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Original Article

Tumor necrosis factor-alpha, transforming growth factor-beta, degree of lower urinary tract symptoms as predictors of erectile dysfunction in benign prostatic hyperplasia patients

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Abstract *Objective:* Erectile dysfunction (ED) is a condition of insufficient penile erection, consistently or recurrently, for sexual activity. Tumor necrosis factor-alpha (TNF-α) induces transforming growth factor-beta (TGF-β), which causes the transition of epithelial cells into mesenchymal cells that affect ED. This study aimed to evaluate the roles of TNF-α, TGF-β, degree of lower urinary tract symptoms, and prostatic volume for the presence of ED in benign prostatic hyperplasia (BPH) patients.
Methods: Our study performed an analytic observational retrospective cohort study using secondary data from four hospitals in Bali, Indonesia, including medical records and other administrative data. The sample was BPH patients with several history qualifications.
Results: Our sample was 83 respondents, ranging from 50 years to 80 years, 61 respondents with ED and 22 with non-ED. The International Prostate Symptom Score showed a significant result, which indicates that ED is more common in patients with higher International Prostate

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Symptom Score ($p=0.002$). Moreover, the TNF-α of $\geq$43.9 pg/mg and TGF-β of $\geq$175.8 pg/mL were significantly associated with the presence of ED in BPH patients ($p<0.0001$). Despite these results, prostate volume is not significant with ED ($p=0.947$).
Conclusion: TNF-α, TGF-β, and lower urinary tract symptoms severity can predict the occurrence of ED in BPH, while prostatic volume was not significant.

1. Introduction

Erectile dysfunction (ED) is a condition of insufficient penile erection, consistently or recurrently, for sexual activity [1]. According to research conducted by the Massachusetts Male Aging Study and the European Male Aging Study, the prevalence of ED is higher in the elderly [2].

Benign prostatic hyperplasia (BPH) is the most common benign tumor in male patients, which is high in elderly patients. The prevalence of lower urinary tract symptoms (LUTS) in the general population increases with aging. The incidences of ED and BPH also increase with higher life expectancy [3]. A multinational study of elderly male patients aged 50–80 years, with more than 12 000 participants in Europe and the USA, showed an association between LUTS and ED. In 83% of sexually active men, the prevalence of LUTS was 90%, while ED was 49% in total patients [4].

Recently, BPH was associated with chronic inflammation, which can induce the release of cytokines and other inflammatory factors. Increasing proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), induced the secretion of anti-inflammatory cytokines, such as transforming growth factor-beta (TGF-β) and fibroblast growth factor [5,6]. Moreover, ED might increase the production of inflammatory markers and mediators, including C-reactive protein, intercellular-1 adhesion molecule, interleukin (IL)-6, IL-10, IL-1, and TNF-α. The other effect was an increase in endothelial or prothrombotic factors, such as fibrinogen, tissue plasminogen activator, plasminogen activator inhibitor-1, and von Willebrand factor [7]. Therefore, our study aimed to evaluate the roles of inflammatory markers and mediators, such as TNF-α and TGF-β, degree of LUTS, and prostatic volume in BPH patients.

2. Patients and methods

This research is an analytic observational retrospective cohort study using medical record data and other administrative data. The data source came from a multicenter study in Denpasar, Bali, consisting of Prof. Dr. I.G.N.G. Ngoerah General Hospital, Surya Husada Hospital, Balimed Hospital, and Darma Yadnya Hospital. This research has received approval from the research ethics committee of the Faculty of Medicine, Universitas Udayana, Prof. Dr. I.G.N.G. Ngoerah General Hospital with No. 2565/UN 14.2.2VII.14/LT/2020, and the authors obtained permission from all hospitals to use the information for this publication. All respondents in this study had afforded informed consents and signed the sheet regarding their participation in this study before data collection.

The inclusion criteria in this study were BPH patients aged 50–80 years from June 2017 to December 2019. The exclusion criteria were any history of central and peripheral nervous disorders, psychiatric illness, sexually transmitted disease, previous penile or pelvic surgery, Peyronie's disease, and endocrine disease, including type 2 diabetes mellitus (DM). ED patients, which were on treatment or taking blood thinners, were also excluded. Type 2 DM patients were excluded due to chronic inflammation, which can affect TNF-α and TGF-β levels. Our study performed total sampling during the period. According to a non-paired cohort hypothesis test with $Z_{\alpha}=1.96$, $Z_{\beta}=0.842$, and a 10% drop-out rate, the minimal sample was 37 respondents.

Our study analyzed the significance of the severity of LUTS with the International Prostate Symptom Score (IPSS), prostatic volume, and TNF-α and TGF-β levels in the prostate related to the presence of ED in BPH patients. The prostate volume was evaluated through pre-operative trans-abdominal ultrasonography, while TNF-α and TGF-β levels were obtained through post-transurethral resection of the prostate. IPSS above 7 was defined as a moderate-severe degree of LUTS. The patients were diagnosed with ED when the International Index of Erectile Function score was below 14.

The cut-off point is made with the receiver operating characteristic (ROC) curve to determine normal limits in TNF-α and TGF-β. The data were analyzed for the data distribution with Kolmogorov-Smirnoff test. Then, data analysis was performed with *t*-test, Mann-Whitney, bivariant, and multivariant analysis using IBM SPSS version 23 for Windows (Chicago, IL, USA).

3. Results

The sample was collected with a non-probability consecutive sampling technique until acquired 83 respondents, 61 patients with ED and 22 non-ED. The patient characteristics are described in Table 1. The results showed a significant risk for IPSS, TNF-α, and TGF-β with $p<0.05$, to the respondents who experienced ED, while prostate volume was not significantly associated with ED with $p=0.947$.

Our study used bivariant analysis to determine the relationship between the variables with risk factors (degree of LUTS, TNF-α, TGF-β, and prostate volume) and the occurrence of ED, presented in Table 2. The cut-off points

Table 1 Characteristics of respondents.

Variable	Presence of ED		Range	*p*-Value
	Yes[a] ($n=61$)	No[a] ($n=22$)		
IPSS	13.2±8.0	7.6±3.0	2.0—35.0	0.002[b,*]
TNF-α, pg/mg	47.5±4.5	40.7±6.3	32.3—58.8	0.000[b,*]
TGF-β, pg/mL	247.2±67.7	158.1±10.7	128.9—387.5	0.000[c,*]
Prostate volume, mL	46.6±18.4	45.4±16.3	20.7—96.3	0.947[b]

ED, erectile dysfunction; IPSS, International Prostate Symptom Score; TNF-α, tumor necrosis factor-alpha; TGF-β, transforming growth factor-beta.
[a] Values are presented as mean±standard deviation.
[b] The data were normally distributed, and independent *t*-test was used.
[c] The data were not normally distributed, and Mann-Whitney *U* test was used.
* The difference was statistic significant.

of TNF-α, TGF-β from the ROC curves are shown in Fig. 1. The area under the curve (AUC), sensitivity, and specificity of TNF-α and TGF-β based on the ROC curves are summarized in Table 3.

The isolated bivariate analysis continued with multivariate tests on the degree of LUTS, TNF-α, and TGF-β and showed a significant result with $p<0.05$. TGF-β significantly affected the occurrence of ED with a positive *b*-value, shown in Table 4. There is a positive relationship between TGF-β in the prostate and ED; TGF-β of ≥175.8 pg/mL has the risk of ED 192.7 times more than that of <175.8 pg/mL, the most dominant variable.

Mean level of TNF-α in the prostate of respondents with ED was 47.5 (standard deviation [SD] 4.5) pg/mg, while with non-ED was 40.7 (SD 6.3) pg/mg. The best cut-off of TNF-α was 43.9 pg/mg with an AUC value of 0.834 (95% CI 0.70—0.96), a sensitivity of 75.4%, a specificity of 81.8%, and a *p*-value of 0.000 (Table 3). In total, 55.4% of patients have ED with TNF-α of ≥43.9 pg/mg, with odd ratio of 13.8 (95% CI 4.03—47.22), which means the higher TNF-α level in the prostate is the higher risk, about 13.8 times of ED.

The mean value of TGF-β in the prostate was 247.2 (SD 67.7) pg/mL in ED patients, while 158.1 (SD 10.7) pg/mL in non-ED patients. The results showed that the best cut-off point of prostate TGF-β was 175.8 pg/mL with an AUC value of 0.983 (95% CI 0.96—1.00), a sensitivity of 91.8%, a specificity of 95.5%, and *p*-value of 0.000 (Table 3). The presence of ED with TGF-β of ≥175.8 pg/mL was 67.5% of the total sample, while only 6% in the non-ED group with an odd ratio of 235.2 (95% CI 25.93—2132.96), which means that patients with TGF-β of ≥175.8 pg/mL had a risk of ED of 235.2 times higher than those with TGF-β of <175.8 pg/mL.

4. Discussion

Research conducted by the European Male Aging Study showed that the prevalence of ED varied from 6% to 64% depending on the differences in age subgroups and increased with age, with a mean of 30% [2]. There is a significant relationship between the degree of LUTS and the occurrence of ED, which is more common in moderate to

Table 2 Bivariate analysis of variables with risk factors for ED in benign prostatic hyperplasia patients.

Variable	Incidence of ED		OR	95% CI	*p*-Value
	Yes[a] ($n=61$)	No[a] ($n=22$)			
Degree of LUTS			4.7	1.66—13.51	0.002*
Moderate to severe (IPSS≥8)	42 (68.9)	7 (31.8)			
Low (IPSS<8)	19 (31.1)	15 (68.2)			
TNF-α			13.8	4.03—47.22	0.000*
High (≥43.9 pg/mg)	46 (75.4)	4 (18.2)			
Normal (<43.9 pg/mg)	15 (24.6)	18 (81.8)			
TGF-β			235.2	25.93—2132.96	0.000*
High (≥175.8 pg/mL)	56 (91.8)	1 (4.5)			
Normal (<175.8 pg/mL)	5 (8.2)	21 (95.5)			
Prostatic volume			0.673	0.247—1.838	0.440
Grade III (31—50 mL)	33 (54.1)	14 (63.6)			
Grade IV (51—70 mL) and V (>70 mL)	28 (45.9)	8 (36.4)			

ED, erectile dysfunction; OR, odd ratio; CI, confident interval; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; TNF-α, tumor necrosis factor-alpha; TGF- β, transforming growth factor-beta.
[a] Values are presented as *n* (%).
* The difference was statistic significant.

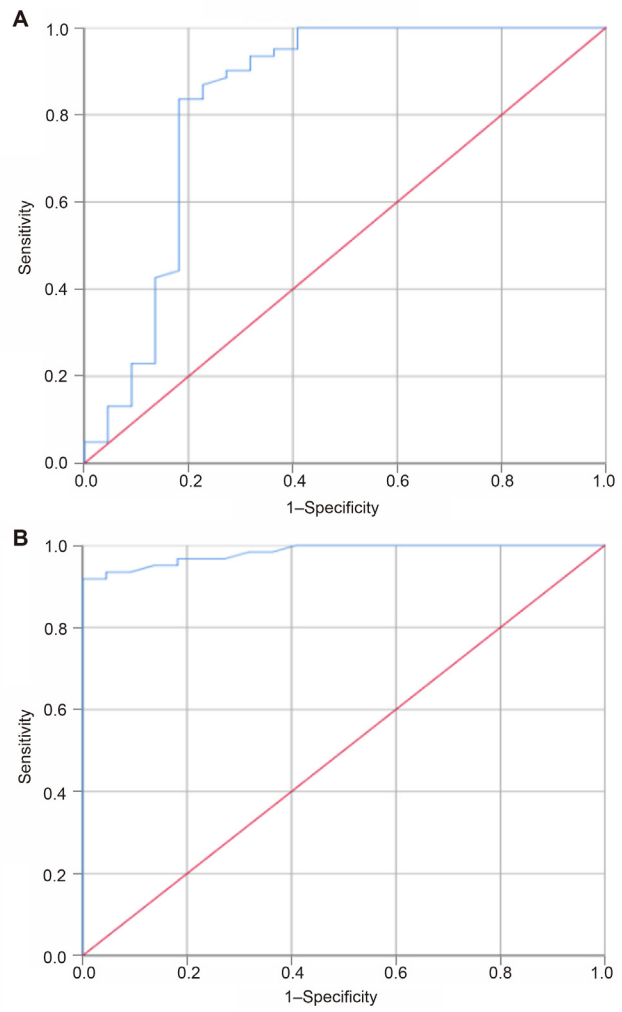

Figure 1 Receiver operating characteristic curves. (A) Tumor necrosis factor-alpha; (B) Transforming growth factor-beta.

severe degrees of LUTS [8]. Similar results were demonstrated by Yafi et al. [9], who found that the presence of LUTS was a risk factor for ED in BPH patients. Its risk was as significant as metabolic diseases, such as obesity, dyslipidemia, type 2 DM, hypertension, and cardiovascular disease.

Pathophysiological mechanisms of LUTS and ED include nitric oxide synthase (NOS) or nitric oxide (NO) and Rho-kinase (ROCK) activation pathways, inflammatory pathways, microvascular dysfunction, autonomic hyperactivity, pelvic ischemia, sex hormones, and psychological factors [10]. The development of phosphodiesterase-5 inhibitors as the first-line therapy for ED encouraged further studies on NO role in the penis and prostate. The NO was synthesized through the catalytic conversion of L-arginine to L-citrulline. NOS in mammals consists of endothelial NOS (eNOS), neuronal NOS (nNOS), and induced NOS. Particularly in the penis, the rapid relaxation of the corpora cavernosa smooth muscle and blood vessels was associated with the nNOS role and initiated by increased blood flow in the corpora cavernosa. Inversely, eNOS is predicted to have an essential role in the flaccid state [11].

Guanylate cyclase catalyzes the synthesis of cyclic guanosine monophosphate (cGMP), which is activated by NO and terminated by cGMP phosphodiesterase. Then the high level of intracellular cGMP induces the activation of protein kinase G (PKG) to inhibit calcium release, followed by smooth muscle relaxation [9]. ED can be affected by an imbalance in the NO/cGMP/PKG pathway or reduced biological NO availability, which is resulted from circulatory changes in penile tissue. Moreover, NO modulates smooth muscle tone in the normal prostate by nitrate innervation from fibromuscular stroma, glandular epithelium, and blood vessels. Particularly in the transition zone of prostate enlargement, the levels of NOS or NO and nitrate innervation are reduced and may increase the contraction of smooth muscle in the prostatic urethra and bladder neck, which leads to voiding symptoms. There was a hypothesis

Table 3 AUC value, sensitivity, and specificity of TNF-α and TGF-β.

Variable	AUC (95% CI)	Sensitivity, %	Specificity, %	*p*-Value	Cut-off
TNF-α	0.834 (0.70–0.96)	75.4	81.8	0.000*	43.9 pg/mg
TGF-β	0.983 (0.96–1.00)	91.8	95.5	0.000*	175.8 pg/mL

AUC, area under the curve; CI, confident Interval; TNF-α, tumor necrosis factor-alpha; TGF-β, transforming growth factor-beta.
* The difference was statistic significant.

Table 4 Results of multivariate analysis.

Variable	*b*-Value	Adjusted OR (95% CI)	*p*-Value
TNF-α (high: ≥43.9 pg/mg)	1.725	5.6 (0.70–44.68)	0.103
TGF-β (high: ≥175.8 pg/mL)	5.261	192.7 (14.09–2647.05)	0.000*
Degree of LUTS (moderate to severe: IPSS≥8)	−0.025	0.9 (0.11–8.10)	0.982

OR, odd ratio; CI, confident interval; TNF-α, tumor necrosis factor-alpha; TGF- β, transforming growth factor-beta.
* The difference was statistic significant.

that urothelium also expresses and releases NO in response to various stimuli, in which nNOS controls smooth muscle tone and gland activity, while eNOS regulates local vascular perfusion [12]. In addition, the association between ED and degree of LUTS is because LUTS seriously affect men's quality of life and then psychologically affect erectile function [13].

The analysis of the TNF-α cut-off point of 46.945 pg/mg has a sensitivity of 73.5% and a specificity of 95.2%, with the AUC area of 0.882 (95% CI: 0.800–0.964; $p=0.000$) [14]. A study by Carneiro et al. [15] demonstrated that TNF-α significantly increased in ED and is suspected of having an essential role in the pathophysiology of ED. The significant difference in TNF-α in the prostate between the groups with ED and non-ED means that TNF-α in the prostate is associated with the occurrence of ED, the mean TNF-α in the prostate being higher in the group with ED.

In vivo administration of TNF-α decreased vascular endothelium-dependent vasorelaxation and reduced NO through increased reactive oxygen species. In addition, TNF-α also plays a role in proatherogenic processes by inhibiting gene promoter activity and destabilizing *eNOS* mRNA in endothelial cells. Therefore, TNF-α results in the suppression of *eNOS* mRNA expression.

The TNF-α binding to TNF receptor-1 in the vascular wall causes atherosclerosis. In endothelial cells, TNF-α induces inflammatory gene transcription and activates RhoA/ROCK pathways causing increased Ca^{2+} sensitivity. ROCK activation allows TNF-α to increase the junctional permeability, and induces rearrangement and apoptosis of actomyosin [15].

Another hypothesis said that BPH was caused by an immune-induced inflammatory disease, according to the association between chronic inflammation and BPH. The role of TNF-α is a pro-inflammatory cytokine produced by macrophages and T cells and induces IL-6, produced by stromal and epithelial cells of the prostate, causing the proliferation of epithelial cells [14,16].

TNF-α can also induce TGF-β by the transition of epithelial cells to mesenchymal cells. TGF-β causes fibroblast migration and proliferation, increases collagen and fibronectin synthesis, and decreases extracellular matrix degradation associated with fibrosis [17]. The TGF-β cut-off point of 207.63 pg/mL has a sensitivity of 73.5% and a specificity of 85.7%, with the AUC of 0.86 (95 % CI: 0.766–0.953; $p=0.000$). TGF-β of above 207.63 pg/mL was considered a high level [14]. There was a significant difference between TGF-β levels in the prostate in the ED and the non-ED group. The higher TGF-β level in the prostate significantly increases the occurrence of ED.

TGF-β, an essential cytokine, is an important factor for the proliferation inhibition and alteration of apoptotic mechanisms. TGF-β consists of three different isoforms, which are TGF-β1, TGF-β2, and TGF-β3. TGF-β1 is secreted by basal epithelial cells and causes inhibition of basal cell proliferation by an autocrine mechanism. Inversely, TGF-β2 from smooth muscle in the prostate causes paracrine modulation through the epithelium receptors. Thus TGF-β helps basal cell regulation by the paracrine mechanism in the prostate gland while inhibiting the proliferation of cells and inducing apoptosis in the prostatic epithelium [16].

Our study in prostate volume showed the highest number of ED occurring at Grade III based on atlas of radiologic measurement, but statistical results of prostate volume did not affect ED. The study by Partin et al. [18] showed a similar result, which supports that the prostate volume does not affect the presence of ED.

Duarsa et al. [14] found that TNF-α levels had a low correlation to prostate volume development ($r=0.392$; $p<0.001$). Each 1 pg/mg increase in TNF-α increased prostate volume by 0.28 mL ($p=0.011$). Furthermore, an increase of 1 pg/mL TGF-β increased prostate volume by 0.015 mL ($p<0.001$).

Prostate volume has been associated with the progression of bladder outlet obstruction. An increased prostate volume will cause the lumen of the prostate to narrow, resulting in urine flow obstruction [19]. The research conducted by Hossain et al. [20] showed that prostate volume and intravesical prostatic protrusion affect the severity of symptoms synergistically. Intravesical prostatic protrusion is a morphological change that occurs because the middle lobe of the prostate gland has grown, which appears as a form of protrusion of the prostate that starts from the neck of the urinary bladder until it reaches the bladder, thereby inhibiting the flow of urine that will come out through the neck of the bladder and causing increased activity in the bladder during the process of urination that will cause symptoms or disturbances when urinating; this term is better known as LUTS [19,20]. Bassey and Isiwele [21] reported an insignificant relationship between the degree of IPSS score and prostate volume in 61 patients; therefore, the size of prostate volume would not determine the severity of LUTS in men with BPH.

Our study brings the analysis of inflammatory markers and mediators, which are statistically significant for the presence of ED in BPH patients, from the multicenter samples in Bali to elaborate on the outcome in the larger community. Even though our study was held in a multicenter study in Denpasar, Bali, our study has limitations on the study duration, which was no longer than 3 years due to the pandemic COVID-19 condition, which also postponed the process of collecting and analyzing data. Moreover, our patients were relatively homogenous, which were dominantly Balinese people. Therefore, the results might be different in different populations and places. We encourage all academicians to conduct further research with massive sample data and heterogeneous patients.

5. Conclusion

The moderate-severe degree of LUTS (IPSS≥8), high level of TNF-α (≥43.9 pg/mg), and high level of TGF-β (≥175.8 pg/mL) were the predictors of ED in BPH patients. TGF-β of ≥175.8 pg/mL is the most dominant variable in the presence of ED in BPH patients.

Author contributions

Study concept and design: Gede W.K. Duarsa.
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Data analysis: Gede W.K. Duarsa, Pande M.W. Tirtayasa.

Drafting of manuscript: Gede W.K. Duarsa, Ronald Sugianto.
Critical revision of the manuscript: Tjokorda G.B. Mahadewa.

Conflicts of interest

The authors declare no conflict of interest.

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