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Prospective evaluation of the association between varicocele and benign prostatic hyperplasia in men over 40 years of age

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Abstract

We investigated the association between varicocele and benign prostatic hyperplasia in men over the age of 40 years. A total of 296 outpatients were evaluated. Prostate volume was measured with transrectal ultrasound. Varicocele was diagnosed by physical examination and ultrasound. Prostatic hyperplasia was defined as prostate volume greater than or equal to 40 ml. Two groups were compared: patients with prostate volume less than 40 ml and patients with prostate volume greater than or equal to 40 ml. There was a statistically significant difference between the groups in terms of mean age, post-void residual, International Prostate Symptom Score and PSA. The percentage of patients with clinical varicocele in the group with a volume less than 40 ml and the group with a volume equal to or greater than 40 ml was 38.2% and 47.7% respectively ($p = .12$). There were no differences between the two groups in the percentage of patients with clinical or subclinical varicocele (43.2% vs. 52.2%, respectively, $p = .12$). No differences were found in the percentage of patients with varicocele when comparing men with prostates smaller than 40 ml and greater than or equal to 40 ml.

KEYWORDS

benign prostatic hyperplasia, lower urinary tract symptoms, prostate-specific antigen, prostatic volume, total testosterone, varicocele

1 | INTRODUCTION

Benign prostatic hyperplasia (BPH) associated with lower urinary tract symptoms (LUTS) is one of the most common problems in men, with an estimated prevalence of 50%–75% in those over 50 years of age (Egan, 2016). Important risk factors include metabolic syndrome, obesity and hereditary pre-disposition (Gray et al., 1991; Roberts et al., 2004). The direct stimulation of the gland's stromal and epithelial growth requires testosterone and its active metabolite, dihydrotestosterone (Gray et al., 1991; Roberts et al., 2004).

The influence of androgens on prostate growth is paradoxical since BPH is more frequent in older men, even though there is a decrease in testosterone levels (Gray et al., 1991; Roberts et al., 2004). Additionally, a correlation between testosterone levels and prostate volume has not been demonstrated (Liu et al., 2007). Gat et al proposed a hypothesis to explain this inconsistency, arguing that prostatic growth occurs because most patients with BPH also have varicocele, and the latter produces pelvic and intraprostatic reflux of venous blood rich in testosterone (Gat et al., 2008).

The relationship between varicocele and BPH has not been clearly demonstrated. Therefore, we carried out the present study in

which we evaluated the prostate volume and the presence of varicocele in a cohort of men over 40 years of age.

2 | MATERIALS AND METHODS

Outpatient volunteers of our Clinic, who were over 40 years of age, were recruited from March 2018 to January 2020. Information was collected prospectively. The following variables were obtained: prostate volume by transrectal ultrasound, presence and degree of varicocele on physical examination, presence of varicocele by doppler ultrasound, body mass index, post-void residue, International Prostate Symptom Score (IPSS), prostate-specific antigen (PSA) and history of arterial hypertension, dyslipidaemia, diabetes, and family history of BPH. The ultrasound was performed with the Philips Clear VUE 650 USD14A0752 equipment, using a 7.5-MHz L12-4 flat transducer, a 2–5 MHz curved C5-2, and a 4–9 MHz C9-4v transrectal. Patients taking pharmacological treatment for BPH were included. The institutional Ethics Committee authorised the study. All patients signed written informed consent.

We excluded patients with the following history: prostate cancer, cryptorchidism, inguinal or scrotal surgery, varicocele surgery, surgery for benign prostatic hyperplasia and neuropathic bladder. Patients taking a 5-alpha-reductase inhibitor and a prostate volume lower than 40 ml by transrectal ultrasound were also excluded.

Body mass index (BMI) was obtained by dividing weight in kilograms over height measured in metres squared. We calculated prostatic volume using transrectal ultrasound according to the prostate ellipsoid formula: height × length × width × 0.52.

BPH was considered a prostate volume greater than or equal to 40 ml. The clinical diagnosis of varicocele was made with palpation of the spermatic cord with the patient standing in a warm room, both at rest and with Valsalva manoeuvres. We used the clinical classification of varicocele according to the World Health Organization: grade 0 is subclinical, grade 1 is palpable only with the Valsalva manoeuvre, grade 2 is invisible but palpable without the Valsalva manoeuvre, and grade 3 is visible (Lorenc et al., 2016). The ultrasound diagnosis of varicocele was made with the patient in the supine position, and the criteria applied was a venous diameter of the pampiniform plexus greater than 2 mm and/or the presence of reflux that lasted longer than 2 s (Liguori et al., 2004; Lorenc et al., 2016). Subclinical varicocele was defined as that identified with ultrasound but not with a physical examination. We calculated the post-void residue with the elongated ellipsoid formula: volume = length × width × height × 0.52 (Hvarness et al., 2002).

2.1 | Statistical analysis

Dichotomous variables were reported with absolute numbers and percentages. Continuous variables were presented with means and standard deviation in case of a normal distribution, and medians and interquartile ranges in non-normal distribution. The Kolmogorov–Smirnov test was used to verify the normal distribution of continuous variables. Differences between groups with continuous variables were obtained with the Student *t* test for variables with normal distribution, and Mann–Whitney *U* test for variables without normal distribution. Differences between groups with categorical variables were calculated with the chi-squared test. A *p*-value of <.05 was considered a statistically significant difference. Statistical calculations were carried out with The Statistical Package for the Social Sciences software (SPSS version 17.0). All *p*-values presented are two-tailed.

3 | RESULTS

A total of 296 men were included in the study. Demographic and health-related characteristics can be seen in Table 1. The mean age was 63 years (±8). The mean prostate volume was 43 ml (±23). PSA value and the post-void residue medians were, respectively, 2.1 ng/ml (interquartile range 1.2–4.3) and 48 ml (interquartile range 17.5–103). A prostate volume greater than or equal to 40 ml was seen in 45% of the patients. Almost half of the patients had clinical or clinical/subclinical varicocele (42.9% and 48.3% respectively). The most frequent medical history was high blood pressure and a family history of BPH (39.8% and 20.2% respectively). Left varicocele was the most frequent (74 patients, 25.0%), followed by bilateral (52 patients, 17.5%) and right (1 patient, 0.3%; Figure 1). Subclinical varicocele was found in 17 patients (5.7%), grade 1 in 19 patients (6.4%), grade 2 in 51 patients (17.2%) and grade 3 in 56 patients (18.9%; Figure 2).

TABLE 1 Demographic and health-related characteristics of the patients

Continuous variables	Mean (±ds)	Median	Interquartile range	Range
Age, years	63.0 (±8)			41–88
Prostate volume (ml)	43.6 (±23)			10–152
PSA (ng/ml)		2.1	1.2–4.3	0.1–18.4
Post-void residual (cc)		48	17.5–103	0–473
Categoric variables			**No.**	**%**
Prostate volume greater than or equal to 40 ml			135	45
Clinic varicocele			129	42.9
Clinic or subclinic varicocele			143	48.3
Dyslipidaemia			43	14.5
Diabetes			31	10.4
Hypertension			118	39.8
Obesity (BMI > 30)			41	13.8
Family history of BPH			60	20.2

Abbreviations: BMI, body mass index; BPH, benign prostatic hyperplasia; ds, standard deviation; PSA, prostate-specific antigen.

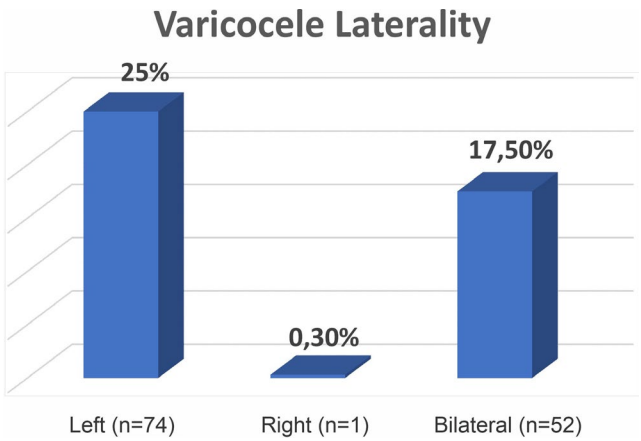

FIGURE 1 Varicocele laterality

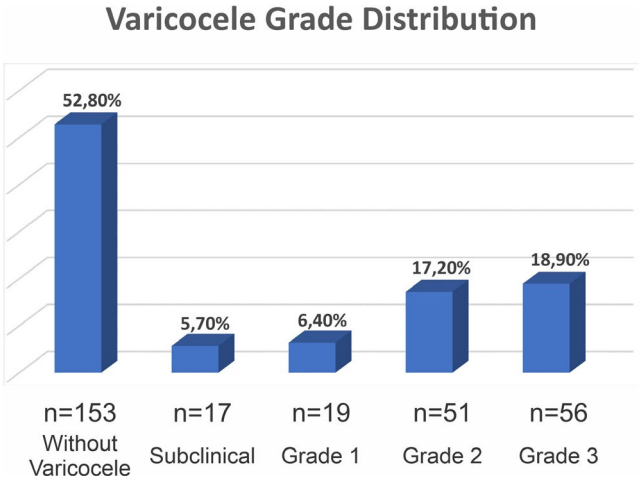

FIGURE 2 Varicocele grade distribution

Table 2 shows the distribution of varicocele by age groups. There was a similar prevalence between the ages of 40 and 79, with values between 38.2% and 48.8%. A higher trend was observed in the range of 80–89 years, with a prevalence of 62.5%.

When comparing patients with a prostate volume less than 40 ml and patients with BPH (prostate volume equal to or greater than 40 ml), there were statistical differences in the median PSA (1.5 ng/ml vs. 3.1 ng/ml, respectively, $p < .001$), the median of post-void residual (35 ml vs. 71 ml, respectively, $p < .001$), the median of IPSS (9 vs. 11, respectively, $p = .04$) and the mean age (62.0 years vs. 65.4 years, respectively, $p = .001$; Table 3). No statistical differences were found in terms of clinical varicocele (38.2% vs. 47.7%, respectively, $p = .12$), clinical or subclinical varicocele (43.2% vs. 52.2%, respectively, $p = .12$), nor grade 3 varicocele (16.6% vs. 20.7%, respectively, $p = .4$; Table 3). There were no statistical differences between the groups in the history of dyslipidaemia, diabetes, hypertension, obesity and relatives with BPH (Table 3).

TABLE 2 The varicocele distribution by age groups

Age group (years)	Clinic or subclinic varicocele, no (%)	Clinic varicocele, no (%)
40–49	7 (46.6)	7 (46.6)
50–59	38 (46.9)	31 (38.2)
60–69	66 (48.8)	61 (45.1)
70–79	27 (43.5)	27 (43.5)
80–89	5 (62.5)	5 (62.5)

TABLE 3 Comparison between groups

	Prostate volume less than 40 ml, $n = 162$	BPH (prostate volume equal to or greater than 40 ml), $n = 134$	p
PSA, ng/ml (median, interquartile range)	1.5 (0.8–2.5)	3.1 (2–6.5)	<.001
Post-void residual, ml (median, interquartile range)	35 (10.6–75)	71 (27.7–144)	<.001
IPSS (median, interquartile range)	9 (5–15)	11 (6–18)	.04
Age, years (mean, ±1ds)	62.0 (±7.6)	65.4 (±8.3)	.001
Clinic varicocele (no., %)	62 (38.2)	64 (47.7)	.12
Clinic or subclinic varicocele (no., %)	70 (43.2)	70 (52.2)	.12
Grade 3 varicocele (no., %)	27 (16.6)	28 (20.7)	.4
Dyslipidaemia (no., %)	26 (15.8)	17 (12.5)	.4
Diabetes (no., %)	16 (9.6)	15 (11.1)	.6
Hypertension (no., %)	62 (37.5)	55 (40.7)	.5
Obesity, BMI > 30 (no., %)	21 (14.0)	20 (16.5)	.5
Family history of HPB (no., %)	30 (18.1)	29 (21.4)	.4

Abbreviations: BMI, body mass index; ds, standard deviation; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen.

4 | DISCUSSION

Prostate growth in men over 40 years of age is a unique process as it occurs despite a progressive decrease in testosterone levels, a hormone that plays a preponderant role in stimulating stromal and epithelial growth of the gland (Feldman et al., 2002; Goren & Gat, 2018; Madersbacher et al., 2019; Roberts et al., 2004). This 'paradox' led Gat et al to formulate a hypothesis according to which the varicocele plays a predominant role in BPH development (De Caestecker et al., 2016; Gat & Goren, 2018; Gat et al., 2008; Goren & Gat, 2018). According to his theory, based on venographic studies, varicocele increases the hydrostatic pressure in the Santorini plexus,

conditioning a flow of venous blood rich in testosterone through the deferential vein towards the pelvis. Once in the pelvis, the blood flows retrogradely towards the prostate because the deferential vein's pressure is much higher than that of the prostatic venous plexus (Gat et al., 2008).

One of the basis of Gat's theory is the increasing prevalence of varicocele with age. According to contemporary series, in young adults over 18 years of age, the prevalence is 4.5%-22%, but it increases to 34%-53% over 40 years (Besiroglu et al., 2019; Canales et al., 2005; Damsgaard et al., 2016; De Rose et al., 2019; Han et al., 2016; Levinger et al., 2007; Liu et al., 2017). Our study included men older than 40 years and showed a clinical varicocele prevalence of 42.9%, consistent with the range described and very similar to that published by Canales (Canales et al., 2005). It is presumed that the hydrostatic pressure supported by the gonadal veins' valves over the years makes them incompetent, as their elastic resistance is affected by factors such as inflammation, mineralisation, the proliferation of smooth muscle cells and abnormalities in the extracellular matrix (Donaldson, 2015; Gat et al., 2008; Levinger et al., 2007; Oklu et al., 2012; Raffetto & Khalil, 2008).

Regarding laterality and grade, the left varicocele was more frequent than the bilateral (25% vs. 17.5% respectively), and grades 2 and 3 were more frequent than grade 1 (17.2%, 18.9%, and 6.4% respectively). These results coincide with other studies by Canales, Han and Besiroglu (Besiroglu et al., 2019; Canales et al., 2005; Han et al., 2016). The lower prevalence of grade 1 varicocele can be explained because its detection depends on the examiner`s subjective perception during the Valsalva manoeuvre. This limitation led us to measure subclinical varicocele (diagnosed only with ultrasound) to reduce measurement bias risk.

Gat and colleagues published studies that support their theory. A retrospective review of 206 patients with BPH who underwent bilateral percutaneous sclerotherapy of the spermatic veins showed a statistically significant reduction in prostate volume and urinary symptoms score in 81.5% of patients after 24 months of follow-up (Gat & Goren, 2018). In another study, they evaluated 901 patients with BPH, aged between 33 and 81 (Goren & Gat, 2018). They found varicocele in all cases, by physical examination, contact thermography and ultrasound with Doppler ultrasound.

In contrast with Gat's theory, some authors dispute the causal relationship between varicocele and BPH. Otunctemur et al prospectively studied 1,040 patients older than 40 years with BPH and found that bilateral varicocele was associated with a lower prostate volume (Otunctemur et al., 2014). Strunk et al performed percutaneous embolisation of the spermatic veins in 30 patients with BPH and did not find a significant decrease in prostate volume after six months of follow-up (Strunk et al., 2015). In addition, De Caesteker measured the levels of testosterone in the periprostatic venous blood of patients undergoing prostatectomy with the Millin technique and compared them with those obtained from peripheral blood, obtaining higher concentrations in the first sample in only 2 of 7 patients who had varicocele and BPH (De Caestecker et al., 2016).

Our results are in the same line as the Otunktemur, Strunk and De Caesteker studies (De Caestecker et al., 2016; Otunctemur et al., 2014; Strunk et al., 2015). We did not find statistically significant differences in the percentage of clinical and subclinical varicocele between patients with prostates under 40 ml and patients with 40 ml or more. One explanation for this finding could be that mild varicoceles do not affect prostate growth, but neither did we find differences between the two groups in terms of the percentage of patients with grade 3 varicocele.

The discrepancy between Gat's publications and what was found in ours and other studies may have different explanations. The first is methodological: in the study that described a decrease in prostate volume by sclerotherapy of the gonadal veins, the result could be affected by the inclusion of patients taking a 5-alpha-reductase inhibitor (Gat & Goren, 2018). The study that described varicocele in all 901 patients with BPH did not have a control group and did not include an evaluation of the prostate volume: the inclusion criterion was the presence of urinary symptoms, and therefore, stating that varicocele is a characteristic of patients with BPH may be inaccurate (Goren & Gat, 2018). In the same study, the very high number of patients identified with varicocele could be explained because a sensitive thermographic method was used for diagnosis, in addition to physical examination and ultrasonography (Goren & Gat, 2018).

A second argument against BPH genesis from varicocele is current knowledge of different pathways to promote prostatic growth independently of serum testosterone levels, described by different authors (Chen et al., 2020; Da Silva & De Souza, 2019; Ho & Habib, 2011; Li et al., 2019; Liu et al., 2007; Poirier, 2003; Wu et al., 2019; Yoo et al., 2019). These include: (a) a persistently high serum and intraprostatic level of dehydrotestosterone produced from androstenedione, due to the high activity of the enzyme 17-beta hydroxysteroid dehydrogenase; (b) stimulation of stromal proliferation at the expense of oestrogens, whose high levels are the product of the persistent activity of the aromatase enzyme; (c) overexpression of the androgen receptor and the oestrogen receptor; and (d) a chronic inflammatory process accompanied by immune dysregulation.

Our study has strengths such as the prospective nature and rigour in measuring prostate volume and varicocele with the support of ultrasonography. However, there are three limitations to discuss. Firstly, Doppler ultrasound was performed with the patients in the supine position and not standing, and some authors recommend the latter to improve the accuracy of the measurement of venous dilation (Kim et al., 2015). Secondly, prostate volume measurement could be affected in some patients taking a 5-alpha-reductase inhibitor (Nickel et al., 2011). However, none of them had a volume lower than 40 ml, and therefore, the drug could affect the calculation of the average volume in patients with prostates greater than 40 ml, but not the configuration of the two groups compared. Finally, given its cross-sectional nature, a study like ours is designed to establish an association between variables, not a causal relationship. We will need a future prospective cohort

study to determine the final answer about the varicocele role in the origin of BPH.

In conclusion, our prospective study did not find a difference in the percentage of patients with varicocele when comparing patients with prostates greater than or equal to 40 ml and under 40 ml. This finding does not support the hypothesis that varicocele is a causal factor of prostate growth. Our findings are compatible with the idea that prostate cell proliferation in people over 40 years of age is a multifactorial phenomenon of a hormonal and inflammatory nature.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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