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Role of varicocele sclerotherapy in the management of benign prostatic hyperplasia and its associated lower urinary tract symptoms (pilot study)

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Abstract

Background: Benign prostatic hyperplasia (BPH) is inescapable with aging and can cause lower urinary tract symptoms, worsening the quality of life. New pathophysiologic mechanisms of BPH development are currently under study to modulate its management. The valvular destruction of the spermatic veins (varicoceles development) incurs a testicular-prostatic hydrostatic pressure gradient, which conveys free undiluted testosterone to the prostate via a testicular-prostatic backdoor passage. Subsequently, prostatic congestion and androgen-dependent prostatic hyperplasia occur resulting in lower urinary symptoms development. The purpose of our study is to detect the effect of testicular venous sclerotherapy on the prostatic enlargement and the related urinary symptoms.

Results: Our single-arm interventional study included 36 patients with an age range of 40–80 years. The patients complained of urinary symptoms and had prostatomegaly with varicoceles by sonography. A median international prostatic symptom score (IPSS) of 19 and a quality of life (QoL) score ranging (3–6) reflected the severity of the urinary symptoms. Venography showed reflux in all cannulated spermatic veins with subsequent sclerotherapy on the left side and bilaterally in 80.6% and 11.1% of the patients, respectively. The technical and clinical success rates reached 91.7% and 83.3%, respectively, with a statistically significant reduction in the IPSS and QoL scores. We observed a statistically insignificant improvement in the sexual satisfaction, prostatic volumes, post-void residual volumes, and PSA levels. Minimal self-limiting complications occurred with an overall rate of 38.9%. Only 16.66% of cases needed further surgery, while the rest had sufficient symptomatic relief post sclerotherapy.

Conclusion: Varicoceles sclerotherapy can be employed to resolve the testicular venous insufficiency and mitigate the severity of the prostatic-related urological symptoms in middle-aged and elderly men, so varicoceles can be considered a confounding variable in the development of the prostatic-related lower urinary tract symptoms.

Keywords: Benign prostatic hyperplasia, Lower urinary tract symptoms, Varicoceles, Sclerotherapy, Dihydrotestosterone

Background

Benign prostatic hyperplasia (BPH) is one of the most prevalent ailments of aging men, affecting nearly 50% and 100% of this population by the time they reach 50 and 80 years of age, respectively, with a detrimental impact on their quality of life (QoL) [1].The prostate grows at a rate of 2.5% per year in higher age groups and the age-related

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prostatic enlargement mainly affects the prostatic periurethral zone [2]. Subsequent prostatic urethral compression occurs with resultant urinary outflow obstruction, urinary bladder hypertrophy and reduction of the bladder volume reservoir [3, 4].

The lower urinary tract symptoms affect up to 74% of adults above 40 years, 42% of whom report a moderate degree of symptoms. In addition, an age-dependent lower urinary symptomatic progression occurs in 5-year increments with a resultant poor sexual life due to erectile and ejaculatory dysfunctions and side effects of antiandrogenic medications [5].

To further explore the underlying mechanisms of prostatic enlargement, Gat et al. [4, 6, 7] proposed that the blood flow mechanics of the anatomically connected prostatic and testicular veins follow Pascal's [8] and Bernoulli's [9] laws, which postulate that the fluid hydrostatic pressure equalizes across communicating vessels. The age-related valvular destruction of the spermatic veins establishes continuous blood columns with elevated hydrostatic pressures (27 and 32 mmHg for 35 and 40 cm columns heights on the right and left, respectively, compared to 6 mmHg for a normal intervalvular blood segment). In addition to collaterals development, the testicular venous elevated pressures establish a pressure gradient, which diverges free testosterone (dihydrotestosterone or DHT) from the testes to the prostate with subsequent prostatic congestion and androgen-dependent prostatic hyperplasia [7] (Fig. 1).

Gat et al. [4, 6, 7] referred to the testicular-prostatic venous backflow as 'the backdoor phenomenon,' which was used to explain the biologic paradox of testosterone-dependent BPH despite age-dependent serum testosterone decline. The Gat theory was confirmed during venography by the visualization of a prostatic capsular blush following the opacification of an impaired testicular vein while applying abdominal compression to simulate the elevated hydrostatic pressure (Fig. 2). Subsequently, Gat considered varicoceles sclerotherapy to be a super-selective intraprostatic androgen deprivation therapy because the occlusion of the refluxing spermatic veins and their vertical bypasses eliminates the testicular-prostatic pressure gradient with back-flow cessation and reversal of the prostatic hyperplasia [7].

Several studies agreed with the Gat theory while others rejected it. The supporting studies included the Strunk and Rauch study [10] that detected an improvement of the urinary symptoms upon sclerotherapy application in patients with prostatomegaly, the Ur Rehmen et al. study [11] that found the pressure in the incompetent left ISV to be 31 mmHg with Valsalva, and the Pejčić et al. study [12] that detected a fourfold rise in the dihydrotestosterone (DHT) quantity of the BPH specimens using mass spectrometry. Some studies observed a direct association between varicoceles and BPH with age [13, 14] while others found that orchiectomy and antiandrogenic medications aid the prostatic volume reduction [15, 16].

On the other hand, studies that rejected the Gat theory disputed the proposed causal relationship between varicoceles and BPH, and claimed that the prostatic enlargement is a multifactorial process caused by androstenedione-dependent DHT, aromatase-dependent

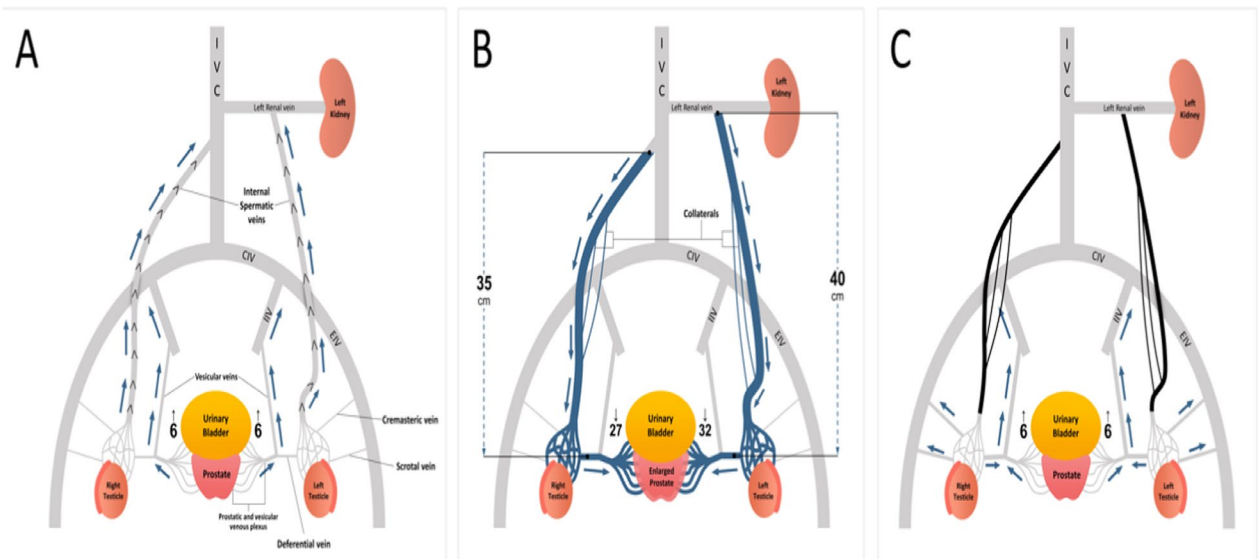

Fig. 1 Diagram showing **A** normal, **B** pathological and **C** post sclerotherapy testicular-prostatic venous changes with emphasis on the hydrostatic pressure changes for blood column lengths (EIV = external iliac vein, IIV = internal iliac vein, CIV = common iliac vein)

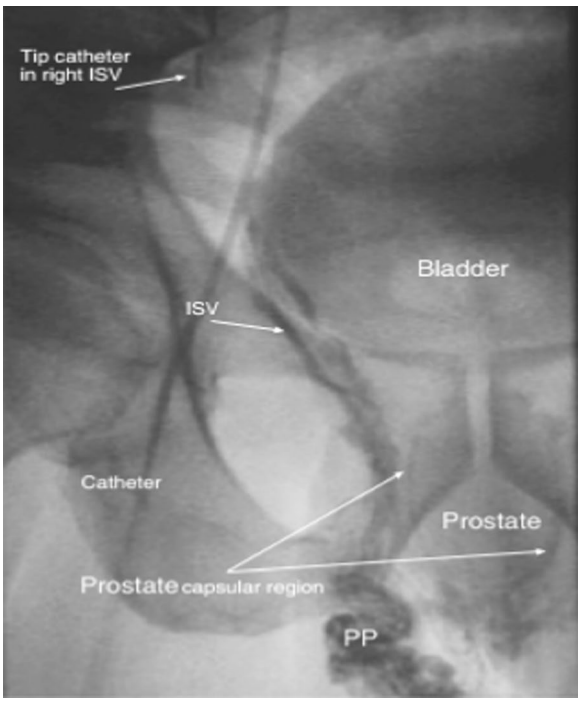

Fig. 2 A prostatic capsular contrast 'blush' (long arrows) following spermatic venous opacification confirms the backdoor phenomenon [7] "Copyright (2022) Wiley. Used with permission from (Gat and Goren, Benign prostatic hyperplasia: Long-term follow-up of prostatic volume reduction after sclerotherapy of the internal spermatic veins, Andrologia, Wiley)" (pp = pampiniform plexus)

estrogen stromal proliferation, androgen and estrogen receptors overexpression, chronic inflammation, and immune dysregulation [17–20]. In addition, two prospective studies published different results from those of the Gat studies [4, 6, 7]; Goana et al. study [21] uncovered no statistical significance in varicoceles percentage between patients with prostatic volumes ≥ 40 ml and < 40 ml and De Caestecker et al. study [22] detected high periprostatic plexus testosterone in only 2 out of 7 patients undergoing Millin prostatectomy for BPH.

The aim of our study is to test the Gat theory via occluding varicoceles and studying the subsequent effect on prostatic volumes and prostatic-related lower urinary tract symptoms in middle-aged and elderly men suffering from benign prostatic hyperplasia.

Patients

For 6 months from June 2021 till November 2021, our single-arm interventional pilot study enrolled 40 cases; 36 of whom were included and the remaining 4 were excluded.

The patients complaining of lower urinary tract symptoms with elevated PSA were referred by the urology clinics of our hospital and nearby centers for prostatic biopsies to exclude any underlying prostatic malignancies. Those patients received complementary scrotal sonographic assessments to detect the presence of refluxing varicoceles and to help determine if they fitted the inclusion criteria of our study.

The inclusion criteria were: males ≥ 40 years having sonographically-detected refluxing varicoceles with concomitant prostatic volumes > 30 cc due to benign prostatic enlargements. All of the enlarged prostatic glands included in the study were biopsied and were pathologically proven to be benign prostatic hyperplasia.

The inclusion criteria also specified patients with lower urinary tract complaints for over a year with little relief on antiandrogenic medications despite compliance for ≥ 6 months, suffering from antiandrogenic drugs side effects or refusing prostatic surgeries. The exclusion criteria comprised young adults complaining of varicoceles-induced infertility or having asymptomatic varicoceles without BPH or LUTS. Any patient with a known urological cancer, a history of urological surgeries, an ongoing infection, having stones, renal failure (creatinine clearance < 30 ml/min), or a bleeding tendency (INR > 2) was also excluded.

Clinical assessment

A comprehensive medical history was obtained from each patient regarding his relevant comorbidities as Diabetes Mellitus. Each patient was also asked about the intake of bladder irritants (tobacco and caffeine), drugs inciting lower urinary tract symptoms as diuretics, and antiandrogenic drugs namely alpha-blockers and 5-alpha-reductase inhibitors. The patients' lower urinary complaints were divided into obstructive, post micturition and storage symptoms. The obstructive urinary symptoms included weak urine streams, straining, intermittency, and hesitancy. The post micturition symptoms included terminal and post micturition dribble while the storage urinary symptoms included frequency, urgency, nocturia, and incontinence.

Each patient was asked to fill an International Prostate Symptom Score (IPSS) and a Quality of Life (QOL) questionnaire (Fig. 3) to determine the severity of his urinary symptoms and was also asked to detail the impact of the urological problems on his sexual performance and satisfaction. Each patient underwent a testicular examination for palpable varicoceles, an abdominal examination for a palpable urinary bladder, and a digital rectal examination (DRE) to assess the prostatic size, mobility, and symmetry.

International Prostate Symptom Score (I-PSS)

Patient Name: _____ **Date of birth:** _____ **Date completed** _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Fig. 3 The international prostatic symptom score (IPSS)

Preprocedural evaluation and preparation

The patients' preprocedural evaluation included laboratory testing, imaging assessment and urodynamic studies. Each patient did a PSA level as a baseline for follow-up and was tested via a urine analysis to exclude infections, a serum creatinine test to rule out renal failure, and a coagulation profile to exclude any bleeding diathesis. As for imaging, each patient underwent a pelvic sonography to measure the prostatic volume and the post void residual volume, and a testicular Doppler to detect and grade subclinical varicoceles. The urodynamic studies confirmed the urine outflow tract obstruction by measuring the maximum urinary flow rate (Q max) and excluded concomitant detrusor over activity.

The preprocedural instructions mainly specified a 48-h stoppage of the intake of nephrotoxic medications including metformin, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. The rest of the instructions entailed preprocedural adequate hydration and bladders evacuation.

Methods and materials

Sonographic assessment

The pre and postprocedural follow-up sonographic assessments were performed by two sonographers (with 5 and 11 years of experience) using the Mindray DC-60 Exp sonographic machine (Mindray, Guangdong, China (Mainland)) with transducers frequencies of 5–7 and 9–12 MHz for pelvic and testicular sonographies, respectively. The sonographers set the examination room at an ambient temperature of 24–30 °C, instructed the patient to properly expose the area in question, applied a copious amount of warm coupling gel to the area and obtained the required images in the transverse and sagittal planes after adjusting the sonographic parameters (gain, depth, focus, and scale) for each examination.

During the pelvic sonography, the prostatic and the post void residual volumes were calculated via the device's proprietary volume algorithm employing the formula: $\text{volume} = (4/3) \times (\pi) \times (Da/2) \times (Db/2) \times (Dc/2)$ where Da, Db, and Dc are the height, the width, and the depth of the measured organ. During the testicular sonography and in the presence of a male chaperone, the patient lay supine holding his penis to his abdomen and covering it with a towel to improve the scrotal exposure and comfort. The transducer was gently placed on the scrotum to detect the presence of varicoceles (≥ 2 mm in diameter). The subsequent color and pulsed-wave Doppler assessments were performed to detect the varicoceles reflux upon straining.

Sclerotherapy technique

Varicocele sclerotherapy was performed at an interventional radiology unit affiliated with a University Hospital by two interventional radiologists: a professor assisted by the principal investigator with 19 and 5 years of experience, respectively. They used an angiographic machine of brand: Philips Allura Xper FD20 (Philips, Amsterdam, The Netherlands) operating via a digital subtraction angiography software, a 360° rotating tube, and a 45/90° tilt table.

Before the beginning of the procedure, the patient was instructed to remain calm and alert the operators if sudden discomfort develops. The procedure began with sterilizing the skin, applying local anesthesia (subcutaneous lidocaine 1%, 1 ml/kg containing 10 mg lidocaine with a maximum dose of 4.5 mg/kg) then employing the Seldinger technique [23] during the jugular access and the testicular venous cannulation. Access was obtained by puncturing the right internal jugular vein with the Seldinger needle, through which the guidewire of the introducer set was passed, followed by needle removal. The 5F introducer sheath (sheath over a dilator) (KDL®, Shanghai Kindly, Shanghai, China) was passed over the introducer set guidewire, followed by withdrawing the wire and the dilator, leaving the sheath in place.

Through the sheath, a 5F vertebral catheter (impress®, Merit Medical Systems, Utah, USA) was advanced over a hydrophilic guidewire (Radifocus®, Terumo, Tokyo, Japan) in Seldinger fashion to catheterize the left renal vein and perform renal venography using low osmolar non-ionic contrast media (Omnipaque® 350, GE healthcare, Cork, Ireland) with a dose of 1.4 ml/kg; not exceeding 140 ml. The left renal venography helped delineate the left gonadal vein orifice(s) for cannulation. Similarly, the right gonadal vein was cannulated using a 5F sidewinder Sim 2 catheter (Tempo®, Cordis Inc., Miami, Florida, USA). The super-selectively catheterized gonadal veins showed contrast reflux during venography with vertical collaterals opacification (Figs. 4, 5).

Upon confirming the ISVs reflux, the sclerosant foamy mixture was prepared via the Tessari method [24] using a three-way stopcock to connect two syringes; one containing 8 cc of unfiltered room air and the other containing 2 cc of polidocanol (Aethoxysklerol® 3%, Kreussler Pharma, Paris, France) with a maximum injectable dose of 4 cc containing 120 mg of lauromacrogol 400.The plungers of the syringes were then pushed back and forth 20 times till the production of foam in a sclerosant-air ratio of 1:4. The foam injection was preceded by a contrast column whose distal displacement aided the fluoroscopic detection of the dispersion of the radiolucent foamy mixture.

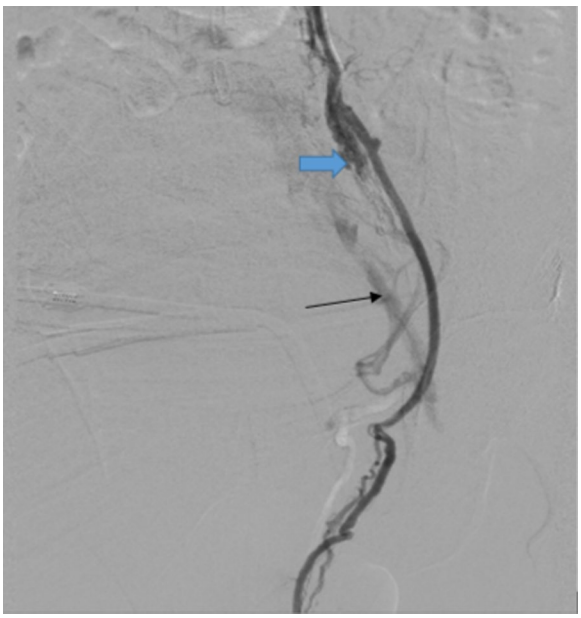

Fig. 4 Case 1 reveals left ISV incompetence with reflux (black arrow) and parallel vertical collaterals (blue arrow), with a zoom on the reflux site

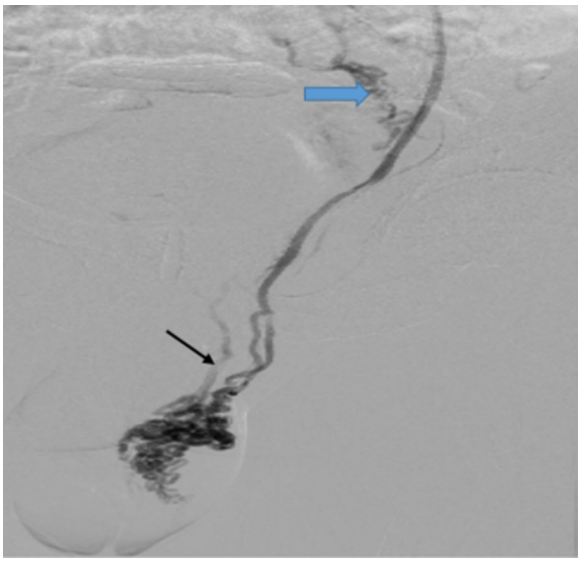

Fig. 5 Case 2 shows the entire length of the left ISV with reflux (black arrow) and parallel vertical collaterals (blue arrow)

During foam injection, the gonadal venous inguinal segment was compressed to stop the foam flow into the scrotal veins. The sclerotherapy process ensued in a stepwise fashion from distal at the inguinal ring to proximal up till the upper third of the renal vein to prevent sclerosant reflux into the renal vein and avoid the non-target renal vein embolization. At each step, the operators performed repeat gonadal venography to detect the patency of the main gonadal veins and their collaterals. The angiographic endpoint was reached when control venography detected occlusion of the distal gonadal veins and their vertical bypasses with no reflux (Fig. 6). At the end of the procedure, the catheter was withdrawn, the sheath removed, and the access site was compressed for 5 min before covering it with a light compression bandage.

Postprocedural care and follow-up

Patients were advised to cut back on caffeinated drinks and stop any antiandrogenic medications postprocedural to properly assess the sclerotherapy effect on prostatic volumes and urinary symptoms without bias. They were instructed to resume their usual activities apart from heavy lifting that required an additional 1–2 weeks of rest. They were also informed to return to the clinic after three months for the follow-up assessment of their postprocedural PSA levels, prostatic volumes, and symptoms severity. They were then discharged after a total of 30 to 60 min post sclerotherapy.

Statistical analysis

The sample size of our study was calculated using the (PASS 11.0) program and the cases were gathered using the Convenience Sampling method. The data of our cases were collected and analyzed via descriptive and inferential statistical tests. The results of the descriptive tests were presented as (means ± standard deviations) with ranges, medians with interquartile ranges (IQR), and numbers with percentages for quantitative variables

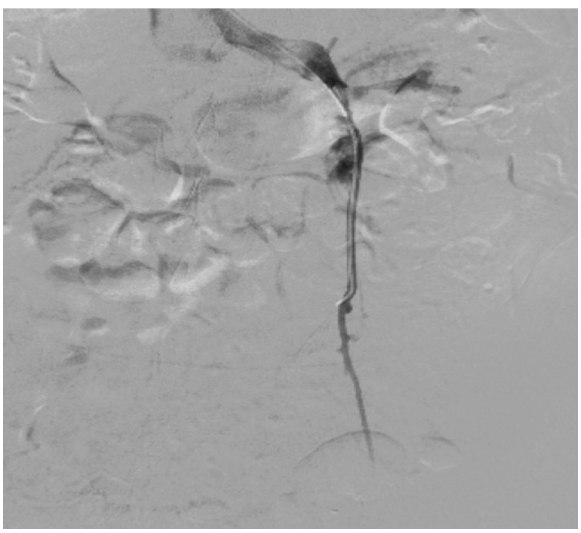

Fig. 6 Post sclerotherapy image showing left ISV stump with no collaterals or reflux (angiographic endpoint)

with parametric distributions, quantitative variables with non-parametric distributions, and qualitative variables, respectively. The inferential statistical tests were the Chi-square test, the Paired t-test and the Wilcoxon Rank test used for comparing qualitative data groups, quantitative data groups with normal distributions, and quantitative data groups with non-normal distributions, respectively. The inferential statistical results having *P* values of less than 0.05 were considered statistically significant with a 95% confidence interval, and were statistically packaged using the Statistical Package for Social Sciences (SPSS) program version 23.

Results

Out of the 40 enrolled patients, four patients were excluded; two had pathologically proven prostatic cancers, one had low creatinine clearance (20 ml/min), and the last one had a bleeding tendency with an elevated international normalized ratio (INR = 4). The other 36 cases were included in our study and stratified into 4 age groups: (40–49) years, (50–59) years, (60–69) years, and (70–80) years noted in 25%, 33.3%, 27.8%, and 13.9% of the cases, respectively.

The obstructive, post micturition, and irritative urinary symptoms affected 50%, 33.3%, and 16.7% of the cases, respectively. The obstructive urinary symptoms affected the higher age groups due to their larger prostatic volumes, whereas the irritative urinary symptoms diminished the bladder storage capacity. The severity of the urinary symptoms was quantified via the IPSS and the QoL scores whose medians were 19 and 5 and ranges were (7–30) and (3–6), respectively, reflecting patients' urological sufferings. A subsequent IPSS grading was applied and stratified the IPSS scores into moderate, severe, and mild grades in 50%, 41.7%, and 8.3% of the cases, respectively. Associated sexual dissatisfaction was noted in 47.3% of cases.

The mean ± standard deviation of the prostatic volumes and the post-void residual volumes were 68.97 ± 17.38 and 124.17 ± 12.57, and their ranges were 40–120 cc and 100–160 ml, respectively. The sonographic interobserver agreements for the prostatic volumes, the post void residual volumes and the varicoceles reflux detections were calculated as 95%, 96%, and 85%, respectively.

Left and bilateral testicular venous cannulations were feasible in 80.6% and 11.1% of the cases, respectively. For each cannulated ISV, venography was performed confirming contrast reflux followed by attempting sclerotherapy, which was considered technically successful upon reflux cessation in the cannulated gonadal vein and its vertical bypasses. The overall technical success rate reached 91.7%, whereas the technical failure rate was only 8.3%; attributed to the catheterization failure of both ISVs mostly because of their narrow ostia.

The post sclerotherapy complications were self-limiting reaching a rate of 38.9% (Fig. 7). The most frequent complications were the post embolization pain and epididymoorchitis that occurred in 27.8% and 8.3% of the cases, respectively, and resolved either spontaneously or with analgesics. Venous dissection occurred in 2.8% of the cases and was successfully embolized in the same sclerotherapy session (Fig. 8). The puncture sites were free with no post-intervention hematomas.

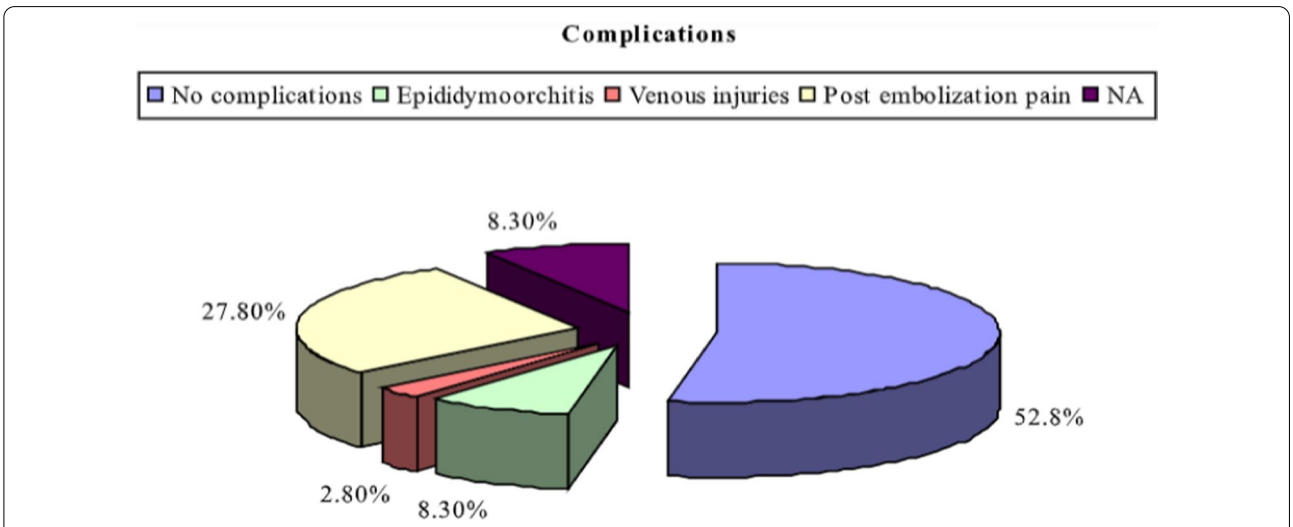

Fig. 7 Pie chart for post-intervention complications percentages (NA = not applicable, due to technical failure where complications cannot be assessed)

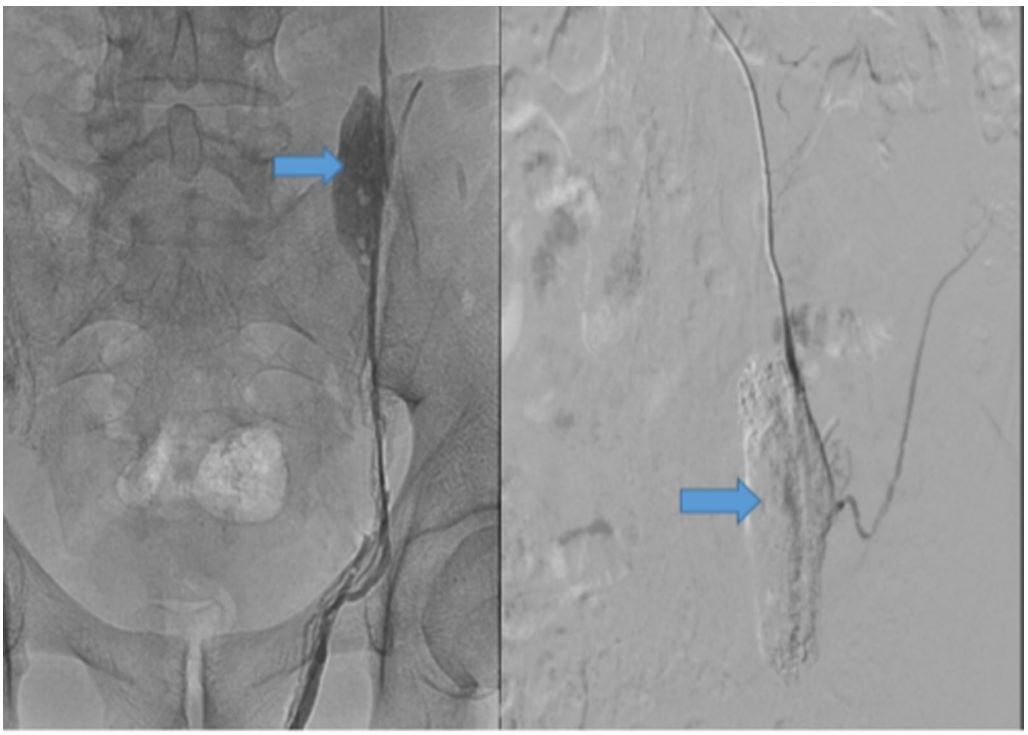

Fig. 8 **A** Venous dissection (blue arrow), **B** post sclerotherapy showing dissection occlusion (blue arrow), in addition to cessation of left gonadal venous opacification with no collaterals or reflux

After 3 months, no patients were lost-to-follow-up. Their follow-up showed no clinical improvement and an inapplicable clinical assessment due to technical failure in 8.3% of the cases for each, with an overall failure rate of 16.66% where cases needed further urinary catheterization followed by transurethral resection prostatectomy (TURP).

The overall clinical success rate was 83.3%, where clinical success was defined as follow-up symptomatic improvements by a minimum of 3 points or a 25% decrease in the initial IPSS score, with or without a change in the initial IPSS grade.

The reduction in the IPSS and the QoL scores were statistically significant (Table 1) as well as the improvement of the IPSS grades (Fig. 9). The data analysis via Box and Whisker charts emphasized the reduction in the median of the IPSS and QoL scores and showed a more prevalent data distribution in the lower quartiles (Fig. 10), pointing to a notable clinical improvement sufficient enough for 83.34% of the cases to not seek further operative alternatives. We also noted other non-statistically significant improvements post sclerotherapy in the prostatic and post-void residual volumes, the PSA levels, and the sexual satisfaction (Table 2).

Table 1 Demonstrates the statistical significance of IPSS and QoL changes post sclerotherapy

	Pre No. = 36	**Post No. = 36**	**Test value**	***P* value**	**Sig**
IPSS scores					
Median (IQR)	19 (15–22.5)	17 (7–19)	−2.425‡	0.015	S
Range	7–30	6–35			
IPSS grades					
Mild (1–7)	3 (8.3%)	9 (25.0%)	13.130*	0.004	HS
Moderate (8–19)	18 (50.0%)	15 (41.7%)			
Severe (20–35)	15 (41.7%)	6 (16.7%)			
NA	0 (0.0%)	6 (16.7%)			
QOL					
Median (IQR)	5 (4–6)	4 (4–6)	−2.546‡	0.011	S
Range	3–6	2–6			

P value > 0.05: non significant (NS); *P* value < 0.05: significant (S); *P* value < 0.01: highly significant (HS)

*Chi-square test

‡ Wilcoxon Rank test

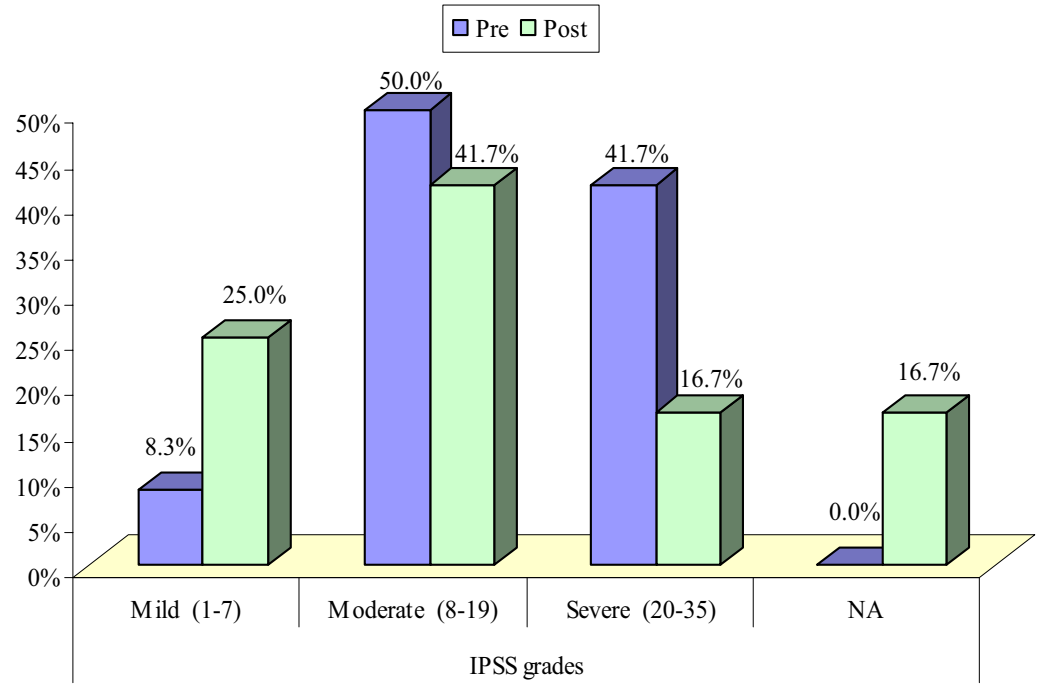

Fig. 9 Diagram demonstrating the change of the IPSS grades post sclerotherapy

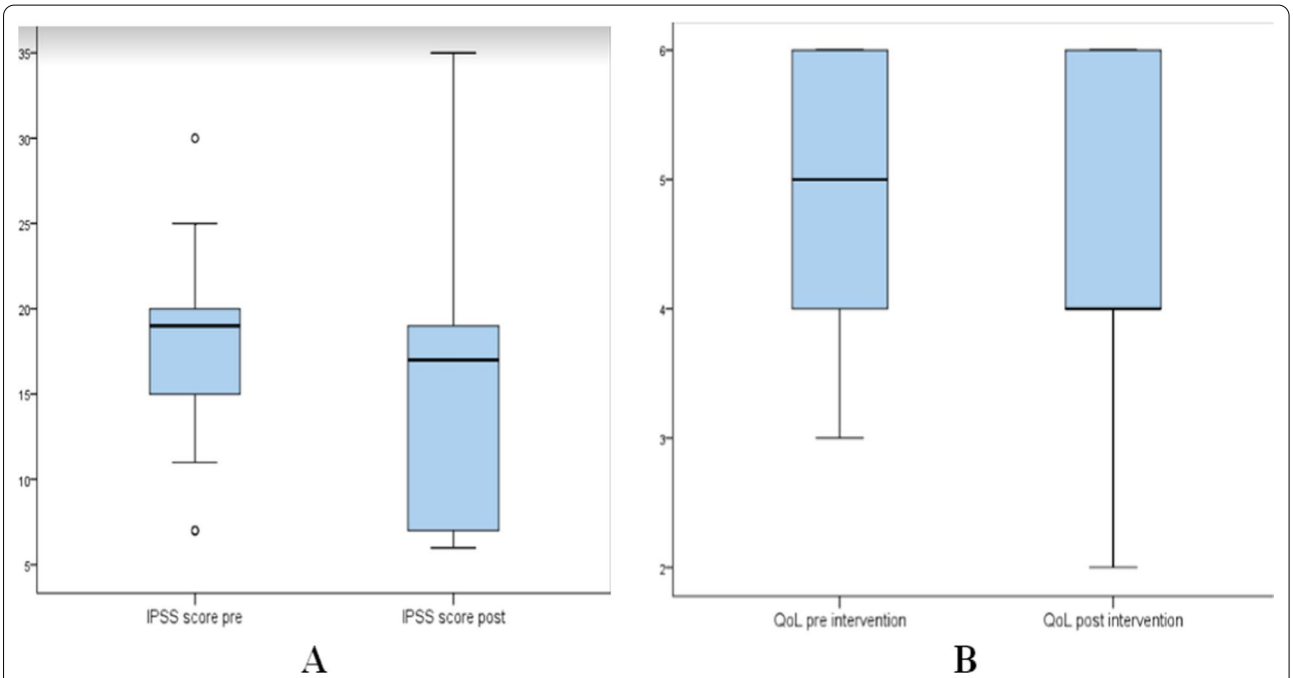

Fig. 10 Box and Whisker charts demonstrating the skewness of the distribution of the pre and post sclerotherapy IPSS and QoL scores

Discussion

To date, there is not a wholesome consensus explaining the mechanism of BPH development, which is inapt given the large burden of the BPH disease and its prevalence among a wide sector of a vulnerable age group. In an effort to present a fresh perspective of the backstage workings of the prostatic enlargement, we conducted our study to test the recent theory proposed by Gat et al. [4,

Table 2 Demonstrates the statistical analysis of the changes in the degrees of sexual satisfaction, prostatic volumes, post-void residual volumes, maximum urinary flow rates, and PSA levels pre and post sclerotherapy

	Pre No. = 36	Post No. = 36	Test value	*P* value	Sig
Post void residual volume (ml)					
Mean ± SD	124.17 ± 12.57	122.48 ± 11.57	− 1.928•	0.063	NS
Range	100–160	100–150			
Prostatic volume (cc)					
Mean ± SD	68.97 ± 17.38	63.85 ± 16.63	− 1.948•	0.060	NS
Range	40–120	30–115			
PSA (ng/ml)					
Median (IQR)	10 (8.5–11)	9 (8.5–10)	− 1.765‡	0.077	NS
Range	7–12	7–12			
Q-max					
Median (IQR)	10 (9–10)	10 (8–11)	− 1.607‡	0.108	NS
Range	7–15	7–15			
Sexual satisfaction					
Dissatisfied	17 (47.3%)	13 (36.1%)	4.337*	0.114	NS
Neutral	16 (44.4%)	11 (30.6%)			
Satisfied	3 (8.3%)	9 (25.0%)			
NA	0 (0.0%)	3 (8.3%)			

P value > 0.05: non significant (NS); *P* value < 0.05: significant (S); *P* value < 0.01: highly significant (HS)

• Paired t-test

‡ Wilcoxon Rank test (*P* value > 0.05: non significant (NS); *P* value < 0.05: significant (S); *P* value < 0.01: highly significant (HS))

6, 7]. The theory suggests that testosterone causing prostatic hyperplasia is not delivered via the arterial supply of the prostatic gland but rather through a venous backflow from the testes to the prostate under the effect of a pressure gradient, incited by the age-related insufficiency of testicular veins whose occlusion can reverse the androgen-dependent prostatic hyperplasia. Furthermore, the Gat et al. studies proposed a causal relationship between varicoceles and BPH based on the significant prostatic volume reduction in 80% of their patients two years after varicoceles sclerotherapy.

Unlike the Gat et al. trials [4, 6, 7] and similar to the Strunk–Rauch [10] analysis, our study detected a discrepancy between the post sclerotherapy urinary symptomatic improvement and the near stationary prostatic sizes. In our opinion, the discrepancy can be attributed to the prostatic periurethral zone's faster response to the post intervention androgen deprivation than the rest of the prostate, resulting in symptomatic improvement before the sonographic detection of the prostatic volume reduction. In addition, failure to perform the intervention bilaterally in the majority of cases may have hindered the detection of the intervention's full effect on the prostatic volumes. Also, the discrepancy can be attributed to the regression of the prostatic congestion as a partial response to sclerotherapy, sufficient enough to ameliorate the urinary symptoms but insufficient to reduce the prostatic sizes. Lastly, the post intervention hormonal deprivation may require a longer period than 3 months to affect a reversal of the prostatic hyperplasia and a subsequent reduction of the prostatic volumes.

Contrary to the Gat et al. confirmation of a causal relationship between varicoceles and BPH, we could not confirm or deny this relationship because our study lacked control and randomization. However, we were able to suggest a connection between varicoceles and BPH by applying the Bradford Hill criteria for causality inference [25] to our observations in the study. Some of the criteria applied to the varicoceles-BPH relationship which were: their strong association, their simultaneous affection of a specific population (the middle-aged and the elderly males), and their connection via a plausible coherent mechanism linking them as cause and effect without confliction with the biological knowledge of the BPH disease.

The inferred varicoceles-BPH connection can impact the understanding of the mechanisms of development of related pathologies including prostatic cancer in elderly men and infertility in middle-aged men. In addition, severing the varicoceles-BPH connection can lead to a better management of the aforementioned pathologies; thus reducing the need for operative alternatives and lessening the morbidity and mortality for higher age groups.

Regarding infertility in middle-aged men, asthenospermia can be attributed to varicoceles that backflow into the periprostatic venous plexus causing its dilatation with subsequent prostatic congestion and malfunction. The malfunctioning prostate does not produce sufficient semen-liquefying secretions to adjust the semen viscosity, hence leads to asthenospermia and infertility.

Thus, varicoceles sclerotherapy yields a better outcome than varicocelectomy in asthenospermia with associated varicoceles and prostatic congestion. In sclerotherapy, the sclerosant agent can reach the distal testicular-prostatic venous channels to occlude them and reverse the periprostatic venous dilatation; thus reducing the prostatic congestion, increasing the prostatic semen-liquefying secretions, enhancing the semen viscosity, and improving the sperm count and motility. In this case, sclerotherapy provides an effective cost–benefit management for middle-aged men suffering from concomitant varicoceles-related infertility and BPH-related lower urinary symptoms, targeting multiple pathologies with one procedure.

With varicoceles, a testicular-prostatic pressure gradient occurs that leads to venous backflow into the prostate carrying a large amount of testosterone, and causes prostatic cellular androgen-dependent hyperplasia with subsequent cellular DNA mutations. Therefore, early application of varicocele sclerotherapy can reduce the risk of androgen-dependent prostatic cancer development.

The technical success rate of our study and Strunk–Rauch's were 91.7% and 100%, respectively. Both studies shared common criteria regarding limited patients' clinical improvement including prostatic volumes $\geq$ 100 ml, large post void residual volumes $\geq$ 120 ml, and mild IPSS grades. Similar to the Strunk and Rauch study, our study showed non-statistically significant improvements in the PSA values and the post void residual volumes as well as minimal self-limiting complications.

Limitations and recommendations

The results and conclusions of our study can only apply to patients suffering from BPH-related lower urinary tract symptoms with concomitant varicoceles, provided that they have not undergone prior urological surgeries.

Our study comprised a confounding variable which is non-urological polyuria incited by Diabetes Mellitus and diuretics intake. The polyuria affected two patients who complained of concomitant obstructive symptoms and were therefore included in the study. To avoid bias, we used additional frequency volume charts for each patient to quantitatively measure their urine outputs pre and postprocedural. Post sclerotherapy, their obstructive symptoms improved despite the stationary amount of their urine outputs.

We recommend further randomized control trials on larger sample sizes to eliminate the effect of confounding variables and to confidently assess the varicoceles-BPH causal relationship, with a follow-up period of no less than a year to fully elucidate the effect of sclerotherapy on prostatic volumes and to properly detect any varicoceles recurrence or symptomatic relapse.

Conclusions

Varicoceles sclerotherapy acts as a mechanical antidote to the mechanical testicular venous valvular failure and can be employed in the mitigation of the severity of the BPH-related lower urinary symptoms; lessening the need for prostatic surgeries and thus impacting the BPH management.

Our study suggests that varicoceles are a contributing factor in the development of BPH in middle-aged and elderly men; however, it is still questionable whether varicoceles act alone or as a part of a systemic disorder to develop BPH.

Abbreviations

BPH: Benign prostatic hyperplasia; DHT: Dihydrotestosterone; DRE: Digital rectal examination; INR: International normalized ratio; IPSS: International prostatic symptoms score; IQR: Interquartile range; ISV(s): Internal spermatic vein(s); IVC: Inferior vena cava; LUTS: Lower urinary tract symptoms; PSA: Prostatic specific antigen; Qmax: Maximum urinary flow rate; QoL: Quality of life; TURP: Transurethral resection prostatectomy.

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Not applicable.

Author contributions

ZA suggested the research idea, set the study design, selected the patients according to the inclusion criteria, collected the patients' data, evaluated the patients' clinical symptoms and performed their sonographic assessments before and after the procedure, assisted in the intervention, drafted the manuscript, and revised it (principal investigator). MG supervised the procedure of patients' selection and data collection, and interpreted the collected data. WH performed the intervention for the patients, revised the collected data and its statistical analysis. KS clinically examined the patients, supervised their pre- and postprocedural sonographic assessments, reviewed the literature, and shared in the statistical analysis. All authors read the final manuscript and approved it for submission.

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Availability of data and materials

The datasets and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Research Ethical and Scientific Committee of Faculty of Medicine at Ain Shams University in Egypt 'The committee's reference number of approval: FWA 000017585.' Patients' privacy and their data confidentiality were guaranteed with a restricted access to the patients' data except for the principal investigator. Written informed consents to participate in the study were obtained from all patients or their legal guardians. The patients were informed of the prostatic hyperplasia current management lines, a detailed explanation of the procedure and possible intervention-related complications: contrast-induced allergic reactions, nephropathy, epididymo-orchitis, accidental arterial puncture, arteriovenous fistula, puncture site hematoma, venous dissection, post embolization pain, non-target embolization, and possible technical failure.

Consent for publication

A consent for publication was obtained for the data of each individual included in the study, given by the patients themselves or their legal guardians.

Competing interests

The authors declare that there are no competing interests.

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