higher mean bone mineral density, mean bone mineral content, mean T score, mean Z score at femoral neck and mean total hip Z score than control. Mean total testosterone and estradiol levels were higher in the dutasteride group. There were no significant differences between the groups in lumbar spine bone density parameters or bone turnover markers. Our results provide evidence that long-term 5α-reductase suppression does not adversely affect bone mineral density. Dutasteride therapy could have beneficial effect on bone density.

***Key words**: bone density, benign prostatic hyperplasia, dutasteride, finasteride*

Introduction

Current clinical practice guidelines recommend 5α--reductase inhibitors (5ARIs), either alone or in combination with alpha-blockers, as appropriate treatment options for benign prostatic hyperplasia BPH[1]. The clinical efficacy of 5ARIs in the treatment of BPH has been firmly established and supported with scientific evidences[2,3]. A marked reduction in prostate volume, improvement in symptoms associated with BPH, a significant reduction in the risk of acute urinary retention and the need for BPH related surgery are all beneficial effects of 5ARIs administration[4,5]. The two widely available 5ARIs are finasteride and dutasteride. Each drug induces marked dihydrotestosterone (DHT) suppression, which is the primary androgen responsible for prostate growth[6,7]. Testosterone is converted to more potent androgen, DHT by two isoenzymes of 5α-reductase. The type 2 isoenzyme predominates in normal and BPH tissue and is inhibited by finasteride, which decreases serum concentrations of DHT by approximately 70%[8]. Dutasteride, a dual 5ARI inhibits both type 1 and type 2 isoenzyms, leading to a 95% decrease in serum DHT concentrations[9]. This difference may be important during long term treatment.

Received for publication June 3, 2014

The long-term effects of altering the androgen balance through 5α-reductase inhibition on other androgen responsive tissues such as bone are less well established. Numerous studies have clarified complex effects of sex hormones on bone cells. The relative role of the androgen receptor, estrogen receptor α and estrogen receptor β in mediating the effect of androgens or their metabolites on bone tissue has been debated[10]. Androgen deficiency in men is associated with premature bone loss and increased frequency of osteoporotic fractures[11]. It has been demonstrated that human osteoblast-like cells express predominantly 5α-reductase type 1[11]. Although there are evidences that androgens exert profound effect on the homeostasis of mature bone in men, the relative importance of androgens and estrogens for bone turnover remains unresolved[10]. There is increasing evidence that at least part of the effects of androgen in men can be explained by their aromatization into estrogens[12]. Despite dramatic decrease in serum DHT, current scientific evidence does not suggest significant impact of 5ARIs on bone tissue despite biological plausibility in either direction. Clinical studies with a type 2 5ARI, finasteride provide evidence that inhibition of type 2 5α-reductase does not adversely affect bone mineral density (BMD), the lack of significant changes in the bone markers is consistent with minimal effect on bone metabolism[13,14,17]. Because of near complete inhibition of 5α-reductase, dutasteride has a far greater potential to interfere with male skeletal homeostasis. Recent finding that type 1 5α-reductase is predominantly expressed in osteoblast supports the absence of effect on bone in clinical studies with type 2 5ARI (finasteride) but rise question about dutasteride effect on bone through inhibition of type 1 5α-reductase[11]. In this study for the first time we examined the effects of long term therapy (more than one year) with dutasteride on BMD.

Materials and Methods

Subjects

The study included a total of 150 male subjects 60 to 78 years old who suffered from BPH. All subjects were regular patients of Department of Urology (University Hospital of Rijeka, Rijeka, Croatia). Finasteride group included 50 subjects who were treated with finasteride 5 mg daily for a period of 24 to 48 months. Dutasteride group included 50 subjects who were treated with dutasteride 0.5 mg daily for a period of 24 to 48 months. Finasteride and dutasteride group were compared with control group which consisted of 50 subjects who had never been treated with 5ARI and were comparable with both groups considering age, body mass index (BMI) and physical activity.

All subjects were free of clinically significant systemic or other disorder which affect bone metabolism like diabetes mellitus, chronic renal failure, parathyroid disorder; smoking; heavy alcohol use; use of medications including anabolic steroids, antiandrogens, estrogen, glucocorticoids, diuretics, seizure medications, warfarin, calcium or vitamin D supplements as determined by patients medical history, physical examination, clinical laboratory test results and baseline questionnaire completed by all subjects. Informed consent was obtained from all subjects and the institutional ethics committee approved this study.

Measurements

BMD was measured at the lumbar spine: anteroposterior view (L1-L4); lateral view (L2-L3) and in the nondominant hip by dual energy x-ray absorptiometry using a Hologic densitometer QDR DELPHI-W#70616W (Hologic, Bedford, USA). Bone densitometry results are reported as bone mineral density (BMD, mg/cm^2), bone mineral content (BMC, mg), T score (compares the BMD to the mean for young normal males) and Z score (compares it with age-matched controls)[17]. T score and Z score are expressed as the number of standard deviations (SD) values by which a given result differs from the mean value for young men and men of equal age respectively. All subjects were assessed by same machine by experienced dual energy X-ray technologists who were provided with study specific standard operating procedure. Instrument-specific normative database was used. All bone density scans were analyzed for acceptability considering artifacts, compression fractures or other confounding factors.

Serum total testosterone and estradiol were measured by electrochemiluminescence immunoassay (ECLIA) using a analyzer Elecsys 2010 (Roche, Meinheim, Germany). The normal range is 6.68–25.7 nmol/L for total testosterone and 28–156 pmol/L for estradiol. The bone turnover markers serum osteocalcin and serum C-terminal telopeptide of type 1 collagen (S-CTX) were measured by ECLIA using analyzer Cobas 601e 2009 (Roche, Meinheim, Germany). The normal range is 14–46 μg/L for osteocalcin and <0.704 μg/L for S-CTX. For hormone and bone turnover markers blood was drawn in the morning and measurements were performed at a central laboratory (University Hospital of Rijeka, Rijeka, Croatia).

Statistical analysis

The collected data were statistically evaluated using data analysis software system STATISTICA 8.0 (StatSoft Inc,Tulsa, OK, USA). The continuous variables were checked for normality of distributions (by Kolmogorov-Smirnov and Shapiro-Wilks tests) and presented by mean and standard deviation. Comparisons of variables between groups were made using ANOVA test, while post-hoc comparisons using Sheffé test. The level of statistical significance was set at 0.05 in all analyses.

Results

Base-line characteristics of hormonal levels and bone turnover markers

There were no significant differences among finasteride, dutasteride and control group in age and BMI.

TABLE 1
COMPARISON OF PATIENT CHARACTERISTICS, HORMONES AND BONE TURNOVER MARKERS (X±SD)

Parameter	Group		
	Control (N=50)	Finasteride (N=50)	Dutasteride (N=50)
Age (years)	68±4	69±5	70±5
BMI (kg/m^2)	26.5±2.6	26.6±2.2	26.8±2.5
Total testosterone (nmol/L)	17.1±6.8	16.4±4.0	20.3±2.9*§
Estradiol (pmol/L)	82.7±29.9	90.6±52.7	116.1±44.8*§
Osteocalcin (μg/L)	17.7± 5.6	17.6±4.6	17.0±2.9
S-CTX (μg/L)	0.25±0.1	0.22±0.08	0.22±0.08

BMI – body mass index, S-CTX – serum C-terminal telopeptide of type 1 collagen; * comparison between dutasteride and control group, $p<0.05$; § comparison between dutasteride and finasteride group, $p<0.05$

TABLE 2
COMPARISON OF BONE DENSITOMETRY PARAMETERS (MEAN±SD)

Parameter	Group		
	Control (N=50)	Finasteride (N=50)	Dutasteride (N=50)
Lumbar spine AP (L1-L4)			
BMC (g)	74.7±15.3	76.7±19.5	77.0±18.1
BMD (g/cm^2)	1.05±0.16	1.08±0.22	1.08±0.18
T score	–0.34±1.5	–0.05±2.0	–0.14±1.6
Z score	0.54±1.5	0.85±2.0	0.77±1.6
Lumbar spine Lat (L2,L3)			
BMC (g)	19.9±5.1	20.8±5.6	20.5±4.3
BMD (g/cm^2)	0.76±0.15	0.80±0.20	0.77±0.14
Femoral neck			
BMC (g)	5.26±0.9	5.45±1.2	5.90±1.3*
BMD (g/cm^2)	0.87±0.12	0.90±0.14	0.94±0.16*
T score	–0.47±0.9	–0.24±1.0	0.09±1.2*
Z score	0.69±0.9	0.96±1.0	1.30±1.1*
Total hip			
BMC (g)	48.40±7.1	49.79±8.6	51.35±10.3
BMD (g/cm^2)	1.02±0.12	1.06±0.13	1.08±0.16
T score	–0.11±0.81	0.16±0.88	0.33±1.03
Z score	0.53±0.8	0.85±0.9	1.02±1.0*

AP – anteroposterior view, Lat – lateral view, BMC – bone mineral content, BMD – bone mineral density; * comparison between dutasteride and control group, $p<0.05$

The dutasteride group had higher mean serum total testosterone levels than finasteride ($p<0.001$) and control ($p=0.006$).The mean serum estradiol levels were higher in the dutasteride group than finasteride ($p=0.015$) and control ($p<0.001$). There were no significant differences between finasteride and control group in mean serum total testosterone and estradiol levels. There were no significant differences among finasteride, dutasteride and control group in serum bone turnover markers; osteocalcin and S-CTX (Table 1).

Bone densitometry parameters

All bone density parameters mean values at femoral neck were significantly higher in the dutasteride group than control: BMD ($p=0.027$), BMC ($p=0.020$), T score ($p=0.028$) i Z score ($p=0.011$). There were no significant differences between dutasteride and finasteride group in bone density parameters mean values at femoral neck: BMD ($p=0.274$), BMC ($p=0.147$), T score ($p=0.277$) i Z score ($p=0.243$). There were no significant differences between finasteride and control group in bone density parameters mean values at femoral neck: BMD ($p=0.552$), BMC ($p=0.687$), T score ($p=0.549$) i Z score ($p=0.394$). The mean total hip Z score was also significantly higher in the dutasteride group than control ($p=0.027$). There were no significant differences between dutasteride and finasteride group in the mean total hip Z score ($p=0.631$). There were no significant differences

between finasteride and control group in the mean total hip Z score (p=0.218). There were no significant differences among finastride, dutasteride and control group in mean values for total hip BMD, BMC and T score. There were no significant differences among finasteride, dutasteride and control group in mean values of lumbar spine bone density parameters. Analyzed parameters were BMD, BMC, T score, Z score in anteroposterior view (L1-L4) and BMD, BMC in lateral view (L2, L3) (Table 2).

Discussion and Conclusion

Although 5ARIs in the treatment of BPH have been used for 20 years, few studies have investigated the skeletal effects of these drugs. The results of studies designed to address the impact of type 2 5α-reductase inhibition with finasteride on bone tissue in men are consistent in showing no effect on BMD or bone turnover markers despite marked serum DHT suppression[13–16]. Our finding that long term inhibition of type 2 5α-reductase with finasteride does not adversely affect bone mineral density in older men with BPH is in agreement with those studies. Important finding that type 1, not type 2 5α-reductase is predominantly expressed in osteoblasts might explain absence of effect on bone in these studies[11].

We found that older men chronically treated with dutasteride because of BPH have significantly greater bone mineral density parameters (BMD, BMC, T score and Z score) at femoral neck and also total hip Z score than controls. The impact of dutasteride, a dual type 1 and type 2 5ARI on bone tissue is less well-established, because studies are currently lacking. In contrast to our finding, Amory at al. showed that dutasteride did not have significant effects on BMD despite profound (94%) serum DHT suppression[16]. In interpreting these results, however, it should be considered that subjects in this study were young man, duration of 5α-reductase inhibition was 1 year and only total hip, not femoral neck BMD was measured.

The dutasteride treated older men in our study had significantly higher mean serum total testosteron and estradiol. The relative roles of testosterone, DHT and estradiol in homeostasis of mature bone are not clear. Testosterone levels have been shown to be directly correlated with BMD in older men, although serum levels of estradiol were more strongly correlated[17]. Higher serum levels of estradiol in our study may be due to shunting of testosterone through the aromatization pathway. Serum DHT levels were not measured in our study and are known from previous studies[16]. Our results suggest that serum estradiol plays a major role in maintenance of BMD in older men, which could be true especially for cortical bone compartment. Therefore conversion of testosterone to DHT may not be necessary for the effect of androgens on BMD in older men. We found no differences in spine BMD between studied groups. It is possible that effects of 5α-reductase inhibition on cancellous and cortical bone are different. It is known that sex hormones act on different way on two different bone compartments[10].

The lack of significant differences between groups in bone turnover markers in our study is consistent with most other studies[13,16].

Our findings imply that dutasteride could have osteprotective effect on cortical bone but whether and to what extent effects on bone density may translate in clinical benefits need further investigation. In a recent study exposure to 5ARIs may lower the risk of hip fracture[18]. Together with long term studies using selective modulation of androgen and estrogen action, to clarify local hormone levels and interactions in bone tissue may be an important part for a comprehensive picture.

Long term use of 5ARIs in treatment of BPH in older men does not adversely affect bone mineral density. Furthermore dutasteride could have osteprotective effect on cortical bone health in terms of bone densitometry parameters. Although long term studies are needed, our data suggest that dutasteride could prevent bone loss and provide protection against osteoporosis in older men.

REFERENCES

1. MADERSBACHER S, ALIVIZATOS G, NORDLING J, SANZ CR, EMBERTON M, DE LA ROSETTE JJ, Eur Urol, 46 (2004) 547. — 2. McCONNELL JD, ROEHRBORN CG, BAUTISTA OM, N Engl J Med, 349 (2003) 2387. — 3. ROEHRBORN CG, SIAMI P, BARKIN J, Eur Urol, 57 (2010) 123. DOI: 10.1016/j.eururo.2009.09.035. — 4. McCONNELL JD, BRUSKEWITZ R, WALSH P, ANDRIOLE G, LIEBER M, HOLTGREWE HL, N Engl J Med, 338 (1998) 557. — 5. DEBRUYNE F, BARKIN J, VAN ERPS P, REIS M, TAMMELA TL, ROEHRBORN C, Eur Urol, 46 (2004) 488. — 6. McCONNELL JD, Br J Urol, 76 (Suppl 1) (1995) 5. — 7. CARSON C, RITTMASTER R, Urology, 61 (2003) 2. — 8. RITTMASTER RS, LEMAY A, ZWICKER H, CAPIZZI TP, WINCH S, MOORE E, J Clin Endokrinol Metab, 75 (1992) 484. — 9. CLARK RV, HERMANN DJ, CUNNINGHAM GR, WILSON TH, MORRILL BB, HOBBS S, Clin Endocrinol Metab, 89 (2004) 2179. — 10. VANDERSCHUEREN D, VANDENPUT L, BOONEN S, LINDBERG MK, BOUILLON R, OHLASON C, Endocr Rev, 25 (2004) 389. — 11. ISSA S, SCHNABEL D, FEIX M, J Clin Endocrinol Metab, 87 (2002) 5401. — 12. KHOSLA S, MELTON III LJ, RIGS BL, J Clin Endocrinol Metab, 87 (2002) 1443. — 13. TOLLIN SR, ROSEN HN, ZUROWSKI K, J Clin Endocrinol Metab, 81 (1996) 1031. — 14. MATSUMOTO AM, TENOVER L, MCCLUNG M, J Urol, 167 (2002) 2105. — 15. MATZKIN H, CHEN J,WEISMAN Y, GOLDRAY D, PAPPAS F, JACCARD N, BRAF Z, Clin Endocrinol, 37 (1992) 432. — 16. AMORY JK, ANAWALT BD, MATSUMOTO AM, J Urol, 179 (2008) 2333. DOI: 10.1016/j.juro.2008.01.145. — 17. KHOSLA S, MELTON LJ III, ATKINSON EJ, O'FALLON WM, J Clin Endocrinol Metab, 86 (2001) 3555. — 18. JACOBSEN SJ, CHEETHAM TC, HAQUE R, SHI JM, LOO RK, JAMA, 300 (2008) 1660. DOI: 10.1001/jama.300.14.1660.

J. Španjol

University of Rijeka, School of Medicine, Department of Urology, Braće Branchetta 20, 51000 Rijeka, Croatia
e-mail: josip.spanjol@medri.uniri.hr

UTJECAJ INHIBICIJE 5α-REDUKTAZE S FINASTERIDOM I DUTASTERIDOM NA GUSTOĆU KOSTIJU KOD STARIJIH MUŠKARACA S BENIGNOM HIPERPLAZIJOM PROSTATE

S A Ž E T A K

Testosteron se pretvara u dihidrotestosteron putem dva izoenzima 5α-reduktaze. Finasterid i dutasteride su 5α-reduktaza inhibitori koji se obično koriste u liječenju benigne prostatične hiperplazije[1–7]. Usporedili smo indekse mineralne gustoće kosti u 50 muškaraca liječenih finasteridom, 50 muškaraca liječenih s dutasteridom i 50 neliječenih muškaraca koji su predstavljali kontrolnu skupinu. Koštana mineralna gustoća kralježnice i kuka mjerene su pomoću dvostruke rendgenske apsorpciometrije. Koštani metabolizam procijenili smo mjerenjem serumskog osteokalcina (pokazatelj stvaranja nove kosti) i mjerenjem serumskog C-terminalnog telopeptida kolagena tipa 1 (pokazatelj razgradnje kostiju). Također. Smo odredili ukupni serumski testosteron i estradiol. Dutasterid skupina imala je značajno višu srednju gustoću kostiju, srednji sadržaj minerala u kostima. Srednja vrijednost serumskog testosterona i estradiola u krvi bila je viša u dutasterid grupi. Nije bilo značajne razlike između skupina u mineralnoj gustoći slabunske kralježnice. Naši rezultati pružaju dokaze kako dugoročna primjena inhibitora 5α-reduktaze ne utječe nepovoljno na mineralnu gustoću kostiju. Terapija dutasteridom može imati blagotvoran učinak na kosti.