Original Article

Serum testosterone and prostate-specific antigen levels are major risk factors for prostatic volume increase among benign prostatic hyperplasia patients

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Abstract *Objective:* Benign prostatic hyperplasia (BPH) is one of the most common diseases found among elderly men. Even though multiple risk factors of BPH have been identified in the past, the risk factors which have a direct impact on prostate volume have not been identified. In this study, we aim to determine the most significant contributing risk factors to prostate volume enlargement by analyzing possible associated risk factors previously studied.
Methods: This is a quantitative study with an analytical observational design, performed using a retrospective cohort approach. Total sampling was performed on 83 patients who underwent transurethral resection of the prostate (TURP) in Sanglah General Hospital from January to February 2019. Bivariate analysis is performed to examine each variable's association with prostate volume followed by a multivariate analysis. All variables were reassessed with path analysis to measure the direct effects, indirect effects, and total effects on prostate volume.
Results: Bivariate analysis shows that serum testosterone (R$=$0.208; $p=$0.059) and prostate-specific antigen (PSA) level (R$=$0.626; $p=$0.001) have a significant association with prostate volume. Multivariate analysis shows that serum PSA (B$=$1.4; $p=$0.001; 95% confidence interval [95% CI]$=$1.039—1.770) and testosterone (B$=$0.024; $p=$0.005; 95% CI$=$0.008—0.041) levels are significant among all the analyzed risk factors. There is a significant and strong effect of PSA to

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prostate volume (c=0.636; *p*=0.001) whereas testosterone has a significant albeit weak effect to prostate volume (c=0.246; *p*=0.009) based on the total effect of the path analysis.
Conclusion: Serum testosterone and PSA levels are significantly associated with prostatic volume increase among BPH patients.

1. Introduction

Interest and focus of urologists have never shifted far from benign prostatic hyperplasia (BPH) as it is one of the most common diseases found among elderly men [1]. Multiple studies worldwide have shown that the prevalence of the disease is at an all-time high especially among people above the age of 60. It is estimated that almost 70 percent of United States men between the age of 60 and 69 years have a certain degree of BPH [2]. Unfortunately, the prevalence rate of BPH in Indonesia has never been studied or published [3]. In Sanglah General Hospital, Bali alone there are 103 BPH patients who underwent transurethral resection of the prostate (TURP) in 2013 [4]. Even though it has been one of the main protagonist of urologic diseases for years, studies focusing on its associated risk factors are still being performed to this day. Latest findings claimed that BPH is no longer considered as a single disease but a manifestation caused by systemic alterations induced by multiple risk factors [5]. Multiple risk factors for BPH have been identified in the past. However, the risk factors which have a direct impact on prostate volume have yet to be identified. As severity progression based on the lower urinary tract symptoms (LUTS) of the disease is closely associated with the increase of prostate volume, it is necessary to identify these factors to evaluate new prevention strategies in the future. Therefore, in this study we aim to determine the most significant contributing risk factors to prostatic volume enlargement by analysing the possible associated risk factors previously studied: Age, urinary tract infection, type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, serum testosterone level, prostate-specific antigen (PSA) level, tumor necrosis factor (TNF)-α and TGF-β levels in prostate tissue.

2. Methods

2.1. Study population

This study is a quantitative study with an analytical observational design, performed using a retrospective cohort approach. Total sampling was chosen as the sampling method analysing 83 patients who underwent TURP in Sanglah General Hospital from January 2018 to February 2019. The inclusion criteria of this study are: Male patients around the age of 50–80 years old, prostate volume ranging from 20 to 80 mL, and have undergone TURP with a histopathology result confirming the diagnosis of BPH. Patients with confirmed infection, uncontrolled diabetes mellitus,

existing bladder stone with length or width longer than 2.5 cm, confirmed bladder tumor, urinary catheter use for more than 1 year, and patients who routinely consumed nonsteroidal anti-inflammatory drugs (NSAID) or aspirin are excluded.

2.2. Study variables

Independent variables included in this study consist of patients' age, body mass index (BMI), fasting plasma glucose level, plasma glucose level 2 h post prandial, testosterone level, PSA level, total cholesterol level, triglyceride level, urine culture results, prostate volume, TNF-α and TGF-β level. Prostate volume is assigned as the dependent variable.

2.3. Statistical analysis

Bivariate analysis is performed to examine each variable's association with prostate volume followed by a multivariate analysis using the logistic regression method. All variables were reassessed with path analysis to measure direct effects, indirect effects, and total effects from each significant risk factor regarding prostate volume. The statistical analysis is performed using IBM SPSS® 23.0 (International Business Machines [IBM] Corporation, New York, USA). The path analysis is performed using IBM SPSS® AMOS.

3. Results

3.1. Subjects' characteristics

Out of the 103 patients who underwent TURP, 83 patients fit the study inclusion criteria. The subjects' variables and characteristics are presented in Table 1.

3.2. Bivariate analysis

Bivariate analysis is performed to evaluate any associations between the risk factors and prostate volume using the Spearman method based on the statistical scale of the data. Both serum testosterone (R=0.208; *p*=0.059) and PSA level (R=0.626; *p*=0.001) have a significant association with prostate volume as shown in Table 2.

3.3. Linear regression analysis

Multivariate analysis is performed using the linear regression method to obtain the most significant risk factors

Table 1 Subjects' characteristics.

Variable	Mean±SD or n (%)	p-Value
Age (year)[a]	64.4±8.2	0.181
Body mass index (kg/m^2)[a]	23±3.3	0.200
Fasting plasma glucose (mg/dL)[a]	103.2±30.2	<0.001
Plasma glucose 2 h post prandial (mg/dL)[a]	131.8±45.4	<0.001
Total cholesterol (mg/dL)[a]	166.4±41.7	0.200
Triglyceride (mg/dL)[a]	144±214.8	<0.001
PSA (ng/mL)[a]	8.1±8.1	<0.001
Testosterone (ng/ml)[a]	412.4±177	0.200
TNF-α (pg/mg)[a]	50.8±22.9	<0.001
TGF-β (pg/mg)[a]	221.1±22.9	<0.001
Urine culture result		<0.001
Negative	71 (85.5)	
Positive	12 (14.5)	
Prostate volume (mL)[b]	46.3±7.8	<0.001

SD, standard deviation; TGF, transforming growth factor; TNF, tumor necrosis factor; PSA, prostate-specific antigen.
[a] The characteristics data collected from the patients were assigned as independent variables for the analysis.
[b] Prostate volume was assigned as the dependent variable for the analysis.

Table 2 Bivariate analysis results between risk factors and prostate volume.

Risk factor	Prostate volume	
	r-score	p-Value
Age (year)	0.098	0.377
Body mass index (kg/m^2)	0.007	0.953
Fasting plasma glucose (mg/dL)	−0.201	0.068
Plasma glucose 2 h post prandial (mg/dL)	−0.147	0.186
Total cholesterol (mg/dL)	0.011	0.922
Triglyceride (mg/dL)	0.002	0.986
PSA (ng/mL)	0.626	0.001
Testosterone (ng/mL)	0.208	0.059
TNF-α (pg/mg)	−0.089	0.423
TGF-β (pg/mg)	0.000	0.998
Urine culture results	−0.117	0.294

PSA, prostate-specific antigen; TNF, tumor necrosis factor; TGF, transforming growth factor.
*Bivariate analysis is performed using the spearman method based on the variables' data scale to evaluate the relationship between each variable and prostate volume.

among all analyzed variables. Serum PSA (B=1.4; p=0.001; 95% CI=1.039−1.770) and testosterone (B=0.024; p=0.005; 95% CI=0.008−0.041) levels are the two risk factors with the highest association significance to prostate volume among the patients as shown in Table 3.

3.4. Path analysis

A path analysis of the variables is performed to examine the dependencies among the risk factors and their relationships to prostate volume.

3.4.1. Two-sided correlation between risk factors
In Table 4, the two significant correlations of risk factors are the correlation between T2DM and obesity (r=0.191; p=0.005; 95% CI=0.057−0.325), between diabetes mellitus type 2 and dyslipidemia (r=0.323; p=0.001; 95% CI=0.155−0.490) and between TNF-α and TGF-β levels (r=0.515; p<0.001; 95% CI=0.352−0.678).

3.4.2. One-sided correlation between risk factors and prostate volume
In Table 4, the one side correlation analysis between risk factors and prostate volume, shows that T2DM has a negative correlation with PSA (r=−0.227; p=0.001; 95% CI=−0.360−0.094). PSA, on the other hand, has a one-way correlation with prostate volume (r=0.636; p=0.001; 95% CI=0.471−0.802). Testosterone also has a weak one side correlation with prostate volume, albeit weak (r=0.246; p=0.013; 95% CI=0.051−0.440).

3.4.3. Direct effect of risk factors to PSA
Analyzing the direct effect of risk factors to PSA, Table 5 shows T2DM has a negative direct effect with PSA

(r=−0.061; p=0.003), whereas other risk factors do not have a significant direct effect to PSA. This indicates that the presence of T2DM lowers the increase of PSA.

3.4.4. Direct effect of risk factors to testosterone
There is no direct effect from other risk factors to serum testosterone levels as shown in Table 5.

3.4.5. Direct effect of risk factors to prostate volume
In Table 5, showing the direct effect of risk factors to prostate volume, PSA has a relatively strong direct effect on prostate volume (r=0.636; p=0.001), whereas serum testosterone has a weak effect to prostate volume (r=0.246; p=0.009).

3.4.6. Indirect effect of risk factors to prostate volume
T2DM has a negative indirect effect with prostate volume (r=−0.187; p=0.005) due to its negative association with PSA.

3.4.7. Total effect of risk factors to prostate volume
There are significant and strong effects of PSA on prostate volume (c=0.636; p=0.001) whereas testosterone has a significant albeit weak effect to prostate volume (c=0.246; p=0.009) based on the total effect shown in Table 6. The

Table 3 Linier regression results of risk factors regarding prostate volume.

Variable	B	95% CI	p-Value	R^2
PSA	1.4	1.039−1.770	0.001	44.3%
Testosterone	0.024	0.008−0.041	0.005	

*Linear regression method performed to assess the most significant variables among the risk factors.
PSA, prostate-specific antigen; CI, confidence interval.

Table 4 Correlation between two risk factor variables.

Correlation	r-score	p-Value	95% CI
Two-sided correlation			
Age ↔ UTI	−0.076	0.511	−0.303−0.151
Age ↔ T2DM	−0.157	0.114	−0.351−0.038
Age ↔ Obesity	−0.187	0.094	−0.407−0.032
Age ↔ Dyslipidemia	−0.123	0.311	−0.362−0.115
Age ↔ TNF	−0.021	0.862	−0.255−0.213
Age ↔ TGF	0.023	0.818	−0.174−0.221
UTI ↔ T2DM	−0.086	0.368	−0.274−0.101
UTI ↔ Obesity	−0.018	0.861	−0.224−0.187
UTI ↔ Dyslipidemia	−0.033	0.745	−0.229−0.163
UTI ↔ TNF	0.174	0.182	−0.081−0.429
UTI ↔ TGF	0.003	0.972	−0.184−0.190
T2DM ↔ Obesity	0.191	0.005	0.057−0.325
T2DM ↔ Dyslipidemia	0.323	<0.001	0.155−0.490
T2DM ↔ TNF	−0.085	0.395	−0.279−0.110
T2DM ↔ TGF	−0.127	0.066	−0.262−0.008
Obesity ↔ Dyslipidemia	0.071	0.504	−0.138−0.281
Obesity ↔ TNF	−0.182	0.167	−0.440−0.076
Obesity ↔ TGF	−0.101	0.361	−0.317−0.116
Dyslipidemia ↔ TNF	0.154	0.121	−0.041−0.349
Dyslipidemia ↔ TGF	0.157	0.108	−0.034−0.348
TNF ↔ TGF	0.515	<0.001	0.352−0.678
One-sided correlation			
PSA ← Age	0.089	0.341	−0.094−0.271
PSA ← UTI	−0.018	0.856	−0.216−0.179
PSA ← T2DM	−0.227	0.001	−0.360−0.094
PSA ← Obesity	−0.000	0.998	−0.222−0.221
PSA ← Dyslipidemia	−0.004	0.968	−0.213−0.204
PSA ← TNF	0.050	0.700	−0.207−0.308
PSA ← TGF	−0.018	0.888	−0.266−0.230
Prostate volume ← PSA	0.636	0.001	0.471−0.802
Prostate volume ← Testosterone	0.246	0.013	0.051−0.440
Prostate volume ← Age	0.036	0.593	−0.097−0.170
Prostate volume ← UTI	−0.038	0.606	−0.183−0.107
Prostate volume ← T2DM	−0.006	0.957	−0.213−0.201
Prostate volume ← Obesity	0.082	0.296	−0.071−0.235
Prostate volume ← Dyslipidemia	0.099	0.191	−0.049−0.247
Prostate volume ← TNF	−0.019	0.852	−0.215−0.178
Prostate volume ← TGF	0.039	0.655	−0.131−0.208
Testosterone ← Age	−0.017	0.881	−0.252−0.216
Testosterone ← UTI	−0.045	0.734	−0.304−0.214
Testosterone ← T2DM	−0.171	0.101	−0.376−0.033
Testosterone ← Obesity	0.087	0.397	−0.114−0.288
Testosterone ← Dyslipidemia	−0.078	0.616	−0.383−0.227
Testosterone ← TNF	−0.014	0.918	−0.282−0.253
Testosterone ← TGF	−0.085	0.458	−0.309−0.140

PSA, prostate-specific antigen; TNF, tumor necrosis factor; TGF, transforming growth factor; UTI, urinary tract infection; T2DM, type 2 diabetes mellitus.
*Path analysis (illustration shown in Fig. 1) exhibiting the correlation between each variable to show that there may be associations between variables not previously discovered.

relationship between each independent variable and their relations to prostate volume based on table is shown below in the path analysis shown in Fig. 1.

4. Discussion

Recent observational studies concluded that age is one of the risk for the onset and progression of the disease [6]. A longitudinal study in Krimnen and Baltimore claimed that prostate size grows with a rate of 2.0%−2.5% each year in elderly males [7,8]. In this study, age with a mean sample age of 64.4 years is not significantly associated with prostate volume based on the bivariate analysis (r=0.098; p=0.377) and the total effect analysis (r=0.088; p=0.379). Even though the prevalence of BPH seems to increase with age, there are other factors with higher level of association with prostate volume. On a healthy elderly male with no comorbidities, the progression of BPH may not be that severe, making the association weaker compared to other risk factors.

Bladder outlet obstruction which increases the occurrence of urinary stasis may promote bacteria to invade the urothelium causing a urinary tract infection [9]. In this study, the presence of UTI as indicated by urinary culture result is not significantly associated with prostate volume based on the bivariate analysis (r=−0.117; p=0.294) and the total effect (r=−0.061; p=0.588). Theoretically a large postvoid residual volume of urine caused by a chronic bladder outlet obstruction would generate a predisposition to UTI. However, currently there is only little evidence based on previous studies which claims that the occurrence of UTI is associated with diseases related to bladder outlet obstruction [10]. There may not be many significant correlation found in studies, due to multiple confounding bias surrounding the pathogenesis of UTI which can't be attributed much to urinary stasis only.

A meta-analysis study in 2012 showed a significant positive association between BMI and BPH-induced lower urinary tract symptoms (LUTS) [11]. Central obesity specifically is often present alongside BPH in multiple studies [12−15]. On the contrary, several prospective studies claimed that there is no association between obesity and LUTS in BPH patients [16,17]. The insignificant association with prostate volume in this study based on the bivariate (r=0.007; p=0.953) and total effect analysis (r=0.103; p=0.380) may be due to the averagely normal BMI among the patients and the lower than average BMI of Indonesian and Asian people compared to American or European people.

An animal model study evaluating the effects of feeding the animals with a high cholesterol diet came to a conclusion that the intervention is able to induce prostatic enlargement [18]. This finding is supported by a study claiming that subjects with symptomatic BPH overall have higher low-density lipoprotein (LDL) cholesterol level and lower high-density lipoprotein (HDL) cholesterol level [19]. Oxidized LDL is believed to be able to increase secretion of growth factors and pro-inflammatory cytokines released by human stromal BPH cells where triglyceride (TG) level do

Table 5 Direct and indirect effects of evaluated risk factors.

Effect	r-score	p-Value
Direct effect to PSA		
PSA ← Age	0.089	0.344
PSA ← UTI	−0.018	0.855
PSA ← T2DM	−0.227	0.003
PSA ← Obesity	−0.000	0.998
PSA ← Dyslipidemia	−0.004	0.968
PSA ← TNF	0.050	0.707
PSA ← TGF	−0.018	0.888
Direct effect to serum testosterone		
Testosterone ← Age	−0.018	0.881
Testosterone ← UTI	−0.045	0.734
Testosterone ← DM	−0.171	0.131
Testosterone ← Obesity	0.087	0.399
Testosterone ← Dyslipidemia	−0.078	0.608
Testosterone ← TNF	−0.014	0.918
Testosterone ← TGF	−0.085	0.455
Direct effect to prostate volume		
Prostate Volume ← PSA	0.636	<0.001
Prostate Volume ← Testosterone	0.246	0.009
Prostate Volume ← Age	0.036	0.590
Prostate Volume ← UTI	−0.039	0.603
Prostate Volume ← DM	−0.006	0.957
Prostate Volume ← Obesity	0.082	0.304
Prostate Volume ← Dyslipidemia	0.099	0.208
Prostate Volume ← TNF	−0.019	0.852
Prostate Volume ← TGF	0.039	0.652
Indirect effect to prostate volume		
Prostate volume ← Age	0.052	0.436
Prostate volume ← UTI	−0.023	0.748
Prostate volume ← T2DM	−0.187	0.005
Prostate volume ← Obesity	0.021	0.768
Prostate volume ← Dyslipidemia	−0.021	0.734
Prostate volume ← TNF	0.029	0.734
Prostate volume ← TGF	−0.032	0.691

PSA, prostate-specific antigen; TNF, tumor necrosis factor; TGF, transforming growth factor; UTI, Urinary Tract Infection; T2DM, type 2 diabetes mellitus.
*Path analysis (illustration shown in Fig. 1) exhibiting the direct and indirect causative effect from each variable to prostate volume to show a cause−effect relationship.

Table 6 Total effect of risk factors to prostate volume.

Effect	Coefficient	p-Value
PSA ← Age	0.089	0.344
PSA ← UTI	−0.018	0.855
PSA ← T2DM	−0.227	0.003
PSA ← Obesity	−0.000	0.998
PSA ← Dyslipidemia	−0.004	0.968
PSA ← TNF	0.051	0.707
PSA ← TGF	−0.18	0.888
Prostate volume ← PSA	0.636	<0.001
Prostate volume ← Testosterone	0.245	0.009
Prostate volume ← Age	0.088	0.379
Prostate volume ← UTI	−0.061	0.588
Prostate volume ← T2DM	−0.193	0.165
Prostate volume ← Obesity	0.103	0.380
Prostate volume ← Dyslipidemia	0.077	0.446
Prostate volume ← TNF	0.010	0.942
Prostate volume ← TGF	0.006	0.956
Testosterone ← Age	−0.018	0.881
Testosterone ← UTI	−0.045	0.734
Testosterone ← T2DM	−0.171	0.131
Testosterone ← Obesity	0.087	0.399
Testosterone ← Dyslipidemia	−0.078	0.608
Testosterone ← TNF	−0.014	0.918
Testosterone ← TGF	−0.085	0.455

PSA, prostate-specific antigen; TNF, tumor necrosis factor; TGF, transforming growth factor; UTI, urinary tract infection; T2DM, type 2 diabetes mellitus.
*Path analysis (illustration shown in Fig. 1) exhibiting the total causative effect from each variable to prostate volume to show a complete cause−effect relationship.

not [20]. On the contrary, in this study the bivariate analysis of cholesterol (r=0.011; p=0.922) and triglyceride (r=0.077; p=0.446) as well as the total effect analysis of dyslipidemia (r=0.077; p=0.446) to prostate volume are insignificant. The results are in line with the findings from studies that fail to find the association between benign prostatic enlargement (BPE) and dyslipidemia [21,22]. This may indicate that the presence of mere dyslipidemia alone without any comorbidities as a part of metabolic syndrome is not enough to affect prostate volume.

Since 1966, researchers have already suspected a connection between BPH and metabolic abnormalities related to glucose metabolism [23]. Following the abundance of literatures evaluating the connection between T2DM and BPH, this study results in an insignificant

bivariate analysis of fasting plasma glucose (r=−0.201; p=0.068) and plasma glucose 2 h post prandial (r=−0.147; p=0.186) as well as an insignificant total effect analysis of the diagnosis of T2D and prostate volume (r=−0.193; p=0.165). However, T2D is indirectly related to prostate volume (r=−0.187; p=0.005) albeit negatively, meaning that the presence of T2D indirectly lowers the risk of prostatic enlargement. Several studies have proposed a significant independent association of T2DM to BPH caused by mechanisms such as hyperinsulinemia and insulin growth factor (IGF) affecting the receptors in stromal and epithelial cells of prostate [23,24]. Insulin resistance is claimed to be an important factor for prostate gland enhancement by some studies [25,26]. High level of insulin may alter the metabolism of sex hormones directly or indirectly through obesity [27]. It is able to increase the amount of androgen and Estrogen affecting prostatic cells by lowering sex hormone-binding globulin levels [20]. Additionally, hyperinsulinemia is able to increase catecholamines in plasma and tissue, which further promotes hyperplasia of the cells [28]. High level of glucose promote the level of calcium in smooth muscle cells and neural tissues, activating the sympathetic nervous system. This activation may increase the tone of prostatic smooth muscles which worsens existing symptoms [29,30]. Sarma et al. [31] performed a prospective study which showed that diabetes may be linked to LUTS
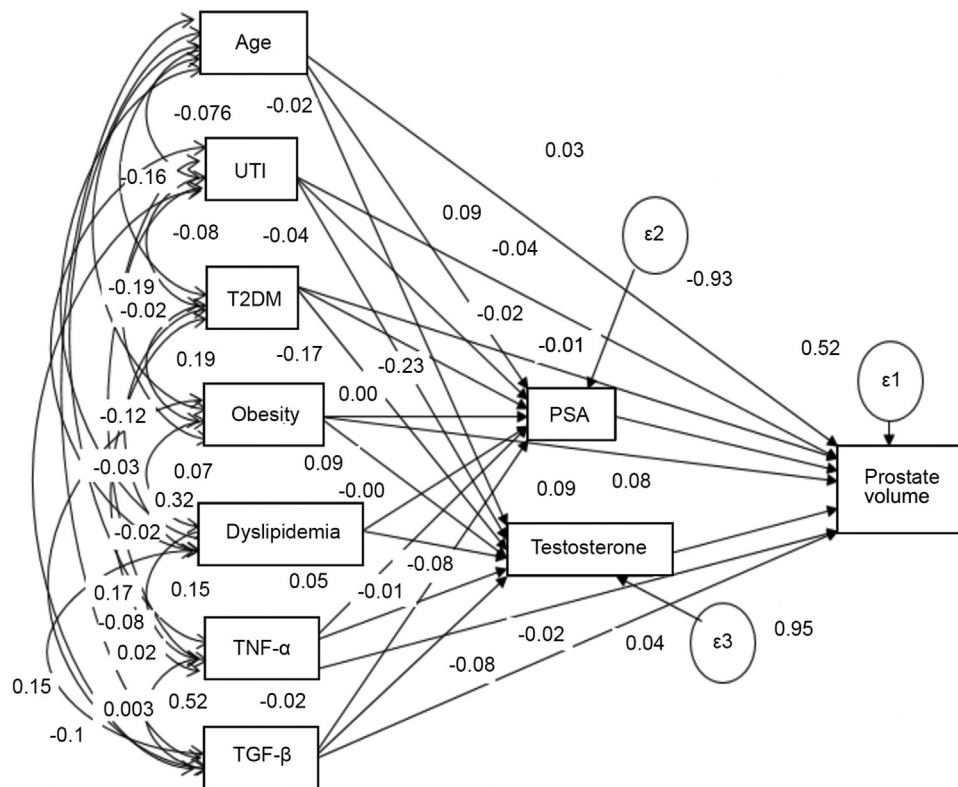
Figure 1 Risk factors for prostatic volume increase path analysis. PSA, prostate-specific antigen; TNF, tumor necrosis factor; TGF, transforming growth factor; UTI, urinary tract infection; T2DM, type 2 diabetes mellitus.

but not prostate volume. A study by Burke et al. [32] also failed to show the connection between T2DM and prostate volume. The association is found to be closely related to the dynamic components of urinary tract functions, but not prostate volume.

Aside from hormonal factors, inflammation is also considered to be responsible for contributing to the development of BPH. The inflammation process explained usually occurs in a systemic level associated with metabolic syndrome or locally in cases like prostatitis [33]. In some ways or another, inflammation has a role in the development of BPH shown by histological findings obtained from biopsies and surgeries [34]. Immune cells like macrophages and T-Cells produce TNF-α as an inflammatory response. The cytokine promotes interleukin-6 (IL-6) which induces proliferation of epithelial cells [35—38]. Previous study conducted by Duarsa et al. [39] in 2018 showed a significant difference of TNF-α expression in LUTS patients after being performed a TURP compared to non-LUTS patients. In this study, we examine the association of the cytokine with prostate volume resulting in a Bivariate analysis (r=−0.089; p=0.423) and total effect analysis (r=0.010; p=0.942). This shows that in relation to prostate volume only, the cytokine is not significantly impactful compared to other possible risk factors. A similar result can be seen with TGF-β. The bivariate analysis (r=0.000; p=0.998) and total effect analysis (r=0.006; p=0.956) reveal an insignificant association. The same study conducted by Duarsa et al. [39] also evaluated the association of TGF-β which is shown to be

significantly higher on BPH patients with LUTS after TURP. In the human body, TGF-β is able to induce proliferation in prostatic stromal cells, however it is also responsible in the pathway of growth arrest of the cells. TGF-β1 at low doses is able to induce proliferation with the help of platelet-derived growth factor (PDGF), however at high doses it is able to cause growth arrest of prostatic stromal cells [40]. This complex dose-dependent mechanism of the cytokine is the result of many systemic processes which cannot be attributed to one pathophysiology process. Thus, the independent association of the cytokine solely with prostate volume is difficult to be proven significant as seen in the results of the study.

Physiologically, unlike other organs the prostate keeps growing throughout the adult male life [41]. An ample amount of studies in the past have explored the role of testosterone in the increase of prostate volume. However, what's interesting is that as age continues to increase, the hormone is actually declining resulting in a seemingly paradoxical correlation between testosterone and BPH [33]. A theory suggests that the metabolite of the hormone, dihydrotestosterone (DHT) should be taken into account as it is able to bind with androgen receptors with greater affinity compared to testosterone [42]. It is found to be responsible in initiating prostate cell's proliferation and growth. van der Sluis and associates reported that DHT activity is highly found in prostate with BPH. In a study examining the effects of hormone replacement therapy (HRT) using testosterone, they discovered that the hormone significantly increases

prostate volume and PSA levels [43]. Several studies have concluded the association with testosterone administration during therapy [33]. Aside from DHT, estradiol, which is also derived from testosterone is also claimed to have an independent effect on prostate volume. The risk for BPH is proven to be related to serum estradiol independently in cohort studies [44]. However its association to prostate volume alone has yet to be proven. A positive association of these metabolites' precursors is seen in this study based on the logistic regression analysis ($B=0.024$; $p=0.005$) and total effect analysis ($r=0.245$; $p=0.009$). The results in this study evidently show that serum testosterone is significantly associated with and directly impacts the increase of prostate volume in BPH. On a different note, in its relation to prostate cancer, serum testosterone levels are usually found to be lower among prostate cancer patients with high Gleason score. Dell'Atti et al. [45] reported that serum testosterone levels change significantly on patients with a confirmed diagnosis of prostate cancer on the second biopsy who were previously found with atypical small acinar proliferation during the first biopsy performed 6 months prior. The next step following the findings of this study should focus on evaluating the serum level of DHT and estradiol among BPH patients and their association with prostate volume.

A study by Deori et al. [46] shows that 52% of male patients with PSA levels ranging between 1.1 and 1.5 ng/mL and 65% of male patients with PSA levels ranging between 1.6 and 2.0 ng/mL have prostate with a volume of more than 30 mL. They concluded that PSA serum of more than 1.5 ng/mL can be used as functional cut off point for screening male patients with prostate with a volume of more than 30 mL. PSA level could be used as estimator for prostate volume measurement according to a study conducted by Putra et al. [47]. In this study, we found that every 1 ng/mL PSA serum increase is related to an increase in prostate volume size by 1.4 mL. The bivariate analysis ($r=0.626$; $p=0.001$); logistic regression analysis ($B=1.4$; $p=0.001$), and total effect analysis ($r=0.636$; $p=0.001$) of PSA in association with prostate volume in this study show significant connections.

Considering the differences of results between this study and previous ones, it has become clearer that prostate volume increase in BPH results from a variety of factors which could occur together coactively or independently at different times. Upon examining the possible risk factors through a multivariate analysis followed by a path analysis, we have determined that as the end process of all risk factors that are related to each other, serum testosterone and PSA level are the major risk factors which are significantly associated to and directly impact prostate volume. Future studies regarding a similar topic building upon the results of this study should attempt to increase the sample size as this study was limited by its sample size.

5. Conclusion

Serum testosterone and PSA levels are significantly associated with prostatic volume increase among BPH patients.

Author contributions

Conflicts of interest

Acknowledgement

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