ORIGINAL PAPER

Risk factors for benign prostatic enlargement: The role of lifestyle habits at younger age. The *#Controllati2017* initiative study group

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Summary

Objective: The risk factors for benign prostatic enlargement (BPE) are not well understood and particularly few data are available from Italian population.
Materials and methods: This was an observational cross sectional study aimed to examine the association between several risk factors and BPE. During the "#Controllati2017" initiative, men aged 18 years or more were invited to attend participating urologic centers for a free of charge visit for counseling about urologic or andrologic conditions. Each participating man underwent a physical examination including digital rectal examination (DRE). Further he was asked about his medical history, urologic symptoms, sexual activity and related problems. Diagnosis of BPE was made by the urologist after DRE.
Results: Out of the 1902 [mean age 54 years (SD 12, range 18-92)] considered men, a total of 603 subjects (31.7%) had diagnosis of BPE. The diagnosis of BPE increased from 9.3% in men aged < = 50 years, to 34.1% in those aged 51-60 years and to 58.7% among men aged > 60 years. A history of hypertension, diabetes, heart diseases, hypercholesterolemia and hypertriglyceridemia were all significantly associated with an increased risk of BPE in the total series and, although not always in a statistically significant way, in strata of age. Physical activity (PA) was significantly associated with a decreased risk of BPE. We have further analyzed the risk of BPE in men with one or more of the identified risk factors (i.e. hypertension, diabetes, heart disease, hypercholesterolemia, hypertriglyceridemia and low PA): the risk of BPE increased with number of risk factors reported by the subjects. The estimated risk were higher among younger men.
Conclusion: In our study a history of hypertension, diabetes, heart disease, hypercholesterolemia and hypertriglyceridemia increased the risk and physical activity lowered the risk of BPE. This risk profile was observed also in men aged < 50 years.

KEY WORDS: *Benign prostatic enlargement (BPE); Hypertension; Diabetes; Hearth disease; Hypercholesterolemia; Hypertriglyceridemia; Physical activity.*

INTRODUCTION

Despite the high prevalence of the conditions, the risk factors for *benign prostatic hyperplasia* (BPH) or *benign prostatic enlargement* (BPE) are not well understood.
Some studies have suggested a role of diabetes or hypertension in the pathogenesis of PBH (1).
Further, HDL-cholesterol levels were an independent predictors of prostate enlargement (2). Other studies have shown that body mass index and waist circumference were positively related with prostate volume (3, 4). All these factors are associated with metabolic syndrome, a condition that increase the risk of cardiovascular diseases (5).
Further, it has been suggested that regular *physical activity* (PA) may decreased the risk of BPE (6).
These findings suggest that healthy life habits may lower the risk of growth of prostatic volume.
Available data on the role of these factors are scanty and particularly few data are available from Italian population.
In June 2017, the *Italian Society of Urology* conducted the "*#Controllati2017*" preventive initiative. In the framework of this preventive campaign, data have been collected on determinants of the risk of BPE.

MATERIALS AND METHODS

This was an observational cross sectional study aimed to examine the association between several risk factors and BPE.
During the "*#Controllati2017*" (1st June-15th July 2017) initiative, males of any age were offered to attend a free of charge visit for counseling about urologic or andrologic conditions in urological centers affiliated to the *Italian Society of Urology* (*Società Italiana di Urologia*).
A pamphlet inviting men for a free of charge check-up and listing participating centers was left in chemists and general practitioners' waiting rooms; an advertising campaign was set in the press and broadcast media.
Each participating man underwent a physical examination including *digital rectal examination* (DRE) and was

asked by the urologist about his medical history, urologic symptoms, sexual activity and related problems.
A total of 173 centers participated to the initiative. Epidemiological data were collected in 61 centers for a total of 2572 men who filled the questionnaire.
Data were recorded with a simple questionnaire used by all centers.
The first section, about age and life habits was completed by the patient. History of hypertension, diabetes, hearth diseases and other medical conditions, and the findings of the clinical examination were recorded by the urologist.
Diagnosis of BPE was made by the urologist after DRE.
Erectile dysfunction (ED) was diagnosed according to the definition of the *NIH Consensus Development Panel* (7).
The 2002 *International Continence Society* definitions were used for frequency, nicturia, urgency, dysuria (intermittency, slow stream, straining, terminal dribble, postmicturition dribble) incomplete emptying (8).

The section on PA included questions on self reported intensity of activity at work and in leisure time separately. Patients were asked about their PA, which were classified into five categories (scores between 1 and 5) corresponding to 'very heavy', 'heavy', 'average', 'moderate' and 'light'. The scores of the two highest levels of occupational and leisure PA were combined, in order to obtain adequate numbers in the categories.
For the purpose of the present paper we compared the characteristics of subjects with and without BPE.
Mean (standard deviation, SD), median (range) or frequency (percent,%) were computed as appropriate.
Odds ratios (OR), and the corresponding 95% *confidence intervals* (CI), were derived using unconditional multiple logistic regression, fitted by the method of maximum likelihood, in which the dependent variable was the presence (case) or absence (control) of BPE and the independent ones were the exposures considered in the analysis. We included in the model potential co-variates

Table 1.
Distribution of 603 subjects with and 1299 without benign prostatic enlargement according to selected factors and strata of age.

	≤ 50 years			51-60 years			≥ 61 years			
	No BPE N = 681 (90.7)	BPE N = 70 (9.3)	adj OR (95% CI)	No BPE N = 382 (65.9)	BPE N = 198 (34.1)	adj OR (95% CI)	No BPE N = 236 (41.3)	BPE N = 335 (58.7)	adj OR (95% CI)	Total series OR (95% CI)
BMI (kg/m^2)										
< 25	340 (50.9)*	35 (50.7)	1	154 (41.1)	61 (31.6)	1	87 (37.3)	116 (35.4)	1	1
≥ 25 - < 30	254 (38.0)	25 (36.2)	1.0 (0.6-1.6)	168 (44.8)	95 (49.2)	1.4 (1.0-2.1)	117 (50.2)	152 (46.3)	1.0 (0.7-1.9)	1.4 (1.1-1.7)
≥ 30	74 (11.1)	9 (10.8)	1.2 (0.5-2.6)	53 (14.1)	37 (19.2)	1.2 (0.6-2.2)	29 (12.4)	60 (18.3)	1.55 (0.9-2.6)	1.9 (1.4-2.5)
Smoking habits										
Never smokers	391 (58.1)	34 (48.6)	1	195 (51.3)	87 (43.9)	1	102 (43.8)	140 (42.3)	1	1
Ever smokers	282 (41.9)	36 (51.4)	1.5 (0.8-2.7)	185 (48.6)	111 (56.1)	1.3 (0.8-2.0)	131 (56.2.)	191 (57.7)	1.1 (0.7-1.7)	1.4 (0-9-1.8)
Occupational PA										
No	122 (18.9)	13 (21.0)	1	77 (21.9)	36 (19.6)	1	43 (22.3)	73 (28.2)	1	1
Low	203 (31.4)	20 (32.3)	0.9 (0.4-1.9)	112 (31.9)	56 (30.4)	1.1 (0.7-1.8)	54 (28.0)	82 (31.7)	0.9 (0.5-1.9)	0.9 (0.6-1.1)
Moderate	193 (29.8)	23 (37.1)	1.1 (0.6-2.3)	108 (30.8)	62 (33.7)	1.2 (0.7-2.0)	79 (40.9)	80 (30.9)	0.6 (0.4-1.0)	0.8 (0.7 -1.1)
Intense	129 (19.9)	6 (9.7)	0.4 (0.2-1.2)	54 (15.4)	30 (16.3)	1.2 (0.7-2.2)	17 (8.8)	24 (9.3)	0.8 (0.4-1.7)	0.6 (0.4-0.9)
Leisure PA										
No	61 (9.1)	5 (7.9)	1	40 (11.0)	30 (16.2)	1	27 (12.3)	41 (12.9)	1	1
Low	195 (29.2)	20 (31.8)	1.3 (05-3.5)	115 (31.7)	51 (27.6)	0.6 (0.3-1.1)	62 (28.2)	90 (28.4)	1.0 (0.5-1.7)	0.7 (0.5-1.0)
Moderate	285 (42.6)	29 (46.0)	1.2 (0.5-3.3)	157 (43.2)	70 (37.8)	0.6 (0.3-1.0)	97 (44.1)	152 (48.0)	1.0 (0.6-1.8)	0.8 (0.6-1.1)
Intense	128 (19.1)	9 (14.3)	0.9 (0.3-2.8)	51 (14.0)	34 (18.4)	0.9 (0.5-1.7)	34 (15.4)	34 (10.7)	0.7 (0.3-1.3)	0.6 (0.4-0.9)
Hypertension										
No	595 (90.6)	50 (76.9)	1	256 (70.0)	106 (56.7)	1	118 (51.8)	150 (45.7)	1	1
Yes	62 (9.4)	15 (23.1)	2.9 (1.5-5.4)	110 (30.0)	81 (43.3)	1.8(1.2-2.6)	110 (48.2)	178 (54.3)	1.2 (0.9-1.8)	3.1 (2.5-3.8)
Diabetes										
No	652 (99.2)	62 (98.4)	1	341 (95.0)	164 (90.6)	1	198 (89.2)	266 (83.4)	1	1
Yes	5 (0.8)	1 (1.6)	2.1 (0.2-18.3)	18 (5.0)	17 (9.4)	2.0 (1.0-3.9)	24 (10.8)	53 (16.6)	1.6 (0.9-2.8)	3.7 (2.5-5.4)
Hearth disease										
No	650 (99.1)	61 (96.8)	1	332 (93.3)	164 (91.1)	1	189 (87.5)	245 (79.8)	1	1
Yes	6 (0.9)	2 (3.2)	3.6 (0.7-18.0)	24 (6.7)	16 (8.9)	1.2 (0.7-2.6)	27 (12.5)	62 (20.2)	1.8 (1.1-2.9)	3.5 (2.5-5.0)
Hypertriglyceridaemia										
No	601 (91.9)	57 (87.7)	1	302 (86.0)	152 (85.4)	1	181 (85.8)	257 (84.3)	1	1
Yes	53 (8.1)	8 (12.3)	1.6 (0.7-3.5)	49 (14.0)	26 (14.6)	1.1(0.6-1.8)	30 (14.2)	48 (15.7)	1.1 (0.7-1.9)	1.4 (1.1-1.9)
Hypercholesterolaemia										
No	533 (81.0)	49 (74.2)	1	263 (73.9)	122 (67.4)	1	157 (71.7)	212 (68.0)	1	1
Yes	125 (19.0)	17 (25.8)	1.5 (0.8-2.7)	93 (26.1)	59 (32.6)	1.4 (0.9-2.0)	62 (28.3)	100 (32.0)	1.2 (0.8-1.7)	1.6 (1.3-2.0)

*OR: odds ratio; CI: confidence interval; *In some cases the sum does not add up the total due to missing values.*

considered as categorical variables. The terms included in the model were those found statistically significantly associated with the risk of BPE in the crude analysis. Further, we computed an overall risk score including all factors found statistically significantly associated with the risk of BPE in the crude analysis of the total series. Subjects were classified according the presence of none, 1,2 3 or more factor and corresponding OR were computed.

RESULTS

Overall, 2572 men were observed in 61 participating centers: the mean number of attending men per center was 42 (median 35, range 4-126). Their mean age was 54 years [standard deviation (SD) 12, range 18-92].
After exclusion of men who did not filled the demographic questionnaire and those who underwent previous partial and complete prostatectomy, we analyzed data from 1902 men, aged 54 years (SD 12, range 18-92). The reason for the visit was urinary symptoms in 318 (16.7%), sexual problems in 234 (12.3%), renal disease in 37 (2.0%) and prostatic problems in 346 (18.2%). Prevention was the only reason for consultation in 1156 subjects (60.8%, each man could indicate one reason or more).
Out of the 1902 considered men, a total of 603 subjects

jects according to the diagnosis of BPE according to class age are shown in Table 1.
A history of hypertension, diabetes, hearth disease, hypercholesterolemia and hypertriglyceridemia were all significantly associated with an increased BPE risk in the total series and, although not always in a statistically significant way, in all the three considered strata of age. PA was significantly associated with a decreased risk of BPE.
We have further analyzed the risk of BPE in men with one or more of the identified risk factors (i.e. hypertension, diabetes, hearth disease, hypercholesterolemia and hypertriglyceridemia and PA): the risk of BPE increased with number of risk factors reported by the subjects. The estimated OR were higher among younger men (Table 2).
Table 3 considers the frequency of urinary symptoms among men with a diagnosis of BPE in strata of age.
The frequency of all symptoms increased with age and dysuria was the most common symptoms at all ages.
Considering subjects for which the information was available, ED was reported in the 39,8% (225/565) of men with BPE and 16.3% (201/1235) of those without BPE (adj chi suare p < 0.05). This difference in the frequency of DE was consistent in the three considered strata of age: in particular considering men aged < 50 years the frequency of ED was 17.5% (11/63) among the men with BPE and 9.9% (64/644) among those without BPE (adj chi square = 0.06).

Table 2.
Association between benign prostatic enlargement (BPE) and number of risk factors.

	≤ 50 years			51-60 years			≥ 61 years			Total series
	No BPE N = 681 (90.7)	**BPE** N = 70 (9.3)	**adj OR** **(95% CI)**	**No BPE** N = 382 (65.9)	**BPE** N = 198 (34.1)	**adj OR** **(95% CI)**	**No BPE** N = 236 (41.3)	**BPE** N = 335 (58.7)	**adj OR** **(95% CI)**	**adj OR** **(95% CI)**
Number of risk factors reported by the subject										
0	494 (72.5)	42 (60.0)	1	187 (49.0)	72 (36.4)	1	82 (34.8)	95 (28.4)	1	1
1	134 (19.7)	17 (24.3)	1.8 (0.8-3.3)	122 (31.9)	75 (37.9)	1.7 (1.1-2.6)	81 (34.3)	105 (31.3)	0.9 (0.6-1.6)	1.3 (1.0-1.8)
2	38 (5.6)	7 (10.0)	2.3 (0.8-6.7)	44 (11.5)	31 (15.7)	1.9 (1.0-3.4)	43 (18.2)	78 (23.4)	1.1 (0.6-1.9)	1.5 (1.0-2.2)
≥ 3	15 (2.2)	4 (5.7)	3.5 (1.0-11.6)	29 (7.6)	20 (10.1)	2.0 (1.0-4.1)	30 (12.7)	57 (17.0)	1.9 (1.0-3.7)	2.1 (1.4-3.3)

AOR: adjusted odds ratio. Including terms for BMI and age.

Table 3.
Association between benign prostatic enlargement (BPE) and urinary symptoms.

	≤ 50 years		51-60 years		≥ 61 years	
	No BPE	**BPE**	**No BPE**	**BPE**	**No BPE**	**BPE**
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Urgency	96 (14.1)*	10 (14.3)	28 (7.3)	32 (16.2)	11 (4.7)	52 (15.5)
Nicturia	52 (7.6)	17 (24.3)	47 (12.3)	61 (30.8)	33 (14.0)	115 (34.3)
Dysuria	86 (12.6)	38 (51.4)	92 (24.1)	108 (54.5)	74 (31.4)	212 (63.3)
Frequency	46 (6.8)	27 (38.6)	48 (12.7)	79 (39.9)	24 (10.2)	131 (39.1)
Incomplete voiding sensation	70 (10.3)	32 (45.7)	54 (14.1)	80 (40.4)	26 (11.0)	142 (42.4)

In some cases the sum does not add up the total due to missing values.

(31.7%) had diagnosis of BPE. The diagnosis of BPE increased from 9.3% in men aged <=50 years, to 34.1% in those aged 51-60 years and to 58.7% among men aged > 60 years. The general characteristics of study sub-

DISCUSSION

The general results of this analysis show that a history of hypertension, diabetes, hearth disease, hypercholesterolemia and hypertriglyceridemia increase the risk of BPE at all ages.
A regular PA tended to decrease the risk. Interestingly these factors were associated with PBE risk also in men aged 50 years or less, thus underlining the role of a healthy life style among younger men.
This suggestion was also confirmed when we have considered the risk BPE among men with one, two or three of the factors found associated with the risk of PBE: the presence of more risk factors was more markedly associ-

ated with the risk of BPE in men aged 50 years or less. The role of modifiable lifestyle factors on the risk of BPH has been widely suggested (9). For example, a review of the literature conducted in the late 2000 and including eight studies has shown, compared to the sedentary group, a pooled odds ratios for BPH or LUTS of 0.70 (95% CI 0.44-1.13, p = 0.14), 0.74 (95% CI 0.60-0.92, p = 0.005), and 0.74 (95% CI 0.59-0.92, p = 0.006) for men engaging in light, moderate, and heavy physical activity, respectively (6). We confirm these findings, in particular the protective effects of PA was more evident among younger men.

Obesity, elevated fasting plasma glucose, diabetes, dyslipidemia, and the metabolic syndrome may all significantly increase the risks of BPH and low urinary tract symptoms (10-12). In our study diabetes, hypercholesterolemia, hypertrigliceridemia were associated with an increased risk of BPE. Further a history of hypertension and hearth diseases increased the risk. All these findings underline that BPE shares similar risk factor with metabolic syndrome and cardiovascular diseases.

The biological link between these risk factors and the prostatic growth is not completely understood.

However, for example, it has been shown that lipids (*oxidized low-density lipoprotein*, LDL) increase in vitro the secretion of growth and pro-inflammatory factors by human stromal BPH cells in culture (13). Along this line in a clinical perspective, the addition of statins to standard therapy for BHP lowered prostate volume (14).

It has been suggested that metabolic syndrome-dependent prostate growth may play a major role among older men (15). An interesting findings of the present study is the observation that the OR of BPE associated with the presence of several risk factors such as PA and hyperlipidemia, diabetes and hypertension were higher (although no statistically significantly different) among younger than older men. This findings underline the role of encouraging healthy lifestyle habits among men under the 50 years of age in order to reduce the risk of BPH.

Limits

As previously discussed in the paper reporting the results of the *#Controllati2016* initiative (16), the major flaw of this study is the fact that the study population were men voluntarily presenting to the participating centers and physicians associated to the *Italian Society of Urology* (SIU). Along this line the observed frequency of BPE in this population, about 30%, is higher than reported in the literature (17).

Further, the participating centers were not randomly identified among all members, so they cannot be considered representative of all Italian centers. However, they were well distributed over the main areas of the country and there were no marked differences in the results among centers in various large Italian areas, giving strong support to the consistency of the general results. Likewise, the prevalence of hypertension and diabetes and overweight were largely similar to the general Italian population.

For example the percentage of hypertensive subjects was largely consistent with that of the Italian population (18) and with the results of the *#Controllati2016* survey (16).

In any case, any inference from the present analysis must be made in strictly comparative terms and strictly referred to men attending urologic services.

The diagnosis of BPE was based on DRE that tends to underestimate the prostatic volume (17). In any case any misclassification of men with or without BPE should lower the observed associations.

The strengths of the study included the fact that it provides information from a large series of men identified in all parts of Italy. Further, the participation rate was very high. Along this line, the patients presented themselves voluntarily to the physician, so their answers to all questions should be truthful.

CONCLUSIONS

In our study a history of hypertension, diabetes, hearth disease, hypercholesterolemia and hypertriglyceridemia increased the risk and physical activity lower the risks of BPE.

These findings are consistent with other studies. The findings suggest that BPE risk is associated with lifestyle habits and modifiable risk factors of cardiovascular disease. Cohort studies are needed to evaluate if modification of lifestyle habits may change the natural history of BPH.

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