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ORIGINAL ARTICLE

Prostate Disease

Clinical correlates of enlarged prostate size in subjects with sexual dysfunction

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Digito-rectal examination (DRE) of the prostate provides useful information on the state of prostate growth and on the presence of suspected peripheral nodules. The aim of this study is to describe the clinical and biochemical correlates of finding an enlarged prostate size at DRE in subjects with sexual dysfunction (SD). A consecutive series of 2379 patients was retrospectively studied. The analysis was focused on a subset of subjects (n = 1823; mean age 54.7 ± 11.4) selected for being free from overt prostatic diseases. Several parameters were investigated. After adjusting for confounders, the presence of an enlarged prostate size at DRE was associated with a higher risk of metabolic syndrome (HR = 1.346 (1.129–1.759); P = 0.030), type 2 diabetes mellitus (HR = 1.489 (1.120–1.980); P = 0.006), increased LDL cholesterol (>100 mg dl^{-1}; HR = 1.354 (1.018–1.801); P = 0.037) and increased mean blood pressure (BP) values (HR = 1.017 (1.007–1.027) for each mmHg increment; P = 0.001). Accordingly, enlarged prostate size was also associated with a higher risk of arteriogenic erectile dysfunction (ED), as well as with other andrological conditions, such as varicocele and premature ejaculation (PE). PSA levels were significantly higher in subjects with enlarged prostate size when compared to the rest of the sample (HR = 3.318 (2.304; 4.799) for each log unit increment in PSA levels; P < 0.0001). Arteriogenic ED, according to different criteria, was also associated with increased PSA levels. In conclusion, our data support the need to examine prostate size either by clinical (DRE) or biochemical (PSA) inspection in subjects with SD, in order to have insights into the nature of the SD and the metabolic and cardiovascular (CV) background of the patient.
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INTRODUCTION

Benign prostatic hyperplasia (BPH) and its related lower urinary tract symptoms (LUTS) are common urological conditions of the aged man affecting about half of subjects older than 50 years and three out of four of those older than 80 years.[1–3] Erectile dysfunction (ED) is another condition often present in the aged man, which is frequently comorbid with LUTS/BPH.[2–4] ED and LUTS/BPH synergistically deteriorate the psychological and relational fitness of patients, finally reducing their overall quality of life.[2,4,5] Despite the wealth of literature supporting a link between ED and LUTS/BPH, recognition of this link is lacking in both primary and secondary care.[2] In addition, the pathogenetic reasons for this association have not been completely clarified. Common alterations in the nitric oxide-cyclic guanosine monophosphate pathway, enhancement of RhoA-Rho-kinase signaling and pelvic atherosclerosis are often considered as the most important mechanisms involved in determining the two conditions.[6] According to the III International Consultation on Sexual Medicine[7] and the Standard Operating Procedures in Sexual Medicine,[8] a correct physical examination should include digito-rectal examination (DRE) of the prostate. This relatively easy medical act can exclude the presence of suspected peripheral prostatic nodules or glandular inflammation and provide useful information on the state of prostate growth. The presence of an enlarged prostate can be suggestive of storage or voiding symptoms. In addition, because the prostate represents one of the main targets of androgen action, a reduced prostate volume may be suggestive of hypogonadism.[9]

So far, no studies have investigated the clinical correlates of measuring prostate size with DRE in subjects with sexual dysfunction (SD). In this particular population, the aim of the present study is to describe the clinical and biochemical correlates of enlarged prostate size.

MATERIALS AND METHODS

A non-selected series of 2379 heterosexual male patients attending our Andrology and Sexual Medicine Outpatient Clinic for SD for the first time was retrospectively studied. Sexual orientation was routinely investigated in all patients using a standard question. Only heterosexual patients were included in this study, to make the results more comparable and to prevent possible bias as described elsewhere.[10]

PSA levels have been postulated as an effective predictor of prostate volume and LUTS severity.[11–14] In this study, the analysis was focused on a subset of subjects (n = 1823) selected for being free from overt

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prostatic diseases. Hence, subjects with a PSA level >4 ng ml^{-1} and/or with a history of prostate disease (n = 556) were excluded, unless otherwise stated. The sociodemographic and clinical characteristics of the selected cohort are reported in **Table** 1.

Table 1: Characteristics of the sample

Characteristics	*Value*
Age (year)	54.7±11.4
Marital status (%)	
Stable relationship living together	77.0
Stable relationship not living together	14.4
Non-stable relationship	8.6
Education (%)	
None/primary school	15.9
Secondary school	34.4
High school	32.7
University	17.0
Morbidities (%)	
Current smoker	29.1
Hypertension	33.4
Diabetes mellitus	24.5
Metabolic syndrome	44.3
CVD at enrolment	14.9
Clinical, laboratory and instrumental parameters	
BMI (kg m^{-2})	27.1±4.2
SBP (mmHg)	135 (125–145)
DBP (mmHg)	85 (80–90)
Mean blood pressure (mmHg)	100 (93–107)
LH (U l^{-1})	4.0 (2.7–5.7)
FSH (U l^{-1})	4.9 (3.3–8.1)
Total testosterone (nmol l^{-1})	15.5±6.2
PSA (ng ml^{-1})	1.0 (0.9–1.1)
Glycemia (mg dl^{-1})	97 (88–114)
Total cholesterol (mg dl^{-1})	202.1±40.3
HDL cholesterol (mg dl^{-1})	47.9±12.2
LDL cholesterol (mg dl^{-1})	126.3±34.4
Triglycerides (mg dl^{-1})	119 (84–168)
Flaccid PSV at PDU (cm s^{-1})	16.8±5.7
Flaccid acceleration (m s^{-2})	2.8±1.4
Dynamic PSV at PDU (cm s^{-1})	50.8±19.3
Dynamic PSV at PDU<35 cm s^{-1}	22.2
Dynamic PSV at PDU<25 cm s^{-1}	5.3
Chronic disease score	2.5±2.6
SIEDY scale score	
Scale 1 (organic domain of ED)	3.3±2.3
Scale 2 (relational domain of ED)	2.0±2.1
Scale 3 (intrapsychic domain of ED)	3.2±2.2
Intrapsychic parameters as derived by MHQ-questionnaire	
MHQ-A score (free-floating anxiety symptoms)	5.5±3.4
MHQ-P score (phobic anxiety symptoms)	4.5±2.5
MHQ-O score (obsessive-compulsive traits and symptoms)	6.0±3.7
MHQ-S score (somatization)	3.7±2.8
MHQ-D score (depressive symptoms)	4.9±3.2
MHQ-H score (hysterical symptoms and traits)	4.8±3.0

BMI: body mass index; CVD: cardiovascular diseases; DBP: diastolic blood pressure; ED: erectile dysfunction; FSH: follicular stimulation hormone; HDL: high density lipoprotein; LDL: low density lipoprotein; LH: luteinizing hormone; MHQ: Middlesex hospital questionnaire; PSA: prostatic specific antigen; PSV: peak systolic velocity at penile doppler ultrasound (PDU) after PGE1 stimulation; SBP: systolic blood pressure; s.d.: standard deviation. Data are expressed as mean±s.d. when normally distributed, median (quartiles) when not normally distributed and as percentages when categorical

All patients enrolled underwent the usual diagnostic protocol applied to newly referred subjects at the Andrology Outpatient Clinic. All the data provided were collected as part of the routine clinical procedure and in line with current guidelines.[15] All patients provided an informed consent to the study. Patients were interviewed prior to the beginning of any treatment, and before any specific diagnostic procedures, using the SIEDY Structured Interview.[16] SIEDY is a 13-item interview made up of three scales, which identify and quantify components concurring with SD.[17–22]

Premature ejaculation (PE) was defined as ejaculation within 1 min of vaginal intromission (as reported by the patient) according to previously described criteria.[23,24] Delayed ejaculation was defined as 'slowness to ejaculate' (as reported by the patient) according to previously described criteria.[23–25]

In addition, patients were asked to complete the Middlesex Hospital Questionnaire (MHQ),[26] a brief self-reported questionnaire for the screening of mental disorders in a nonpsychiatric setting. The total score of MHQ (ΣMHQ) provides an index of mood and anxious spectrum psychopathology.[27,28] Patients were asked to report any kind of drugs used. Chronic Diseases Score, an index of concomitant morbidities, was calculated as previously described.[29] This is an aggregate comorbidity measure based on current medication used and originally validated for use as a predictor of physician-rated disease status, self-rated health status, hospitalization and mortality.[29]

Main outcome measures

All patients underwent a complete physical examination, with measurement of BP (mean of three measurements 5 min apart, in sitting position, with a standard sphygmomanometer), height, weight and body mass index. Blood samples were drawn in the morning, after an overnight fast, for determination of blood glucose (by glucose oxidase method; Aeroset Abbott, Rome, Italy), total cholesterol, high density lipoprotein cholesterol and triglycerides (by automated enzymatic colorimetric method; Aeroset Abbott, Rome, Italy) and follicular stimulating hormone, luteinizing hormone, prostatic specific antigen (PSA) and total testosterone (by electrochemiluminescent method, Modular Roche, Milan, Italy). Low density lipoprotein (LDL) cholesterol was calculated according to Friedewald equation. Metabolic syndrome (MetS) was defined according to the International Diabetes Federation (IDF) criteria.[30]

All patients also underwent a colored penile Doppler ultrasound (PDU) examination performed in the flaccid state and 20 min after a PGE1 (10 μg) intracavernous injection (dynamic evaluation), as previously described.[31] We decided to use the same protocol for PDU in all patients studied in order to make the results fully comparable. The following parameters were considered: flaccid peak systolic velocity (PSV) and penile acceleration and after PGE1 stimulation, dynamic PSV.[31] PDU procedure was performed as recommended in 'Standard Practice in Sexual Medicine', produced by the International Society of Sexual Medicine Standards Committee[32] and the 3rd International Consultation on Sexual Medicine.[33] In particular, according to International Society of Sexual Medicine Standards Committee[32] and the 3rd International Consultation on Sexual Medicine[33] different pathological dynamic PSV thresholds (<25 and 35 cm s^{-1}) were considered. In addition, we recently reported that in subjects seeking medical care for ED, a flaccid acceleration threshold of 1.17 m s^{-2} showed a threefold increase in incidence of major adverse cardiovascular (CV) events.[34] Hence, even this cutoff was considered.

An unselected subset of (n = 51) patients underwent transrectal colored PDU, using the ultrasonographic console Hitachi H21 (Hitachi Medical System, Tokyo, Japan) as previously described.[35] The

characteristics of this subset did not differ from the rest of the sample (not shown). In particular, transrectal prostate color-Doppler ultrasound was prescribed during normal routine clinical practice, as second level examination in the presence of prostate pain or suspected prostate cancer at DRE according to European Association of Urology guidelines.[3,36] Patients with enlarged prostate size at DRE have a significantly higher prostate volume, when evaluated at ultrasound (**Figure 1**). Accordingly, receiver operating characteristic curve analysis showed that the detection of an enlarged prostate size at DRE provided a specificity of 99.5%, sensitivity of 68% and an accuracy of 93% in predicting an enlarged volume (>30 ml) at ultrasound.

Statistical analysis

Data were expressed as mean ± standard deviation when normally distributed, and as median (quartiles) for parameters with non-normal distribution, unless otherwise specified. Differences were evaluated with one-way analysis of variance or Kruskal-Wallis test, according to normal or non-normal distribution. Correlations were assessed using Spearman's or Pearson's method when not normally or normally distributed, respectively. Unpaired two-sided student's *t* -tests were used for comparison of means of normally distributed parameters. When distribution could be normalized through logarithmic transformation such as in the case of PSA, the same test was applied to logarithmically transformed data. In all other cases (i.e., not normally distributed variables), Mann-Whitney U test was used for comparisons between groups. Stepwise multiple linear or logistic regressions were applied for multivariate analysis, for continuous or categorical dependent variably, respectively. All statistical analysis was performed on SPSS (Statistical Package for the Social Sciences; Chicago, USA) for Windows 17.1.

RESULTS

Among the selected patients studied, ED, PE and delayed ejaculation were reported by 77.3%, 25.7% and 8.9%, respectively. In particular, erection not sufficient for penetration, according to SIEDY Appendix A question 1C, was reported in <25% of cases by 1067 (58.5%), in 25%–50% by 190 (10.4%), in 50%–75% by 252 (13.8%) and in >75% by 314 (17.3%) subjects. In addition, 589 (32.3%) had an enlarged prostate volume at DRE.

Prostate size and metabolic parameters

In the selected population (i.e., without prostatic diseases or high PSA), after adjusting for confounders (including age, total testosterone, gonadotropins, body mass index and associated morbidities), subjects with an enlarged prostate size had a higher risk of metabolic syndrome (MetS), as defined by IDF criteria (HR = 1.346 (1.129–1.759); $P = 0.030$). In addition, a higher risk of type 2 diabetes mellitus (T2DM, HR = 1.489 (1.120–1.980); $P = 0.006$), increased LDL cholesterol (>100 mg dl^{-1}; HR = 1.354 (1.018–1.801); $P = 0.037$) and increased mean BP values (HR = 1.017 (1.007–1.027) for each mmHg increment; $P = 0.001$) were observed in patients with an enlarged prostate size.

Prostate size and clinical (sexual and non) parameters

After adjusting for the aforementioned confounders, no association between an enlarged prostate size at DRE and risk of erection not sufficient for penetration was observed (HR = 1.078 (0.989; 1.175); $P = 0.088$ for each increment in the score of question 1C of SIEDY Appendix A). When the same model was evaluated in the population stratified according to median age the association was found in older (age ≥54-years-old; HR = 1.115 (1.007; 1.234); $P = 0.037$ for each increment in the score of question 1C of SIEDY Appendix A), but not in younger subjects (not shown). Accordingly, the presence of an enlarged prostate size at DRE was associated with reduced flaccid acceleration and dynamic PSV in older (**Figure 2**; HR = 0.783 (0.697; 0.880) and HR = 0.984 (0.975; 0.991); for each increment in acceleration and PSV after adjusting for confounders; both $P < 0.0001$), but not younger patients (not shown).

Enlarged prostate size was also associated with a higher risk of PE (HR = 1.426 (1.115; 1.823); $P = 0.005$). When the population was divided according to median age, the association was confirmed in younger (HR = 1.736 (1.185; 2.543); $P = 0.005$), but not in older subjects (not shown). Conversely, no association between delayed ejaculation and enlarged prostate size was observed (not shown).

Among nonsexual clinical parameters, the presence of left clinical-derived varicocele was another condition significantly related to an increased risk of an enlarged prostate size (HR = 1.293 (1.119–1.494); $P < 0.001$). The association between varicocele and an enlarged prostate size was confirmed even when patients complaining of PE were excluded from the analysis (HR = 1.292 (1.085–1.539), $P = 0.004$).

Prostate size relational and intrapsychic parameters

Subjects with an enlarged prostate size more often reported an impaired couple relationship as derived from SIEDY Scale 2 score; a validated instrument to score relational factors in subjects with SD (2.42 ± 2.26 *vs* 1.59 ± 1.81; $P < 0.0001$). After adjustment of the aforementioned confounders, the association between an enlarged prostate size at DRE and pathological SIEDY Scale 2 score (≥2) was confirmed in the whole selected population (HR = 1.286 (1.023; 1.6161); $P = 0.031$),

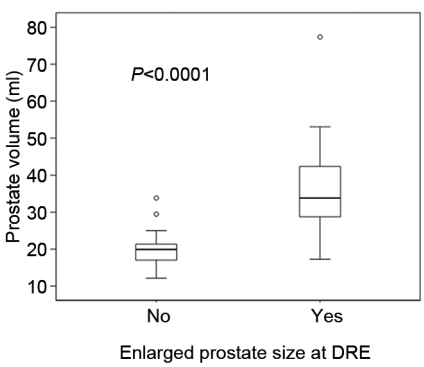

Figure 1: Prostate volume in patients with or without enlarged prostate size at digito-rectal examination (DRE). HR: hazard ratio.

Figure 2: Penile vascular parameters at Doppler ultrasound in subjects with or without enlarged prostate size at DRE. (**a**) Acceleration evaluated in flaccid state (before PGE1 stimulation); (**b**) peak systolic velocity evaluated in dynamic condition (after PGE1-stimulation). The inset indicates the age, body mass index, total testosterone, gonadotropin and associated morbidity adjusted data. DRE: digito-rectal examination; PGE1: prostaglandin E1.

and in older subjects (HR = 1.600 (1.206; 2.123); $P = 0.001$), but not in younger patients (not shown).

Similarly, after the adjusting for previous confounders, antidepressant medication and Σ-MHQ, older but not younger patients with an enlarged prostate size had a significantly higher risk of depressive symptoms, as derived from MHQ self-reported questionnaire (HR = 1.335 (1.083–1.646); $P = 0.007$ for each increment in MHQ-D score quartile).

Prostate size and PSA

PSA levels were significantly higher in subjects with enlarged prostate size when compared to the rest of the sample (**Figure 3a**). This association was confirmed after adjusting for confounders (HR = 3.318 (2.304; 4.799) for each log unit increment in PSA levels; $P < 0.0001$). Similar results were observed when the same model was applied to both young or old subjects, as categorized according to median age (HR = 2.283 (1.182; 4.441); $P = 0.014$ and HR = 3.944 (2.530; 6.150); $P < 0.0001$ for each log unit increment in PSA, respectively for young and old patients; see also **Figure 3b** and **3c**).

Subjects reporting an erection not sufficient for penetration in more than 25% of cases had significantly higher PSA levels when compared to the rest of the sample (**Figure 4a**, HR = 1.373 (1.021; 1.846), $P = 0.036$ after adjustment for confounders). However, when the same analysis was performed according to median age, the association between ED and PSA was confirmed only in older, but not in younger, patients (**Figure 4b** and **4c**, HR = 1.472 (1.003; 2.160), $P = 0.048$ and HR = 1.136 (0.709; 1.822); $P = 0.595$, respectively). Similarly, in older subjects, a negative association between PSA levels and pathological flaccid acceleration (<1.17 m s^{-2}) was observed (**Figure 5a**; HR = 1.853 (1.075; 3.194); $P < 0.0001$ after adjustment for confounders). In addition, in older but not younger (not shown) subjects, arteriogenic ED, according to different criteria, was associated with increased PSA levels (**Figure 5b** and **5c**). Accordingly, the risk of arteriogenic ED significantly increased as a function of PSA and Chronic Diseases Score increment; whereas, it was inversely related to total testosterone levels (**Figure 5d**).

In line with these data, older subjects with pathological LDL cholesterol (>100 mg dl^{-1}) had significantly higher PSA levels after adjusting for the aforementioned confounders (HR = 1.995 (1.225–3.249); $P = 0.005$).

Finally, it is interesting to note that all the previous results were confirmed when the entire, unselected, population of patients with SD was considered (not shown).

DISCUSSION

We here reported that, in a cohort of subjects with SD, the evaluation of prostate size, through DRE, is a simple, inexpensive and informative clinical procedure that can provide insights not only into urological health but also into sexual and CV health. Hence, in our opinion, DRE should be systematically performed by healthcare professionals on each patient with SD. The presence of an enlarged prostate size at DRE was in fact related not only to other andrological conditions, such as varicocele and PE, but also to arteriogenic ED and MetS. Finally, depressive symptoms and impairment of couple fitness were more often present in subjects with an enlarged prostate size.

The association between enlarged prostate size and MetS is not surprising. We recently performed a review of the available evidence showing that subjects with MetS had a significantly higher total and transitional zone prostate volume.[37] The reasons for the association between MetS and BPH have not been completely clarified, but we recently demonstrated that, in a rabbit model, the MetS condition was associated with prostatic inflammation, hypoxia and fibrosis along with a condition of hypogonadotropic hypogonadism.[38] Interestingly, treating hypogonadism reduced MetS-associated inflammation and restored oxygenation.[38] An association between MetS, hypogonadism and BPH was also found in human studies.[39] Among the Mets components, previous studies indicated that higher serum LDL levels are associated with greater risk of BPH[40] and that dyslipidemia might be one of the important risk factors in the pathogenesis of BPH.[41] Accordingly, we here reported that subjects with an enlarged prostate at DRE had higher LDL levels when compared to the rest of the sample. How MetS and dyslipidemia can boost prostate inflammation and/or enlargement is a matter of speculation. However, in isolated human stromal BPH cells we recently demonstrated that oxidized LDL and insulin stimulate the secretion of other proinflammatory (IL-6, IL-8 and IL-7) and growth-promoting (e.g., bFGF) factors,[42] therefore sustaining an immune-mediated growth response. Even in this *in vitro* model, androgen receptor activation can blunt prostatic cell response to metabolic (oxLDL) or proinflammatory (TNFα) stimuli.[38] Therefore, MetS-associated hypogonadism has been proposed as a possible bridge between chronic prostatic inflammatory response and metabolic alterations in both animal[38] and human experimental studies.[42] However, in the present study, the association between an enlarged prostate size

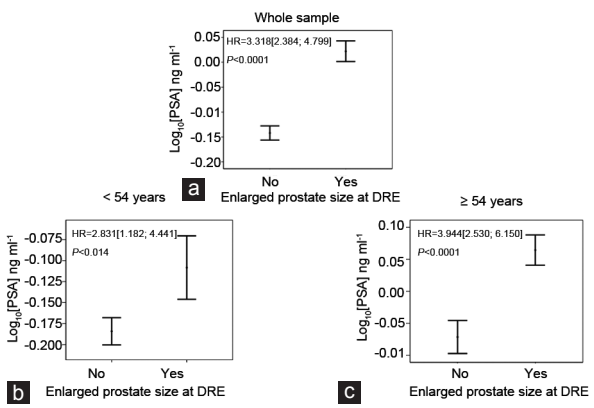

Figure 3: PSA levels in patients with or without enlarged prostate size at DRE. (**a**) Whole population; (**b**) patients younger and (**c**) older than median age of the sample (54 year old). The inset indicates the age, body mass index, total testosterone, gonadotropins and associated morbidities derived data. DRE: digito-rectal examination; PSA: prostate-specifi c antigen.

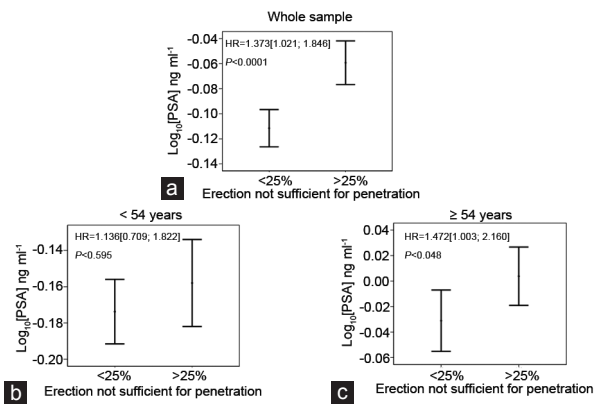

Figure 4: PSA levels in patients with or without severe erectile dysfunction (erection not sufficient for penetration in >25% of cases according to SIEDY Appendix A; see reference 16). (**a**) Whole population, (**b**) patients younger and (**c**) older than median age of the sample (54-years-old). The inset indicates the age, body mass index, total testosterone, gonadotropins and associated morbidities derived data. PSA: prostate-specific antigen.

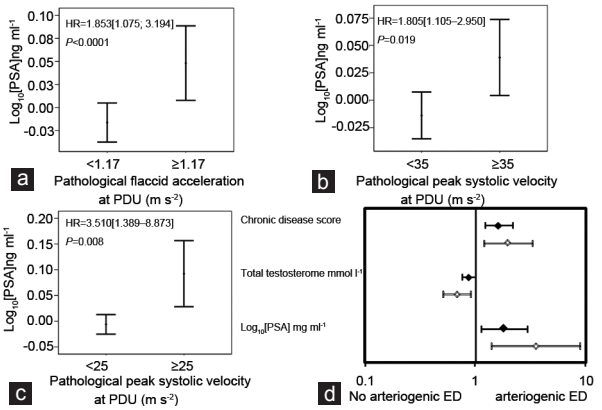

Figure 5: PSA levels according penile doppler ultrasound (PDU) parameters in older (>54-years-old) subjects. (**a**) Relationship between PSA levels and pathological acceleration (<1.17 m s^{-2}) evaluated in flaccid condition (before PGE1 stimulation). (**b** and **c**) PSA levels in patients with and without arteriogenic erectile dysfunction (ED) according to different criteria (peak systolic velocity (PSV) evaluated in dynamic conditions, after PGE-1 stimulation, <35 and 25 cm s^{-1}). (**d**) Risk of arteriogenic ED (PSV <35 cm s^{-1} black diamonds and <25 cm s^{-1} white diamonds) as a function of specific increment of chronic disease score (an index of associated morbidities, each 5 score increment; see reference 29), testosterone levels (each 5 nmol l^{-1} increment) and PSA levels (each log unit increment). The inset indicates the age, body mass index, total testosterone, gonadotropins and associated morbidities derived data. PSA: prostate-specifi c antigen.

and MetS was confirmed even after the adjustment for testosterone and gonadotropin levels. Hence, it can be hypothesized that, besides hypogonadism, MetS-associated dyslipidemia could induce per se an increase in prostate size. In addition, MetS and dyslipidemia are well-known risk factors for ED, which explains the observed link between enlarged prostate size and arteriogenic ED.[43,44] The prevalence of ED in subjects with MetS ranges from 27% to 80%, and is strictly associated with the number of MetS components and endothelial function impairment.[43,44] Longitudinal data from the Massachusetts Male Aging Study showed that ED could also be predictive of incident MetS.[45] The MASM-7 study, the largest multinational survey conducted in the US and six European countries, systematically investigating the relationship between BPH/LUTS and SD, demonstrated that LUTS is an independent risk factor for ED, most probably because of an impaired blood supply.[46] Interestingly, patients with severe vascular diseases and BPH symptoms had a significantly lower perfusion of the transition zone of the prostate than healthy controls, thus suggesting that an impairing of blood supply to the prostate plays a key role in the development of BPH.[47,48] Pinggera *et al*.[49] demonstrated that LUTS are associated with chronic ischemia of the prostate and urinary bladder, which could be improved by the treatment with alpha-blockers. Although we did not specifically investigate LUTS symptom severity, we found that an enlarged prostate size was associated with penile atherosclerosis, at least as detected by an impaired penile blood flow.

PSA levels have been postulated as an effective predictor of prostate volume and LUTS severity.[11-15] Serum PSA may be utilized as an alternative way of estimating prostate size, particularly when the key question is whether or not the prostate is above or below a threshold volume. For example, as reported by Roehrborn *et al*.[11] and confirmed by other investigators[12] to achieve a specificity of 70% while maintaining a sensitivity between 65% and 70%, approximate age-specific criteria for detecting men with prostate glands exceeding 40 ml are: PSA >1.6, >2.0 and >2.3 ng ml^{-1} for men with BPH in their 50, 60 and 70 s, respectively. Recently Park *et al*.[50] published data on more than 30 000 men involved in the Korean Prostate Health Council Screening Program. They showed that serum PSA was a strong predictor of prostate volume and significantly correlated with LUTS severity. Our data are in line with this evidence. Subjects with an enlarged prostate size at DRE had higher PSA levels, a higher risk of arteriogenic ED and increased LDL cholesterol. The observed link between arteriogenic ED, enlarged prostate size at DRE and elevated PSA levels was not confirmed in younger subjects, when the population was categorized according to the median age. It can be speculated that other factors might mitigate the latter associations in younger individuals. In addition, in the youngest subjects, PSA is more dependent on the androgen milieu,[9] which also influences penile blood flow.[51]

Among other symptoms and signs, enlarged prostate size was related to PE and varicocele. We previously reported that varicocele is an independent risk factor for PE, closely associated with clinical and ultrasound features of prostatitis.[52] Gat *et al*.[53] demonstrated the presence of direct communication between deferential veins and the vesicular prostatic plexus. Hence, it can be speculated that a back-flow of venous blood from the testis to the prostate can lead to an intrapelvic venous congestion, facilitating the onset of prostatitis symptoms, which in turn can induce the development of PE as previously described.[54] On the other hand, an enlarged prostate size could reflect the presence of prostate inflammations/infection, which is one of the most important causes of acquired PE, along with hyperthyroidism.[23,24,54-56] Accordingly, the use of alpha-blockers and phosphodiesterase type 5 inhibitors, which might also reduce prostate inflammation,[57,58] could be beneficial even in subjects with PE.[59] Hence, the evaluation of the prostate is mandatory in subjects complaining of PE.[60] A large body of evidence has emphasized the importance of SD, including PE and ED, in reducing couple satisfaction and quality of life.[61] Present data suggest that the presence of enlarged prostate size in subjects with SD could even exacerbate this couple impairment. In fact, depressive symptoms and an impaired couple relationship, as detected by pathological SIEDY Scale 2 score, were observed in patients with an enlarged prostate size. It is important to note that the partner data were derived from patients' perception and not from an interview with the partner. However, the data are relevant because they represent the scenario the patient is often dealing with, and therefore it mirrors the true couple relationship, at least as perceived by the patient. In addition, the cross-sectional nature of the present study does not allow any speculation on causal relationship. In fact, in this sample, depressive symptoms and couple impairment could be considered a consequence of either SD or BPH. No specific data on LUTS severity were available, but Mitropoulos *et al*.[62] confirmed that partners of subjects with LUTS suffered from a reduction in quality of life specifically related to an inadequate sex life, disruption of social life and fear of cancer and surgery.

Several limitations of the present study should be recognized. First of all, estimating prostate size by DRE is notoriously unreliable. In particular correlation coefficients between DRE and transrectal ultrasound measurements vary widely from 0.4 to 0.9, although it has been reported that training with a dedicated model may improve the precision.[63,64] In general, smaller prostates are overestimated and larger glands are underestimated with the degree of underestimation increasing as actual size increases.[63,64] In our unit, all the physicians were systematically trained to estimate prostate size, as a part of their andrology formation. However, we cannot infer that, during the study, variability of prostate size estimation during DRE by different investigators could have occurred. Nonetheless, our results–obtained in a large series of patients seeking medical care for SD–showed that this procedure might be an important source of clinical information not

only for urological health, but also for metabolic and CV stratification. In addition, present results are derived from patients consulting an Italian Andrology Clinic for SDs, which could have different characteristics from those consulting general practitioners or not seeking medical care. Furthermore, it should be recognized that results obtained in specific clinical settings cannot be easily generalized to wider populations. Conversely, phenomena observed in samples from the general population cannot always be extended to patients seeking treatment for a specific condition.

In conclusion, our data support the need to examine prostate size either by clinical (DRE) or biochemical (PSA) inspection in subjects with SD, in order to have insights into the nature of the SD and the metabolic and CV background of the patient. On the other hand, because BPH/LUTS represents a significant and growing public health challenge, evaluating its sexual counterparts might help in choosing the most appropriate treatment. In fact, ED medications, such as the phosphodiesterase type 5 inhibitors; have recently proven to have a beneficial effect not only on sexual symptoms and couple satisfaction, but also on LUTS.[65] Accordingly, Tadalafil has recently been licensed in several countries for the treatment of LUTS, most probably because this ED medicament increases prostate[66] and bladder[67] oxygenation and reduces prostate inflammation.

AUTHOR CONTRIBUTIONS

GC, E Maseroli, GR and AS contributed to the data collection. MG, LV, GF and E Mannucci contributed to the intellectual revision of the manuscript. GR and ED helped to draft the manuscript. All authors read and approved the final manuscript. GC and MM conceived of the study, participated in its design and coordination, performed the statistical analysis and helped to draft the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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