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Correlation between testosterone level, serum prostate-specific antigen level, and diabetes mellitus with grade inflammation of the prostate



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ABSTRACT

Introduction: Benign Prostate Hyperplasia is the most common degenerative disease in men, characterized by an increase in prostate epithelial and stromal cells, that leads to impairment of urinary flow. The risk factor of BPH was uncertain, some studies showed that reduced testosterone level leads to BPH. Evidence suggests that modifiable factors may influence the risk of BPH, such as diabetes mellitus, PSA level, and inflammation. Pro-inflammatory mediators regulate the proliferation and differentiation of prostate tissue. This study aimed to determine correlation between testosterone level, PSA level, and blood glucose and grade inflammation of prostate.

Methods: An analytic cross sectional study was done in 72 BPH patients of Sanglah Hospital Urology clinic. All samples underwent PSA level, testosterone, blood glucose measurement before transurethral resection of the prostate procedure. The grade inflammation of

prostate was then determined by pathologist. All data obtained were analyzed by univariate, bivariate, and multivariate analysis using SPSS version 20.0 statistical software.

Results: Seventy-two samples included in this study with age range from 50 to 84 years old. Grade inflammation of prostate was significantly correlated with PSA level with p-value 0,006 and prevalence ratio (PR) 2 with 95% CI (1.129-3.544). Testosterone level was not significantly correlated with grade inflammation of prostate (PR 1.233; 95% CI: 0.804-1.891; p=0.334). Blood glucose level and grade inflammation of prostate showed PR 1.943 with 95% CI (1.542-2.447) with p-value 0.058, but after multivariate analysis the p-value was 0.022.

Conclusion: Grade inflammation of prostate was significantly correlated with blood glucose level and serum PSA level.

Keywords: BPH, grade inflammation prostate, PSA, testosterone, diabetes mellitus

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INTRODUCTION

Benign prostate hyperplasia (BPH) is one of the most common male degenerative diseases. The risk of BPH increases with age, and around 70% of men over the age of 60 years were diagnosed with it. According to WHO data, the prevalence of BPH is between 0.5-1.5 per 100,000 worldwide. In Sanglah General Hospital, there were 103 patients with BPH in 2013 who underwent surgery, among 1161 patients undergoing urologic surgery. The risk factors for BPH are still unclear, some studies have led to predisposition of decreased testosterone levels. Diabetes and PSA level are also associated with prostate hyperplasia. Sjahmuhidajat in 2011 stated that change of testosterone-estrogen balance occurred in elderly because of reduced testosterone production and testosterone was converted into estrogen in peripheral adipose tissue.¹

Daniels, et al. found that prostatitis occurred in 83% patients with BPH. Prostatitis increased the risk of BPH eight times higher.² Reduce et al.

suggested inflammation occurred in 78,4% BPH patients, while 21,6% without.³

Elevated Prostate-specific antigen (PSA) level turned out to be substantial marker for prostate diseases, such as BPH.⁴ Some studies showed that grades inflammation of prostate tissue positively correlated with PSA level. Inflammation increased PSA serum level as a result of prostate duct damage which secreted PSA from the lumen of prostatic ducts and acini to interstitial tissue.⁵

Bourke and Griffin were the first who showed the relationship between diabetes mellitus and BPH, based on data that stated the highest prevalence male underwent prostatectomy was diagnosed with DM. Lots of evidence regarding the role of insulin resistance that secretes various cytokines through the inflammatory process (low-grade chronic inflammation), resulting in prostate enlargement.⁶

From the explanation above, it can be concluded that the degree of inflammation in patients with

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BPH is associated with or influenced by many factors. We tried to investigate whether an increase in the degree of inflammation in BPH patients was associated with testosterone levels, increased serum PSA levels and diabetes mellitus.

METHODS

A cross sectional study was done at Urology Department in Sanglah Hospital Denpasar in July 2016 to July 2017. The target population was all male patients with BPH who came to the Urology polyclinic or were hospitalized at Sanglah General Hospital. The inclusion criteria were patients with prostate enlargement based on ultrasound examination. Exclusion criteria were patients who refused to participate in the study, had undergone prostate surgery before, or patients with malignancy. The selection of samples in this study was by consecutive sampling technique with a sample size of 37 samples.

A total of 72 men met the study inclusion criteria within the study period. Blood collected from samples for blood glucose, serum PSA, and testosterone examination. Transabdominal ultrasound (TAUS) or transrectal ultrasound (TRUS) was done to determine prostate volume by urologist. Prostate tissue was examined after TURP to determine the grade of inflammation. Inflammatory aspects associated with prostate tissue can be classified using a hypothetical histologic grading on the basis of extension of inflammatory cells.⁷ Grade 0 defined as no inflammatory cells, grade 1 finding was scattered inflammatory cell infiltrate without nodules, grade 2 was nonconfluent lymphoid nodules, and grade 3 was defined as large inflammatory area with confluence.

Analysis of data was carried out using SPSS. Data collected were analyzed with univariate analysis, bivariate analysis, and multivariate analysis. Univariate analysis was used to feature the characteristic of subjects, while bivariate analysis was used to determine association between variables. Multivariate analysis was done to investigate the

pure effect of one independent variable as a risk factor for the occurrence of dependent variables after taking into account the other independent variables, including direct influence or indirect influence on dependent variables.

RESULTS

Baseline characteristics

A cross sectional analytic study was done to male patients with benign prostate hyperplasia. Total samples in this study were 72 patients. The age of the patients in this study was 50 to 84 years old. The mean of body mass index was 22,91 (2.91 SD). The mean of blood glucose and cholesterol were 132.72 (47.13 SD), and 149.44 (230.08 SD) respectively. While PSA and testosterone level in this study were 10.67 (11.67 SD) and 399.35 (169.69 SD) (Table 1).

Relationship between grade of prostate inflammation, blood glucose level, prostate-specific antigen level, and testosterone level

As shown in Table 2 increased blood glucose level positively correlated with grade of prostate inflammation, but failed to show a statistical significance, with p-value 0.058; prevalence ratio 1.943 (CI 95%: 1.542-2.447). Level of serum PSA was significantly correlated with grade of prostate inflammation with p-value 0.006; PR 2 (CI 95%: 1.129-3.544), but not with testosterone level, p-value 0.334; PR 1.233 (CI 95%: 0.804-1.891 CI).

Multiple regression analysis of correlation between grade of prostate inflammation and other clinical and laboratory parameters

As shown in table 3, in multiple adjusted linear regression analysis, grade of prostate inflammation was significantly associated with blood glucose level (p=0.022) and PSA level (p= 0.042). However, testosterone level and others parameters were not related to grade of prostate inflammation.

Table 1 Baseline characteristics of the BPH samples

Variable	Mean	Standard Deviation	Range
Age (years old)	64.51	8.41	50 - 84
BMI (kg/m ³)	22.91	2.91	16.70 – 28.51
Blood glucose (gr/dl)	132.72	47.13	89 – 357
Cholesterol (mg/dl)	149.44	230.08	46 – 1761
PSA (ng/dl)	10.67	11.67	0.22 – 60.36
Prostate Volume (cc)	44.57	17.77	20.68 – 97.50
Testosterone (kg/ m ²)	399.35	169.69	52.20 – 863.30

BMI, body mass index; PSA, prostate-specific antigen

Table 2 Relationship between blood glucose level, PSA level, testosterone level and grade of prostate inflammation

Parameters	Grade of Prostate Inflammation		P	PR (95% CI)
	High grade (%)	Low grade (%)		
Blood glucose				
≥ 200	5.6	0	0.058	1.943 (1.542-2.447)
< 200	49.6	45.8		
PSA level				
High	41.6	20.8	0.006	2 (1.129-3.544)
Low	12.6	25		
Testosterone				
≥ 399.35	29.1	19.4	0.334	1.233 (0.804-1.891)
<399.35	25	26.5		

Table 3 Multiple regression analysis of correlation between grade of prostate inflammation and other clinical and laboratory parameters

Parameters	Estimate (β)	Standardized Coefficients	P value
Age (years)	0.003	0.051	0.676
BMI (kg/m ³)	-0.023	-0.133	0.260
Blood glucose (gr/dl)	-0.003	-0.304	0.022
Cholesterol (mg/dl)	0.000	0.098	0.402
PSA (ng/dl)	-0.010	-0.242	0.042
Testosterone (kg/ m ²)	-0.001	-0.197	0.095
Prostate volume (cc)	-0.002	-0.063	0.609

BMI, body mass index; PSA, prostate-specific antigen

DISCUSSION

Prostate Specific Antigen (PSA) is a protease that is produced by most prostate epithelial cells, so that PSA is considered a specific examination for the prostate organ. Increased serum PSA levels are important markers of various prostate diseases, including BPH, prostatitis, and prostate cancer.⁴

The average PSA (ng/dl) level in this study was 10.67 with a standard deviation of 11.6. Research by Singh et al. (2017) found that PSA levels in BPH patients were 4-10 ng/ml, while the study by Mosli et al. stated that the average PSA in BPH patients was 6.87 ng/ml. The Shetty et al. study stated that PSA levels in BPH patients were 4.01-10 ng/dl, although there were 4 patients with PSA levels of 20-100 ng/dl. In this study the cut-off value of PSA to detect malignancy was 19.5 ng/dl with a sensitivity of 96.3%, specificity of 86.2%.⁸⁻¹⁰

Level of serum PSA was significantly correlated with grade of prostate inflammation with p-value 0.006; PR 2 (1.129-3.544 CI). The normal value of PSA is below 4 ng/ml.¹¹ Some studies show that the level of inflammation in prostate tissue is positively correlated with PSA values. Inflammation

increased PSA serum level as a result of prostate duct damage which secreted PSA from the lumen of prostatic ducts and acini to interstitial tissue.⁵ One of the earliest studies of PSA levels with histological inflammation was carried out by Brawnet al. with the conclusion that inflammation in the prostate causes an increase in serum PSA levels. The study by Irani et al. shows an association between aggressive inflammation and increased PSA levels. Simardi et al. concluded that the extent of inflammation correlated with an increase in serum PSA. Kandirali et al. modified the grading method of Irani et al. and showed a broad and aggressive relationship of inflammation in the prostate with increased levels of PSA and PSA density (PSAD) and decreased levels of free PSA (fPSA). Gui-zhong et al. uses the classification of prostatitis from the National Institute of Health (NIH), showing the extent and degree of inflammation associated with elevated serum PSA levels.⁵

The average blood sugar level (gr/dl) in this study was 132.72 with a standard deviation of 47.13. In a review of studies conducted by Breyer

et al. it was shown that hyperglycemia and insulin resistance increased the risk of BPH and LUTS. In hyperglycemia states various condition occurred, such as increase of sympathetic tone, stimulation of prostate tissue growth by insulin and associated trophic factors, changes in expression of sex steroid hormones, induction of systemic inflammation and oxidative stress.¹² Ferreira et al. (2014) in their study reported that DM associated with LUTS, mainly the symptom of nocturia.¹³ Whereas Qu et al. (2014) reported that DM (characterized by 7 mmol/l fasting blood sugar, or 2-hour postprandial blood sugar 110 mg/dl) had a greater prostate volume (41.18 vs. 51.52 cm, $p = 0.005$) and increased PSA levels (1.94 vs. 3.23, $p = 0.013$).¹⁴

Several hypotheses have been developed to explain the relationship between DM and BPH. IGF axis dysregulation (insulin growth factor) is associated with BPH and prostate cancer. The IGF axis regulates physiologic and pathophysiologic growth organs including the prostate. The structure of IGF which is similar to insulin, causes insulin combines to IGF receptor to enter the prostate cells, resulting in receptor activation to induce growth and proliferation.^{12,15,16,17}

Insulin can increase gene transcription or translation of proteins involved in the metabolic processes of sex hormones, and affect hormonal milieu in the prostate. Hyperinsulinemia is associated with lower levels of sex hormone-binding globulin, thus increasing the number of sex hormones that enter the prostate cells and affect their growth. Also, chronic pro-inflammatory cytokines associated with metabolic syndrome, hyperglycemia and hyperinsulinemia contribute to BPH / LUTS.¹⁸⁻²¹

In our study increased blood glucose level positively correlated with grade of prostate inflammation, but failed to show a statistical significance, with p -value 0,058; prevalence ratio 1,943 (1.542-2.447 CI). In multiple adjusted linear regression analysis, grade of prostate inflammation was significantly associated with blood glucose level ($p = 0,022$). Diabetes mellitus contributes simultaneously and significantly to prostate inflammatory grade. There are no other studies that show a relationship between blood sugar levels and prostate inflammation grade in BPH patients.

Several studies investigated the role of diabetes mellitus and metabolic syndrome induce inflammation in BPH. Various cytokines secreted in metabolic syndromes such as IL-6, IL-8, bFGF, which are markers of prostate inflammation in human prostate myofibroblast cells. Also, the metabolic syndrome is also associated with increased levels of c-reactive protein, IL-6, IL-8, and TNF- α . Metabolic syndrome correlates with prostate inflammation followed by wound healing and proliferation of

prostate tissue. A multicenter cohort study of BPH patients ($n=244$) was done to investigate the association of metabolic syndrome and prostate inflammation in BPH. Inflammatory infiltrate scores in prostate specimens showed association with metabolic syndrome factors ($p = 0.001$). The study concluded that fat and insulin have a negative effect on prostate health, increase inflammation, and were keys pathogenic factors for BPH.²²

Testosterone is the most important androgen in humans. Androgens are a group of steroids that have anabolic and masculinizing effects in both men and women. Testosterone was formed since the fetus for ten weeks or more after birth. Furthermore, basically no testosterone was produced during childhood until approximately the age of 10-13 years. Then testosterone production increases rapidly under the stimulation of the anterior pituitary gonadotropin hormones at the beginning of puberty and ends throughout life, decreasing rapidly above the age of 50 years. At the age of 80 years the decrease in testosterone can reach up to 20-50% of peak levels. Testosterone level was not significantly correlated with grade of prostate inflammation with p -value 0,334; PR 1.233 (0.804-1.891 CI). There were no previous studies that discussed the relationship between testosterone levels and prostate inflammation grade.

Some evidence showed three hypotheses for the occurrence of BPH. Bacterial/viral infections with and without clinical symptoms can trigger prostate inflammation which can then recur or continue due to metabolic changes, including DM, hypercholesterolemia. Hypogonadism and/or hyperestrogenism can maintain an inflammatory atmosphere in the prostate. The combination of these conditions leads to excessive TLR expression, transformation of prostate cells into antigen presenting cells (APC) and activation of prostatic lymphoid tissue, leading to excessive production of growth factor, induction of prostate remodeling and prostate enlargement.²²

Liu et al. conducted a male BPH screening study of more than 45 years in China. In this study age was positively correlated with prostate volume, IPSS and PSA levels. Testosterone levels did not correlate significantly with prostate volume or IPSS.²³

Favilla et al. investigated the relationship between degrees of LUTS and sex hormone levels in men with BPH who underwent surgical therapy. The IPSS score correlated positively with age ($r = 0.405$, $p < 0.001$) and total testosterone (TT) ($r = 0.298$, $p = 0.020$). The study was divided into 2 subgroups, 40 samples with IPSS < 19 and 82 others with IPSS > 19, and obtained median TT levels of 346.80 ng/ml and 425.69 ng/ml respectively. The risk of LUTS was increased in men with higher TT

levels, although the average testosterone value was still normal.²⁴

Some studies focused on the relationship between serum androgen concentration and BPH in older patients, but the results were not always consistent. Joseph et al. reported that large prostate volume was associated with an increase in testosterone levels in African-Americans, but Meikle et al. found a correlation between prostate volume and TT levels in 214 twin men in the white population. Other studies found no significant association between TT levels and prostate volume. Apart from this there was no consistent correlation between TT and free testosterone with LUTS in other studies, but there was a relationship between androstenediolglucuronide (DHT metabolite) and E2 levels. However, there were several studies that have found that prostate volume is not related to free testosterone levels after controlling for age variables.²⁴

Testosterone deficiency is a proinflammatory state because adipose tissue secretes various substances such as proinflammatory cytokines, adipokine, FFA (Free Fatty Acid) and estrogen. All of these substances contribute to the development of prostate inflammation as well as in androgen deficiency conditions.²⁵

Visceral fat is an active secretory tissue, proinflammatory cytokines, adipokines, biochemical modulators and other proinflammatory factors such as IL-6, IL-1 β , PAI-1, TNF α , angiotensinogen, vascular endothelial growth factor (VEGF) and amyloid serum A.²⁶

All of these factors contribute to systemic and peripheral inflammation and dysfunction of the vascular. FFA activates nuclear factor- κ B pathways which are then produced by TNF α . TNF α activates lipolysis followed by increased synthesis of IL-6 and macrophage chemoattractant protein-1 (MCP-1) which will increase macrophage mobilization and insulin sensitivity modulation. Increased TNF α also increases the expression of adhesion molecules in the endothelium and vascular smooth muscle cells. IL-6 stimulates the synthesis of C-reactive protein by hepatocytes. Aromatase is an enzyme that converts testosterone to estradiol, especially in adipose tissue. Testosterone has been shown to influence insulin sensitivity, which means can modulate insulin sensitivity directly.²⁶

In conclusion, this study revealed that grade inflammation of prostate was correlated with PSA serum level and blood glucose, but not with testosterone level. Inflammation of prostate was one of factor that contributes to the occurrence of BPH.

Further studies examining those factors and others need to be done to investigate the role of inflammation as the risk of developing BPH.

CONCLUSION

Grade inflammation of prostate was significantly correlated with blood glucose level and serum PSA level. On the other hand testosterone does not correlate with the degree of inflammation of the prostate.

CONFLICT OF INTEREST

The author declares there is no conflict of interest regarding all elements in this study.

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