Sexual Medicine

Vascular damage as a risk factor for benign prostatic hyperplasia and erectile dysfunction

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OBJECTIVE

To assess benign prostatic hyperplasia (BPH) and erectile dysfunction (ED), both considered to be associated with urogenital ageing, in ageing men in a cross-sectional population study, comparing them with healthy controls by using symptom scores and contrast-enhanced colour Doppler ultrasonography (CDUS).

PATIENTS, SUBJECTS AND METHODS

Transrectal CDUS and quantitative measurement of colour pixel intensity (CPI) are excellent minimally invasive techniques for assessing normal and pathological blood flow. CDUS was performed using the microbubble-based ultrasound enhancer for evaluating prostate, bladder neck and corpus cavernosum vascularity in young healthy men, men with BPH, and men with severe vascular damage (diabetes mellitus type 2). Resistive index measurements and computer-assisted quantification of CPI were used to objectively evaluate perfusion. The International Prostate Symptom Score (IPSS) and the International Index of Erectile Function (IIEF) were applied to quantify the symptoms.

RESULTS

In patients with BPH, perfusion of the transition zone (TZ) of the prostate was significantly lower and the resistive index of the TZ significantly higher (both $P < 0.001$) than in healthy controls. The perfusion patterns of men with BPH and those who also had severe vascular damage (diabetes mellitus type 2) showed that vascularity in the latter group was lower in the prostatic TZ and the corpora cavernosa. In patients with BPH the IPSS, quality-of-life and IIEF scores were significantly worse than in the control group. Men with concomitant atherosclerosis had even worse symptom scores.

CONCLUSION

These results strongly support the hypothesis that age-related impairment of blood supply to the lower urinary tract is important in the development of BPH and ED. Vascular damage may cause chronic ischaemia and thus be a contributing factor in the pathogenesis of BPH and ED.

KEYWORDS

atherosclerosis, BPH, diabetes mellitus, hypoxia, transrectal colour Doppler ultrasonography

INTRODUCTION

In elderly men BPH is common; ageing is associated with profound morphological and functional changes in the lower urinary tract. According to the Massachusetts Male Aging Study, neither BPH nor LUTS significantly affect erectile function [1], but nevertheless there is increasing evidence of an association between BPH and erectile dysfunction (ED) [2–4]. Moreover, it was suggested that ED may be a clinical manifestation of a more generalized disorder which also affects penile blood flow [5] and therefore might be an early warning sign of coronary heart disease.

Although there is evidence that androgens and oestrogens are involved in the growth of stromal and epithelial cells and the induction of fibromuscular overgrowth in the prostate, the cause of BPH remains unclear and seems to be multifactorial. It was postulated that hyperplasia in the stromal and glandular compartments may be induced by stromal growth secondary to hypoxia, which in turn results from abnormal blood flow patterns [6]. In a recent study using a cell-culture model of human prostatic stromal cells, the cells responded to hypoxia by up-regulating the secretion of several growth factors *in vitro*, which suggests that hypoxia may trigger prostatic growth [7]. In the prostate hypoxia might occur in patients with generalized or localized vascular damage, and indeed several studies suggested an association between prostatic disease and the presence of vascular disorders such as coronary heart disease or diabetes mellitus [8,9]. A recent study showed a clear association between hypoxia and neovascularization in the rat bladder [10]. However, to date no definite causal relationship between vascular damage and BPH has been established.

The use of colour Doppler ultrasonography (CDUS) opened new fields for ultrasonography in medicine by allowing the real-time display of blood flow. The vascular anatomy of the prostate as shown by power CDUS shows a reproducible and symmetrical flow pattern. Power CDUS is highly sensitive in depicting blood flow, and the number, course and continuity of vessels more readily than other imaging methods. Power CDUS can process the 'noise' differently from the signal, restricting it to a narrow range of lower amplitudes and displaying it as a background of uniform appearance. All signals above this level of background noise are assigned a colour different from that of noise and can be clearly differentiated, even at the weakest of levels. This allows the user to increase the colour gain and thus increase the sensitivity of detecting blood flow. Although CDUS is a useful noninvasive method for assessing blood flow, it is only of limited value if the data are quantified subjectively. On the contrary, computer-assisted quantification by calculating colour pixel intensity (CPI) is a reliable technique that allows an accurate assessment of organ and tissue perfusion. A method for quantifying CDUS data in organs was developed using statistical image analysis. Based on standardized image recording, data are acquired from the video output of any ultrasound scanner using a colour frame-grabber in a personal computer. The digitized colours are recognized according to their position in the CDUS palette bar, typically resulting in an 8-bit colour image with a proportion of identified pixels of >99.9%. Within the region of interest (ROI) the statistics of the detected flow patterns can be calculated. It was shown clearly that this analysis can be used for comparative or longitudinal studies, and for an objective evaluation and assessment of CDUS in complex vascular studies. Its diagnostic impact was reported in several studies [11,12].

The resistive index (RI) obtained by pulsed-wave CDUS is related to both blood flow and pressure, and is one of the most reliable indicators of vascular damage to small vessels in the prostate [13]. The present cross-sectional population study was conducted to investigate whether there is a potential causal relationship between vascular damage and BPH and/or ED by assessing prostatic blood flow using contrast-enhanced CDUS and symptom scores.

PATIENTS, SUBJECTS AND METHODS

From September 2003 to November 2004, 83 men were enrolled; the cohort was divided into three subgroups, the first of which comprised patients with BPH and manifest type 2 diabetes mellitus (defined as a fasting glucose level of ≥7.8 mmol/L on several occasions) for at least 5 years; the second group comprised nondiabetic patients with BPH (IPSS ≥ 7) with a prostate volume of ≥30 mL, and the third, a control group of healthy men with no clinical signs of BPH (IPSS < 7 and prostate volume <30 mL) or ED.

Patients with prostate cancer or a history of previous prostate surgery were excluded from the study, as were men being treated with 5α-reductase inhibitors or α-blockers. Men with clinically evident prostatitis, acute UTI or a contraindication to the ultrasonography contrast-agent SonoVue™ (Bracco, Milano, Italy), e.g. New York Heart Association stage IV heart failure, were also excluded.

Thirty-seven diabetic patients with BPH were referred for a routine urological assessment from other departments of the hospital, while 28 nondiabetic patients presented to our clinic with LUTS from BPH; 18 healthy men served as controls. Informed consent was obtained from all patients and subjects.

At the initial examination a history of type 2 diabetes mellitus, cigarette smoking, and the use of medications was elicited by a standardized interview. Obesity was determined on the basis of the body mass index (BMI); patients with a BMI of >25 kg/m^2 were considered obese. Blood pressure and pulse were measured with a standard sphygmomanometer after the patient had been seated for ≥5 min. Fasting lipid levels (total cholesterol, high-density and low-density cholesterol, triglycerides), fasting glucose levels and glycosylated haemoglobin (HbA1c) values were determined. Uroflowmetry was performed and residual urine, serum testosterone, homocysteine and PSA/free PSA levels were assessed in all patients. If the PSA levels were high a TRUS-guided prostate biopsy was taken to exclude prostate cancer. Patients with biopsy-confirmed prostate cancers were excluded from the study. The International Index of Erectile Function (IIEF) [14] was used to assess erectile function, while LUTS were evaluated using the IPSS.

All ultrasonography investigations were done by one experienced radiologist (F.F.) using contrast-enhanced CDUS with the high-frequency end-fire probe EC10C5 fitted to a Sequoia unit (Acuson, Mountain View, CA, USA). With the patients in the left lateral decubitus position, care was taken to minimize probe pressure on the rectal wall. The patient was examined with an empty (or nearly empty) bladder to preclude compression of the intraprostatic and bladder neck vessels. Contrast-enhanced CDUS was

TABLE 1 The clinical characteristics of the patients; data are expressed as the median (25–75th percentile). Differences among the three groups were analysed with the Kruskal–Wallis test, which when statistically significant, was followed by the Mann–Whitney U-test, with statistical significance defined at P < 0.05. After Bonferroni's correction for three comparisons, P < 0.017 was considered to indicate statistical significance

Variable	Diabetics with BPH (DM)	BPH only	Control (C)	P BPH vs DM	P BPH vs C	P DM vs C
N	37	28	18			
Age, years	60 (52–67.5)	64 (58.25–69.75)	36.5 (28.75–43.25)	0.043	<0.001	<0.001
CPI (TZ)	183 (156.5–201.5)	217 (193.75–244)	299.5 (280.25–338.75)	<0.001	<0.001	<0.001
CPI (PZ)	239 (199–251)	236 (216.25–251.75)	270 (254.75–301)	0.952	<0.001	<0.001
RI (TZ)	0.87 (0.85–0.89)	0.82 (0.77–0.85)	0.66 (0.60–0.70)	<0.001	<0.001	<0.001
RI (PZ)	0.85 (0.83–0.89)	0.82 (0.78–0.85)	0.72 (0.70–0.80)	0.019	0.002	<0.001
CPI (bladder neck)	40 (29.5–50)	46.5 (39–54.25)	60 (53.5–70)	0.040	0.001	<0.001
RI (bladder neck)	0.96 (0.9–1.0)	0.92 (0.88–0.96)	0.84 (0.8–0.9)	0.088	0.008	<0.001
RI (corpus cavernosum)	1 (1–1)	0.98 (0.94–1)	1 (0.9–1.02)	0.001	0.286	0.631
Acceleration time, s (corpus cavernosum)	0.1 (0.09–0.12)	0.06 (0.05–0.07)	0.02 (0.01–0.02)	<0.001	<0.001	<0.001
IPSS	14 (11–22)	8.5 (7–15)	0 (0–3)	0.001	<0.001	<0.001
Quality-of-life score	3 (2–4)	2 (1–3)	0 (0–0)	0.006	<0.001	<0.001
IIEF score	26 (17–32)	42 (32.5–52)	66 (60–68.25)	<0.001	<0.001	<0.001
Homocysteine, μmol/L	11.5 (9.8–14.7)	12.2 (11.5–13.9)	11.0 (10.2–12.6)			
HbA1c, %	8.1 (7.2–9.9)	5.5 (5.4–5.7)	5.35 (5.2–5.6)	<0.001	0.185	<0.001
Testosterone, ng/mL	3.4 (2.85–4.25)	4.3 (3.13–5.35)	4 (3.13–5.83)			
PSA, ng/mL	0.95 (0.55–1.35)	1.56 (0.88–2.33)	0.47 (0.32–0.76)	0.035	<0.001	0.002
Prostate volume, mL	42 (36–50)	43.5 (36.5–50)	19 (16.75–24)	0.786	<0.001	<0.001

DM, diabetes mellitus; C, control.

used to measure the RI and visualize the arteries of the prostate transition zone (TZ), the peripheral zone (PZ) and the bladder neck. CDUS was performed in a transverse plane at the base, midportion, and apex of the prostate. For assessing the RI, pulsed-wave spectral Doppler analysis was used in the arteries of the PZ and the TZ in each plane. Subsequently, the mean of each plane was calculated.

The Doppler signal intensity in both zones (TZ and PZ) and the bladder neck was determined using computer-assisted quantification of CPI. The ROI was placed in areas with the highest detectable blood flow. For this purpose the red-green-blue output of the ultrasound unit was digitized with an IBM-compatible computer. The digitized images were post-processed with the USA National Institutes of Health image software package (version 1.62). In each man, the CPI was quantified using computer assistance for areas of the outer and the inner gland. The digitized 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 minimize background noise the threshold value for the blue and red colour channels was set in the middle of the brightness value dynamic range, i.e. at 128 for both colours. Within the defined ROI only colour pixels showing a brightness value of >64 were counted.

Furthermore, the RI and the acceleration time were assessed in penile arteries of the corpora cavernosa. The acceleration time was measured by spectral-wave CDUS from the beginning of the systolic upstroke to the highest systolic peak in the waveform. Any break in the systolic upstroke before the peak was reached was ignored.

Data were expressed as the median (25–75th percentile) and differences among the three groups analysed using the Kruskal–Wallis test. If this test indicated statistical significance, the Mann–Whitney *U*-test was the applied, with statistical significance defined as $P < 0.05$. After Bonferroni's correction for three comparisons, $P < 0.017$ was considered to indicate statistical significance.

RESULTS

The study included 83 patients (37 with BPH and type 2 diabetes mellitus, 28 nondiabetic with BPH, and 18 healthy controls). In the diabetic group the mean (range) interval after a diagnosis of type 2 diabetes was 8.7 (5–14) years and the mean HbA1c 8.5 (5.8–12.7)%. The participants' clinical characteristics are shown in Table 1.

Perfusion of the TZ of the prostate was significantly lower in patients with BPH, with a median CPI of 217 (155–287), than in healthy controls, at 299.5 (254–397; $P < 0.001$). In patients with severe vascular damage (diabetes type 2) perfusion of the TZ was worse, with a median CPI of 183 (112–344), than in nondiabetic patients with BPH ($P < 0.001$). The TZ CPI in both diabetic and nondiabetic patients was significantly lower than in the controls ($P < 0.001$), whereas in terms of blood flow in the PZ there was no significant difference between nondiabetic patients with BPH and those with diabetes ($P = 0.952$).

By contrast, the RI of the TZ in nondiabetic patients was significantly higher than in the controls, with a median RI of 0.82 (0.70–0.89) vs 0.66 (0.56–0.82) ($P < 0.001$), and in diabetic men the RI of the TZ was even higher, at 0.87 (0.74–0.92) ($P < 0.001$). However, the RI of the PZ was no different between men with severe vascular damage (diabetes type 2) and nondiabetic patients with BPH.

In patients with BPH the CPI and RI values at the bladder neck were significantly worse than in the control group ($P = 0.001$ and 0.008, respectively), but there was no difference between diabetic and nondiabetic patients with BPH ($P = 0.040$ and 0.088, respectively).

The RI measured in the arteries of the corpora cavernosa were no different between the nondiabetics with BPH and controls ($P = 0.286$), but the mean arterial inflow was significantly slower in diabetic patients than in nondiabetics with BPH ($P < 0.001$), and slower in the nondiabetics with BPH than in the control group ($P < 0.001$).

There was no significant difference in blood pressure, pulse rate, fasting total cholesterol, and high- or low-density lipid levels, serum testosterone, homocysteine levels and cigarette smoking among the three groups. In diabetics the mean triglyceride levels were higher than in nondiabetic patients ($P = 0.001$) but they were no higher than in the control group ($P = 0.027$). The median BMI was lower in the control group than in diabetics with BPH ($P = 0.004$), whereas there was no difference between the nondiabetic BPH group and the diabetics ($P = 0.083$) and controls ($P = 0.166$).

The IPSS, quality-of-life and IIEF scores in patients with BPH were significantly worse than in the control group ($P < 0.001$). In men with concomitant atherosclerosis these symptom scores were even worse. For the mean IPSS there was a significant difference between the diabetic and nondiabetic BPH group ($P = 0.001$), and quality-of-life and IIEF scores in diabetic patients were significantly worse than in the nondiabetic BPH group ($P = 0.006$ and <0.001, respectively).

There was no significant difference in prostate volume, maximum flow rate and residual urine volume between diabetic and nondiabetic patients with BPH, but all these variables were better in the controls than in the patients.

DISCUSSION

Recent studies show that a significant proportion of men with BPH have sexual dysfunction [15] and furthermore, that there is an association between the development of BPH and manifestations of atherosclerotic disease such as noninsulin-dependent diabetes mellitus, hypertension or dyslipidaemia. This suggests that BPH is a component of the metabolic syndrome and that the underlying cause of BPH might be systemic rather than local. Diabetic patients had significantly faster annual prostate growth rates than in men presenting with LUTS [16]. Also, diabetes was associated with greater BPH symptom severity despite age-adjustment [8].

The mechanisms responsible for erectile problems in men with BPH are still poorly understood. In the past the association between BPH and ED was attributed to the sympathetic nervous system [15] or psychological factors [17]. However, it has been shown that patients with severe vascular damage are at least three times more likely to develop ED than are men in the general population [18]. Nevertheless, the causal relationship between vascular damage on the one hand and ED and BPH on the other remains unclear, although there is increasing evidence that oxidative stress may have a role in the induction of cell growth. This is supported by observations suggesting that there is a common pathogenetic mechanism responsible for both vascular smooth muscle cell growth and prostate smooth muscle proliferation.

While the RI was relatively low in healthy prostatic vessels, arteries in the PZ may be compressed by the TZ in patients with advanced BPH, which was found to lead to a markedly greater RI in the capsular arteries. These findings were confirmed, as the RI in the nondiabetic BPH group was slightly higher in the PZ than in the TZ (0.824 vs 0.818), whereas in the diabetic group the RI values in the TZ were higher (0.87) than in the PZ (0.85). This indicates that the latter patients have greater vascular resistance arising from the significant vascular damage, particularly in the TZ. In healthy subjects the vascular resistance was clearly lower than in men with BPH; notably, in controls the vascular resistance in the outer gland (PZ) was higher than in the inner gland (TZ).

Interestingly, diabetic patients with BPH had a significantly greater RI in the TZ than nondiabetic patients ($P < 0.001$), whereas there was no significant difference between the groups in the RI in the PZ ($P = 0.019$). These findings were confirmed by CPI analysis, which is an objective method for analysing tissue perfusion. Virtually identical results were obtained for the PZ (median 239 in the diabetic group vs 236 in the group with BPH; $P = 0.952$), whereas the values were significantly different for the TZ (median 183 vs 217, respectively; $P = 0.001$).

The mechanism responsible for the markedly greater RI and the lower CPI in the TZ of men with BPH and ED is still poorly understood. It was suggested that the TZ might compress and thus cause mechanical obstruction of the vessels in the PZ [19]. As the TZ is contained within a dense capsule, it seems likely that a high pressure is accumulated within the TZ, which, in BPH and even more so in diabetic men with BPH, may result in compression of the vessels supplying the TZ. However, the significantly higher RI and the significantly lower CPI in the TZ of patients with long-standing diabetes compared to nondiabetic patients indicate that there might be additional contributing factors in patients presenting with vascular damage. Patients with arterial ischaemia had lower pO_2 levels, as assessed by laser Doppler flowmetry [20], a method that has been shown to be comparable to CDUS in assessing blood-flow [21]. The higher RI of the TZ in diabetic patients with BPH clearly indicates a higher vascular resistance, which seems to be related to diabetic vascular damage. Hypoxia induces the expression not only of hypoxia-inducible factor 1 but also of angiogenic growth factors such as vascular endothelial growth factor, fibroblast growth factors (-2 and -7) and TGF-β, as well as cytokines like interleukin 8 [7,22,23]. Long-term exposure of the prostatic stroma to increased growth factor levels secondary to chronic hypoxia may cause stimulation of stromal growth over years, and thus contribute to the pathogenesis of BPH.

Research into the causes of microcirculatory dysfunction in diabetic patients shows an

interplay of numerous factors. It was repeatedly shown that diabetic neuropathy can lead to vasodilatation, which would result in the opposite of the present findings. Recent research suggests that diabetes mellitus influences the production and/or transport of endogenous nerve growth factor and consequently, that deprivation of this neurotrophic factor may account for the functional deficits known to occur in diabetic neuropathy, such as impaired catecholamine transmitter synthesis.

ED is frequently of vascular origin and an association between ED and ischaemia resulting from endothelial disease of penile arteries has been suggested. Consequently, ED may be considered a clinical manifestation of a more generalized vascular disorder that also affects penile circulation [5]. It is well known that a significant increase in arterial inflow to the corpora cavernosa is required to obtain an erection and that even minor haemodynamic abnormalities can cause ED [5]. The present data appear to support these findings. Although the RI of the cavernosal arteries did not differ significantly among the three groups, the acceleration time was significantly lower in patients with LUTS than in controls ($P < 0.001$). The lower IIEF scores in diabetic patients with BPH than in nondiabetics ($P < 0.001$) and the control group ($P < 0.001$) confirms the significant role of vascular damage in the pathogenesis of ED.

A potential limitation of the present study is that patients with diseases that may affect sexual function, e.g. liver cirrhosis, impaired renal function and hypothyroidism, were not excluded. A second limitation is the lower age of the controls than the diabetic and nondiabetic patients. However, to exclude men with clinical BPH the control group had to comprise younger men, as ≈60% of men aged >60 years present with symptoms of clinical BPH.

In conclusion, the present results strongly support the hypothesis that age-related impairment of blood supply to the lower urinary tract has a key role in the development of BPH-induced LUTS and ED. Vascular damage may cause chronic ischaemia and thus be a contributing factor in the pathogenesis of BPH and ED. Consequently, reducing tissue hypoxia by improving oxygen delivery, which is a major goal in the management of atherosclerosis in general and diabetes in particular, might be beneficial in BPH and ED.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **ED**, erectile dysfunction; **CDUS**, colour Doppler ultrasonography; **CPI**, colour pixel intensity; **ROI**, region of interest; **RI**, resistive index; **BMI**, body mass index; **HbA1c**, glycosylated haemoglobin; **IIEF**, International Index of Erectile Function; **TZ**, transition zone; **PZ**, peripheral zone.