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The Effects of Lovastatin on Conventional Medical Treatment of Lower Urinary Tract Symptoms with Finasteride

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ABSTRACT

Objective: To explore whether or not statins have any impact on the progression of components of benign prostatic hyperplasia (lower urinary tract symptoms severity, prostate volume and serum prostate specific antigen (PSA) when combined with other agents inhibiting growth of prostate cells.
Materials and Methods: This was a preliminary, clinical study. Eligible patients were aged > 50 yrs, with International Prostate Symptom Score (IPSS) between 9 and 19, total prostate volume (TPV) > 40 mL, and serum PSA > 1.5 ng/mL. Patients were divided in two groups: those with and those without lipidemia. After selection, eligible BPH patients with lipidemia (n = 18) were prescribed lovastatin 80 mg daily and finasteride 5 mg daily, while eligible patients without lipidemia (n = 15) were prescribed only finasteride 5 mg daily. IPSS, TPV and serum PSA were evaluated at end point (4 months).
Results: There was no difference between the two groups on the primary end point of mean change from baseline in IPSS (p = 0.69), TPV (p = 0.90) and PSA (p = 0.16) after 4 months of treatment.
Conclusions: Short-term lovastatin treatment does not seem to have any effect on IPSS, TPV and PSA in men with prostatic enlargement due to presumed BPH.

Key words: *prostate; benign prostate hyperplasia; volume; PSA; statins; finasteride*
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INTRODUCTION

The etiology of benign prostatic hyperplasia (BPH) is still largely unresolved. Multiple partially overlapping and complementary systems (nerve, endocrine, immune, vascular) and local factors are likely to be involved (1), and therefore, several etiologic factors for BPH have been proposed to date (2). Primary interest has been focused on the steroid hormones, especially testosterone estrogen and their metabolites (3). Of the currently used BPH pharmacotherapeutic treatments, only the 5a-reductase inhibitors have been demonstrated to modify the underlying pathology (4).

A competitive inhibitor of the enzyme, type-II 5a-reductase, blocks the reduction of serum testosterone to the more active dihydrotestosterone (DHT). In fact, DHT and not testosterone is the major intraprostatic androgen (5,6). As a result, intraprostatic DHT levels decrease by 80-90% while serum testosterone levels remain unchanged. Although the role of these agents is not fully defined, a regression of the epithelial component of BPH causing a reduction of prostate volume (approximately 30%) (7) and a decrease in the 'static' component of bladder outlet obstruction resulting in improvements in lower urinary tract symptoms (LUTS) and urinary flow have been documented in flow rates, symptom

scores and imaging studies (8). The best results have occurred in men with large prostates (> 40 grams), while all the 5a-Reductase Inhibitor's (5ARI) effect takes approximately 3 to 6 months to occur (9). To our knowledge, of the currently used BPH pharmacotherapeutic interventions only the 5a-RI's have been shown to modify the underlying pathology.

Statins are commonly prescribed agents to lower cholesterol and the associated risks of vascular events. They act by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. Stimulation of liver low-density lipoprotein (LDL) receptors by inhibition of this enzyme in the liver results in an increased clearance of LDL from the bloodstream and a decrease in blood cholesterol levels.

Since cholesterol is a required intermediate in sex steroid synthesis, a decrease in blood cholesterol levels results in a decrease in sex steroid synthesis. Indeed, epidemiological studies have demonstrated that alteration of hormonal levels results in modifications of hormonal activity in the prostate gland (10). Although the multiple interactions in the biochemical pathways and the molecular signaling of steroid hormones and its impact in the development of BPH in cellular level are poorly understood, it could be assumed that alteration of sex steroid synthesis leads to changes in local networks of epithelial, stromal and luminal factors necessary for the BPH development (11). Under those circumstances, it is possible that statins influence BPH development through effects on steroid hormone through interference of the 5a-RI's molecular mechanisms. Experimental studies have demonstrated that steroid hormones contain characteristic effects on prostatic smooth muscle cells (12) which can be altered by statins (13). Although the exact mechanism is not known, the impact of statins on hypertrophic prostate cells growth could be attributed to the apoptotic properties of statins. Effects of statins in both prostate stromal and epithelial cells could be also attributed to the anti-oxidative properties of statins. In fact, there is increasing evidence that oxidative stress might play a role in the induction of prostate cells growth and thus contribute to the pathogenesis of BPH (14,15).

Since most patients with symptomatic BPH are aging men and are likely to use additional drugs for the treatment of concomitant diseases, the identification of those which may interfere with BPH molecular mechanisms and enhance the efficacy of conventional BPH treatment would be useful to patients following conservative treatment alone. Given that the efficacy of 5aRI's in treating LUTS suggestive of BPH is limited (9), statins probably represent the perfect candidate.

The aim of the present study was to explore an approach to the treatment of men with LUTS and prostatic enlargement that involves simultaneous management of serum lipid levels, by evaluating the impact of lovastatin on conventional treatment with finasteride in men with BPH.

MATERIALS AND METHODS

Patients complaining of lower urinary tract symptoms who presented at the outpatient Department of Urology at the General Hospital of Thebes from June 2006 to February 2007 were asked to complete the International Prostate Symptom Score (IPSS). In collaboration with the Department of Cardiology, they underwent a serum total cholesterol, HDL and LDL examination. The only criterion for classifying a man as lipidemic, was a fasting serum low-density lipoprotein level > 100 mg/dL in two consecutive measurements. Inclusion criteria were as follows: age > 50 yrs., IPSS between 9 and 19, total prostate volume (TPV) > 40 mL, and serum prostate specific antigen (PSA) > 1.5 ng/mL at baseline. Patients who met the inclusion criteria were considered eligible for this study independently of their lipidemic status. Exclusion criteria were previous medical history, evidence, or suspicion of prostate cancer; history of urologic surgery or procedures that may have altered prostate anatomy/architecture cystoscopy, prostate biopsy or catheterization within 15 days of study entry, urinary tract infection; chronic prostatitis, bladder stone, severe infection or major surgical operation within 3 mo prior to study entry. Subjects with clinically significant impaired hepatic or renal function; clinically significant elevation in serum creatinine phosphokinase or TG levels were excluded from the study.

The study was approved by the local ethics committee and was performed in accordance with

the International Conference on Harmonization Guidelines for Good Clinical Practice (1996), which represents the international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve participation of human subjects.

Study Design

Preliminary, clinical study in men with BPH and LUTS. Both study group and controls were regular patients who presented at the outpatient department of the General Hospital of Thebes. Eligible patients were aged > 50 yrs., with an IPSS between 9 and 19, TPV > 40 mL, and serum prostate-specific antigen (PSA) > 1.5 ng/mL. They were selected among first time-diagnosed patients with BPH who were scheduled to receive the appropriate treatment. Study medication was only prescribed to those patients who were found to suffer from LUTS suggestive of BPH and lipidemia. After a nine-month screening period, selected patients were divided into two groups accordingly to their lipidemic status. In order to reduce potential bias, both groups were consisted of selected patients with similar demographics who met the same selection criteria.

Outcome Measures

The mean changes from baseline of IPSS, TVP and PSA as efficacy parameters were defined. Efficacy evaluations were performed at baseline and at four month of treatment. A GE 2000 ultrasound device was used to determine total prostate volume measurements. The TPV was calculated by using the formula for a prolate ellipse (width x length x height x 0.52). Symptom improvement was assessed using the International Prostate Symptom Score Questionnaire, whereas lipidemia was monitored through fasting low-density lipoprotein measurements..

RESULTS

The screening period was between June 2006 and February 2007. Eligible patients were divided in the two study groups between April and June 2007 (baseline) according to the lipidemic status. The remaining patients were prescribed the appropriate treatment accordingly to the bothersome of LUTS and the levels of serum LDL. Of 98 patients initially screened only 37 meeting the inclusion criteria had similar demographics: There was no statistically significant difference between the two groups regarding median age, body height, total cholesterol and LDL level at baseline. Patients with lipidemia (serum low-density lipoprotein > 100 mg/dL at baseline) were prescribed lovastatin 80 mg daily and finasteride 5 mg daily, while patients without lipidemia were prescribed only finasteride 5 mg daily. Two of the selected patients however did not receive treatment; one patient left the study due to adverse events, while another patient discontinued the study. Finally, 33 patients (18 with lipidemia and 15 without lipidemia), completed the study in October 2007.

The change in mean IPSS from baseline (14) to end point (7.5) was considered statistically significant ($p = 0.00$) in patients with lipidemia (statin-finasteride group). The change in mean IPSS from baseline (14.8) to end point (8.7) was considered statistically significant ($p = 0.00$) in patients without lipidemia (finasteride group) also.

The change in mean TPV from baseline (58.7) to end point (46.8) was statistical significant ($p = 0.00$) in patients with lipidemia (statin-finasteride group). The change in mean TPV from baseline (57.2) to end point (44.7) was considered statistically significant ($p = 0.00$) in patients without lipidemia (finasteride group).

The change in mean PSA from baseline (2.87) to end point (1.89) was considered statistically significant ($p = 0.00$) in patients with lipidemia (statin-finasteride group). The change in mean PSA from baseline (3.09) to end point (2.37) was not considered of statistical significance ($p = 0.2$) in patients without lipidemia (finasteride group).

There was no difference between the two groups on the primary end point of mean change from baseline in IPSS ($p = 0.69$), TPV ($p = 0.90$) and PSA ($p = 0.16$) after 4 months of treatment (Table-1).

COMMENTS

The fact that both BPH and metabolic syndrome are very common conditions - particularly

Table 1 – *Patient demographics.*

	Patients Without Lipidemia (finasteride group)	**Patients With Lipidemia** (statin-finasteride group)
Mean age	65.7	66.2
Mean weight	78.2	80.8
Mean IPSS (baseline)	14.8 (3.27)	14 (3.18)
Mean IPSS (end point)		7.5 (2.95)
Mean TPV (baseline)	57.2 (18.01)	58.72 (16.92)
Mean TPV (end point)		46.69 (14.74)
Mean PSA (baseline)	3.067 (1.92)	2.87 (1.58)
Mean PSA (end point)	2.37 (2.09)	1.89 (1.1)

IPSS = International Prostate Symptom Score; PSA = prostate specific-antigen; TPV = total prostate volume (standard deviations are in parentheses)

among older men- and the observation that most BPH patients share similar metabolic abnormalities as patients with the metabolic syndrome, have led several investigators to point out a relationship between those two conditions (16,17). Although the specific mechanism is not clearly understood it could be assumed that it involves an interplay between several hormonal pathways: since lipids impact both on cardiovascular disease development and the production of sexual hormones, it is plausible that they might affect the risk for BPH development through the increase of DHT levels (18). Epidemiologic data demonstrated a significantly higher prevalence of cardiovascular diseases and dyslipidemia in men with BPH (3,19) and studies linking dyslipidemia with the rate of benign prostatic growth and with LUTS (20,21) further support the above-mentioned hypothesis. In confirmation of the above, an experimental study demonstrated that a high cholesterol diet, and subsequently high serum cholesterol levels, led to histological changes in the rat prostate that resembled prostatic hyperplasia (22) while, recently, statins have been proven to affect circulating androgens (23).

Only two clinical trials (24,25) to date have addressed the potential use of statins in the treatment of men with LUTS and BPH. In the study of Marino et al., simvastatin was used along with mepartricin, a polyene macrolide antibiotic with unknown composition, for the treatment of symptomatic BPH in a small sample of patients. In contrast Mills et al., assessed the efficacy of atrovastatin in the treatment of LUTS and prostate enlargement in a large, double blind, placebo-controlled trial. The results of these previous studies are controversial; while treatment with simvastatin achieved a 38-40% clinical response in the first study (24), treatment with atrovastatin did not show an effect on urinary symptoms, flow rate, quality of life, or prostate size and morphology and PSA in the second (25). Given the similarities in the pharmacological profile between simvastatin and atrovastatin it could be easily assumed that the effects on observed in the study of Marino et al., are more likely to be attributed to the mepartricin whose efficacy in the treating of BPH related symptoms was further investigated (26-28). Although a potential role of mepartricin in decreasing estrogen plasmatic levels and their concentration in the prostate has been proposed (29), it is more likely to be attributed to its antibacterial action. Indeed, a reduction in prostate size has not been achieved in any of these studies, while more recent studies linked the mepartricin induced LUTS improvement in cases of chronic nonbacterial prostatitis/chronic pelvic pain syndrome (30).

None of the previous studies, however, has evaluated the efficacy of BPH treatment with statins in combination with a 5a-reductase inhibitor. Currently,

it is still not clear which effect of 5ARIs is responsible for their benefits; current evidence suggests a apoptotic process restricted to epithelial cells (31). To our knowledge, BPH is caused by an increase in prostate epithelial and stromal cells, especially the latter. The observation that statins have pro-apoptotic effects in prostate stromal cells (32,33), justified the rationale for the complementary use of statins in the treatment of BPH: since BPH stromal cells have a long life span and are not very responsive to androgen withdrawal (32), pharmacologically inducing apoptosis in these cells could probably lead to a further reduction of hypertrophic prostate volume and to a consequent improvement of LUTS. Unfortunately, similar to the previous studies, statins did not show any effect of on IPSS, nor boosted the 5ARI's effect on TPV. However, serum PSA values seemed to be generally lower in the statin/finasteride arm compared to finasteride arm alone. This finding is interesting, as statins have been previously reported to decrease serum PSA (34). It could be assumed that statins also impact on the growth of prostate epithelial cells through an intervention in the pathway of androgen synthesis (35). Although, data suggest that treatment with statins may lower serum PSA with time, results must be confirmed in a larger study population while controlling for potential confounders. Finally, our finding of a non statistically significant change in mean PSA from baseline to end point in patients without lipidemia (finasteride group) could be probably attributed to the relatively low sample as well as to the relatively low duration of the study. In fact, it is not uncommon for therapies to not impact LUTS objective measures (prostate volume, PSA, flow rate) but still result in real patient improvement in IPSS scores (as in pde5i inhibitors).

CONCLUSION

Since the study period was very short, any long-term effects could not be discussed based on these results. It is probable that no effect of statins on IPSS, TPV and PSA would have been detected even if the study had lasted over a longer period of time. However, it is also possible the statins would have had an effect via metabolic pathways or atherosclerotic mechanisms only after max finasteride effect had occurred (minimum of 6 months f/u). Against a background of increased interest on the impact of steroid hormones in the development of BPH current knowledge is limited and no data indicate whether or not statins independently from their impact on circulating androgen levels does influence the natural history of BPH.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Stamatiou and colleagues are to be lauded on presenting this "negative results" study. The conclusions of the study are reasonable based on the given preliminary data. However, additional assessment of the study's endpoints at the one year mark and beyond while on therapy is crucial. As the authors mention, the maximum effect of finasteride is often not seen until 6 months of therapy has been utilized; this study yields data after only 4 months of intervention. Perhaps more importantly, determination of any synergistic effect of lovastatin with finasteride on LUTS via either metabolic syndrome or a pelvic atherosclerosis mechanism (both long term processes) would likely also require a more robust length of follow-up to note a significant difference between the study's treatment arms.

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EDITORIAL COMMENT

Finasteride, a 5α-reductase inhibitor is currently an established part of medical management of benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS). Inhibition of 5α-reductase lowers serum levels of dihydrotestosterone, the active androgen metabolite. This leads to reduction in prostate volume and serum prostate specific-antigen (PSA) values.

Experimental studies have reported that statins, a widely used group of cholesterol-lowering drugs, can reduce proliferation of prostate stromal and epithelial cells in vitro (1). This effect seems to

be at least partly mediated by inhibition of the enzyme HMG-CoA reductase that, in addition to precursors of cholesterol, also produces isoprenoids essential in control of cell cycle and apoptosis. However, also other mechanisms of action have been proposed (1).

Thus, it is within possibilities that statins could be effective in treatment of LUTS due to BPH. In this issue of the International Braz J Urol, Stamatiou et al. report results from a clinical experiment, in which they recruited 33 men with BPH, and treated hypercholesterolemic men with combination of finasteride and lovastatin (2), while normolipidemic men were treated conventionally with finasteride only.

The study setting is interesting. As the mechanisms for action in the prostate tissue are likely separate for lovastatin and finasteride, they could in theory have a synergistic effect in BPH treatment.

However, the observed decrease in clinical parameters of BPH was similar for both groups. After four months treatment there was no significant difference in prostate volume, serum PSA or IPSS symptom score between the study groups, i.e. there was no advantage for combining lovastatin with finasteride. Still, the PSA level was lower among hypercholesterolemic men both at the base line and after four months treatment, which suggests that serum cholesterol level could also affect PSA.

This is among the first clinical studies on this subject. The results in general concur with previous studies (2). Thus, based on the present evidence, the answer for the title question seems to be "no". Lovastatin does not enhance the effect of finasteride treatment for lower urinary tract symptoms or prostate volume, and statins cannot be currently endorsed for treatment of LUTS.

However, the follow-up time in this study was only four months, and thus long-term effects cannot be ruled out. While lovastatin does not appear to have any immediate treatment effect in BPH (based on the absence of synergistic effect with finasteride), it still remains unclear whether lovastatin could reduce progression of BPH. Due to slowly progressing nature of BPH this kind of treatment effect would take years, instead of months, to become evident in a clinical study.

Additionally, the two study groups differed systematically according to their lipidemic status. Serum cholesterol affects prostate growth (3), and it is possible that this difference could have changed the treatment response between the study groups.

In spite of these uncertainties, the study by Stamatiou et al. shows that, despite the drug's beneficial cardiovascular effects, lovastatin does not seem to have any short-term effect against BPH and does not bring any benefit over the conventional medical management of the condition. Thus, based on the current evidence, we cannot recommend lovastatin to patients for treatment of BPH and LUTS.

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