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Vascular damage induced by type 2 diabetes mellitus as a risk factor for benign prostatic hyperplasia

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Abstract *Aims/hypothesis:* The aim of this study was to evaluate the relationship between benign prostatic hyperplasia (BPH) and arteriosclerosis shown in a model of type 2 diabetes in a trans-sectional population study using contrast-enhanced colour Doppler ultrasound for exact assessment of prostatic blood flow. *Methods:* Contrast-enhanced transrectal colour Doppler ultrasound was performed using a microbubble-based ultrasound enhancer SonoVue for evaluating prostate vascularity (transitional zone [TZ] and peripheral zone [PZ]) in diabetic BPH patients, non-diabetic BPH patients and healthy subjects. Computer-assisted quantification of colour pixel intensity (CPI) was used to objectively evaluate the prostate vascularity. Resistive index measurements were obtained in the TZ and the PZ. Findings were compared between these three groups. *Results:* TZ-CPI was significantly lower in diabetic patients than in non-diabetic BPH men (p=0.001), whereas the CPI of the PZ showed no difference between these two groups (p=0.978). TZ-CPI of patients with diabetic and non-diabetic BPH were significantly lower than in controls (p<0.001), but no difference was found between diabetic and healthy patients in the PZ (p=0.022) and borderline significance was seen when comparing patients of the BPH group with the control patients (p=0.019). Resistive index values of the TZ in diabetic patients showed significantly higher values (p<0.001) than the BPH and control groups. *Conclusions/interpretation:* The significantly lower CPI and higher resistive index values of the TZ in diabetic patients compared with patients with non-diabetic BPH and healthy subjects indicate considerable vascular damage in the TZ of these patients. Diabetic vascular damage may cause hypoxia and may contribute to the pathogenesis of BPH.

Keywords Arteriosclerosis · Benign prostatic hyperplasia · Diabetes mellitus · Hypoxia · Transrectal colour Doppler ultrasound

Abbreviations BPH: benign prostatic hyperplasia · CDUS: colour Doppler ultrasound · CPI: colour pixel intensity · ED: erectile dysfunction · IIEF: International Index of Erectile Dysfunction · PZ: peripheral zone of prostate · RI: resistive index · TZ: transitional zone of prostate

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Introduction

Dysregulation in the prostatic stromal cells is of decisive importance in the pathogenesis of benign prostatic hyperplasia (BPH), the most common non-malignant proliferative disorder in the ageing male. In spite of evidence that androgens and oestrogens are involved in the growth of stromal and epithelial cells in the prostate and induction of fibromuscular overgrowth, the true aetiology of BPH remains unclear and seems to be multifactorial.

It has been postulated that a reawakening of the inductive properties of the prostatic stroma induces hyperplasia in the stromal and glandular compartment [1], and that abnormal blood flow patterns might contribute to hypoxia-stimulated prostate growth [2]. In a recently published study using a cell culture model of human prostatic stromal cells, it was

shown that prostatic stromal cells respond to hypoxia by upregulation of secretion of several growth factors in vitro suggesting that hypoxia may trigger prostatic growth [3]. Hypoxia in the prostate may occur in patients who present with generalised or localised vascular damage, and indeed several studies have suggested an association between the presence of vascular disorders such as coronary heart disease or diabetes mellitus and prostatic disease [4–7]. The earliest report that discusses the association of diabetes mellitus with vascular degenerative complications goes back to the early 1950s [8]. A recent study clearly demonstrated the association between hypoxia and increased angiogenesis and growth in the rat bladder [9]. However, to date, no clear causative correlation has been found between vascular damage and BPH.

Colour Doppler ultrasound (CDUS) is a non-invasive method for the determination of blood flow, but subjective quantification of the CDUS data has shown limited efficacy [10]. In contrast, computer-assisted quantification of CDUS by calculation of the colour pixel intensity (CPI) has been shown to be an accurate technique that allows for exact assessment of organ and tissue perfusion [11, 12].

The resistive index (RI) obtained by pulsed-wave Doppler ultrasound is related to both blood flow and pressure and represents one of the most relevant indicators of vascular damage in the analysis of small vessels in the prostate [13].

This trans-sectional population study was performed to test the hypothesis of a causal relationship between BPH and type 2 diabetes mellitus by assessment of prostatic blood flow using contrast-enhanced CDUS.

Subjects and methods

From September 2003 to September 2004 a total of 64 men were enrolled to participate in the present study. The cohort was divided into three subgroups. The first subgroup included patients with manifest type 2 diabetes mellitus (defined as repeated fasting glucose levels ≥7.8 mmol/l) for a minimum duration of 5 years. The second group comprised men with BPH (International Prostate Symptom Score [IPSS] of ≥7) and a prostate volume of 30 cm^3 or higher. The control group consisted of healthy men with no signs of BPH (IPSS <7 and a prostate volume lower than 30 cm^3).

Patients with prostate cancer or who had undergone prostate surgery prior to the study were excluded, as well as men taking medication of 5-alpha reductase inhibitors or alpha blockers. Subjects with clinically evident prostatitis, acute urinary tract infection, or contraindication to the ultrasound contrast agent SonoVue (Bracco, Milano, Italy) including New York Heart Association stage IV heart failure were also excluded.

Twenty-eight diabetic patients were referred from the Department of Internal Medicine for routine urological check-up; 24 non-diabetic patients presented to our clinic with lower urinary tract symptoms due to BPH; and 12 healthy patients served as a control group. All patients provided informed consent, and the investigations were approved by the local ethics committee.

Information obtained by standardised interview at initial examination included history of type 2 diabetes mellitus, cigarette smoking and use of medications. Obesity was estimated using BMI (kg/m^2). A patient with a BMI above 25 was considered obese. Blood pressure and pulse count were measured using a standard sphygmomanometer after the patient had been sitting for at least 5 min. Fasting lipid levels (total cholesterol, HDL and LDL cholesterol, triglycerides) as well as fasting glucose levels and the HbA_1C value were determined in the hospital diagnostic laboratory. Uroflowmetry and measurement of residual urine was performed in every patient, as well as determination of serum testosterone and prostate-specific antigen/free prostate-specific antigen. Patients with elevated prostate-specific antigen levels underwent ultrasound-guided prostate biopsy in order to rule out prostate cancer. Patients with biopsy-proven prostate cancer were excluded from the study.

For assessment of erectile function the International Index of Erectile Dysfunction (IIEF) [14] was used. Lower urinary tract symptoms were evaluated using the International Prostatic Symptom Score (IPSS).

All ultrasound investigations were carried out with one single experienced radiologist (F. Frauscher) performing contrast-enhanced CDUS with the high-frequency end-fire probe EC10C5 fitted to a Sequoia unit (Acuson, Mountain View, CA, USA). Patients were in the left lateral decubitus position. During imaging, care was taken to minimise probe pressure on the rectal wall. Patients underwent examination with an empty or nearly empty bladder so that compression of the bladder did not affect intraprostatic and bladder-neck vessels. Contrast-enhanced CDUS was used to visualise arteries of the transition zone (TZ) and peripheral zone (PZ) as well as the bladder neck, and to measure the RI. CDUS was performed in a transverse plane at the base, mid and apex of the prostate. Pulsed-wave spectral Doppler analysis for assessment of the RI was performed from arteries of the PZ and the TZ in each plane. The mean of each plane was calculated.

Doppler signal intensity in both zones (TZ and PZ) as well as for the bladder neck was evaluated using computer-assisted quantification of CPI. The region of interest was placed in areas with the highest detectable blood flow. To perform this, the red–green–blue output of the ultrasound unit was digitised using an IBM-compatible computer. The digitised images were post-processed using the NIH image software package (version 1.62, National Institutes of Health). For each subject, an area from the outer and inner gland underwent computer-assisted quantification of CPI. The digitised colour image was divided into its three colour components. Each colour channel consists of 256 brightness values according to the brightness of the colour. To minimise background noise, the threshold value for the blue and red colour channels was set to the middle of the brightness value dynamics range, namely at 128 for both colours. Within the defined region of interest, only colour pixels showing a brightness value greater than 64 were counted (Fig. 1).

Additionally, the RI and the acceleration time in penile vessels (corpora cavernosa) were evaluated. The acceleration time was measured by spectral wave Doppler ultra-

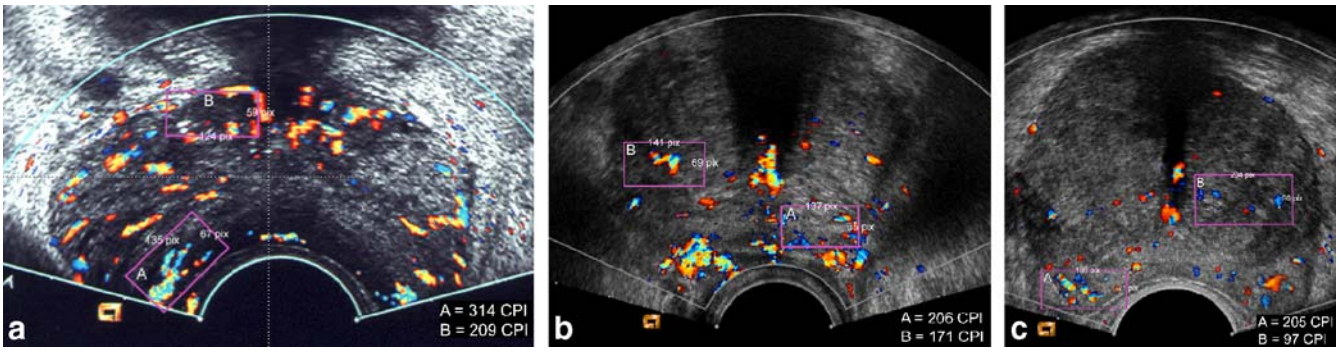

Fig. 1 Measurement of CPI: contrast-enhanced colour Doppler ultrasound images showing the defined *rectangles* around the regions of interest (20 mm^2) in a non-diabetic patient with normal prostate (21 cm^3, *upper panel*), a non-diabetic patient with BPH (74 cm^3, *middle panel*) and a diabetic patient with BPH (81 cm^3, *lower panel*)

Table 1 Clinical characteristics of the patients enrolled in the study

	Diabetic patients (*n*=28)	BPH patients (*n*=24)	Control group (*n*=12)	Kruskal–Wallis test *p* value	Mann–Whitney *U*-test *p* value		
					BPH vs diabetic	BPH vs control	Diabetic vs control
Age (years)	60.5 (53/68)	63 (58.25/69.75)	33 (28.25/42)	<0.001	0.186	<0.001	<0.001
CPI (TZ)	183.5 (150.75/205.5)	217 (193.75/247)	294 (277.25/333.75)	<0.001	0.001	<0.001	<0.001
CPI (PZ)	239.5 (191/262.75)	236 (216.25/252.5)	266 (256.25/300.75)	0.004	0.978	0.019	0.022
RI (TZ)	0.88 (0.84/0.89)	0.8 (0.77/0.84)	0.63 (0.6/0.68)	<0.001	<0.001	<0.001	<0.001
RI (PZ)	0.85 (0.83/0.89)	0.81 (0.77/0.87)	0.72 (0.7/0.8)	<0.001	0.019	0.015	<0.001
CPI (bladder-neck)	39.5 (28.5/51)	46.5 (39/57.25)	61.5 (49/71.5)	0.003	0.057	0.018	0.002
RI (bladder-neck)	0.96 (0.9/1)	0.92 (0.89/0.99)	0.84 (0.79/0.96)	0.01	0.305	0.019	0.006
RI (corpora cavernosa)	1 (1/1)	1 (0.95/1)	1 (1/1.08)	0.002	0.11	0.018	0.286
Acceleration time (corpora cavernosa/s)	0.11 (0.09/0.12)	0.05 (0.04/0.07)	0.02 (0.01/0.02)	<0.001	<0.001	<0.001	<0.001
IPSS	14 (11/21.75)	8 (6/15)	0 (0/2.75)	<0.001	0.004	<0.001	<0.001
Quality of life score	3 (2/4)	2 (1/3)	0 (0/0)	<0.001	0.011	<0.001	<0.001
IIEF score	26 (18/32)	42 (34.25/52.75)	66 (60/68.75)	<0.001	<0.001	<0.001	<0.001
RR systolic BP (mm Hg)	140 (122.5/160)	140 (130/150)	130 (110/140)	0.149			
RR diastolic BP (mm Hg)	80 (71.25/90)	80 (71.25/80)	75 (70/80)	0.203			
Pulse rate (bpm)	74.5 (66.5/86)	72 (66.5/80)	70 (62.5/76)	0.222			
Cholesterol (mmol/l)	4.89 (4.31/5.44)	4.80 (4.10/5.26)	4.77 (3.90/5.29)	0.798			
Triglycerides (mmol/l)	2.40 (1.69/3.11)	1.52 (0.92/1.98)	1.36 (0.93/2.52)	0.004	0.001	0.96	0.049
BMI	26.5 (24.25/29)	24.5 (22.25/27.5)	24 (22/25)	<0.001	0.031	0.224	0.002
Glucose (mmol/l)	9.73±2.94	5.59±0.56	5.03±0.48	<0.001	<0.001	0.002	<0.001
HbA_1c (%)	8.15 (7.15/10.25)	5.5 (5.4/5.7)	5.35 (5.23/5.6)	<0.001	<0.001	0.379	<0.001
Testosterone (ng/ml)	3.35 (2.83/4.28)	4.55 (3.25/5.48)	4.5 (3.3/5.88)	0.05	0.03	0.804	0.069
Prostate-specific antigen (ng/ml)	1.05 (0.55/1.36)	1.78 (0.88/2.73)	0.39 (0.25/0.78)	<0.001	0.046	<0.001	0.005
Prostate volume (cm^3)	44 (40/53.75)	43.5 (38.25/50.75)	19 (17/24)	<0.001	0.607	<0.001	<0.001
Maximum flow (ml/s)	16.5 (9.68/18)	16 (12.08/20.5)	29.6 (26.8/40.1)	<0.001	0.526	<0.001	<0.001
Average flow (ml/s)	7.95 (5.18/11)	8.45 (5.7/11.75)	17.7 (14.3/22.15)	<0.001	0.7	<0.001	<0.001
Residual urine (ml)	40 (21.25/87.5)	30 (0/67.5)	0 (0/0)	<0.001	0.323	0.001	<0.001

Data are expressed as medians and 25th and 75th percentiles. Differences between the three groups were analysed by the Kruskal–Wallis test. If the Kruskal–Wallis test indicated statistical significance, Mann–Whitney *U*-tests were performed. Statistical significance was defined as $p<0.05$. After Bonferroni's correction for three comparisons, *p* values of less than 0.017 were considered to indicate statistical significance

sound from the beginning of the systolic upstroke to the highest systolic peak in the waveform. Any break in the systolic upstroke before it reached its peak was ignored.

SPSS for Windows 12.0 software (Chicago, IL, USA) was used for all analyses. Data were expressed as medians and 25th and 75th percentiles. Differences between the three groups were analysed by Kruskal–Wallis tests. If these tests indicated statistical significance, Mann–Whitney *U*-tests were performed. Statistical significance was defined as p being less than 0.05. After Bonferroni's correction for three comparisons, p values of less than 0.017 were considered to indicate statistical significance.

Results

Sixty-four patients were evaluated in the present study, among them 28 patients diagnosed with type 2 diabetes mellitus, 24 patients with non-diabetic BPH and 12 healthy patients who served as controls. Mean time interval after diagnosis of type 2 diabetes in the diabetic group was 8.4 years (range 5–14 years). Mean HbA_1c value in the diabetic group was 8.15% (range 5.8–12.7%). The clinical characteristics of the patients are presented in Table 1.

CPI of the TZ was significantly lower in diabetic patients than in patients with non-diabetic BPH (median 183.5 [range 112–244] vs 217.0 [range 155–287]; p=0.001), whereas CPI of the PZ showed no difference between these two groups (mean 239.5 [range 165–341] vs 236.0 [range 176–312]; p=0.978). TZ-CPI in patients with both diabetic and non-diabetic BPH were significantly lower compared with the controls (p<0.001), but no difference was found between diabetic and healthy patients in the PZ (p=0.022), and a borderline significance was seen when comparing patients of the BPH group with the control patients (p=0.019).

RI values of the TZ in diabetic patients (mean 0.88 [range 0.74–0.92]) showed significantly higher values (p<0.001) compared with non-diabetic BPH patients (mean 0.80 [range 0.70–0.89]) and the control group (mean 0.63 [range 0.56–0.70]). RI measured in the PZ was not different between diabetic and non-diabetic BPH patients (mean 0.85 [range 0.77–0.92] vs 0.81 [range 0.68–0.91]; p=0.019), but was significantly different between the control group and the diabetic and non-diabetic BPH groups (p<0.001).

CPI and RI values measured at the bladder neck did not show any difference between diabetic and non-diabetic BPH patients (p=0.057 and p=0.305, respectively). There was a significant difference in CPI and RI between diabetic patients and the control group (p=0.002 and p=0.006, respectively), but no difference was observed in the CPI and RI values between the BPH patients and the control group (p=0.018 and p=0.019, respectively).

RI measured in arteries of the corpus cavernosum did not show any difference between the three groups, but mean increase of arterial inflow was significantly slower in diabetic patients than in the BPH (p<0.001) and control (p<0.001) groups.

There was no significant difference between the three groups in terms of blood pressure, pulse count, fasting cholesterol levels (total, HDL and LDL), serum testosterone and cigarette use. Mean triglyceride levels were higher in diabetic patients compared with the BPH group (p=0.001) but not compared with the control group (p=0.049). Median BMI was lower in the control group than in diabetic patients (p=0.002), whereas there was no difference in BMI between the BPH group and the diabetic (p=0.031) and control groups (p=0.224).

Mean IPSS showed a significant difference between the diabetic and non-diabetic BPH men (p=0.004), and quality of life scores and IIEF scores were significantly worse in diabetic patients compared with non-diabetic BPH patients.

Mean prostate volume, maximum flow rate and residual urine volume did not show significant difference between diabetic and non-diabetic BPH patients (p=0.607, p=0.526 and p=0.323, respectively), but all these parameters were better in the control group compared with in the diabetic group and patients with non-diabetic BPH.

Discussion

Previous studies have shown an association of arteriosclerotic disease manifestations such as type 2 diabetes mellitus, hypertension or dyslipidaemia and the development of BPH, indicating that BPH is a component of the metabolic syndrome and that the causal factor for BPH might be a systemic rather than a local factor. Recent studies demonstrated a significantly faster annual growth rate in diabetic patients compared with in other men presenting with lower urinary tract symptoms [15], and that diabetes is associated with greater BPH symptom severity even after age adjustment [6]. Long-lasting diabetes mellitus has repeatedly been shown to be an indicator disease for arteriosclerosis and to represent an independent predictor of significant arteriosclerosis [16, 17], as diabetes is significantly and positively associated with intima media thickness [18–20]. Up to now, however, the causal association of vascular damage and BPH remains unclear. There is an increasing recognition of the role of oxidative stress as an inductor of cell growth. Relevant to this are observations suggesting that there is a common pathogenetic mechanism for vascular smooth muscle cell growth and remodelling and prostate smooth muscle proliferation.

While in healthy prostatic vessels the RI is relatively low, in patients where BPH is advanced, arteries between the PZ and the TZ may be compressed, which has been found to lead to a marked increase in the RI of the capsular arteries [21]. The RI measurements in the symptomatic BPH patients as a group confirm the above-mentioned findings by showing higher RI values in the PZ than in the TZ (0.81 vs 0.80). In contrast, however, in the diabetic patients, higher RI values were measured in the TZ (0.88) than in the PZ (0.85), indicating significant vascular damage with increased vascular resistance particularly in the TZ of these patients. An important finding is the statistically significant increase of RI in the TZ of diabetic patients in contrast to non-diabetic BPH patients (p<0.001), whereas the RI of the PZ did not reveal any significant difference between these groups (p=0.019).

CPI analysis as an objective analysis method for tissue perfusion confirmed these findings, showing almost identical results for the PZ (median 239.5 in the diabetic group vs 236.0 in the non-diabetic BPH group; p=0.978) but significantly different values for the TZ (median 183.5 in the diabetic group vs 217.0 in the group with BPH alone; p=0.001). While other studies investigating the vascular anatomy of the normal prostate found no significant difference between the RI values of the PZ and the TZ [22], in the present study there was a clear difference between these two areas in the control group (0.72 in the PZ vs 0.63 in the TZ). Although the values are both significantly below the corresponding values measured in diabetic and non-diabetic BPH patients, in healthy subjects the vascular resistance seems to be higher in the outer gland (PZ) than in the inner gland (TZ).

TZ and PZ were defined according to the definition of McNeal [1, 23]. Differentiation between the PZ and the TZ was adequately performed in all patients using the high-end ultrasound unit. No RI and CPI measurements were performed within a distance of 3 mm of the urethra to avoid any influence of urethral blood flow.

The mechanism behind the markedly increased RI and decreased CPI values in the TZ has not been clarified to date, but it has been suggested that mechanical obstruction by TZ might compress vessels of the TZ [24]. As the TZ is contained within a dense capsule, it seems reasonable that a high pressure is built up within the transition zone, which, in turn, will cause an increased compression of the vessels to the TZ in BPH and even more so in diabetic patients. However, the significantly higher RI values and the significantly lower CPI values of the TZ in diabetic patients compared with non-diabetic BPH patients indicate that in patients with vascular damage there might be additional reasons for these findings. Decreased pO_2 levels have been demonstrated in patients with arterial ischaemia using laser Doppler flowmetry [25], a method that has been shown to be comparable to CDUS in assessing blood flow [26]. The association between diabetes and the higher RI of the TZ clearly demonstrated a higher vascular resistance which seems to be related to diabetic vascular damage. Hypoxia induces not only expression of the transcription factor hypoxia inducible factor 1 (HIF1) but also expression of angiogenic growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factors 2 and 7 (FGF-2 and FGF-7) and TGF-β as well as cytokines like IL8 [3, 27, 28]. Long-term exposure of the prostate stroma to increased growth factor levels as a result of chronic hypoxia may cause a stimulation over years and may contribute to the pathogenesis of BPH.

Although it is known that long-standing diabetes can cause lower urinary tract symptoms because of autonomic neuropathy, this has been shown to be due to functional parasympathetic, and to a lesser extent sympathetic, denervation of the detrusor muscle, so that diabetes primarily affects detrusor function [29, 30].

Interestingly, an inverse association between diabetes and prostatic cancer has been repeatedly described [4, 31]; this is compatible with a potential cancer-promoting role for endogenous testosterone, the level of which is lower in diabetic patients, which was also found in our patient cohort. However, the difference in testosterone levels between the diabetic and non-diabetic groups was not statistically significant (p=0.03). A risk-reducing effect of antidiabetic diet or hypoglycaemic agents may also contribute to the lower incidence of prostate cancer in diabetic men. On the contrary, others found hyperinsulinaemia to be a promotor of prostate cancer [32], and a significant association of coronary heart disease with the occurrence of prostate cancer has been described [5].

Erectile dysfunction (ED) is frequently of vascular origin, and an association between ED and ischaemia has been suggested as a consequence of endothelial disease of penile arteries. Thus, ED may also be considered to be the clinical manifestation of a disease affecting penile circulation as a part of a more general vascular disorder [33]. It is known that the increase of arterial inflow within the corpora cavernosa needed to obtain an erection is significant and minor abnormalities of this haemodynamic change are sufficient to cause ED [33]. Present data appear to support these findings. Although the RI values of arteries of corpora cavernosa did not significantly differ between the three groups, the acceleration time was significantly lower in diabetic patients compared with in non-diabetic BPH patients (p<0.001) and the patients in the control group (p<0.001). The lower IIEF score in diabetic men compared with non-diabetic BPH patients (p<0.001) and the control group (p<0.001) confirms the major role of diabetes as a risk factor for ED due to its vascular and neural involvement. However, a potential limitation of the present study is that patients with diseases that could alter sexual activity such as liver cirrhosis, impaired renal function and hypothyroidism were not excluded. Another limitation is the lower age of patients in the control group compared with men with BPH and diabetic patients. However, because about 60% of men aged 60 present with symptoms of clinical BPH, the control group had to consist of younger men to exclude men with clinical BPH.

Experimental studies have shown that lower urinary tract symptoms are associated with reduced blood flow in the detrusor muscle. A recently published study investigating the RI values in 29 patients demonstrated a significant difference in the arterial blood flow of the detrusor in obstructed vs non-obstructed patients with a full and an empty bladder [34]. Other studies also showed an influence of detrusor hypoxia in the pathogenesis of BPH [35]. However, in the present study no significant difference was found between RI (p= 0.305) and CPI (p=0.057) values between diabetic and non-diabetic BPH patients. On the other hand, differences between diabetic men and the control group were significant, whereas differences between non-diabetic BPH patients and controls were not (p=0.019 for RI and p=0.018 for CPI). Thus data on correlation between decreased perfusion of detrusor and lower urinary tract symptoms remain unclear, and additional studies are warranted to clarify this specific issue.

In conclusion, the significantly lower CPI and higher RI values of the TZ in diabetic patients compared with non-diabetic BPH and healthy subjects indicate considerable vascular damage in the TZ of the diabetic patients. Vascular damage may cause hypoxia, which induces not only ex-

pression of the transcription factor HIF1 but also expression of angiogenic growth factors as well as cytokines. Long-term exposure of the prostate stroma to increased growth factor levels as a result of chronic hypoxia may cause a stimulation over years and contribute to the pathogenesis of BPH. The WHO has estimated that the number of diabetic people worldwide will double within the next 20 years [36]. Therefore, reduction of tissue hypoxia through the improvement of oxygen delivery by sufficient therapy of arteriosclerosis in general, and of diabetes in particular, might have implications in BPH therapy.

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