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Original Article

Magnetic resonance imaging and morphometric histologic analysis of prostate tissue composition in predicting the clinical outcome of terazosin therapy in benign prostatic hyperplasia

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Abstract

Purpose: To determine whether magnetic resonance imaging (MRI) or quantitative color-imaged morphometric analysis (MA) of the prostate gland are related to the clinical response to terazosin.

Methods: Thirty-six male patients with symptomatic benign prostatic hyperplasia (BPH) with a serum prostate-specific antigen level of 4–10 ng/mL underwent MRI with body coil, transrectal prostate ultrasonography and biopsy prior to terazosin therapy. For MRI-determined stromal and non-stromal BPH, the ratio of the signal intensity of the inner gland to the obturator internus muscle was evaluated. Histologic sections were stained with hematoxylin and eosin. The MA of the specimens was performed by Samba 2000. Results of the two techniques were interpreted according to the terazosin therapy results.

Results: The mean stromal percentage was $60.5 \pm 18.0\%$. No statistically significant relationship was found between the clinical outcome of terazosin and the MRI findings. The MA results showed a significant relationship between the percentage of stroma and the percent change of the peak urinary flow rate, but not with the percent change of the international prostate symptom score after terazosin therapy ($P < 0.05$).

Conclusion: Magnetic resonance imaging alone is not sufficient in predicting the response to terazosin therapy. Morphometric analysis of BPH tissue composition can be used in predicting the clinical outcome of terazosin therapy but it is suitable only in patients for whom prostatic biopsy is necessary in order to rule out prostate cancer.

Key words benign prostatic hyperplasia, biopsy, histologic analysis, magnetic resonance imaging, terazosin.

Introduction

Benign prostatic hyperplasia (BPH) is the most common benign tumor afflicting men and constitutes a major factor impacting the health of men all over the world. The condition of BPH, when it interferes with bladder neck urine flow, frequently requires treatment. Prostatectomy, the only widely accepted effective treatment option in BPH, is invasive and is associated with varying degrees of morbidity. Thus, over the past few years, several studies regarding minimally invasive or non-invasive treatment methods for BPH have been undertaken. The development of non-surgical therapy for BPH has been empirical, as the specific biochemical, physiologic and morphometric properties of the prostate adenoma predisposing to the development of infravesical obstruction have not been elucidated.[1]

Pharmacotherapy, with the use of an α-adrenergic receptor blocker or 5α-reductase inhibitor, has been considered as an alternative treatment method.[2,3] How-

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ever, pharmacotherapy, with its own limitations, does not produce results approaching those achieved by surgery and is effective only in a select number of patients.[4,5] The key to successfully achieving the development of an effective pharmacologic approach to BPH is a thorough understanding of the cellular and chemical basis of the cause of BPH.[1] Benign prostatic hyperplasia is a proliferative process that involves both the stromal and epithelial elements of the prostate.[6–13] The success of pharmacologic agents may depend upon the percent area of stroma or epithelium, as determined by histologic studies.[7,9] α-Adrenergic receptor blockers, such as terazosin, seem to be more effective in BPH patients with stromal hyperplasia.[7] Morphometric histologic interpretation of the prostate could be done with computerized color image analysis.[8–13] Tissue samples for histologic determination could be obtained by the use of transrectal prostate biopsy, an invasive method with a considerable morbidity rate.[14]

Recently, magnetic resonance imaging (MRI) has been advocated as a non-invasive imaging modality of choice for evaluating the prostate gland. The anatomy of the prostate gland and surrounding structures has been well characterized with MRI. It has been reported that the MRI features of BPH are variable, but relatively predictable and depend upon the distribution and size of the glandular elements as well as the composition of the surrounding stroma.[15–17] Magnetic resonance imaging seems to be a potential method of non-invasive assessment of the stromal percentage of the prostate in predicting the outcome of pharmacotherapy.

The main objective of the present study was to determine whether MRI or color-assisted quantitative morphometric image analysis (MA) are related to the clinical response to terazosin, a long-acting α-1 blocker. An additional aim of the study was to assess the value of MRI for determining the histologic composition of the prostate by comparing the MRI scans with the histologic specimens obtained from transrectal prostate biopsy.

Methods

The study was conducted at the Urology Department of Gazi University School of Medicine, Turkey. Patients with symptomatic BPH were evaluated with a complete history and physical examination, complete blood count, routine biochemical analysis, serum prostate-specific antigen (PSA), urinalysis and uroflowmetry. The severity of symptomatic BPH was evaluated using the International Prostate Symptom Score (IPSS) questionnaire. Serum PSA was measured in patients before any prostatic manipulation, using the Tandem-R assay method (Hybritech, San Diego, CA, USA).

Forty-three male patients who had an IPSS greater than 7, a peak urinary flow rate (Qmax) of less than 15 mL/s and a serum PSA of 4–10 ng/mL underwent MRI, transrectal prostate ultrasonography and transrectal prostate biopsy prior to commencing terazosin therapy. The MRI was performed before the transrectal prostate biopsy in order to prevent image misinterpretation due to intraprostatic hemorrhage. Of the 43 patients, 36 whose transrectal prostate biopsy revealed BPH were included in the study. The mean age of the 36 patients was 62.8 (range 51–81) years. The mean pretreatment findings were IPSS 17.7 ± 3 (range 13–27) ng/mL, serum PSA 5.7 ± 1.5 (range 4.1–9.8) ng/mL, Qmax 10.5 ± 2.1 (range 6–13) mL/s, and prostate volume 35.5 ± 5 (range 16–65) mL.

Any patients with a history of urethral stricture, neurogenic disease, diabetes mellitus, bladder neck or urethral operation or previous treatment for BPH were excluded from the study. Patients with any abnormality at digital rectal examination, blood or urine analysis, MRI and transrectal ultrasonography were also not included in this study.

The Wiest Urocompact 6000 Uroflowmeter (Wiest, Irvine, CA, USA) was used for uroflowmetry throughout the study. If the patient voided less than 150 mL, another attempt was encouraged after additional fluid intake. The MRI was performed with a 1.0 Tesla superconducting unit (Signa; GE Medical Systems, Milwaukee, WI, USA) and conventional body coils. T1-weighted spin-echo (SE) axial and T2-weighted fast SE axial, sagittal and fat-suppressor axial images were obtained for all patients. Data acquisition was performed twice, and the field of view was 32 × 32 cm. Inferior and superior saturation pulses were applied.

After MRI, prostate ultrasonography was performed using the 7 MHz Brüel and Kjær transrectal transducer (3535 scanner, 8551 rectal probe; Brüel and Kjær, Nærum, Denmark) by the same urologist. A computer software program based upon the assumption that the prostate is an elliptical structure estimated the prostate volume. Following rectal enema and prophylactic antibiotic (500 mg ciprofloxacin orally 1 h before and 6 h after the procedure) eight random biopsies of the prostate including six from the peripheral zone and two from the transitional zone were taken.

Magnetic resonance imaging method

The MRI scans were prospectively read twice, blinded to time sequence, by two radiologists with the know-

ledge that each patient had clinically suspected prostate cancer. In cases of incompatibility, the two radiologists reviewed the sections again and an agreement between the two observers was reached after careful interpretation. When the two observers could not agree, the senior radiologist decided.

The volume of the inner gland (transition zone plus central zone plus periurethral tissue), the peripheral zone and total prostate gland on T2-weighted images were recorded. The prostatic volume and inner gland volume were calculated by multiplying total prostatic area and inner gland area by 0.8, respectively.

According to the MRI findings, patients were divided into two groups: stromal and non-stromal. Non-stromal BPH was diagnosed according to the following three criteria:[15]

1. The nodules in the inner gland were characterized as having high heterogenous signal intensity on T2-weighted images.
2. Surgical capsule was present.
3. The inner gland volume to total volume ratio was greater than 0.75.

When none of these findings were present, stromal BPH was diagnosed. The surgical capsule was seen as a low-signal-intensity band at the back of inner gland on T2-weighted images. Fibrous and muscular tissue in the non-glandular zone of the prostate was differentiated. While determining the signal intensity (SI) of the hyperplastic inner gland, a large region of interest was used. In order to calibrate the measurements, the ratio of SI of the hyperplastic inner gland to the obturator internus muscle in the same section was determined.

Histologic method

The histologic samples were transrectal prostate biopsy specimens fixed in buffered formalin, embedded in paraffin, and sectioned at 5 μm. Tissue sections were stained with hematoxylin and eosin (H&E).

Morphometric analysis of stroma, glandular epithelium and glandular lumina was performed using the Samba 2000 software image analyzer system (Samba, Canberra, ACT, Australia) combined with a Leitz light microscope (Leitz, Stuttgart, Germany) equipped with a Sony color video camera and MPR II 14-inch color monitor (Sony, New York, NY, USA). Samba 2000 is a color system image analyzer which discriminates color differences of stained tissue sections. The area densities corresponding to each of these tissue components were calculated for each full screen of the monitor, digitized by personal computer. At least 20 different fields (×400) were examined from each tissue section. All glandular epithelium and glandular lumina were subtracted from the total specimen area and percentage of stroma was calculated for each patient.

Terazosin dose

Terazosin was titrated to a daily dosage of 5 mg over a 10-day interval, providing adverse events were not observed. The titration schedule proceeded as follows: 1 mg, days 1–3; 2 mg, days 4–10; and 5 mg, days 11–90. Terazosin was always administered at bedtime. All 36 patients tolerated 5 mg dosage for 3 months. All patients were evaluated with IPSS, serum PSA level, urinalysis and Qmax at the third month. Clinical response to terazosin therapy was defined by changes in IPSS and Qmax.

Statistical method

The relationships between clinical response to terazosin and MRI or histologic interpretation were evaluated by using paired-samples *t*-tests and linear regression tests.

Results

The mean ± SD post-treatment IPSS was 13.4 ± 4.2 (range 9–21) and the mean ± SD Qmax level was 17.5 ± 5.0 (range 7–29) mL/s at the third month of therapy. After the terazosin therapy the mean ± SD improvement in IPSS and Qmax were 23.5 ± 15.9% and 66.1 ± 54.9%, respectively. Improvements in these parameters were statistically significant ($P < 0.001$, paired-samples *t*-test). Only mild dizziness associated with terazosin was observed in 3 patients (8.3%).

Magnetic resonance imaging findings

With MRI, it was determined that 14 patients (38.9%) had stromal and 22 patients (61.1%) had non-stromal hyperplasia (Fig. 1). Pretreatment and post-treatment IPSS and Qmax values in the MRI stromal and non-stromal groups are summarized in Table 1. The change in IPSS and Qmax values was statistically significant for both MRI groups.

No statistically significant relationship was found between the ratio of SI of the hyperplastic inner gland to the obturator internus muscle and the percent change of IPSS ($r = –0.23$, $P > 0.05$) or Qmax ($r = –0.20$, $P > 0.05$).

Histologic findings

By using MA, the mean ± SD percentage of stroma (SP) of the patients was 60.5 ± 18.0%. The relationship

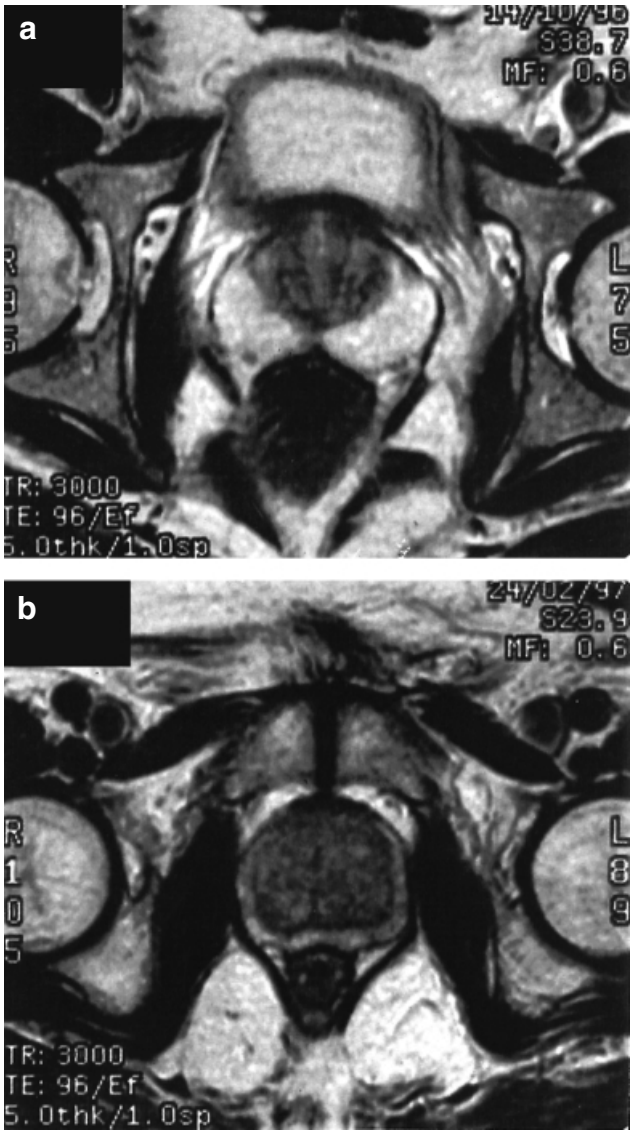

Fig. 1 T2-weighted axial magnetic resonance image of a patient with (a) stromal hyperplasia (percent epithelium of inner gland, 5%; ratio of signal intensity of the inner gland to the obturator internus muscle, 4.32); and (b) non-stromal hyperplasia (percent epithelium of inner gland, 20%; ratio of signal intensity of the inner gland to the obturator internus muscle, 6.02).

between SP and the percent change of IPSS and Qmax according to MA are shown in Fig. 2. Although a statistically significant relationship was not found between the SP and the percent change of IPSS after terazosin therapy ($P > 0.05$), there was a statistically important relationship between SP and the percent change of Qmax ($P < 0.05$).

The mean ± SD MA-detected SP was 60.9 ± 19.8% in the MRI stromal group and 60.3 ± 29.0% in the MRI non-stromal group. The difference between two groups was not statistically different ($P > 0.05$).

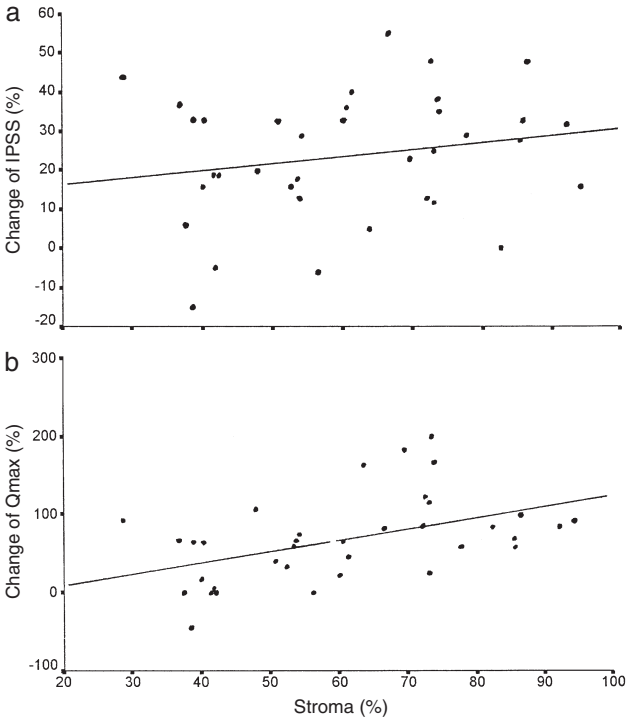

Fig. 2 The relationship between percent of stroma according to Samba 2000 and (a) the percent change of the international prostate symptom score (IPSS; $r = -0.20$, $P > 0.22$); and (b) the percent change of the peak urinary flow rate (Qmax; $r = -0.48$, $P = 0.002$).

Discussion

Terazosin, approved for symptomatic BPH, has an excellent safety profile and efficacy, and is likely to achieve a prominent role in the treatment of this common chronic disease. The clinical response following terazosin therapy observed in the present study is much better than the other reported experiences.[3,5,7] The mean change in Qmax (7 mL/s) at the third month was higher than other reports.[5,7] It might be attributable to the small number or distribution, with regard to percent of stroma, of patients included in the study. Furthermore, the overall mean change in Qmax of 66% was not too different from the result of 58% obtained by Shapiro *et al.*[7]

It has been reported that terazosin is not uniformly effective in relieving BPH-related symptoms and flow restriction. Moreover, baseline clinical or urodynamic parameters are also not directly related to the clinical

Table 1 Pretreatment and post-treatment IPSS and Qmax values for magnetic resonance image-determined stromal and non-stromal groups

	Stromal	*P*-value*	Non-stromal	*P*-value*
IPSS		< 0.01		< 0.001
Pretreatment	18.8 ± 3.3		17.1 ± 2.4	
Post-treatment	14.2 ± 3.5		12.9 ± 3.1	
Qmax (mL/s)		< 0.001		< 0.001
Pretreatment	11.5 ± 1.7		9.7 ± 2.1	
Post-treatment	19.6 ± 6.7		16.6 ± 5.0	

* Paired-samples *t*-test. IPSS, international prostate symptom score; Qmax, peak urinary flow rate.

response to α-blockade in subjects with BPH.[3] An explanation for the varying response to terazosin may be the variation in prostate tissue composition noted in different individuals. The proposed mechanism of α-1 blockade in BPH is a reduction of prostatic urethral resistance secondary to relaxation of prostate smooth muscle, the locus of the α-adrenergic receptors.[7,18] Theoretically, a man with a stromal-rich prostate would respond better to terazosin than a man with an epithelial-rich prostate and it is important to evaluate the histologic type of BPH before instituting pharmacologic treatment.[7,9] Currently, this can be done either by quantitative histopathologic analysis[7] or by MRI.[15,19,20]

Due to its complications, including hematuria, hemospermia, pain, urinary retention, urinary infection and septicemia, transrectal prostate biopsy can not be used in routine clinical practice in order to determine the histologic composition of BPH.[14] However, in the PSA era, a subset of patients with BPH are inevitably biopsied because of suspicious PSA levels and their pathologic specimens can easily be examined for tissue composition also. From this point of view, MRI was used in the present study as a non-invasive method to select the most appropriate patients for terazosin therapy on the basis of histologic components, and the MRI was compared with transrectal prostate biopsy specimens.

Magnetic resonance imaging has been used increasingly in the evaluation of the prostate gland. T1-weighted images (T1WI) reveal the overall prostatic outline and volume correctly but rarely show significant intraprostatic anatomic characteristics.[16] On T1WI the prostate, seminal vesicles and periprostatic veins are of homogenously low SI, similar to that of skeletal muscle. The surrounding musculature, the levator ani and the obturator internus muscles have a relatively low SI.[17] The prostate is divided into the central, transitional and peripheral zones and internal zonal anatomy can be relatively well displayed by T2-weighted images (T2WI).[16] The peripheral zone demonstrates a higher SI than the central and transitional zone because of its high water content and the loose acinar structure of the glands.[17] The central and transitional zones cannot be reliably distinguished on MRI and are often considered inner or central gland.[16,17] The SI of inner gland is greater than that of muscle but less than that of periprostatic fat.[17] The MRI appearance of BPH on T2WI may produce a variety of heterogenous or nodular patterns.[16,17] As the inner gland enlarges, the outer gland is compressed and may be visible only as a thin rim of tissue posteriorly on T2WI, referred to as surgical capsule.[16] A BPH that is predominantly glandular appears as high SI while a stromal BPH has a more homogenously low SI.[16,19]

In the present study, the criteria described by Ishida *et al*. was used for assessing BPH as stromal or non-stromal according to the MRI.[15] Mimata *et al*. proposed that comparing the inner gland of the prostate to the bone marrow of the head of the proximal femur as an internal standard predicts the α-blocker response in patients with BPH.[20] Because these criteria are not accepted worldwide, the ratio of SI of the hyperplastic inner gland to the obturator internus muscle was also determined. It should be noted that small glands within glandular hyperplasia would show low SI and assessment only by SI might give limited diagnostic information. Although it has been found that MRI correlates with histologic tissue heterogeneity and α-1 blockade therapy outcome,[15,19,20] the present study found no statistically significant relationship between the MRI findings and the clinical outcome of terazosin or the histopathologic composition of the prostate. Failure of correlation between MRI findings and histologic interpretation regarding stromal or non-stromal appearance could show that the criteria of MRI are not

clear-cut. If a set of strict criteria for stromal or non-stromal distinction can be found, MRI might possibly predict the clinical outcome of terazosin.

Gadolinium-enhanced MRI or endorectal coil were not used in the present study. Endorectal surface coils have now been developed that yield high resolution of images of the prostate and better demonstrate the zonal anatomy of the gland, and more of the anatomy is imaged in detail.[16] Magnetic resonance imaging with endorectal coil may ultimately have a role in identifying histologic parameters that predict the outcome of alternative pharmacotherapies for BPH. However, the use of gadolinium enhancement or endorectal surface coil increases the cost of MRI.

Bartsch *et al*.[6] and Siegel *et al*.[8] reported the quantitative morphometric analysis of the prostate by using a point stereology method. Shapiro *et al*. described the first application of computer-assisted color image analysis and/or double immunoenzymatic staining with specific antibodies for smooth muscle and epithelium in the prostate in order to determine the percentage area density of smooth muscle, connective tissue, glandular epithelium and glandular lumen in prostate gland.[11–13] It was reported that BPH was primarily a stromal process especially in symptomatic patients.[6,8,9,11,13] The present study found that the mean SP of the patients was 60.5% using MA. These results confirm previous reports indicating that hyperplastic prostates result mainly from a stromal tissue hyperplasia.

The present study found a direct relationship between the SP obtained from MA and the clinical outcome of terazosin. Our hypothesis was that men with stromal-rich prostates would respond better to the terazosin while optimal pharmacologic treatment of men with epithelial-rich prostates is 5α-reductase inhibitors. Supporting our hypothesis, SP obtained from MA was significantly correlated with the percent change of Qmax but not with IPSS, following terazosin therapy. These result parallel closely the results obtained by Shapiro *et al*.[7] They observed a direct relationship between the percent area density of prostate smooth muscle and the percentage increase in peak urinary flow rate (but not with the percentage decrease in total symptom score) which suggests that the therapeutic response to terazosin therapy is related to relaxation of prostate smooth muscle. This lack of correlation between post-treatment IPSS and Qmax may also indicate the role of detrusor overactivity or hypocontractility in BPH which was found in up to 50% of patients, and prostatism symptoms are not BPH specific.[21]

With the use of special staining methods, the stroma can be further differentiated into separate smooth muscle and fibrous compartments, the relative amounts of which may also vary considerably between different prostates.[12,13] Although Shapiro *et al*. have demonstrated the utility of this subdivision,[7] using immunoenzymatic staining techniques to correlate prostatic smooth muscle density and BPH responsiveness to α-blocking agents, subdivision of the stroma may not be practical by using a conventional H&E stain,[13] as in the present study. The study indicates that SP obtained from conventional H&E-stained histologic tissue sections may have a role in predicting an individual's treatment response to α-blocking agents. Results obtained from subdivision of stroma, with double immunoenzymatic color image analysis, would also be of interest and further clinical studies confirming the validity of this method are indicated.

To what extent does a limited tissue sample accurately reflect whole-gland prostatic histologic type? Although major differences in primary BPH tissue composition may exist between prostate glands, it has been shown that within individual prostates the process is rather symmetric and, in fact, as little tissue as a single biopsy core may allow accurate characterization of a hyperplastic prostate gland.[10,22]

In conclusion, our findings suggests that MRI with body coil is not appropriate for determining the clinical outcome of terazosin and not correlated with the histologic composition of BPH. Because it is an invasive diagnostic procedure, pathologic assessment of BPH composition with transrectal prostate biopsy is not suitable. However, for patients in whom prostatic biopsy is necessary to rule out prostate cancer, histologic interpretation of BPH with quantitative color-imaged MA methods may be helpful in predicting the clinical outcome of terazosin therapy.

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