Annals of Medical Research

Original Article

DOI: 10.5455/annalsmedres.2019.09.576 2020;27(1):237-43

Does dutasteride have any cardioprotective effect in elderly men? A prospective randomised controled study

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Abstract

Aim: To investigate whether the increased serum levels of testosterone secondary to Dutasteride therapy has any protective effect on cardiovascular system.

Material and Methods: A prospective analysis of 50 patients diagnosed benign prostatic enlargement between May 2015 and May 2017 was performed. After randomization 25 patients treated with daily administration of 0.5 mg dutasteride (Dutasteride Group), and 25 patients were not given dutasteride (Control Group). We analyzed some serum novel cardiaovascular marker levels at baseline and after 6 months of the treatment. Echocardiography, carotid intima-media thickness and brachial artery resistive index (RI) were evaluated at baseline and after 6 months of the treatment.

Statistical analyses were performed using SPSS, version 21. While "t test" was used for comparison the independent groups, paired t test was used in the matched groups. Statistical significance was considered at $p<0.05$.

Results: The differences in serum Lp a, hs-CRP and NT-proBNP levels were not statistically significant ($p>0.05$). Additionally, echocardiographic parameters, carotid intima-media thickness and brachial artery RI were similar before and after dutasteride tratment.

Conclusion: After the short-term use of dutasteride, there was not a statistically significant difference in serum Lp a, hs-CRP and NT-proBNP levels. Additionally, echocardiographic parameters, carotid intima-media thickness and brachial artery RI were also similar.

Keywords: Dutasteride; cardioprotective effect; elderly men

INTRODUCTION

Cardiovascular disease (CVD) is the major cause of death worldwide. CVD and benign prostate hyperplasia (BPH) are both related to advanced age, and 39.2% of patients who are on medication for BPH use cardiovascular drugs. (1,2)

It is well known that dutasteride decreases serum dihydrotestosterone (DHT) levels by more than 90% and also increases serum testosterone (TT) levels by inhibiting type I and type II 5-alpha-reductase isoenzymes. TT deficiency is related to increased risk of adverse cardiovascular outcomes and favorable effects of TT on cardiovascular system have been described recently.(3,4)

The present study purpose to investigate whether the increased serum TT level caused by dutasteride therapy has any effect on cardiovascular system.

MATERIAL and METHODS

After having obtained approval of National Medicines And Medical Devices Agency Ethics Committee, we performed

Received: 30.09.2019 **Accepted:** 17.12.2019 **Available online:** 18.02.2020
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a prospective analysis of 50 patients diagnosed BPH between May 2015 and May 2017. After randomization, 25 patients treated with daily administration of 0.5 mg dutasteride (Dutasteride Group), and 25 patients were not given dutasteride (Control Group). Twenty four patients in the Dutasteride Group and 23 patients in the Control Group completed the study (Figure 1). Sixteen patients in the Dutasteride Group were given alpha-blockers along with dutasteride and 8 patients were given dutasteride alone. While 14 patients in the Control Group were given alpha-blocker, 9 patients were not given any drug treatment for BPH and observation was prefered according to the symptoms. The main inclusion criteria were the existence of indication for the treatment of BPH.

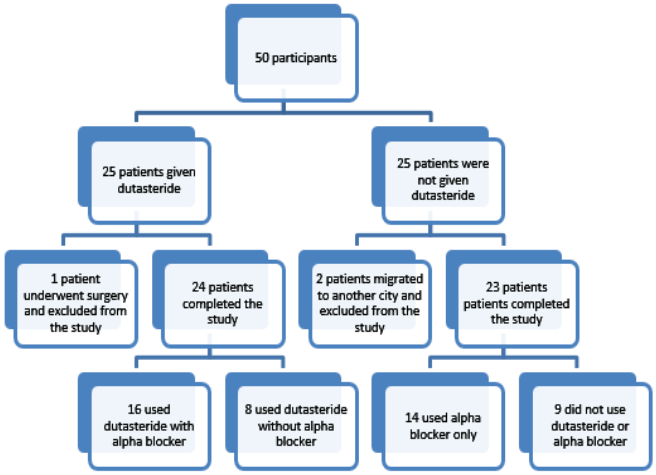

Figure 1. Study flow chart

Serum luteinized hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), total and free prostate specific antigen (PSA), TT, DHT, Lipoprotein a (Lp a), high-sensitive C-reactive protein (hs-CRP) and N-terminal pro b-type natriuretic peptide (NT-proBNP) levels were analysed at baseline and after 6 months of the treatment. After a 10-12 hours overnight fasting, venous blood samples were taken to the clot activator vacuum blood tubes and the serum samples were then obtained by centrifugation. The samples were aliquoted and rapidly frozen, and then were stored at -80°C until analysis. Serum levels of LH, FSH, E2, total PSA, free PSA, T, lipoprotein (a), hsCRP, and NT-proBNP were determined by commercially available kits using c 501 and e 601 modules of Cobas® 6000 modular analyzer series (Roche Diagnostics, USA). Serum levels of DHT were determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS).

Echocardiography (ECO) was performed by the same cardiologist and carotid intima-media thickness and brachial artery resistive index (RI) were evaluated by the same radiologist who were aware of the study design at baseline and after 6 months of the treatment. Echocardiographic evaluation was performed by an experienced physician using a Hitachi Aloka prosound a6 echocardiography device by using 2.5-3.5 MHz transducer in the lateral decubitis position according to American Echocardiography Association guidelines. All images were recorded digitally and specific measurements were made by the average of three to five cardiac cycles. Left ventricle end-systolic diameter, left ventricle end-diastolic diameter, posterior wall and interventricular septum thickness were measured on the M-mode tracing at the papillary muscle level. Simpson's method was used to calculate ejection fraction in the apical four-chamber view. An oscillometric Mobil-O-Graph® PWA Monitor device (I.E.M GmbH, Stolberg, Germany) with integrated ARCSolver® software was used to obtain arterial stiffness parameters. A brachial blood pressure cuff is placed on the left upper arm while the patient was lying in a resting supine position. An oscillometric blood pressure measurement is performed by the device and then the pulse waves at the level of brachial artery are recorded. Measurements were taken after 30 minutes of rest. Measuring the arterial stiffness is based on the physiological process of pulse waves. The software system then provides quantification of aortic systolic blood pressure, aortic diastolic blood pressure, augmentation Index (AIX) and PWV. All participants were asked to avoid drinking alcohol or coffee, and smoking at least 1 hour before the measurements. Cardiologist, radiologist and the author who evaluated the results were unaware as to whether patients were in the dutasteride or non-dutasteride arm of the study (in-house blind).

All statistical analyses were performed using SPSS, version 21. “t test” was used to compare the independent groups and paired t test was used in the matched groups. Statistical significance was described at $p<0.05$.

RESULTS

Mean age of the patients were 65.6 (51-81) years and 64.3 (51-81) years in Dutasteride and Control Groups, respectively ($p>0.05$).

Mean serum TT level increased from 5.07 ng/ml to 5.85 ng/ml and DHT level decreased from 415 pg/ml to 131 pg/ml by the treatment of dutasteride in the Dutasteride Group ($p=0.0001$) An increase in the serum E2 was also observed (21.6 pg/ml to 24.6 pg/ml) but the difference was not statistically significant ($p>0.05$). (Table 1) There was also not a significant increase in FSH and LH levels in the Dutasteride Group ($p>0.05$).

Although there was a slightly decrease in the levels of serum Lp a (11.4 mg/dl to 10.4 mg/dl), hs-CRP (1.58 mg/L to 1.36 mg/L) and NT-proBNP (92.3 pg/ml to 84.4 pg/ml), there was no statistically significant difference ($p>0.05$). Additionally, all of the echocardiographic parameters with brachial artery RI and carotid intima-media thickness were similar before and after dutasteride treatment. ($p>0.05$)

There was not any difference in any of the parameters in the Control Group ($p>0.05$)

All data regarding biochemical, echocardiographic and radiologic evaluation of the Dutasteride and Control groups are presented in Table 1 and Table 2, respectively.

Table 1 .The difference of parameters before and after the dutasteride treatment in Dutasteride Group

	ID					Paired t test	
	n	Mean	Median	Minimum	Maximum	ss	t	p
FSH (mIU/ml) (before)	24	8.71	7.81	2.64	24.31	4.75		
FSH (mIU/ml) (after)	24	8.77	7.95	2.54	23.02	4.29	-0.2	0.838
LH (mIU/ml) (before)	24	7.63	6.80	5.17	12.48	2.25		
LH (mIU/ml) (after)	24	8.10	7.65	5.77	16.54	2.17	-1.1	0.296
E2 (pg/mL) (before)	24	21.56	20.17	5.00	38.44	9.12		
E2 (pg / mL) (after)	24	24.60	23.62	4.28	47.22	10.77	-1.4	0.178
T.Testosteron (ng / ml) (before)	24	5.07	5.07	2.33	8.11	1.64		
T.Testosteron (ng / ml) (after)	24	5.85	5.60	4.22	8.22	1.31	-4.7	0.0001**
Carotis Intima-media thickness (mm) (before)	24	1.24	1.10	.52	2.40	.42		
Carotis Intima-media thickness (mm) (after)	24	1.18	1.00	.56	2.10	.41	0.9	0.355
brachial artery RI (before)	24	.93	.94	.85	.96	.03		
brachial artery RI (after)	24	.93	.93	.87	.97	.03	-0.3	0.794
left ventricular ejection fraction (%) (before)	24	64.3	65.0	50.0	68.0	3.6		
left ventricular ejection fraction (%) (after)	24	64.1	65.0	48.0	68.0	4.0	0.5	0.651
left ventricular end diastolic diameter (mm) (before)	24	4.7	4.7	4.0	5.5	.4		
left ventricular end diastolic diameter (mm) (after)	24	4.7	4.7	4.0	5.4	.4	0.1	0.928
left ventricular end sistolic diameter (mm) (before)	24	2.8	2.9	2.2	3.8	.4		
left ventricular end sistolic diameter (mm) (after)	24	2.8	2.6	.9	4.2	.7	0.3	0.788
left ventricular septal thickness (mm) (before)	24	1.1	1.0	.8	1.3	.2		
left ventricular septal thickness (mm) (after)	24	1.0	1.0	.8	1.4	.2	0.4	0.678
left ventricular anterior wall thickness (mm) (before)	24	1.0	1.0	.7	1.3	.2		
left ventricular anterior wall thickness (mm) (after)	24	1.0	1.0	.8	1.3	.2	0	1
puls wave velocity (m/s) (before)	24	10.0	9.8	7.0	15.0	2.1		
puls wave velocity (m/s) (after)	24	8.7	8.8	0.0	13.5	2.8	1.9	0.071
augmentation index % (before)	24	21.5	21.5	3.0	47.0	10.8		
augmentation index % (after)	24	21.0	18.0	0.0	45.0	11.2	0.3	0.783
Lp (a) (mg/dL) (before)	24	11.4	6.5	3.0	90.0	17.4		
Lp (a) (mg/dL) (after)	24	10.4	6.9	3.0	63.8	13.0	0.8	0.428
DHT (pg/mL) (before)	24	415.01	331.56	83.19	1281.50	270.18		
DHT (pg/mL) (after)	24	131	92	10	377	103	5.2	0.0001*
hsCRP (mg/L) (before)	24	1.58	1.35	.20	4.40	1.05		
hsCRP (mg/L) (after)	24	1.36	1.02	.32	6.00	1.18	1.1	0.273
NT-proBNP (pg/mL) (before)	24	92.3	52.0	8.0	427.0	100.1		
NT-proBNP (pg/mL) (after)	24	84.4	44.0	5.0	650.0	127.7	0.5	0.601

FSH: follicle stimulating hormone, LH: luteinized hormone, E2: estradiol, T.Testosteron: Total testosteron, RI: resistive index, Lp (a): Lipoprotein a, DHT: dihydrotestosterone, hsCRP: high-sensitive C-reactive protein, NT-proBNP: N-terminal pro b-type natriuretic peptide

Table 2 .Parameters baseline and after 6 months in Control Group

	Control					Paired t test	
	n	Mean	Median	Minimum	Maximum	ss	t	p
FSH (mIU/ml) (before)	23	3.96	3.59	1.74	9.83	1.83		
FSH (mIU/ml) (after)	23	4.10	3.91	2.02	9.24	1.67	-1.2	0.242
LH (mIU/ml) (before)	23	4.51	4.37	.95	8.74	1.84		
LH (mIU/ml) (after)	23	4.84	4.22	1.11	11.72	2.47	-1	0.318
E2 (pg/mL) (before)	23	19.33	14.66	5.00	40.45	10.04		
E2 (pg / mL) (after)	23	15.77	13.65	5.00	36.30	9.48	2.3	0.059
T.Testosteron (ng / ml) (before)	23	4.26	3.94	1.47	6.23	1.27		
T.Testosteron (ng / ml) (after)	23	4.38	4.26	1.65	7.39	1.44	-0.6	0.537
Carotis Intima-media thickness (mm) (before)	23	1.00	1.00	.50	2.00	.40		
Carotis Intima-media thickness (mm) (after)	23	.99	1.00	.50	1.90	.38	0.1	0.953
brachial artery RI (before)	23	.91	.93	.78	.95	.05		
brachial artery RI (after)	23	.91	.92	.79	.96	.04	-1.1	0.278
left ventricular ejection fraction (%) (before)	23	64.3	64.0	55.0	69.0	2.9		
left ventricular ejection fraction (%) (after)	23	64.0	64.0	55.0	68.0	2.4	0.6	0.539
left ventricular end diastolic diameter (mm) (before)	23	4.7	4.7	3.8	5.4	.4		
left ventricular end diastolic diameter (mm) (after)	23	4.7	4.8	3.8	5.3	.3	-0.2	0.814
left ventricular end sistolic diameter (mm) (before)	23	2.8	2.9	2.1	3.5	.4		
left ventricular end sistolic diameter (mm) (after)	23	2.8	2.9	2.1	3.5	.4	0.8	0.411
left ventricular septal thickness (mm) (before)	23	1.0	1.0	.7	1.3	.2		
left ventricular septal thickness (mm) (after)	23	1.0	1.0	.8	1.2	.1	0	1
left ventricular anterior wall thickness (mm) (before)	23	1.0	1.0	.7	1.3	.2		
left ventricular anterior wall thickness (mm) (after)	23	1.0	1.0	.8	1.2	.1	-0.1	0.888
puls wave velocity (m/s) (before)	23	8.7	7.6	5.8	14.8	2.4		
puls wave velocity (m/s) (after)	23	8.8	7.5	5.7	14.4	2.5	-1.8	0.084
augmentation index % (before)	23	18.8	21.0	1.0	35.0	10.6		
augmentation index % (after)	23	19.3	20.0	1.0	35.0	11.1	-0.3	0.737
Lp (a) (mg/dL) (before)	23	18.7	6.6	3.0	80.9	26.1		
Lp (a) (mg/dL) (after)	23	17.5	5.5	2.9	81.8	24.6	0.8	0.433
DHT (pg/mL) (before)	23	333.13	324.07	77.49	550.50	113.02		
DHT (pg/mL) (after)	23	322	249	106	970	195	0.2	0.813
hsCRP (mg/L) (before)	23	1.67	1.20	.30	4.20	1.17		
hsCRP (mg/L) (after)	23	1.67	.93	.49	5.18	1.43	0.01	0.994
NT-proBNP (pg/mL) (before)	23	44.5	37.0	5.0	94.0	26.2		
NT-proBNP (pg/mL) (after)	24	44.8	34.0	5.0	134.0	35.2	-0.1	0.953

FSH: follicle stimulating hormone, LH: luteinized hormone, E2: estradiol, T.Testosteron: Total testosteron, RI: resistive index, Lp (a): Lipoprotein a, DHT: dihydrotestosterone, hsCRP: high-sensitive C-reactive protein, NT-proBNP: N-terminal pro b-type natriuretic peptide

DISCUSSION

Aging is a consociate risk factor for both CVD and BPH. It was demonstrated that 39.2% of patients who were prescribed treatment for BPH for the first time had also been using cardiovascular drugs (1,2). Beside aging, androgens are also accepted to be associated with both CVD and BPH. Androgens play an important role in the pathogenesis of prostatic growth, insulin sensitivity, bone metabolism and endothelial function (1-6).

In contrast to some limited articles claiming that TT is harmful for cardiovascular health (7-8), majority of the studies in the literature demonstrate favorable effects of TT on cardiovascular system (9-13). Low TT level results in endothelial dysfunction, vascular stiffening, calcification and increase of arterial wall thickness by causing an increase in the level of pro-inflammatory markers. Low TT level is also associated with mitochondrial dysfunction and oxidative stress resulting in increased risk for cardiovascular events. In addition, it was demonstrated that higher serum TT level in elderly men has a cardioprotective effect (14-16). It is also well known that patients who were given androgen deprivation therapy due to prostate cancer are at an increased risk of cardiovascular events (17-19).

5-alpha-reductase inhibitors such as Dutasteride and Finasteride which are important medicaments used for the treatment of BPH decrease serum DHT levels by more than 90% and increase serum TT levels by inhibiting type I and type II 5-alpha-reductase isoenzymes. So it was investigated whether 5-alpha-reductase inhibitors has any effect on the cardiovascular system after 2000s. However, there is limited numbers of article about this topic in the literature. First study investigates the effect of 5-alpha-reductase inhibitors on CVD was published by Souverein et al. in 2002. They presented that there was not an association between the use of alpha-blockers or finasteride and hospital administration for ischemic heart disease in their population-based study (20). In 2015, Hsieh et al. printed a population-based study by using the National Health Insurance Research Database to evaluate whether 5 ARI are associated with cardiovascular disease in Taiwan. They monitored the patients who were given 5 ARI and also patients who were not given 5 ARI for five years. They found that the rate of cardiovascular disease was significantly lower in patients using Dutasteride (8.4% vs. 11.2%) (21). Skeldon et al. found that Dutasteride did not increased the risk for cardiovascular events as well as Finasteride (22). In contrast to these results, Chou et al. (6) presented that patient who were using 5 ARI had an increased risk of acute coronary syndrome. This was again a population-based study.

To the best of our knowledge, the present study is unique in terms of investigating the effects of the Dutasteride on cardiovascular system by using novel cardiaovascular markers. Lp a is a cardiac marker which is associated with increased LDL- Cholesterol and decreased left ventricular ejection fraction (23). Recent studies have shown that lp a which is an aterogenic lipoprotein has an important role on the pathway of the atherosclerotic cardiovascular diseases (24). In the present study we explored the association between Dutasteride and lp a. In our study, there was a slight decrease in Lp a levels in the Dutasteride group (11.4 mg/dl to 10.4 mg/dl). However this decrease was not statistically significant.

A systemic inflammation marker, hs-CRP, is another important biomarker that has been used to evaluate the risk of cardiovascular events (25). Although there are multiple risk factors, inflammatory process plays a main role in the initiation and progression of atherosclerosis. It is also known that active inflammatory process is associated with elevated CRP (26). According to our results, a statistically insignificant decrease in hs-CRP levels was observed in the Dutasteride group (1.58 mg/L to 1.36 mg/L)

NT-proBNP has also been widely used as a novel cardiac biomarker after 2000s. NT-proBNP is a kind of B-type natriuretic peptide which is mainly released by the cardiomyocytes. Ventricular dilatation and volume overload cause an increase of secretion of this hormone. So, in patients with heart failure, a prominent increase in the serum levels of NT-proBNP is detected. Longer half-time and expression time of NT-proBNP is another advantage to be a biomarker for cardiac dysfunction (27). We used NT-proBNP as a biomarker to evaluate the effect of Dutasteride on the heart failure. There was a decrease in mean value of NT-proBNP levels in Dutasteride group (92.3 pg/ml to 84.4 pg/ml) but the decrease was not statistically significant.

Brachial artery resistive index (RI) is a non-invasive method to evaluate endothelial function (28). In addition, carotid intima-media thickness (CIMT) which is quite easy to measure by using ultrasound is an independent predictor of cardiovascular risk (29). Endothelial dysfunction triggers atherosclerosis and this process results in an increase in intima-media thickness of the arteries (30). Since CIMT and brachial artery RI are simple tools to evaluate the risk for cardiovascular events, we used these parameters in order to investigate the effects of Dutasteride on cardiovascular outcomes. Our study results revealed that there was not a statistically significant difference in both parameters between Dutasteride and Control groups.

There are some limitations of the present study. First, although this is a prospective, randomized, in house blind study, it is not placebo controlled. So we could not evaluate the placebo effect on the results. Second limitation of the study is the low number of the participants. And third, we evaluated short-term results of Dutasteride on cardiovascular system. So long term results of such study may give different results. Despite the limitations mentioned above, to our knowledge, this is the first study evaluating the effects of Dutasteride on cardiovascular system by using novel cardiovascular biomarkers.

CONCLUSION

As a conclusion, after the short-term use of dutasteride, there was no statistically significant difference in levels of serum Lp a, hs-CRP and NT-proBNP which are well known as markers of heart failure and cardiovascular disease. Carotid intima-media thickness, brachial artery RI and echocardiographic parameters were statistically similar. In addition follow up of these patients will be rational in terms of monitoring long term results.

Contributions: Conception and Design: UO, AT. Data acquisition: AK, UO. Data analysis and interpretation: UO, AK, AT, ED, MU, EÖ, EK, MK. Drafting the manuscript: UO. Critical revision: UO, BB, MHK, OY. Statistical analysis: UO. Supervision: MHK, BB, OY.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: This study was financially supported by Scientific Project Office of Giresun University. Project number: SAG-BAP-A-250414-68.

Ethical approval: All procedures performed in study involving participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was performed after having obtained approval of "National Medicines And Medical Devices Agency Ethics Committee".

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