MRI characterization of the dynamic effects of 5α-reductase inhibitors on prostate zonal volumes

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Introduction: *Prior studies of volumetric effects of 5α-reductase inhibitors (5ARIs) on the prostate have used transrectal ultrasound which provides poor differentiation of prostatic zones. We utilized high-resolution prostate MRI to evaluate the true dynamic effects of 5ARI in men who underwent multiple MRIs.*

Materials and methods: *A retrospective study of patients who underwent serial 3.0 Tesla prostate MRI from 2007 to 2012 and were treated with 5ARI were studied. Nineteen patients who had a baseline MRI prior to 5ARI initiation and subsequent MRI follow up were selected. A randomly selected group of 40 patients who had not received any form of therapy was selected as the control cohort. Total prostate volume (TPV), transition zone volume (TZV), and peripheral zone volume (PZV) were calculated using 3D reconstructions and prostate segmentation from T2-weighted MRI. Changes in volumes were correlated with the duration of treatment using linear regression analysis.*

Results: *Following over 2 years of treatment, 5ARI decreased TPV significantly (16.7%, $p < 0.0001$). There were similar decreases in TZV (7.5%, $p < 0.001$) and PZV (27.4%, $p = 0.0002$) from baseline. In the control group, TPV and TZV increased ($p < 0.0001$) while PZV remained stable. When adjusted for the natural growth of prostate zonal volume dynamics seen in the control cohort, approximately 60% of the reduction of the TPV from 5ARI resulted from changes in the TZV and 40% of the reduction from changes in the PZV.*

Conclusions: *3.0 Tesla MRI characterizations of the dynamic effects of 5ARI on prostate zonal volumes demonstrate significant decreases in TPV, TZV, and PZV. 5ARI blocks the natural growth of TZV as men age and decreases both TZV and PZV below their baselines. As imaging technology improves, prostate MRI allows for more accurate assessment of drug effects on dynamic prostate volumes.*

Key Words: prostate volume, MRI, BPH, 5α-reductase inhibitors

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Introduction

The benign growth of the prostate occurs naturally in men as they age. As this hyperplasia progresses with time, more men begin to experience lower urinary tract symptoms (LUTS) with an estimated 50% of men in their 60s experiencing LUTS.[1] The Medical Therapy of Prostate Symptoms (MTOPS) study showed men with

larger prostates benefited more from the combination of alpha-blockers and 5α-reductase inhibitors (5ARI) in preventing progression and improving symptoms than from just alpha-blockers alone.[2] Unlike alpha-blockers, which provide symptomatic relief, 5ARI, including finasteride and dutasteride, are an anti-androgenic class of medication that target the underlying disease process and reduce prostate size. Prior studies have demonstrated that finasteride and dutasteride have equal efficacy in reducing prostate volumes[3] and that 5ARI selectively affects the transition zone (TZ) while sparing the peripheral zone (PZ).[4-6] Studies using transrectal ultrasound (TRUS) found that 5ARI reduce total prostate volume (TPV) by approximately 17%-46% and transition zone volume (TZV) by 7%-25% within the first year of therapy.[7-9] A study by Tempany and colleagues in 1993 evaluated the effect of finasteride and dutasteride on TPV, TZV, and PZV using 1.5 Tesla MRI, considered to be high resolution MR technology at the time; this group found that 5ARI reduced TZV by 7% and PZV by 13.7% compared to the placebo group, however their results on PZV shrinkage did not reach statistical significance.[5]

Therefore, given this 20 year time span and improvements in MR imaging techniques, we sought to evaluate the temporal changes in TPV, TZV, and PZV as seen by prostate imaging segmentation on 3.0 Tesla MRI for men with enlarged prostates on 5ARI therapy compared with a control cohort. We not only assessed the apparent changes of prostatic volumes on medication compared to baseline measurements but we also determined the global effects of 5ARI, taking into account the natural growth of the prostate as men age.

Materials and methods

Study design, setting, and participants

This is an Institutional Review Board-approved retrospective cohort study of patients who underwent serial 3.0 Tesla prostate MRI from 2007 to 2012 in the setting of prostate-specific antigen (PSA) elevation. Patients who had a baseline MRI prior to 5ARI initiation and subsequent MRI follow up were selected. A group of patients who did not receive any form of treatment was randomly selected as the control cohort.

MRI data acquisition and prostate volume measurement

All prostate MRI studies were performed with a 3.0 Tesla MRI Scanner (Achieva, Philips Healthcare, Best, The Netherlands) using a combination of an endorectal coil (BPX-15 or BPX-30, Medrad, Pittsburgh, Pennsylvania, USA) and a six or sixteen-channel cardiac coil placed over the pelvis (SENSE, Philips Healthcare, Best, The Netherlands) as previously described.[10,11] Axial T2W-MR images were used for prostate volume measurements. The total prostate gland and the TZ were contoured using a semi-automated prostate segmentation software platform as previously described.[10,12] The TZ of the prostate is characteristically recognizable since a thin band of fibromuscular tissue (pseudocapsule), which is low in signal intensity on T2W MRI, defines the border between the TZ and PZ. Once outlined manually on three initial T2W MRIs, the software platform allowed segmentation of both whole prostate and its zones and calculation of both TPV and TZV. The PZV was calculated by subtracting the TZV from the TPV. Volumes for each patient were measured by the same radiologist who was blinded to the patient cohort assignment.

Outcome measures and statistical analyses

Objective baseline urinary symptoms were assessed using the International Prostate Symptom Score (IPSS). For patients in the control cohort, the first MR scan served as the baseline volumetric analysis and for the 5ARI group the last MRI prior to starting 5ARI was used. Primary endpoints of the study were temporal changes in TPV, TZV, and PZV. Results were grouped into three time points, from baseline to 12 months, 12 to 24 months, and beyond 24 months follow up for the control group and baseline to 6 months, 6 to 12 months, 12 to 24 months, and beyond 24 months on medication for the 5ARI group.

To control for expected growth in prostatic volumes, we adjusted the TPV, TZV, and PZV changes observed from the 5ARI treatment cohort to include the expected growth as observed in the control group. Adjustments in prostate zonal volume dynamics were made by subtracting the interval volume changes in each prostate zone in the control cohort from that of the 5ARI treatment cohort. Because the control cohort did not have the baseline to 6 months endpoint, volume dynamics for this time period were not adjusted.

Data were analyzed using STATA version 12.1 (Stata Corp., College Station, Texas, USA). Statistical analyses of the change from baseline for continuous parameters (TPV, TZV, and PZV) were performed using a univariate linear model. Categorical variables were compared using Fisher's exact tests. The differences in the primary outcomes observed between the control and treatment cohort were analyzed using Welch's t-test. All results were considered statistically significant at two-sided $p < 0.05$.

TABLE 1. **Patient demographics and characteristics**

	Control cohort	5ARI cohort	p value
Number of patients	40	19	-
Number of MRI per patient, n (%)			
2	30 (75.0)	12 (63.2)	-
3	8 (20.0)	5 (26.3)	-
4	2 (5.0)	2 (10.5)	-
Median age in years (IQR)	62.5 (57-69)	64.2 (57-69)	0.5
Race, n (%)			0.4
Black	7 (17.5)	2 (10.5)	-
Asian	2 (5.0)	3 (15.7)	-
Caucasian	31 (77.5)	14 (73.6)	-
Treatment, n (%)			
Dutasteride	-	9 (47)	-
Finasteride	-	10 (53)	-

5ARI = 5α-reductase inhibitors

Results

Patient demographics

A total of 139 patients were identified with multiple prostate MRI, of whom 19 (13.7%) met selection criteria for the 5ARI arm. Of the remaining patients, 40 were selected randomly as the control cohort. In the treatment group, 10 patients were on finasteride and nine were on dutasteride. There was no significant differences in volumetric effects between the subset analyses of patients administered finasteride versus dutasteride and so they were analyzed as a single cohort. The demographic and baseline characteristics of patients in both cohorts are described in Table 1.

Baseline measurements and analysis

Baseline measurements, including mean PSA, TPV, TZV and PZV, were similar in the control and treatment cohorts ($p > 0.05$, Table 2). Patients in both cohorts had enlarged prostates with by TPV > 30 cc. Baseline measurements in both control and treatment cohorts were combined for correlation and linear regression analyses, Table 3.

Volumetric data analysis

Prostate zonal volume dynamics represented over short and long term imaging are summarized in Table 3. In the control cohort, there were increases in both TPV and TZV over time. Nearly 100% of the increase in TPV arose from TZV increase. There was a small decrease in PZV (-0.4 cc ± 0.5 cc overall), which did not reach statistical significance. In the treatment group, a significant reduction in all three prostate volumes: TPV, TZV, and PZV, was achieved in the first 6 months

TABLE 2. **Baseline measurements; IPSS reported with median value (IQR); PSA, TPV, TZV, and PZV reported with mean values (SD)**

	Control cohort	5ARI cohort	p value
IPSS	9.5 (5-13)	16.0 (10-23)	0.01
PSA, ng/mL	5.8 ± 3.6	6.5 ± 3.0	0.4
TPV, cc	49.9 ± 25.0	54.9 ± 21.4	0.5
TZV, cc	29.8 ± 22.2	33.6 ± 18.0	0.5
PZV, cc	20.1 ± 6.0	21.2 ± 6.1	0.5

5ARI = 5α-reductase inhibitors; IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; TPV = total prostate volume; TZV = transition zone volume; PZV = peripheral zone volume

TABLE 3. **Longitudinal changes in prostate zonal volumes. N = number of patients. Changes are reported in absolute volume change (cc), percent change compared to baseline (%), and standard error (SE)**

Time interval (months)	Zonal volume	Control cohort cc, SE	Control cohort %, SE	5ARI cohort cc, SE	5ARI cohort %, SE	p value
0-6	**N**			**6**	**6**	N/A
	TPV			-9.8, 2.9	-14.4, 2.2	
	TZV			-5.0, 2.1	-10.5, 2.6	
	PZV			-4.8, 0.9	-22.3, 2.3	
6-12	**N**	**18**	**18**	**5**	**5**	
	TPV	2.1, 0.7	4.4, 1.8	-5.1, 1.9	-11.7, 4.3	<0.0001
	TZV	1.8, 1.0	5.5, 6.1	-1.4, 0.9	-5.6, 3.5	<0.0001
	PZV	0.27, 0.7	1.6, 3.7	-3.7, 1.9	-17.1, 9.2	N.S.
12-24	**N**	**22**	**22**	**10**	**10**	
	TPV	4.8, 1.2	9.1, 2.2	-9.9, 1.3	-16.7, 1.4	<0.0001
	TZV	5.2, 1.2	18.9, 3.7	-3.6, 0.8	-9.9, 1.9	<0.0001
	PZV	-0.4, 0.8	-2.5, 3.7	-6.3, 1.2	-25.6, 3.2	0.0001
> 24	**N**	**10**	**10**	**4**	**4**	
	TPV	4.7, 2.1	8.8, 3.9	-7.9, 1.7	-16.7, 2.3	0.0001
	TZV	6.2, 2.9	21.2, 9.1	-2.1, 0.9	-7.5, 3.4	0.01
	PZV	-1.5, 1.3	-4.1, 5.3	-5.8, 1.2	-27.4, 3.1	0.002
Overall effects	TPV	3.8, 0.7	7.3, 1.4	-8.6, 1.0	-15.2, 1.2	<0.0001
	TZV	4.2, 0.9	14.5, 3.3	-3.3, 0.6	-8.8, 1.3	<0.0001
	PZV	-0.4, 0.5	-1.3, 2.3	-5.3, 0.7	-23.4, 2.3	<0.0001

5ARI = 5α-reductase inhibitors; TPV = total prostate volume; TZV = transition zone volume; PZV = peripheral zone volume; N.S. = not statistically significant, $p > 0.05$

following initiation of 5ARI, Table 3. These volumetric effects were sustained for greater than 2 years. The largest zonal volume reduction was seen in the PZ—17.1 to 27.4% decline from baseline PZV ($p < 0.0001$). Even though both TZV and PZV decreased in the 5ARI cohort, approximately 70% of the reduction in the TPV came from PZV decrease. When the effects of 5ARI on TPV, TZV, and PZV were adjusted for the natural growth of prostate zonal volume dynamics, the corrected changes in the TZV were greater than PZV (7.5 cc versus 4.9 cc absolute volume reduction). Therefore, on 5ARI, approximately 60% of the TPV reduction resulted from the change in TZV versus 40% from the change in PZV.

Discussion

The extended clinical utility of 5ARI beyond relief of BPH and LUTS for the prevention and diagnosis of prostate cancer has been studied in recent years. Two major clinical trials found 5ARI decrease the incidence of prostate cancer;[13,14] however, The Prostate Cancer Prevention Trial (PCPT) found finasteride associated with increased risk of high-grade carcinoma.[13] Currently the FDA has not approved 5ARI for chemoprevention of prostate cancer. Preliminary studies suggested that 5ARI might improve the detection of prostate cancer if administered daily for 2 weeks prior to contrast-enhanced color Doppler ultrasound prostate biopsy because it can suppress Doppler flow to benign prostate tissue.[15-17] However, the published results from these studies have been conflicting. New improvements in MRI technology and increasing interests in 5ARI set the stage for our study.

Our study assesses prostate zonal volume dynamics in men with serial MRIs on 5ARI therapy using a high resolution 3.0 Tesla MRI with endorectal and surface coils. We found that in patients who were not taking

5ARI, TPV increases over time which is mainly driven by increasing TZV while the PZV remains relatively stable. In patients on 5ARI treatment, prostate zonal volumes decreased as early as 6 months after treatment initiation.

Our findings also demonstrated that in addition to shrinking the prostate from baseline, 5ARI also prevented the natural growth of untreated prostates, particularly in TPV via TZV augmentation. When the natural growth course is accounted for, the data further demonstrated the effect of 5ARI on the TZ is greater than on the PZ. In the adjusted zonal volume analysis, the contributions to TPV reduction are 60% from TZV and 40% from PZV changes.

While the TPV and TZV dynamics in response to 5ARI have been widely accepted, there has been conflicting evidence in the literature regarding the effect of 5ARI on PZV. One study involving TRUS evaluation of men on finasteride demonstrated a selective decrease in TPV and TZV only.[4] Tempany and colleagues used MRI and found a larger reduction in PZV though not reaching statistical significance likely due to limited sample size and older technology.[5] Other longitudinal, double-blinded studies using volumetric assessment with TRUS found decreases in PZV and TZV similar to our findings.[7,18,19]

MRI has been shown to be more reliable in prostate imaging, particularly in delineation of zonal anatomy, compared to TRUS. TRUS requires compression of the prostate to ensure adequate imaging which is highly operator dependent. Furthermore, MRI allows for more accurate differentiation and segmentation of the TZ and PZ.[20,21] Turkbey and colleagues validated 3.0 Tesla MRI-derived TPV with the weights of human radical prostatectomy specimens.[11] The utilization of high resolution MRI in this study allows for accurate assessment of drug-induced zonal prostate volume changes.

Limitations of this study include its retrospective nature and potential biases that result. MRIs were obtained with an endorectal coil, which compresses the gland posteriorly. Despite the gland deformation, endorectal coil does not affect zonal volume measurements. Rather, the endorectal coil provides imaging with superior resolution for delineating the prostate boundaries which is critical for accurate volume determinations.

Conclusion

3.0 Tesla MRI characterizations of prostate zonal volume dynamics demonstrates significant decreases in TPV, TZV, and PZV in patients on 5ARI therapy compared to a control cohort over both short and longer term therapy. 5ARI block the natural growth of the TZ and further decreases TZV below baseline volume. 5ARI also reduce both TZV and PZV, contributing to an overall decrease in TPV. As imaging technology improves, high resolution prostate MRI allows for more accurate assessment of drug effect and evaluation of patients with benign prostatic hyperplasia.

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