Original Article

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Long-term dutasteride therapy in men with benign prostatic hyperplasia alters glucose and lipid profiles and increases severity of erectile dysfunction

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Abstract:
Background: Dutasteride has been successfully used in treatment of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). However, dutasteride inhibits 5α-reductase type 1 and type 2 enzymes and may compromises glucocorticoids and androgen metabolism and alters metabolic function resulting in undesirable metabolic and sexual adverse side effects.
Aim: The aim of this study was to investigate the long-term adverse effects of dutasteride therapy in men with BPH on: i) blood glucose, ii) glycated hemoglobin (HbA_{1c}), iii) low density lipoprotein-cholesterol (LDL-C); high density lipoprotein-cholesterol (HDL-C) and total cholesterol (TC), iv) testosterone (T), v) liver alanine and aspartate aminotransferases (ALT and AST) and vi) erectile dysfunction (ED).
Methods: A retrospective registry study, with a cohort of 230 men aged between 47 and 68 years (mean 57.78 ± 4.81) were treated with dutasteride (0.5 mg/day) for LUTS, secondary to BPH. A second cohort of 230 men aged between 52 and 72 years (mean 62.62 ± 4.65) were treated with tamsulosin (0.4 mg). All men were followed up for 36–42 months. At intervals of 3–6 months, and at each visit, plasma glucose, HbA_{1c}, TC, LDL-cholesterol, T levels and liver alanine amino transferase (ALT) and aspartate aminotransferase (AST) were determined. Further patient assessment was made by the International Index of Erectile Function (IIEF-EF) questionnaire, the Aging Male Symptom (AMS) and International Prostate Symptom Scores (IPSS).
Results: Long-term treatment with dutasteride therapy is associated with significant improvements in LUTS, as assessed by reduction in prostate volume, IPSS and prostate specific antigen (PSA). Long-term dutasteride therapy, however, resulted in increased blood glucose, HbA_{1c}, TC and LDL levels, ALT and AST activities, AMS Score and reduced T levels and worsened ED as assessed by the IIEF-EF scores. No worsening of ED, glucose, HbA_{1c}, ALT, AST, AMS were observed in men treated with tamsulosin. Most importantly, long-term dutasteride therapy resulted in reduction in total T levels, contributing to a state of hypogonadism.
Conclusion: Our findings suggest that long-term dutasteride therapy produces worsening of ED, reduced T levels and increased glucose, HbA_{1c} and alters lipid profiles, suggesting induced imbalance in metabolic function. We strongly recommend that physicians discuss with their patients these potential serious adverse effects of long-term dutasteride therapy prior to instituting this form of treatment.

Keywords: dutasteride, glucose, lipid profiles, sexual adverse effects, testosterone
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Introduction

5α-Reductase inhibitors (5α-RIs) finasteride and dutasteride and α-adrenergic receptor blockers (ARB), such as tamsulosin, are widely used treatments of lower urinary tract symptoms (LUTS), secondary to benign prostatic hyperplasia (BPH) [1], [2]. 5α-RIs therapy with finasteride is also widely used for treatment of male pattern hair loss (MPHL) commonly known as androgenetic alopecia (AGA) [3], [4]. However, among the main concerns of

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5α-reductase inhibitors therapy is the potential serious adverse sexual side effects [1], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19].

Recently, Upreti et al. [20] reported that inhibition of 5α-reductases (type 1 and 2) by dutasteride reduced stimulation of glucose disposal by high dose insulin and reduced suppression of non-esterified fatty acids (NEFA). These findings suggested that dutasteride inhibition of critical biochemical pathways mediated by 5α-reducatases negatively alter metabolic function [20]. Dutasteride treatment also increased fasting homeostatic model assessment of insulin resistance (HOMA-IR) and increased plasma insulin levels [20]. Dutasteride increased body fat and reduced insulin-mediated suppression of non-esterified fatty acids (NEFAs) [20]. These findings are consistent with the findings of Joyce et al. [21] who reported that, among older men, levels of 5α-dihydrotestosterone (5α-DHT) were inversely associated with insulin resistance (IR) and risk of diabetes.

The potential role of 5α-reductase type 1 in carbohydrate and lipid metabolism is inferred from studies in animals lacking 5α-reductase type1 (knockout, KO). When these animals were fed a high fat diet they exhibited increased susceptibility to weight gain, hyperinsulinemia, fasting hyperglycemia, increased ratios of insulin to glucose and liver fat accumulation [22]. Furthermore, in 5α-reductases type 1-KO mice, liver fatty acid β-oxidation and gluconeogenesis were impaired and gene expression for enzymes catalyzing triglyceride esterification and cholesterol synthesis and excretion were elevated. Animals lacking 5α-reductase type1 also showed greater hepatic fibrosis than wild type mice. Furthermore, inhibition of 5α-reductases (type 1 and type 2) in male Zucker rats, increased plasma glucose and insulin levels [22]. These findings suggest that 5α-reductase type 1 plays an important role in metabolic disease, and may contribute to hepatic steatosis, which leads to enhanced susceptibility to fibrotic liver injury and accelerated progression to nonalcoholic fatty liver disease (NAFLD). These findings emphasize the potential adverse metabolic function in men treated with dutasteride.

Cross-sectional clinical studies have shown that low testosterone concentrations are associated with increased hepatic steatosis in men [23], [24] and are consistent with findings in rodent models, suggesting that 5α-DHT treatment can decrease hepatic lipid accumulation [25], [26].

5α-RIs therapy has critical clinical implications not only in terms of predisposing individuals to development of hepatic steatosis, but also to the large numbers of patients prescribed 5α-reductase inhibitors. As the long-term metabolic consequences of these medications have not been fully assessed, we undertook this study to determine the long-term effects of dutasteride therapy in men with BPH on glucose, HbA_{1c}, TC, LDL-cholesterol and testosterone (T) levels. In addition, we assessed the effects of dutasteride on liver alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities as well as erectile dysfunction (ED).

Methods

(T) All subjects had sought urological consultation in a single urologist's office for LUTS due to BPH. A cohort of 230 men between age 57 and 68 years (mean age 57.78 ± 4.81 years), with total plasma testosterone (T) levels at base line between 310 and 740 ng/dL) (mean 517 ± 100.25 ng/dL) were treated with dutasteride (0.5 mg/day). A second cohort of 230 men between age 53 and 72 years (mean age 62.62 ± 4.65 years), with total plasma T levels at baseline between 310 and 740 ng/dL (mean 533 ± 123 ng/dL) were treated with tamsulosin (0.4 mg). The choice of treatment drug was based on patient's preference after discussion with their urologist.

All subjects on dutasteride and tamsulosin were followed up for 36–42 months. Total plasma T levels, fasting glucose levels and hemoglobin A_{1c} (HbA_{1c}), lipid profile [total cholesterol (TC), low-density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholestero] and liver transaminases were measured as described previously [10], [27], [28]. We also assessed prostate volume, prostate-specific antigen (PSA). The following questionnaires were also completed: International Prostate Symptom Score (IPSS), Aging Males' Symptoms (AMS), and International Index of Erectile Function, Erectile Function domain (IIEF-EF). There were 121 men with diabetes, 58 of them were in the dutasteride group (25.5%) and 63 men with diabetes were in the tamsulosin group (27.4%). In the dutasteride treated group, 45 men (19.57%) were on phosphodiesterase type 5 inhibitors (PDE 5i) therapy and 61 men (26.4%) were on statins therapy at baseline.

At each visit, blood was sampled between 8.00 and 11.00 h after overnight fasting. Plasma T levels were measured using standardized routine laboratory methods [28]. Prostate volumes (PV) were measured using Sonoace SA 8000 SE with ultrasound probes [28] (Samsung Electronics GmbH, 65824 Schwalbach/Taunus, Germany). Baseline PSA levels were determined (ng/mL) as described previously [28]. The IPSS was assessed at each visit (3 months), men completed the AMS and the IIEF questionnaire, maximum score 30 [29]. Prostate size was assessed by ultrasonography [29]. Liver function test was also carried out as described previously [27]. Adherence to treatment was excellent. All patients gave their informed consent to be included in this study, and in accordance to the rules of the German Medical Association for evaluation of patient data from patients receiving standard therapy.

Statistical analyses

The Proc Mixed reference is SAS/STAT Software, Version 9.3 (2011) by SAS Institute Inc was utilized in these analyses. For ontinuous variables, the mean, median, standard deviation, range, minimum, maximum and sample size for the overall sample were reported at each time point. For categorical variables, the frequency distribution was reported. We tested the hypotheses regarding change in outcome scores across the study period by fitting a linear mixed effects model to the data. A random effect was included in the model for the intercept. Estimation and test of change across time were determined by computing the differences in least square means at baseline vs. the score at each follow-up interview, as described previously [10]. Because there were differences in the parameters measured at baseline among the two groups (Table 1), we presented our findings as percent change from baseline values.

Data were expressed as mean change from baseline and plotted as a function of duration of follow-up.

Table 1: Baseline characteristics of patients in the registry treated for long-term with dutasteride and tamsulosin.

Characteristic	Overall (n = 460)	Dutasteride (n = 230)	Tamsulosin (n = 230)	p-Value
Age at baseline				
Mean ± SD	63.13 ± 4.4	63.64 ± 4.1	62.62 ± 4.65	0.013175
Median and range	63 (53.5–72.3)	64 (55–72)	62.65 (53.5–72.3)	
Waist circumference				
Mean ± SD	104.13 ± 6.22	102.91 ± 4.27	105.36 ± 7.5	0.000021
Median and range	104 (93–122)	103 (96–110)	105 (93–122)	
Weight				
Mean ± SD	88.2 ± 8.84	86.67 ± 7.52	89.73 ± 9.77	0.000196
Median and range	86 (72–113)	85 (74–113)	89 (72–110)	
Prostate volume, sonography				
Mean ± SD	48.58 ± 8.79	50.73 ± 8.43	46.42 ± 8.63	9.199E-8
Median and range	49 (32–71)	51 (32–71)	46 (32–60)	
IPSS				
Mean ± SD	9.07 ± 1.6	8.98 ± 1.76	9.17 ± 1.42	0.220268
Median and range	9 (5–12)	9 (5–12)	9 (7–11)	
AMS total = Aging Males' Symptoms questionnaire'				
Mean ± SD	22.09 ± 4.83	23.62 ± 5.95	20.56 ± 2.58	3.12E-12
Median and range	21 (17–47)	22 (17–47)	21 (17–30)	
IIEFEF				
Mean ± SD	22.18 ± 2.77	24.28 ± 1.57	20.07 ± 2	4.41E-88
Median and range	23 (17–29)	24 (20–29)	20 (17–23)	
Hematocrit				
Mean ± SD	45.77 ± 1.69	45.7 ± 1.93	45.83 ± 1.41	0.408396
Median and range	46 (42–50)	46 (42–50)	46 (43–49)	
Leukocytes				
Mean ± SD	7.11 ± 1.02	7.26 ± 0.93	6.95 ± 1.09	0.001094
Median and range	7.1 (5.2–8.9)	7.3 (5.6–8.9)	7 (5.2–8.8)	
Creatinine				
Mean ± SD	1.02 ± 0.15	1.05 ± 0.17	0.99 ± 0.12	0.000027
Median and range	1 (0.8–1.3)	1.05 (0.8–1.3)	1 (0.8–1.2)	
Glucose				
Mean ± SD	101.1 ± 6.76	101.59 ± 7.53	100.62 ± 5.88	0.124383
Median and range	99 (92–125)	99 (92–125)	100 (92–118)	
AST/GOT				
Mean ± SD	27 ± 6.06	29.82 ± 7.04	24.19 ± 2.82	3.8E-26
Median and range	26 (18–42)	30 (18–42)	24 (19–29)	
ALT/GPT				
Mean ± SD	30.29 ± 5.8	32.33 ± 7.04	28.25 ± 3.06	6.57E-15
Median and range	29 (20–45)	33 (20–45)	28 (22–35)	
CRP				
Mean ± SD	1.27 ± 0.96	1.51 ± 0.89	1.02 ± 0.97	4.531E-8
Median and range	1 (0.1–4.6)	1.5 (0.1–2.9)	0.8 (0.1–4.6)	
PSA				

Mean ± SD	2.6 ± 1.11	2.92 ± 0.9	2.27 ± 1.21	1.26E-10
Median and range	2.7 (0.2–5.2)	2.9 (1.1–5.2)	2.3 (0.2–4.2)	
Testosterone				
Mean ± SD	4.94 ± 1.11	4.55 ± 0.81	5.33 ± 1.23	1.21E-14
Median and range	4.8 (2.5–7.4)	4.7 (2.5–6.2)	5.5 (3.1–7.4)	
Diastolic blood pressure				
Mean ± SD	80.64 ± 19.52	89.03 ± 14.62	72.26 ± 20.23	4.06E-22
Median and range	81.5 (40–135)	97 (51–103)	69 (40–135)	
Hemoglobin				
Mean ± SD	14.65 ± 0.5	14.71 ± 0.57	14.59 ± 0.41	0.011981
Median and range	14.6 (13.8–15.6)	14.6 (13.8–15.6)	14.6 (13.9–15.3)	
Total cholesterol				
Mean ± SD	234.17 ± 37.21	240.08 ± 27.39	228.26 ± 44.21	0.000618
Median and range	236.5 (144–327)	242 (177–290)	226 (144–327)	
LDL				
Mean ± SD	130.26 ± 50.1	104.26 ± 42.72	156.27 ± 42.97	3.51E-33
Median and range	131 (31–239)	111 (31–193)	154.5 (82–239)	
HDL				
Mean ± SD	49.03 ± 16.08	41.42 ± 13.72	56.64 ± 14.61	4.09E-27
Median and range	48.5 (18–88)	41 (18–66)	56 (27–88)	
HbA_{1c}				
Mean ± SD	5.82 ± 1.29	5.75 ± 1.34	5.88 ± 1.23	0.270069
Median and range	5.2 (4–9.8)	5.1 (4–9.8)	5.3 (4.7–8.4)	

Baseline characteristics by treatment.

Results

The data in Table 1 provide baseline characteristics of 460 patients included in this retrospective registry study. Two hundred and thirty men were treated with dutasteride and a second group of 230 men were treated with tamsuloisn. All the men were treated for LUTS, secondary to BPH, in one single urologic clinic. At baseline the two groups were similar in some parameters, however, men in the tamsulosin group had larger waist circumference, body weight and elevated LDL and HDL values, and lower AMS score at baseline than those in the dutasteride group.

Long-term dutasteride therapy in men with BPH increases glucose and HbA_{1c} levels

As shown in Figure 1 (upper panel), long-term dutasteride treatment produced a progressive rise in fasting blood glucose (mean difference from baseline value 6.77 ± 0.55 mg/dL; $p < 0.0001$). The increase in blood glucose is paralleled by increased HbA_{1c} (lower panel) (mean difference from baseline value 0.7 ± 0.02%; $p < 0.0001$). In contrast, there were no increases in fasting blood glucose levels or HbA_{1c} levels in the tamsulosin treated men. The percent change from baseline was markedly different among the two groups with continued increase in blood glucose and HbA_{1c} in the dutasteride treated group but not in the tamsulosin treated group, as follow-up continued.

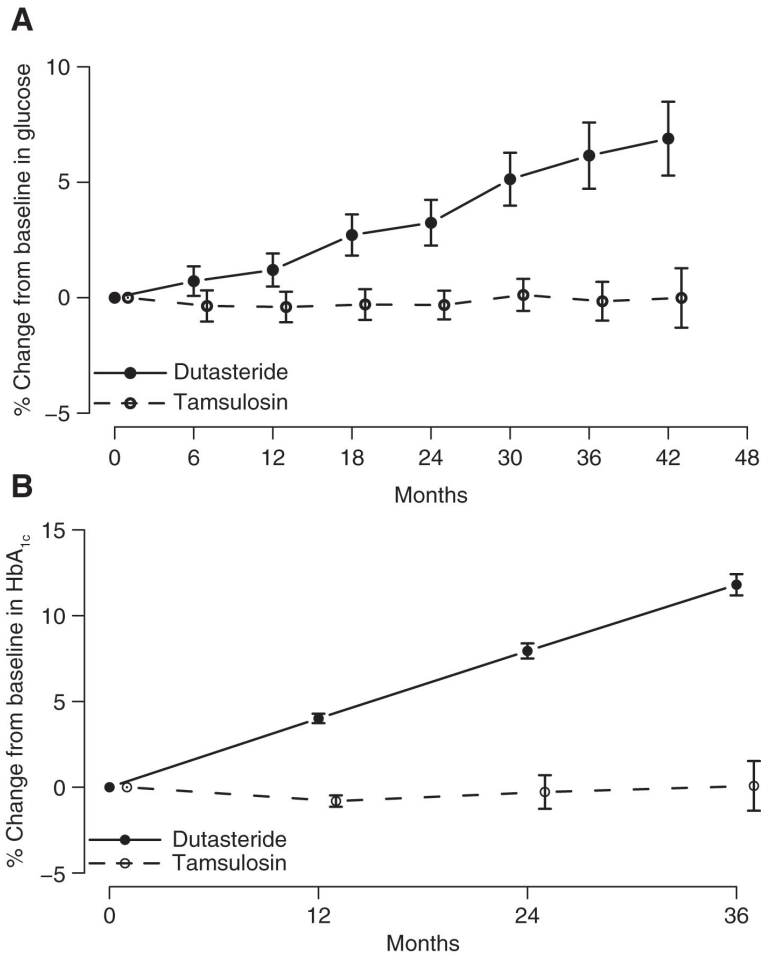

Figure 1: Effects of long-term dutasteride therapy or tamsulosin treatment on fasting blood glucose and HbA_{1c} levels in men treated for BPH. Data are presented as % change from baseline with duration of therapy.

Long-term dutasteride therapy in men with BPH increases LDL-cholesterol and TC levels

As shown in Figure 2, long-term dutasteride therapy in men with BPH increased LDL-cholesterol levels in parallel to that of TC within the first 6 months of therapy and remained at a higher level throughout the follow-up period (mean difference from baseline value 15.87 ± 1.15 mg/dL; $p < 0.0001$) (Figure 2A). Parallel increases were also observed in the tamsulosin treated group. Interestingly, however, there were no significant changes in HDL with dutasteride treatment, but a marked increase in the tamsulosin group was noted (Figure 2B). TC was increased in both treatment groups (Figure 2C). The increased TC with dutasteride (mean difference from baseline value 16.09 ± 1.09 mg/dL; $p < 0.0001$) is, in part, attributed to increased LDL levels. However, the marked increase in TC in the tamsulosin treated group is attributed to significant increases in HDL levels.

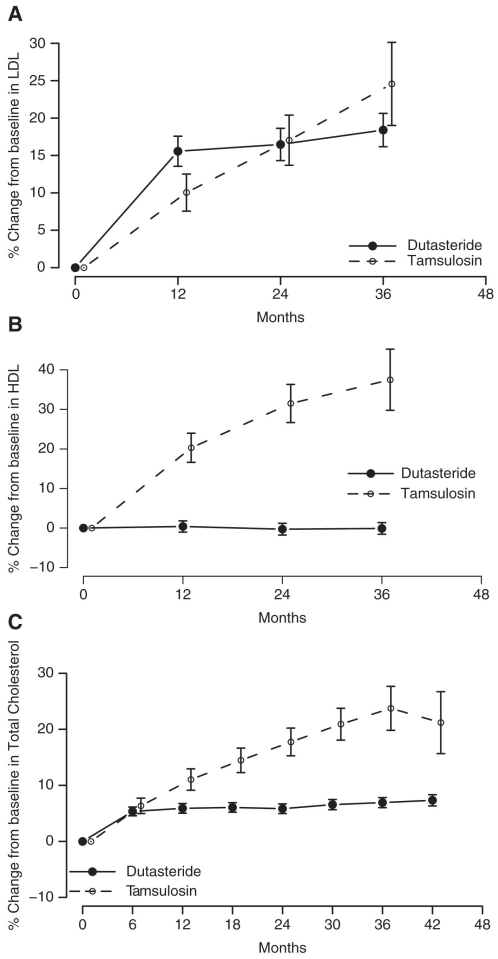

Figure 2: Effects of long-term dutasteride therapy or tamsulosin treatment on low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C) and TC in men treated for BPH. Data are presented as % change from baseline with duration of therapy.

Long-term dutasteride therapy in men with BPH increases the activities of alanine and aspartate amino transferases

An intriguing observation in this study is the increased activity of liver aspartate transaminase (AST) and alanine aminotransferase (ALT) in response to dutasteride but not with tamsulosin (Figure 3A, B). These findings suggest that inhibition of 5α-Rs in liver brings about biochemical changes in liver function and may represent alterations in liver metabolism and/or increased inflammation, increased glucocorticoids levels concomitant with reduced androgen levels.

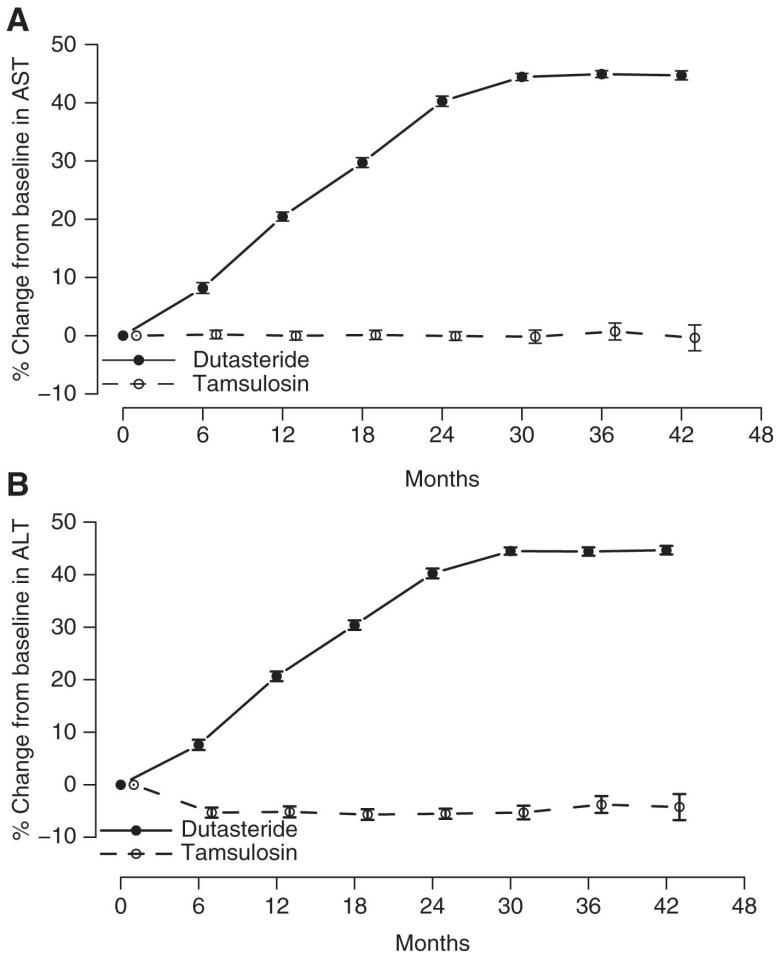

Figure 3: Effects of long-term dutasteride therapy or tamsulosin treatment on alanine and aspartate amino transferases in men treated for BPH. Data are presented as % change from baseline with duration of therapy.

Long-term dutasteride therapy in men with BPH reduces total testosterone levels

We have previously reported that long-term finasteride therapy resulted in reduced total T plasma levels [10]. Here we also noted that patients receiving long-term dutasteride therapy had progressive and significant decline in total T levels (mean difference from baseline value −0.43 ± 0.01 ng/mL; $p < 0.0001$) (Figure 4). The reasons for this reduction in T levels remain unclear. Interestingly, however, no decreases in T levels were noted with tamsulosin treatment (Figure 4) [10].

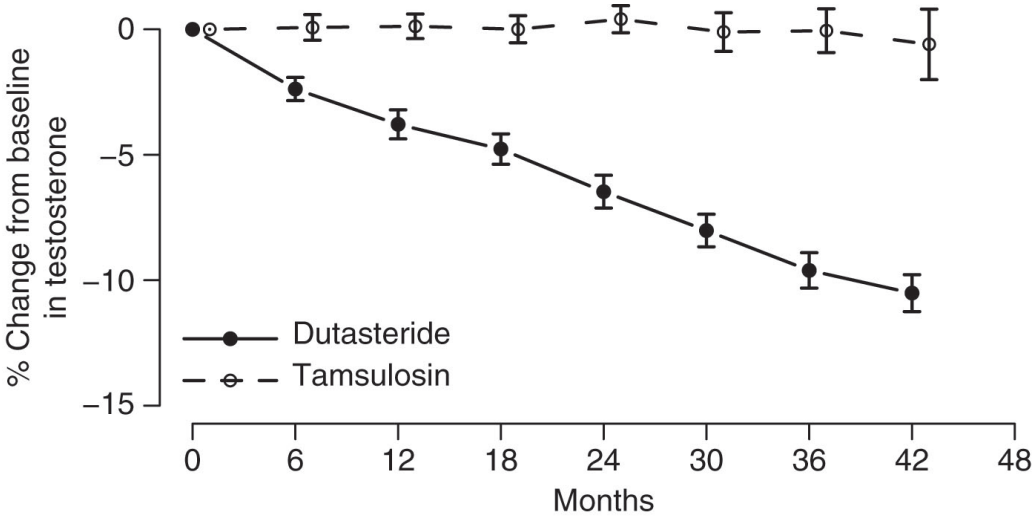

Figure 4: Effects of long-term dutasteride therapy or tamsulosin treatment on testosterone levels in men treated for BPH. Data are presented as % change from baseline with duration of therapy.

Long-term dutasteride therapy in men with BPH increases aging male symptom score

As shown in Figure 5 the AMS increased in men treated with dutasteride (mean difference from baseline value 5.63 ± 0.23; $p < 0.0001$) but not in men treated with tamsulosin. This increase in the AMS score with dutasteride suggests increased adverse events, which impacts the overall quality of life in patients treated with dutasteride. Our findings are consistent with those of Fwu et al. [30], [31] who reported that quality of life was improved significantly during 4 years in men assigned to the doxazosin and combination therapy groups but not in the group assigned to the dutasteride only arm.

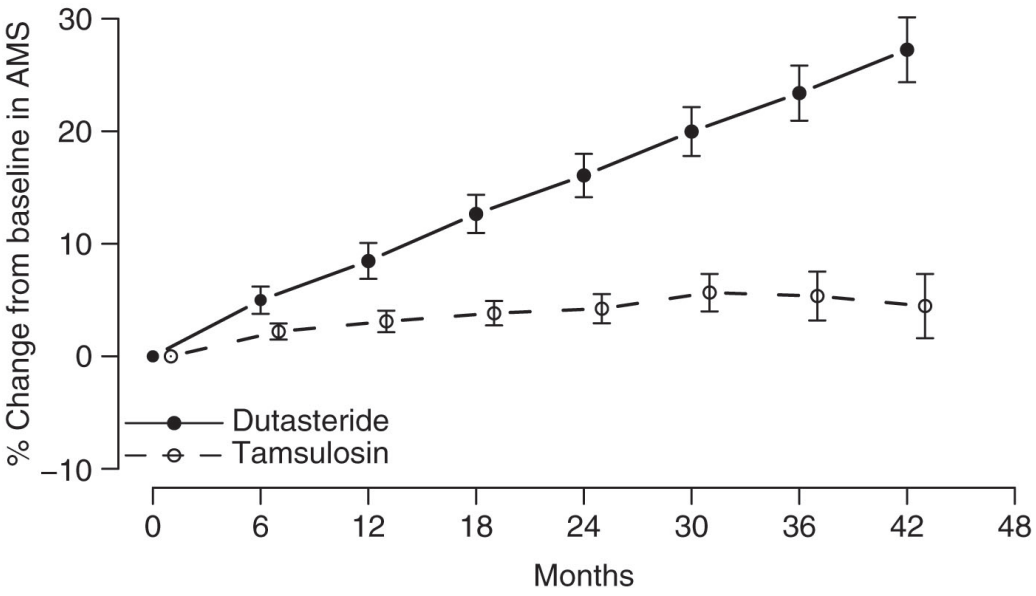

Figure 5: Effects of long-term dutasteride therapy on aging male symptom score in men treated for BPH. Data are presented as % change from baseline with duration of therapy.

Long-term dutasteride therapy in men with BPH increases ED

As shown in Figure 6, treatment with dutasteride, but not tamsulosin, in men with BPH resulted in a significant gradual decrease in erectile function, as assessed by the IIEF-EF score (mean difference from baseline value −3.09 ± 0.08; $p < 0.0001$). The decrease was progressive and was sustained over the 42 months of follow-up.

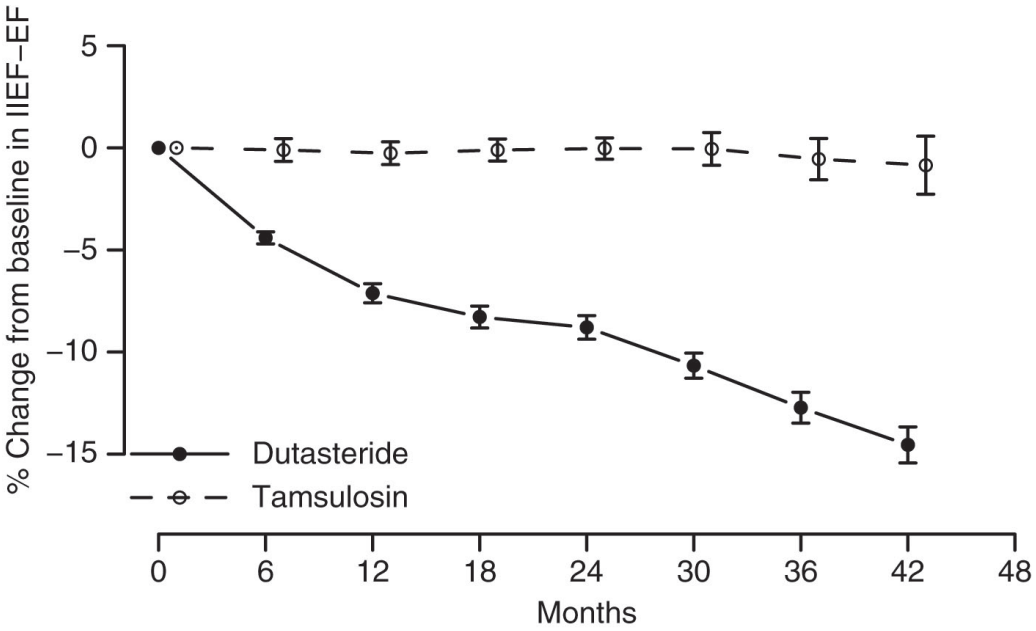

Figure 6: Effects of long-term dutasteride therapy on erectile function in men treated for BPH. Data are presented as % change from baseline with duration of therapy.

Long-term dutasteride therapy in men with BPH reduces prostate volume, IPSS score and prostate specific antigen

As expected, long-term dutasteride treatment resulted in marked reduction in prostate volume (mean difference from baseline value −20.42 ± 0.16 mL; $p < 0.0001$) (Figure 7A), IPSS (mean difference from baseline value −3.55 ± 0.05; $p < 0.0001$) (Figure 7B) and prostate specific antigen (PSA) levels (mean difference from baseline value −0.59 ± 0.01 ng/mL; $p < 0.0001$) (Figure 7C), consistent with previous reports [1], [10], [32], [33], [34]. Tamsulosin treatment resulted in small increases in prostate volume but no significant changes in the PSA values. As expected, tamsulosin treatment produced marked improvement in IPSS (Figure 7A–C).

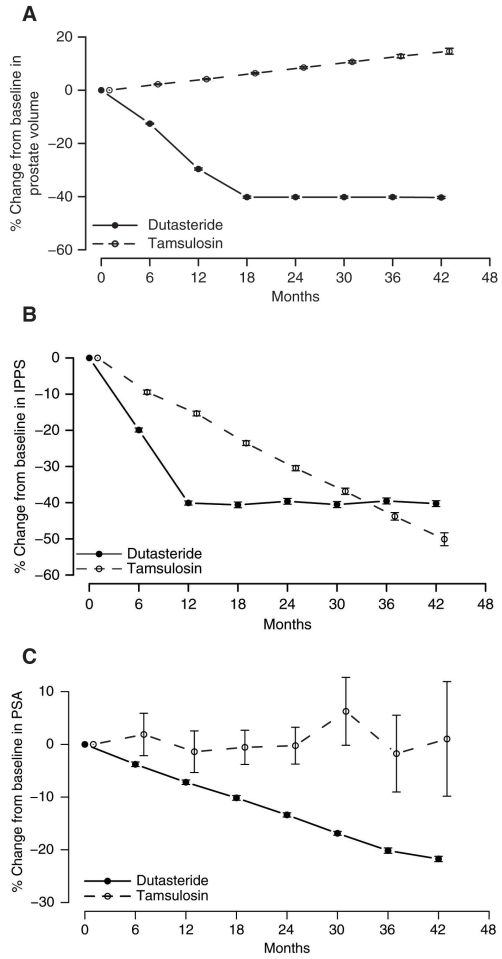

Figure 7: Effects of long-term dutasteride therapy on prostate volume, IPSS score and prostate specific antigen in men treated for BPH. Data are presented as % change from baseline with duration of therapy.

Discussion

Here we report that long-term dutasteride therapy in men with BPH alters metabolic functions. In this retrospective observational study, long-term dutasteride therapy produced a progressive increase in blood glucose and glycated hemoglobin (HbA_{1c}) levels. No significant changes in blood glucose or HbA_{1c} were observed in men treated with tamsulosin. These findings are consistent with observations reported by Upreti et al. [20], in which dutasteride treatment decreased glucose disposal during high-dose insulin infusion, consistent with impaired insulin sensitivity in peripheral organs, including skeletal muscle and/or adipose tissue. Furthermore, Upreti et al. [20] also noted that dutasteride reduced insulin-mediated suppression of non-esterified fatty acids (NEFAs) again suggesting impaired insulin sensitivity in adipose tissue.

Joyce et al. [21] reported that in older men who are free of cardiovascular disease (CVD) and diabetes, baseline levels of 5α-DHT were strongly associated with lower risk of diabetes and with less insulin resistance (IR), as assessed by HOMA-IR [21]. These findings are also consistent with those reported by Hazlehurst et al. [35], in which endogenous glucose production rate was significantly increased after dutasteride treatment and is consistent with increased hepatic IR. Our findings are also consistent with those of Hazlehurst et al. [35] in which, dutasteride had a significant effect on lipid metabolism, in the fasted state. Hazlehurst et al. [35] demonstrated that intrahepatic lipid increased after dutasteride treatment and was associated with increased rates of de novo lipogenesis and adipose tissue lipid mobilization was decreased by dutasteride treatment [35]. These findings suggest that dutasteride treatment is associated with hepatic IR, hepatic lipid accumulation, and decreased adipose lipid mobilization without impacting peripheral insulin sensitivity [35]. Dowman et al. [36] reported that 5α-reductase type 1-deficient mice developed IR and decreased insulin receptor expression. Furthermore, 5α-reductase type 1 deletion accelerated development of hepatic steatosis and reduced hepatic expression of genes involved in insulin signaling, supporting a critical role of 5α-reductase type 1 in the evolution of non-alcoholic fatty liver disease (NAFLD) [36]. Thus, it is possible that long-term dutasteride therapy inhibits 5α-reductase

type 1 function and contributes to alterations in the aforementioned metabolic processes. We also observed an increase in LDL and TC levels but not HDL with dutasteride treatment, suggesting alteration in cholesterol metabolism. Indeed, we also recorded that tamsulosin therapy increased LDL but also HDL thus, contributing to a higher TC levels. The potential mechanism for this increase in LDL and HDL remains unclear.

The role of 5α-reductase type 1 activity in the liver was thought to involve regulating insulin sensitivity and lipid metabolism [22], [37]. In 5α-reductase type 1-KO mice, glucose intolerance was detected at 3 months of age, and a trend to hyperinsulinemia during glucose tolerance test (GTT) was detected at 5 months [22], [37]. 5α-reductase type 1-KO mice had increased susceptibility to hyperinsulinemia fasting hyperglycemia, increased ratios of insulin to glucose and liver fat accumulation [22], [37]. These 5α-Reductase type 1-KO mice exhibited suppression of liver lipolysis and induction of gene transcripts encoding enzymes involved in fatty acid β-oxidation and gluconeogenesis when animals fed a high-fat diet, while transcripts of genes favoring triglyceride esterification and cholesterol synthesis and excretion were disproportionately increased [22], [37]. These findings strongly suggest a critical role for 5α-reductase type 1 in glucose and lipid metabolism. Zhang et al. [25] have reported that treatment with 5α-DHT resulted in a marked decrease in the concentrations of TC, LDL-c, and ApoB. Possible mechanisms are thought to involve androgen/androgen receptor (AR) pathway by mainly suppressing hepatic steatosis by increasing carnitine palmitotyltransferase 1(CPT-1)-mediated β-oxidation and decreasing cholesterol synthesis. Altogether, 5α-DHT is postulated to modulate hepatic lipid metabolism and normalizes the mitochondrial function.

As human liver expresses both 5α-reductase type 1 and type 2 enzymes and these isoforms play a significantly critical role in glucocorticoid metabolism and clearance and inhibit androgen action via blocking 5α-DHT formation, it is possible that inhibition of 5α-reductase type 1 activity increases endogenous glucocorticoid activities concomitant with reduction of androgenic activity producing marked alterations in glucose and lipid homeostasis and resulting in IR and lipid accumulation [9], [20], [22], [35], [36], [37].

We also noted that long-term dutasteride therapy resulted in a reduction in total circulating T levels consistent with previous observation with long-term finasteride therapy [10]. It is possible that reduction in T and/or 5α-DHT levels may contribute to altered glucose and lipid metabolism as well as liver dysfunction. Joyce et al. [21] reported that baseline levels of 5α-DHT were strongly associated with lower risk of diabetes and IR, as assessed by HOMA-IR. In patients undergoing androgen deprivation therapy (ADT) for treatment of prostate cancer, Mohammedali et al. [38] reported increased blood glucose and lipids in men undergoing one year of ADT. Similarly, Oka et al. [39] reported that 1 month after ADT, TC, HDL-C, and LDL-C increased significantly from 185.5 (± 34.1) to 206.2 (± 33.6) mg/dL ($p < 0.001$), from 51.2 (±11.3) to 59.0 (±15.0) mg/dL ($p < 0.001$), and from 108.1 (±31.3) to 119.2 (±32.9) mg/dL ($p < 0.001$), respectively.

In view of our findings and those reported by others [20], [22], [35], [36], it is important to consider the potential long-term consequences of dutasteride therapy on metabolic function, particularly, IR and lipid accumulation in liver. Because hepatic steatosis is a precursor to progression to more advanced stages of NAFLD including nonalcoholic steatohepatitis, it is likely that long-term therapy with dutasteride may contribute to onset of NAFLD. Our findings and those cited here in [20], [22], [35], [36], suggest that inhibition of 5α-reductase type 1 and 2 with dutasteride elicits metabolic dysfunction with potential adverse ramifications. As dutasteride is widely prescribed for men with BPH, it is important that such adverse metabolic function be seriously taken into account prior to commencing such therapy.

We should point out that Andriole et al. [34] did not report changes in total cholesterol, LDL-cholesterol, glucose or glycated hemoglobin levels in the placebo and treated arms of the Reduce Trial. In view of the adverse metabolic changes in glucose, lipids and liver function, it is not surprising that the authors noted increased incidence of heart failure in patients treated with dutasteride for up to 4 years [34]. Andriole et al. [34], reported that "there was an unexpected imbalance in a composite event termed "cardiac failure," which included conditions such as congestive heart failure, cardiac failure, acute cardiac failure, ventricular failure, cardiopulmonary failure, and congestive cardiomyopathy." Although there was no significant difference between the two groups in the overall incidence of cardiovascular events or deaths from cardiovascular events, the authors noted that "there was a higher incidence of the composite event of cardiac failure in the dutasteride group than in the placebo group (0.7% [30 of 4105 men] vs. 0.4% [16 of 4126 men], $p = 0.03$; relative risk estimate, 1.91; 95% CI, 1.04 to 3.50)". The authors reported that "except that in our study, as compared with previous studies, the relative incidence of the composite category of cardiac failure was higher in the dutasteride group than in the placebo group (0.7% [30 men] vs. 0.4% [16 men], $p = 0.03$)" [34]. We should note that a recent population study attempted to investigate the effects of dutasteride on cardiovascular safety [40]. Interestingly however, the study compared the events in the dutasteride group with those in the finasteride group and completely omitting any comparison with a control group (placebo). For this reason, the findings of such study [40] did not support cardiovascular safety of dutasteride, in absence of comparable data in a control group.

Here, we also report an increase in AMS scale with dutsteride therapy suggesting that patients treated with dutasteride have deteriorated quality of life, which may be attributed to decreased T levels, increased adverse

sexual side effects. Further, the observed increase in liver ALA and AST transaminases with dutasteride but not with tamsulosin suggests that dutasteride altered liver metabolic function [20], [22], [35], [36], and may contributed to increased inflammation.

As with finasteride [10], here we report that long-term dutasteride therapy adversely affected erectile function in BPH patients. This observation is consistent with data reported over a 4-year period by Fwu et al. [30], [31], which showed progressive worsening of erectile function. Andriole et al. [33], [34] also reported that dutasteride showed adverse effects of sexual dysfunction in men with BPH during a 4-year period in a prostate cancer prevention clinical trial. Kaplan et al. [41] performed a retrospective analysis of 378 consecutive men treated with 5α-reductase inhibitor monotherapy (197 on finasteride and 211 on dutasteride) in a single clinic and reported that the incidences of ED, ejaculatory dysfunction and decreased libido resulting in discontinuation from therapy was significantly ($p < 0.01$) higher in the dutasteride compared with the finasteride group. Furthermore, the data from consecutive patients treated with dutasteride or finasteride resulted in significantly more sexual side effects than noted with placebo. Similarly, Park and Choi [42] performed a systematic review and meta-analysis and demonstrated that pooled data indicated adverse events and drug-related adverse events were significantly more common in patients treated with dutasteride compared with placebo.

Mechanistically, the effect of dutasteride on ED was demonstrated elegantly in the animal model. Treatment of mature male animals with dutasteride produced significant reductions in the intracavernosal pressure (ICP) [43], [44]. Electrical field stimulation (EFS) or acetylcholine-induced smooth muscle relaxation was significantly attenuated in corpus cavernousm tissues from dutasteride-treated animals. Dutasteride treatment increased deposition of connective tissue with concomitant reduction in the smooth muscle content of the cavernosal tissue. Neuronal nitric oxide synthase (nNOS) expression was significantly attenuated by dutasteride, concomitant with increased expression of inducible NOS (iNOS).

The dutasteride-induced adverse side effects on IIEF-EF domain reported here did not resolve with continued therapy, as was suggested previously [19], [45], [46], [47], [48], [49]. Our findings are inconsistent with those of Debruyne et al. [47] who suggested that long-term use of dutasteride showed no safety issues over 4 years of treatment and therefore this therapy is deemed safe and effective. Debruyne et al. [47] concluded that the onset of drug-related adverse events was reported most frequently at the start of therapy and declined over time in patients receiving dutasteride. This view is consistent with the reported data by Tsunemi et al. [50] in which most of the sexual adverse effects were shown to be drug-related. Chi and Kim [51] showed that after 1 month of treatment, dutasteride therapy resulted in a significant reduction in all investigated sexual functions. The authors noted that recovery in sexual function was noted at 3 months, and orgasmic function and sexual desire were restored to baseline levels at 6 months. However, erectile function was still significantly reduced even at 12 months. More importantly, our findings strongly support previous reports suggesting that, dutasteride treatment increased ED and may increase the severity of ED in BPH patients treated with this drug [31], [32]. It should be noted that there was no resolution of the side effects by continued treatment, as suggested previously. A number of recent reports showed that sexual adverse events do not resolve with continued treatment [18], [50], [52], [53], [54], [55], [56], [57], [58], [59].

The findings in our study are further supported by the data from the MTOPS study, which showed similar worsening of the EF-domain over a 4-year period, when compared with placebo [31], [32]. Recently, Ganzer et al. [18] reported that persistent sexual side effects of 5α-RI therapy were prevalent in a large number of subjects. Furthermore, our findings are contrary to previous claims suggesting that 5α-reductase inhibitors had minimal adverse effects on erectile function and these adverse events resolve with continued treatment [19], [34], [45], [46], [47], [48], [49], [51], [60], [61].

In this study, we report that dutasteride treatment resulted in a significant reduction in T levels over the 36–42 months of treatment. This finding is inconsistent with prior reports in which T levels were shown either to remain unchanged subsequent to 5α-reductase inhibitors therapy or relative increase in T levels were reported with 5α-reductase inhibitors therapy [20], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73], [74], [75], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86]. Kacker et al. [87] did not find any changes of T levels in men receiving dutasteride treatment but there was a clear tendency for a decline in T which, however, did not reach statistical significance.

Hong et al. [82] and Roehrborn et al. [81] reported that dutasteride treatment in men with BPH led to a significant increase in serum T level among patients with lower baseline serum T levels but not in those with higher baseline T levels. Hong et al. [82] reported that the increase in T levels was only noted in the group with baseline T of <360 ng/dL but not in the group with T levels of >540 ng/dL. Similarly, Roehrborn et al. [81] showed that the increase was only in the group with T levels of ≤330 ng/dL but not in the group with baseline T levels of >471 ng/dL. These findings suggest that the baseline T levels may modify the response to 5α-reductase inhibitors therapy.

It is worth noting that 5α-reductase type 3 is highly expressed in many peripheral tissues [88], suggesting that this isoform likely to play an important role in metabolism of such tissues [9], [10], [89]. Also, this isoform

is required for the conversion of polyprenol to dolichol phosphate, which is essential for N-linked protein glycosylation [90] and inhibition of this isoform by dutasteride may be associated with metabolic dysfunction [10], [90]. Dutasteride inhibits 5α-reductase type 3 and such inhibition may contribute to the observed disruptions in metabolic function [90]. It is imperative to point out that 5α-DHT is a potent androgen and transformation of T to 5α-DHT may be important in maintaining the functional metabolism in peripheral tissues [20], [22], [25], [35], [36], [37]. Also, inhibition of the 5α-reductase family of enzymes (types 1, 2 and 3) by dutasteride contribute to a significant reduction (97%) in circulating 5α-DHT levels which are detrimental to metabolic function.

Study strengths and limitations

This study has some limitations including its retrospective nature and a comparison with tamsulosin instead of a control group. Also, a proportion of patients are taking statins, which may influence cholesterol and LDL levels. Similarly, another proportion of patients are taking phosphodiesterase type 5 inhibitors, which may influence results on ED. The strengths of this study are the large number of patients, the long-term follow up of 36–42 months, the inclusion of a comparison group and the real-life setting (no inclusion or exclusion criteria) in which the effects of dutasteride were evaluated clinically.

Summary

This study suggests that long-term dutasteride therapy is associated with increased blood glucose, HbA_{1c}, LDL-cholesterole and TC, potentially leading to increased onset of IR and NAFLD. In addition, dutasteride increased liver transaminase activity and AMS score suggesting increased inflammation and reduced quality of life. Dutasteride therapy also worsened ED and resulted in reduction in T levels. These findings raise serious safety concerns regarding metabolic dysfunction and adverse sexual side effects of long-term dutasteride therapy. Clinicians are strongly urged to discuss these potential health adverse effects of dutasteride treatment with their patients prior to instituting this form of therapy.

Author Statement

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Informed consent: All patients gave their informed consent to be included in this study, and in accordance to the rules of the German Medical Association for evaluation of patient data from patients receiving standard therapy.

Ethical approval: The research related to human use complied with all the relevant national regulations and institutional policies and was performed in accordance to the tenets of the Helsinki Declaration and has been approved by the author's institutional review board or equivalent committee.

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