IS INFLAMMATION AN AGE-RELATED CAUSE OF BPH PROGRESSION

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ABSTRACT

Objective: *To find the role of inflammation in BPH progression represented by prostate enlargement compared between age group.* ***Material & method:*** *Tissue samples of BPH were collected from biopsy, transurethral resection or open surgery. Clinical information was collected including such as patient age, prostate volume, serum prostate specific antigen (PSA) and history of retention before procedure. Patients were divided into three groups, below 63 years old (young adult), 63 - 69 years old (older adult) and equal or above 70 years old (elderly). The samples were analyzed to define the microscopic structure of the hyperplasia (stromal or glandular) and to detect prostatic intraepithelial neoplasia, atypical stromal acinic proliferation, atypical acinar hyperplasia or prostate cancer. Prostate cancer was excluded from study samples. Grade of inflammation was determined by a pathologist depending on number of inflammatory cells. Grade of inflammation was classified in two groups, with mild inflammation or moderate-to-severe inflammation.* ***Results:*** *A total of 1189 patients were reviewed, 1172 were diagnosed with BPH. There were 381 patients (32,5%) with age below 63 years old (young adult), 380 (32,4%) between 63-69 years old (older adult) and 411 (35,1%) in equal or above 70 years old (elderly). In young-adult group, median of prostate volume between mild and moderate to severe inflammations was 42,56 and 45,75 (p = 0,500), for older adult group median was 45,00 and 51,00 (p = 0,038), for elderly group median was 49,00 and 51,98 (p = 0,621).* ***Conclusion:*** *Inflammation has a role in progression of prostate enlargement especially for the older adult group.*

Keywords: *Inflammation in BPH progression, prostate volume, age, PSA.*

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INTRODUCTION

The prostate has been the subject of much study because it is the site of infection as well as benign and malignant neoplasm.[1]

Many factors are known to have a role in prostate enlargement, such as age, hormonal (testosterone), endocrine disease like diabetes mellitus, vascular disease, growth factor, inflammation, and many others.[2] Kessler et al (1998) reported from experimental evaluation of inflammation in rats that immunoinflammatory stimulators might play a role in the prostatic epithelial cell growth and proliferation processes, most probably by modulation of the cytokine system.[3] Nickel and Roehrborn (2007) reported that inflammation in the prostate gland appears to be more closely related to BPH than the clinical syndrome chronic prostatitis.[4]

In the last 5 years, specific inflammatory mediator pathways have been studied in detail to elucidate the potential role of these pathways in BPH pathogenesis. T cells are known to produce and secrete a variety of other growth factors, including HB-EGF and bFGF/FGF-2.[5] A large number of cytokines and their receptors are seen in BPH tissue.[6] Specifically, significant levels of IL-2, IL-4, IL-7, IL-17, interferon γ (IFN-γ), and their relevant receptors are found in BPH tissue.[7,8] IL-2, IL-7, and IFN-γ stimulate the proliferation of prostatic stromal cells in vitro.[7] Prostatic epithelial cell senescence results in increased expression of IL-8, which can promote proliferation of

prostatic stromal cell in vitro.[7] Prostatic epithelial cell senescence results in increased expression of IL-8, which can promote proliferation of nonsenescent epithelial and stromal cells.[9] Macrophage inhibitory cytokine 1 is expressed in normal prostate tissue but significantly downregulated in BPH.[10,11] Chronic inflammation in BPH is also associated with focal upregulation of cyclooxygenase-2 (COX-2) in the glandular epithelium.[12]

An additional source of growth factors in human BPH tissue may be due to the inflammatory cell infiltrates seen in many men with BPH. In the 1990s, descriptive studies suggested a link between inflammation and BPH-related growth. Theyer and associates in 1992 reported extensive infiltration of human BPH tissues by activated T cells.[13] Peripheral blood and tumor infiltrating T cells are known to express VEGF (vascular endothelial growth factor), a potent epithelial mitogen.[14,15] T cells are known to produce and secrete a variety of other growth factors, including HB-EGF and bFGF/FGF-2.[5] Thus, T cells present in the local prostate environment were thought to be capable of secreting potent epithelial and stromal mitogens that promote stromal and glandular hyperplasia.[14]

Delongchamps et al (2008) studied prevalence of inflammation in benign and malignant prostate glands and reported that chronic inflammation infiltrates of the prostate were commonly identified in autopsies regardless of the presence of cancer. The prevalence and location of chronic inflammation were significantly associated with benign prostate hyperplasia. In contrast, no significant association between chronic inflammation and prostate cancer was found.[15]

Prostate enlargement is widely accepted to be age related, with older patients having larger prostates. Hormones also play a role in prostate enlargement and inflammation, but both will deteriorate with aging. To date however, no firm cause-and-effect relationships have been established between prostatic inflammation and related cytokine pathways and stromal-epithelial hyperplasia. Di Silverio et al (2007) and Roehrborn et al (2007) demonstrated a statistically significant correlation between prostate volume, PSA level, and both acute and chronic inflammation, with neutrophil or mononuclear infiltrates,[16,17] but this study only compared between inflammation groups, not compared between age.

OBJECTIVE

The aim of this study is to study the role of inflammation in BPH progression represented by prostate enlargement compared between age groups.

MATERIAL & METHOD

Tissue samples of BPH patients were collected from prostate biopsy, transurethral resection of the prostate or prostate open surgery. Pathologists examined the specimens for histological type and degree of inflammation. Clinical information such as patient age patient and prostate volume was collected.

The patients were divided into tertile groups, the division of age was under 63 years old (young adult), 63 to 69 years old (older adult) and equal or above 70 years old (elderly). This age division was based on another study about disease prevalence in a community-based population of 502 men (55 - 74 years of age) without prostate cancer, to determine relative impact on prevalence rates of the inclusion of these different parameters (and of different cut off values for these parameters) in a case definition of BPH.[18]

The samples were analyzed to define the microscopic structure of the hyperplasia (stromal or glandular) and to detect Prostatic Intraepithelial Neoplasia, Atypical Stromal Acinic Proliferation, Atypical Acinar Hyperplasia. Prostate cancer was an exclusion criteria. In our study BPH progression was defined by prostate volume. Larger prostates were considered more progressive. Inflammation was graded as mild, moderate or severe depending on number of inflammatory cells scattered. Pathologists determined degree of inflammation.

Prostate volume was statistically evaluated within the age group with Anova to find difference in BPH progression within age and degree of inflammation groups.

Each age group was classified according to degree of inflammation, but due to the small numbers in moderate and severe inflammation during calculation, we combined moderate and severe inflammation into one group (moderate to severe inflammation), and mean prostate volume of each inflammation group were compared using T-test.

RESULTS

There were 1172 samples with BPH who met inclusion criteria that could be reviewed. Seventeen samples were excluded. Distribution of prostate volume according to age is seen below.

Table 1. Data characteristic.

	N (%)
Age Group	
Younger adult	381(32,5)
Older adult	380 (32,4)
Elderly	411(35,1)
Degree of Inflammation	
Mild	798 (68,1)
Moderate	143 (12,2)
Severe	231 (19,7)

Number of cases in moderate and severe inflammation group was too small, therefore we combined moderate inflammation and severe inflammation into one group (moderate to severe).

Table 2. Comparison of mean prostate volume in each group of age.

Age Group	Mean ± SD	*p*
Younger adult	48,67 ± 22,14	
Older adult	51,29 ± 24,22	0,001
Elderly	54,92 ± 26,60	

Figure 1 showed differences of prostate volume between mild and moderate to severe inflammation according age group. In young adult group, mean prostate volume was larger for moderate to severe inflammation compared to mild inflammation but not significantly different. In older adult group, mean prostate volume for moderate to severe inflammation was also larger than mild inflammation and mean difference was statistically significant. But in the elderly group difference in mean prostate volume was not statistically significant between groups.

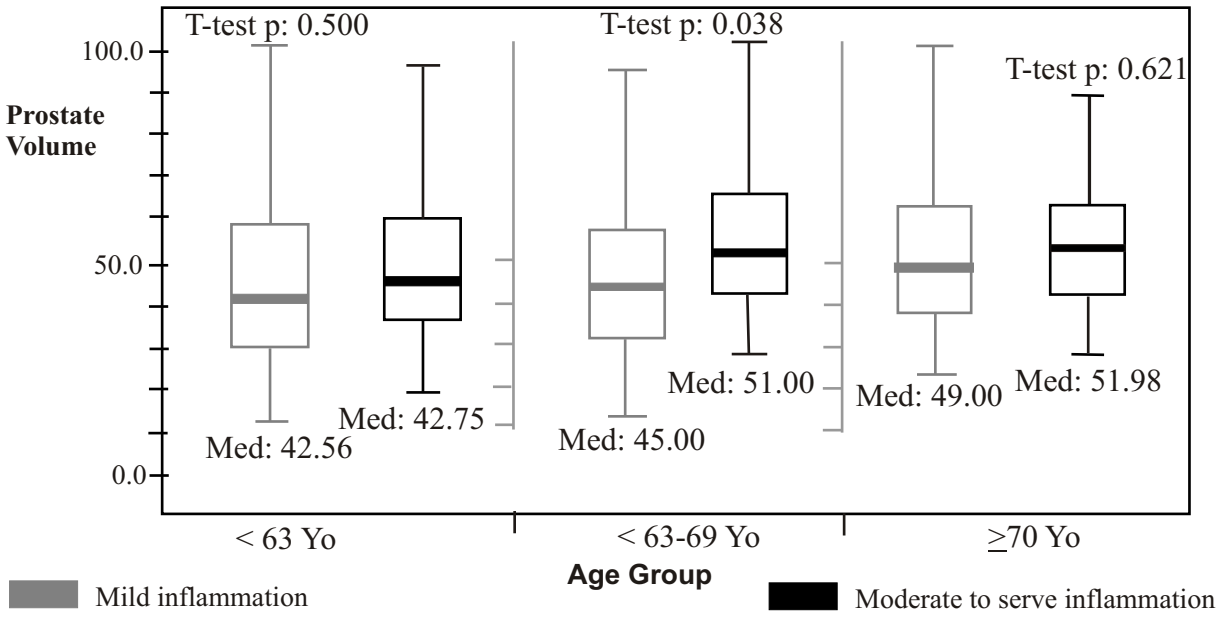

Figure 1. Mean difference of prostate volume between mild and moderate to severe inflammation groups distributed according to age group.

Table 3. Frequency distribution between age group and simplified grade of inflammation.

Grade of inflammation	Group of age			*p*
	Young adult	Older adult	Elderly	
Mild inflammation N (%)	244 (64,0)	267 (70,3)	287 (69,8)	0,118
Moderate to severe inflammation N (%)	137 (36,0)	113 (29,7)	124 (30,2)	

DISCUSSION

The pathogenesis of BPH is still poorly understood, although it is presumed that there is no single pathomechanism, but inflammation seems to play an important role in the initiation, development as well as evolution of BPH, suggesting that BPH is an inflammatory disease. The evidence regarding the role of inflammatory pathways in different clinical entities of BPH has significantly been accumulated. Primary studies have showed that inflammation is a contributor for BPH, or BPH is at least partially driven by inflammation.[19] Other authors also considered that probably it is too early to definitely integrate inflammation in a risk stratification analysis for prostate diseases because (1) a reliable, reproducible diagnosis of prostate inflammation is not possible at the moment and (2) men suspected of having prostate inflammation cannot be clinically assumed eligible for a specific oncologic surveillance. But on the other hand the author also said that, all data presented are very suggestive and certainly prostate inflammation cannot now be considered only as a simple tissue inflammation.[16] Nickel et al (2007) found that chronic histologic inflammation was found in more than 78% of men with enlarged prostates in the REDUCE chemoprevention trial and they also showed that prostate volume was larger in grade 1 - 3 chronic inflammation compared to grade 0.[17]

In this study the effects of inflammation are more obvious in older adult group than young adult and elderly group, we assume that probably the inflammatory response are stronger in younger age. El Yousfi et al (2005) reported that the inflammatory response in older man were decreased, and our results support a general lack of inflammatory response in the elderly exposed to an immune challenge, suggesting that immune deficiency may concern both early and late responses.[20] Age related changes in clonotypic immune system are well documented. For instance, involution of the thymus gland is an early feature of the immune reconfiguration and several age related alterations of T or B cell compartments have been described. Studies on age-associated changes of innate immunity are not as advanced as those of the clonotypic immune system. However, investigations from aged mice showed a functional decline of monocytes and macrophages.[21]

Nicolas et al (2008) shows that chronic inflammation was a common finding in autopsied prostates. It appears to be directly associated with the presence of benign prostatic hyperplasia but not with cancer.[22] A review by Italian authors reported that clinical and experimental data suggest a possible role for inflammation and apoptosis in the development of BPH and prostate cancer. To date, the factors that trigger the imbalance in prostate growth leading to BPH are mostly unknown, but several details of the molecular pathways are well-known, the author suggest further research to understand completely the etiology of the disease.[23]

There was no detailed study of the correlation between inflammation and size of tumor, number or grade of chronic inflammatory cells correlated with size of tumor or inflammatory mediators correlated to the tumor size previously, to find out a better understanding in role of inflammations to the prostate enlargement, when it start to influence, when it stops, and where it works, what influences it or what other factors that is working together with it, and finally how it works on enlargement of prostate.

From our previous study on PSA and prostate volume showed that prostate volume in moderate/severe inflammation (median = 49,9 g) was larger than in mild group (median = 45 g) (p = 0,009).[24] This study showed that inflammation level also has

effect on prostate enlargement whereas in younger adult and older adult shows a larger prostate size in moderate and severe inflammation group compare to mild inflammation group, but in equal or above 70 years old group the mean of prostate size in each inflammation grade was almost equal. Probably, inflammations has effect on earlier age below 60 years old and seems have it peak in seventh decade of life.

Navarette et al (2003) reported that inflammations whether been treated with anti inflammation (permixon 160 mg) shown to reduce the inflammation cells in prostate and the patients were improve in IPSS but the prostate volume not significantly reduce after the treatment.[25] Data from a population-based cohort of 2,447 Caucasian men in Olmsted County, Minnesota, said that their data suggest that NSAID use may prevent, delay, or retard hyperplasia and/or inflammatory processes in the prostate, resulting in a decreased incidence of BPH.[26]

Limitations of this study included the following, the pathology results were not read by a single pathologist, the inflammation degree of inflammatory cells scattering evaluation was determined by pathologist experience. The progression of prostate enlargement is a dynamic process and not only influenced by inflammation. This study was a cross sectional study that evaluated static conditions in a single exposure and a single variable studied influenced the prostate. We did not evaluate the hormonal state that influences the prostate. More thorough and continuous follow up (cohort study) is needed to study the role of inflammation in progression of prostate enlargement and relationship to age, and its correlation with hormonal or other variables.

CONCLUSION

This was the first study that showed the role of inflammation in progression of prostate enlargement especially in older adult group.

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