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Age, lipid profile, testosterone, and prostate-specific antigen are predictors of erectile dysfunction in benign prostatic hyperplasia

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Abstract---Erectile dysfunction (ED) is a condition with a higher prevalence in the elderly. A multinational survey of elderly men conducted in America, France, Germany, Italy, the Netherlands, Spain, and England showed an association with ED in >12,000 men aged 50-80. There is an increasing prevalence of hypercholesterolemia and hypertriglyceridemia in men with ED. Testosterone deficiency is

the most common hormonal cause of ED and has recently been considered a global health problem associated with cardiovascular morbidity and mortality. Prostate-specific antigen (PSA) affects prostate volume associated with high testosterone. This study aims to determine age, lipid profile, testosterone, and PSA levels are predictors of ED incidence in BPH patients. Using analytic observational retrospective cohort design, years) with $p=0.003$, OR 0.2 (95% CI: 0, 07-0.58) which means that there is an increase of 0.2 times ED at age >60 years, lipid profile obtained $p=0.016$, OR 3.7 (CI95%: 1.22-11.45) which means an increase in cholesterol lipid profile total > 200 mg/dL/ TG > 150 mg/dL occurred 3.7 times ED, testosterone $p=0.049$ OR 3.5 (95% CI: 0.95-13.44) means low testosterone levels <193 pg/ml cause ED 3.5 times, and PSA $p = 0.020$, OR 0.3 (95% CI: 0.45-3.33) which means the level of >4 pg/mg causes ED 0.3 times. This conclusion is >60 years of age, high lipid profile, low testosterone levels, and increased PSA can be used as predictors of ED

Keywords---BPH, age, lipid profile, testosterone, PSA.

Introduction

Benign prostatic hyperplasia (BPH) is a common benign tumor that develops in men and is troubling in elderly patients. Erectile dysfunction is a condition with a higher prevalence in older people based on surveys from the Massachusetts Male Aging Study (MMAS) and European Male Aging Study (EMAS) and in $>12,000$ men aged 50-80 years in America, France, Germany, Italy, the Netherlands, Spain, and the UK (Corona *et al.*, 2010). A Canadian primary care physician study found that ED was independently associated with cardiovascular disease. However, this study failed to establish dyslipidemia as an independent risk factor. Smith *et al.* reported a high prevalence of newly diagnosed hypercholesterolemia and hypertriglyceridemia in men with ED (Smith *et al.*, 2007). In a large cohort study of 272,325 patients with ED, the prevalence of hyperlipidemia was 20.2%. In addition, ED has a significantly higher prevalence in individuals with dyslipidemia, coronary artery disease, and metabolic syndrome. In another study, the prevalence of ED was significantly higher in patients who had hypercholesterolemia and hypertriglyceridemia (Pittaras *et al.*, 2015).

Testosterone deficiency is the most common hormonal cause of ED and has recently been considered a global health problem associated with cardiovascular morbidity and mortality (Grossmann and Wu, 2014). Testosterone is an essential factor for maintaining vascular integrity. Testosterone acts via an androgen receptor-mediated mechanism or vascular endothelial growth factor (AR/VEGF) and promotes angiogenesis, stimulating endothelial cell proliferation. Furthermore, testosterone deprivation may directly affect endothelial function and the differentiation, maturation, migration, and homing of circulating endothelial progenitor cells (EPCs) via the availability of nitric oxide (NO), a crucial marker of endothelial function. According to research by Omar *et al.*, there was significant hypogonadism and ED and increased expression of EPCs and endothelial microparticles in patients with vasculogenic ED (Omar *et al.*, 2017).

Prostate-specific antigen (PSA) is synthesized by prostate epithelial cells and is organ-specific but not cancer-specific. Serum PSA levels increased in inflammation after manipulation of the prostate (prostate biopsy or TURP), acute urinary retention, catheterization, prostate malignancy, and advancing age. Serum PSA can be used to predict the disease course of BPH; in this case, if the PSA level is high, it means: (a) faster prostate volume growth, (b) complaints due to BPH/urine emission rate are worse, and (c) more prone to acute urinary retention (Mochtar *et al.*, 2015). In this condition, researchers are interested in knowing age, lipid profile, testosterone, and PSA levels are predictors of ED incidence in BPH patients.

Materials and Methods

This research is a retrospective cohort analytic observational analysis using secondary data and other administrative data derived from medical records of Sanglah Hospital, Balimed Hospital Denpasar, Surya Husada Hospital Denpasar, and Darma Yadnya Hospital Denpasar, all patients diagnosed with BPH during June 2017 to December 2019. Ethics in this study with No. 2565/UN 14.2.2VII.14/LT/2020 from the research ethics committee of the Faculty of Medicine, Udayana University/ Sanglah Central General Hospital Denpasar. Inclusion criteria in this study: (1) adult patients aged 50-85 years, (2) Signed *informed consent*, and (3) diagnosed with benign prostate hyperplasia. Exclusion criteria: (1) endocrine disease other than type 2 DM, (2) history of sexually transmitted diseases, (3) history of psychiatric illness, (4) history of central and peripheral nervous disorders, (5) history of previous penile or pelvic surgery, (6) Peyronie's disease, (7) in the treatment of erectile dysfunction, (8) taking blood thinners. Data analysis using SPSS Version 23 for windows with t-test, Mann Whitney, bivariate and multivariate test.

Results and Discussions

The research sample came from an affordable population of 83 respondents who met the inclusion criteria using a non-probability-consecutive sampling technique until the sample size was met. The data is described based on the mean and standard deviation in Table 1.

Table 1 Characteristics of respondents

Variable	Incidence of erectile dysfunction		Min-max	p
	Yes (n=61)	No (n=22)		
Age (years)	66.4±8.2	58.9±5	50-84	<0.001**
Total cholesterol	178.2±46.6	166.7±33.5	81-295.4	0.290*
Triglycerides	122.6±49.3	101.2±41.8	46-272.5	0.063**
Testosterone	372.9±217.4	344.9±139.3	52.2-863.3	0.765**
PSA	9.27±8.71	4.95±5.18	0.22-43.20	0.009**
PSA Density	0.15 ±0.12	0.17±0.19	0.01-0.95	0.959**

*Independent t-test

** Mann Whitney u test

† Significant

In the results of the comparison between respondents who experienced ED and not ED, it was known that $p < 0.05$ on the results of age and PSA which was statistically significant while total cholesterol $p = 0.290$, triglycerides $p = 0.063$, testosterone $p = 0.765$ and PSA density $P = 0.959$ was not significant. In this study, a bivariate analysis was carried out to determine the relationship between age, lipid profile, testosterone levels, and PSA as predictors of the incidence of ED in BPH patients. $p=0.003$ with OR 0.2 (95% CI: 0.07-0.58) which means age >60 years causes ED 0.2 times, lipid profile obtained $p=0.016$ OR 3.7 (CI: 1.22 -11.45) which means a high lipid profile can cause erectile dysfunction as much as 3.7 times. On testosterone, it was found that $p = 0.049$ OR 3.5 (IK: 0.95-13.44), which means that low testosterone levels can cause erectile dysfunction as much as 3.5 times. At PSA $p = 0.020$ OR 0.3 (95% CI: 0.45-3.33) which means PSA levels >4 pg/mg caused DE 0.3 times while PSA density was not statistically significant with $p=0.687 > 0.05$.

Table 2 Bivariate analysis of variables with risk factors for erectile dysfunction in BPH. Patients

Variable	Incidence of erectile dysfunction		OR	95% CI	P*
	Yes (n=61)	No (n=22)			
Age	60 years	49 (59%)	0.20	0.07-0.58	0.003
	< 60 years old	12 (14.5%)			
Lipid profile	High (total cholesterol > 200/TG > 150)	32 (38.6%)	3.7	1.22-11.45	†0.016
	Normal (Cholesterol < 200/TG < 150)	5 (6%)			
Testosterone	Low (<193 pg/ml)	29 (34.9%)	3.5	0.95-13.44	†0.049
	Normal (193-740 pg/ml)	17 (20.5%)			
PSA	> 4 /mg	40 (48.1)	0.30	0.11-0.83	0.020
	≤4pg/mg	8 (9.6%)			
PSA Density	> 0.15 pg/mg	21 (25.3%)	1.23	0.45-3.33	0.687
	0.15 pg/mg	14 (16.8%)			

*Chi-Square; † Significant

The results of the multivariate test on age, lipid profile, testosterone levels, and PSA in this study using logistic regression test all variables obtained in table 3 with the results of a significant factor playing a role in ED is age with $p = 0.027 < 0.05$ which means there is a significant relationship Positive relationship between old age > 60 years causes ED in BPH as much as 0.27 times and is the most dominant variable causing ED in BPH.

Table 3. Results of multivariate analysis

Variable	B	Adj OR	95% CI	p
old age > 60 years	-1,293	0.27	0.08-0.86	†0.027
High profile lipids	1,892	6.6	0.52-84.19	0.145
Low testosterone	1.366	3.9	0.23-66.16	0.344

high PSA	-0.728	0.48	0.16-0.15	0.208
High-density PSA	0.251	1.28	0.44-3.75	0.647

† Significant

The results of the study were 83 respondents, age of 61 respondents with ED with a mean of \pm SD (66.4 \pm 8.2 years), while there was non-ED in 22 respondents with a mean of \pm SD (58.9 \pm 5 years) and found a significant difference between age ED and Non-ED. *Massachusetts Male Aging Study* (MMAS) and the *European Male Aging Study* (EMAS) state that ED is a condition with a higher prevalence in older people. MMAS shows the prevalence of mild to moderate ED in 52% of men aged 40-70 years. ED strongly correlates with age, health status, and emotional function (Corona *et al.*, 2010)

Aging and androgens are two risk factors that play a role in developing BPH. Prostate tissue repair in the transition area is characterized by (1) hypertrophic basal cells; (2) changes in the luminal secretion of cells leading to calcification, duct obstruction, and inflammation; (3) lymphocytic infiltration with the production of proinflammatory cytokines; (4) increased radical oxygen production of species that damage epithelial and stromal cells; (5) increase the production of fibroblasts and basic TGF- causing stromal proliferation, transdifferentiation, and production of extracellular matrix; (6) altered autonomic innervation reduces relaxation and leads to high adrenergic tone and (7) altered neuroendocrine cell function and release of neuroendocrine peptides (Madersbacher, Sampson and Culig, 2019).

Erectile dysfunction is highly prevalent in the elderly, but several studies have examined the prevalence of ED in men aged <40 years. It was found that ED in young men is caused mainly by psychogenic factors. Signs of ED caused by psychogenic factors are sudden onset, good quality of spontaneous erection or self-stimulation, and previous psychogenic problems. Management of ED at a young age remains a concern because ED can be an early sign of severe organic disease (Yafi *et al.*, 2016).

The study results were based on blood cholesterol levels, the lowest value was 81, and the highest was 295.4. The blood cholesterol of respondents with erectile dysfunction was obtained with a mean of 178.2 (SD: 46.6), while erectile dysfunction did not occur with a mean of 166.7 (SD: 33.5). The blood triglycerides of respondents with erectile dysfunction were obtained with a mean of 122.6 (SD: 49.3), while erectile dysfunction did not occur with a mean of 101.2 (SD: 41.8). DE and LUTS in patients with BPH have a high prevalence in elderly men and have similar risk factors such as hypertension and cardiovascular disease, smoking, obesity, dyslipidemia, diabetes mellitus, metabolic syndrome, stress, anxiety, and depression (Seftel, Sun and Swindle, 2004).

Erectile dysfunction is independently associated with cardiovascular disease. Smith (2007) reported a high prevalence of newly diagnosed hypercholesterolemia and hypertriglyceridemia in men with ED (Smith *et al.*, 2007). The results of this study found that there was a relationship between lipid profiles based on total cholesterol and triglyceride levels with erectile dysfunction. A high lipid profile with erectile dysfunction was obtained (38.6%) with an OR value of 3.7 (CI: 1.22-

11.45), meaning that a high lipid profile could cause erectile dysfunction as much as 3.7 times.

In a large cohort study of 272,325 patients with ED, the prevalence of hyperlipidemia was 20.2% (Seftel, Sun and Swindle, 2004). In addition, ED has a significantly higher prevalence in individuals with dyslipidemia, coronary artery disease, and metabolic syndrome. In another study, the prevalence of ED was significantly higher in patients who had hypercholesterolemia and hypertriglyceridemia (Pittaras *et al.*, 2015). Several other studies have shown that lifestyle modification and pharmacotherapy on cardiovascular risk factors improve sexual function in men with ED. However, further research is needed to determine whether lifestyle and exercise modifications can prevent or treat ED (Gandaglia *et al.*, 2014).

The consensus results of the 2015 Fourth International Consultation on Sexual Medicine, risk factors for ED in men and women are biological, psychological, and socio-cultural conditions. Biological factors that influence the occurrence of ED in men are age, diabetes mellitus, obesity, hypertension, smoking, testosterone levels in the blood, urinary tract infections, and chronic diseases (McCabe *et al.*, 2016).

The results based on the respondents' blood testosterone levels with erectile dysfunction were obtained with a mean \pm SD (372.9 ± 217.4 mg/dL), while erectile dysfunction did not occur with a mean \pm SD (344.9 ± 139.3) in patients with BPH. Testosterone deficiency is the most common hormonal cause of ED and has recently been considered a global health problem associated with cardiovascular morbidity and mortality (Grossmann and Wu, 2014). The results showed a significant relationship between low testosterone levels and erectile dysfunction. Low testosterone levels were obtained as much as 26.5% with an OR of 3.5 (IK: 0.95-13.44), meaning that low testosterone levels can cause erectile dysfunction as much as 3.5 times.

In Omar *et al.* (2017) research, testosterone is essential for maintaining vascular integrity. Testosterone acts via an androgen receptor-mediated mechanism or vascular endothelial growth factor (AR/VEGF) and promotes angiogenesis, stimulating endothelial cell proliferation. Furthermore, testosterone deprivation may directly affect endothelial function and the differentiation, maturation, migration, and homing of circulating endothelial progenitor cells (EPCs) via the availability of nitric oxide (NO), a crucial marker of endothelial function. The study by Omar *et al.* showed a significant association between hypogonadism and ED and an increased expression of EPC and endothelial microparticles in patients with vasculogenic ED (Omar *et al.*, 2017).

The prostate is an organ that depends on male hormones. Therefore, male hormones are crucial in maintaining the prostate's growth, reproduction, and function. Testosterone and DHT, in particular, play an essential role in the prostate cell cycle. In prostate cells, testosterone is converted by 5AR2 to DHT, an androgen that is five times more active than testosterone. Elevated DHT concentration in prostate tissue is one of the representative clinical markers of BPH. DHT binds to the androgen receptor (AR) and acts biologically as a ligand-

reactive transcription factor. In addition, androgen receptor coactivators, such as SRC-1, interact with AR to regulate AR transactivation (Rosen *et al.*, 2003; Choi *et al.*, 2019).

Consequently, the binding between DHT, AR, and SRC-1 increases PSA and growth factor expression in prostate cells. In men with decreased testosterone levels due to aging, The expression of 5AR2 and AR is increased to control endocrine homeostasis (Nicholson and Ricke, 2011). As a result, an increase in DHT and AR, which in turn plays a crucial role in the development of BPH. Meanwhile, 5-alpha reductase inhibitors that block the conversion of testosterone to DHT are commonly used to attenuate BPH symptoms. Finasteride is one of the 5-alpha reductase inhibitors currently used in treating BPH. However, finasteride is reported to have some side effects (Choi *et al.*, 2019).

In this study, the results obtained for PSA levels >4 pg/mg caused ED 0.3 times, $p=0.020$ OR 0.3 (95% CI: 0.45-3.33). PSA levels and testosterone levels affect prostate volume. For every one ng/ml increase in PSA value, there will be an enlargement of the prostate volume by 1.4 ml ($p < 0.001$), and for every one ng/ml increase in testosterone levels, there will be an enlargement of the prostate volume by 0.024 ml ($p = 0.005$). PSA and testosterone levels are the most influencing factors for prostate volume (Bernard, Scior and Do, 2012). The growth of prostate gland volume can be predicted based on PSA levels. The higher the PSA level, the faster the prostate growth rate. The average prostate volume growth rate each year at PSA levels of 0.2-1.3 ng/dl is 0.7 mL/year, while at PSA levels of 1.4-3.2 ng/dl is 2.1 mL/year. Years and a PSA level of 3.3-9.9 ng/dl is 3.3 mL/year. Serum PSA can be elevated in the event of acute urinary retention, and levels gradually decrease, especially after 72 hours of catheterization (Madersbacher, Sampson and Culig, 2019).

PSA examination with digital rectal is superior to digital rectal examination alone in detecting the presence of prostate carcinoma. Therefore, at the age of over 50 years or over 40 years (in the high-risk group), a PSA examination becomes very important to detect the possibility of prostate carcinoma. If the PSA level is >4 ng/ml, a prostate biopsy is considered after discussion with the patient (Madersbacher, Sampson and Culig, 2019). The weakness of this study is the short duration of the study. This study used subjects in specific populations in certain places; hence, this study's results cannot describe the same conditions in different populations and places. Further research is needed to improve this study's results using larger sample size and cohort perspective.

Conclusion

Age > 60 years, total cholesterol lipid profile > 200 mg/dL/TG > 150 mg/dL, low testosterone <193 pg/ml and elevated PSA >4 pg/mg can be used as a predictor of ED in BPH.

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currently accepting manuscripts for upcoming issues based on original qualitative or quantitative research.

Ethical Approval

This research has received approval from the research ethics committee of the Faculty of Medicine, Udayana University/ Sanglah Central General Hospital Denpasar with No. 2565/UN 14.2.2VII.14/LT/2020, and all respondents in this study had obtained informed consent and signed the sheet regarding their participation in this study before data collection

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