

The Role of Inflammation in the Benign Prostatic Hyperplasia Pathogenesis

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Abstract: ***Background:** This study aimed to analyze the role of proinflammatory cytokines TNF α and anti-inflammatory IL-10 in the pathogenesis of benign prostatic hyperplasia. **Methods:** This research is an correlative analytical study with validity test, comparing the levels of pro-inflammatory cytokines TNF- α and anti-inflammatory mediators IL-10 with prostate volume in benign prostatic hyperplasia patients. **Result:** Based on correlation test in BPH patients with prostatitis, prostate volume strongly relates with TNF α and IL-10. This showed in the significant value of less than 0.05. So, TNF- α and IL-10 has a strong relationship with the size of the prostate volume in BPH patients. There is tendency when the TNF- α and IL-10 increased, prostate volume is also increased. Based on the normality data test for prostate volume, obtain result sig = 0.113 > 0.05, that mean the data is concomitant with the normal distribution. Then analyzed by linear regression, the results showed that each increase of TNF α 1 pg / ml, the prostate volume will also tend to increase by 3.345 ml. The value of R^2 at 29.4% provides that the effect of TNF α to the prostate volume is 29.4%, the remaining (70.6%) is came from other factors. When the IL 10 increased 1 level, the prostate volume tends to increased by 1.196, the determination coefficient (R^2) is 15% which means that only 15% of the effect of IL-10 on prostate volume, the remaining 85% comes from other factors. **Conclusion:** Levels of TNF- α and IL-10 have a very strong correlation with the prostate volume in benign prostatic hyperplasia patient. If there is an increased of TNF- α , the prostate volume will also increased. Same as IL-10. Inflammatory mediators play a role in the increasing of prostate volume and prostate proliferation cell inflammatory grading. So it can be concluded that chronic inflammation plays a role in the pathogenesis of benign prostatic hyperplasia.*

Keywords: benign prostatic hyperplasia, tumor necrosis factor α , interleukin-10

1. Introduction

Benign prostate enlargement, or better known as benign prostatic hyperplasia (BPH) is often found in the middle-aged man¹

The BPH term is actually has histopathological meaning, the hyperplasia of stromal cells and epithelial cells of prostate gland^{1,2,3}. BPH could found in approximately 40-50% of patients 51-60 years, the prevalence increased to 70% in patients 61-70 years, and will increase to 90% in patients over 80 years.^{1,4}

They complaints about Lower Urinary Tract Symptoms (LUTS) consisting of urinary obstruction (voiding symptoms) and irritation of storage (storage symptoms), ie. increased of micturition frequency, urgency, nocturia, weakness of micturition emission and often discontinuous (intermittency). The patients unsatisfied after micturition, and urinary retention occurred in the next stage^{1,2,4}

Lots of factors may play roles in the benign prostate gland proliferation. Generally the growth of a prostate found in middle-age patients and and have a normal testes function (produce testosterone). The influence of other hormones (ie. estrogen, prolactin), certain diets, obesity, diabetes, physical activity and chronic inflammation are also suspected in the cells proliferation of prostate gland.^{5,6}

In an inflammatory prostate tissue, cytokines produced from the inflammatory cells which will increase the production of growth factors and angiogenesis. Furthermore, this growth factor plays a role in promoting the proliferation of cells of the prostate gland.^{2,7} In the empirical researches, there are

strongly relationship between the degree of inflammation and LUTS complaints, prostate volume and progression of BPH. This study aims to analyze the role of proinflammatory cytokines TNF α and anti-inflammatory IL-10 in the pathogenesis of benign prostatic hyperplasia.

2. Methods

2.1. Patient and Selection Control

This research is an correlative analytical study with validity test, comparing the levels of pro-inflammatory cytokines TNF- α , anti-inflammatory mediators IL-10, and a prostate volume in benign prostatic hyperplasia patients.

Patients with benign prostatic hyperplasia used as study subjects were 60 respondents. All respondents were through Trans-Urethral Resection of the Prostate (TUR-P) surgery procedure. TNF- α and IL-10 blood serum were analyzed before operation. The prostate tissue specimen from the TUR-P procedure were analyzed in Pathology laboratory. The pathological results showed there were 14 respondents with high grade prostate adenocarcinoma and intraepithelial prostate neoplasm. We remove them from the list.

2.2. Serum Separation and Elisa

Immediately after blood sampling, serum was obtained by centrifugation at 2000 r/min for 15 min at 4° C and stored at -80° C until later analysis. Serum TNF- α (R&D systems ELISA kits) levels were determined using ELISA kits as per standard protocol of manufacturers.

3. Results

3.1. Descriptive Age Respondents patients of benign prostatic hyperplasia (BPH) with Prostatitis

The number of patients with benign prostatic hyperplasia (BPH) is as much as 46 respondents. Age of respondents ranged from 54 years to 85 years. Patients under 60 years are 7 people, or approximately 15.22%, and the age group 60-70 years as many as 23 people or about 50%, and the age group above 70 years as many as 16 people, or approximately 34.78%.

Table 1: The frequency distribution of benign prostatic hyperplasia (BPH) respondent patients by age

Age Group	BPH patients	
	Frekuensi	%
< 60 years	7	15,22
60 – 70 years	23	50,00
> 70 years	16	34,78
Total	46	100

Source: Primary data processing, 2015

These results indicate that benign prostatic hyperplasia (BPH) respondents with prostatitis, both in chronic and acute prostatitis are in the 60-70 years group or older group (no productive).

3.2. Relation between Factors Studied and Prostate Volume in Benign Prostatic Hyperplasia (BPH) Patients

Based on correlation test in BPH patients with prostatitis, prostate volume strongly relates with TNF α and IL-10. This showed in the significant value of less than 0.05. So, TNF- α and IL-10 has a strong relationship with the size of the prostate volume in BPH patients. There is tendency when the TNF- α and IL-10 increased, prostate volume is also increased.

Correlation between prostate volume with	BPH patients	
	r	Sig
TNF α	0,542	0,000
IL-10	0,388	0,008

Source: Primary data processing, 2015

Based on Table 2, in patients with BPH, prostate volume relates very strongly and positively with TNF α , and IL-10. This is indicated by the correlation value and the significance of each of these factors. Ie with TNF α obtained $r = 0.542$, and the IL-10 was obtained $r = 0.388$ means TNF- α factor and IL-10 has a very strong relationship with the volume of the prostate in patients. Ie there is a tendency when TNF- α and IL-10 increased, prostate volume also increased. Likewise with TGF $\beta 1$ values obtained significant (sig) < 0.05 indicates that TGF $\beta 1$ have a strong relationship with prostate volume in patients with chronic prostatitis, although not as strong as with TNF α and IL-10.

3.3. TNF α and IL-10 Influence Test Against Prostate Volume of BPH Patients with Prostatitis

Based on the normality data test for prostate volume, obtain result $\text{sig} = 0.113 > 0.05$, that mean the data is concomitant with the normal distribution. Then analyzed by linear regression. The TNF- α obtained regression equation as shown in Table 3,

$$\text{Prostate volume} = 34.561 + 3.345 \text{ TNF } \alpha$$

The above equation shows that each increase of TNF α 1 pg/ml, the prostate volume will also tend to increased 3.345. The value of R^2 at 29.4% provides that the effect of TNF α to the prostate volume is 29.4%, the remaining (70.6%) is came from other factors.

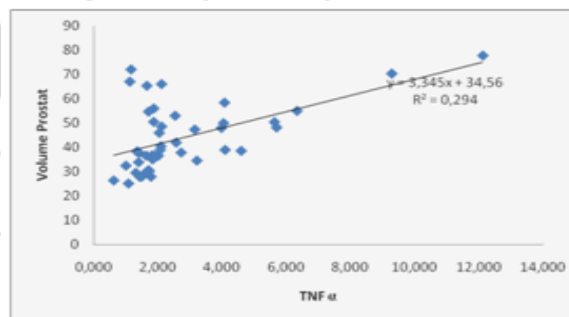
Furthermore, the regression equation for IL-10 with prostate volume are as follows:

$$\text{Prostate volume} = 41.259 + 1.196 \text{ IL-10}$$

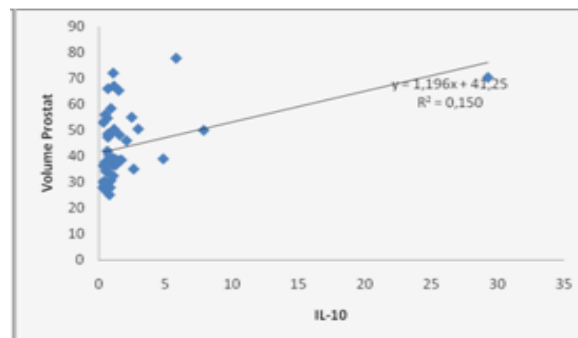
This means that when IL-10 was up 1, the volume of the prostate tends to increase by 1,196, the coefficient of determination (R^2) is 15% which means that only 15% of the effect of IL-10 on prostate volume, the remaining 85% comes from other factors.

Table 3: Results of simple linear regression between TNF α and IL-10 with a prostate volume of BPH patients with prostatitis

Factor	b_0	b_1	R^2
TNF α	34,561	3,345	29,4%
Sig	0,000	0,000	
IL-10	41,259	1,196	15%
Sig	0,000	0,008	



(a)



(b)

Figure 1: (a) The regression curve between TNF α and prostate volume in BPH and prostatitis patients; (b) The regression curve between IL-10 and prostate volume in BPH and prostatitis patients.

4. Discussion

The number of patients with benign prostatic hyperplasia (BPH) with prostatitis in this study were as many as 46 respondents. Age of respondents ranged from 54 years to 85 years. Patients under 60 years are 7 people, or approximately 15.22%, and the age group 60-70 years as many as 23 people or about 50%, and the age group above 70 years as many as 16 people, or approximately 34.78%. These results indicate that respondents of benign prostatic hyperplasia (BPH) with prostatitis are in the group of 60-70 years. This study is similar with that obtained by Parsons JK (2007)⁴. He said that the highest incidence in the United States are in the age group 60-69 years. Based on correlation test, prostate volume relates very strongly and positively with TNF α , and IL-10. This is demonstrated by the significant value of less than 0.05. That is a factor of TNF- α and IL-10 has a strong relationship with the size of the prostate volume in patients. There is a tendency when TNF- α and IL-10 increased, prostate volume is also increased.

Inflammation increased the blood flow due to vasodilation at the site of infection or tissue damage. Capillaries become more permeable to liquids, large molecule and leukocytes pouring out from the blood vessels and entering the tissues. Leukocytes, particularly neutrophils and monocytes, moving toward a target due to chemotaxis. There was also a radical process of proteases release^{8,9}

Excessive cytokine production and sustainable are the responses to lipopolysaccharide (LPS) bacterial or superantigen which are a characteristic response of systemic inflammatory. Distribution of bacterial products induce the production of proinflammatory cytokines such as TNF α , IL-1, IL-6, IL-8, which activated more immune cells and recruited into infection area¹⁰. In excessive amounts the proinflammatory cytokine can damage the vascular wall and resulting organ dysfunction. To compensate the proinflammatory cytokine release, the inflammatory mediators as IL-10 and TGF β are also release. They inhibit the release of cytokines proinflamasi.^{11,12} At the beginning of infection, activated phagocytic cells kill bacteria directly with swallowing and secrete a variety of toxic substances such as free radicals. But this toxic substance on the other hand can damage healthy cells, then the cells that become damaged induce further inflammation. In simplified, acute inflammatory response begins with a pathogen that stimulates early inflammatory responder with the aim to kill pathogens. This early inflammatory mediators activate slow inflammatory mediators that can trigger further initial mediator. Ideally, the inflammatory response must be able to eliminate the pathogen. In some circumstances, the immune response is not strong enough to get rid of pathogens. In other circumstances may occur positive feedback between the early and slow pro-inflammatory mediator release which is resulting unsubsidi immune respons.¹³

Chronic inflammation can be started from the settled of acute inflammatory agents destroyer, but more often that the inflammatory response is a chronic inflammatory response

since the beginning. Unlike the changes or extensive vascular damage and neutrophil infiltration seen in acute inflammation, chronic inflammation showed characteristics of tissue infiltration with mononuclear cells such as macrophages, lymphocytes and plasma cells is accompanied by tissue destruction. Macrophages are a key players of the chronic inflammatory response. This is caused by a number of bioactive products or mediator release. These mediators are part of the immune system that is very strong against the invasion of foreign bodies and tissue damage. The disadvantage is the continuous activation of macrophages that resulting advance tissue damage.¹⁴ In a variety of proven research, the inflammatory environment supports the development of tumors and concomitant with the environment around the tumor. The tumor's environment includes the presence of cytokines, chemokines, leukocytes, lymphocytes and macrophages contribute to the occurrence of vascular dilatation, neovascularization, immune suppression promotes tumor growth and keep them from the immune system. In the tumor microenvironment is no anti-tumor immunity of the host with the pro-inflammatory activity derived from tumors that weaken the anti-tumor activity. This activity depends on the mediators released by inflammatory cells from the host and tumor cells. When the anti-tumor activity of host immunosuppression activity is weaker than that waged by the tumor, the tumor cells avoid the attack of the immune response and growing rapidly. Conversely, if the anti-tumor activity is stronger than the immunosuppressive activity of tumor cells, the tumor cells can eliminated.¹⁵

The result of persistent inflammatory microenvironment are the promotion of tumor growth, accelerated progression and angiogenesis. Cytokine IL-10 can be secreted by tumor cells or by macrophages, and between the effect it produces is IL-10 inhibits the cytotoxic T cells and thereby inhibit the immune response against tumor.¹⁵ Histologically, BPH is characterized by progressive hyperplasia of glandular and stromal tissue. Histological inflammation often found in BPH specimens, and local inflammation in the prostate is an important cause of enlarged prostate and BPH. Prostate inflammation is caused by several factors, such as infectious agents, hormonal changes, dietary habits, reflux of urine and physical trauma, but the relationship between prostate inflammation and bacteria or other foreign antigens still unclear. The cause of BPH is definitely still unclear and multifactorial. Some systemic diseases or lifestyle factors, such as obesity, diabetes mellitus, dyslipidemia, atherosclerosis and smoking, have been reported to be associated with BPH. The possibility of BPH is part of the metabolic syndrome, and the exact cause of BPH is more systemic than lokal.¹⁰

5. Conclusion

Levels of TNF- α and IL-10 has a very strong correlation with the prostate volume in patients with benign prostatic hyperplasia with chronic protatitis. Thus concluded that there is a tendency when TNF- α increased the prostate volume will also increase, as well as with IL-10.

Inflammatory mediators play a role in the increase of prostate volume, and increased prostate inflammatory cell proliferation grading. So it can be concluded that chronic inflammation plays a role in the pathogenesis of benign prostatic hyperplasia. The role of TNF α levels in the blood can be a predictor of the enlarged prostate.

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