BENİGN PROSTAT HİPERPLAZİSİ VE PROSTAT KANSERİNİN RUTİN İNCELEMLERE İLAVETEN ERKEN ÖNGÖRÜLMESİ

The Early Prediction of Prostate Cancer and Benign Prostate Hyperplasia Additional to Rutin Examination

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ÖZET

Amaç: Tanı prosedürleri esnasında BPH'den Prostat Kanserinin ayırtedilmesinde yeni tahmin araçlarını tanımlamak.

Materyal ve Metod: BMI 3 kategori altında değerlendirildi: BMI-1 (18.5-24.9 kg/m2), BMI-2 (25.0-29.9 kg/m2), ve BMI-3 (30.0 kg/m2 veya üzeri). Yeni formülasyonlar, CRP/NLR, CRP/PSA, NLR/PSA, NLR/BMI, (CRP/PSA)/(yaş/100),NLR/(PSA/yaş),NLR/(BMI/yaş),ve (CRP*PSA*yaş)/100; yaş, göbek çevresi, lenfosit ve nötrofil sayıları ve PSA ile dört kategori üzerinden değerlendirmeler yapıldı. İstatistik analizde non-parametric Mann-Whitney U test and Kruskal-Wallis testi kullanıldı. p<0.05 değeri anlamlı olarak kabul edildi.

Sonuçlar: Tüm patoloji sonuçları (BPH and PCa) BMI ile birlikte (BMI-1, -2 ve -3) düşünüldüğünde, göbek çevresi; BPH-BMI-3 (p=0.000), NLR; BMI-1 (p=0.000), PSA; PCa-BMI-3 (p=0.000) grupta anlamlı en yüksekti. Prostat Ca'da BMI analiz edildiğinde; yaş (71.64+1.32) (p=0.003) ve CRP/PSA ortalaması (0.42+0.35) (p=0.048) BMI-1 grupta en anlamlı yüksekken PSA (58.85+46.30) (p=0.020) ve göbek çevresi (82.19+9.66) (p=0.009) BMI-3 grubunda daha anlamlıydı.

Sonuç: Prostat Ca'nın tanısı için halen gerekli olan TRUS rehberliğinde biyopsi öncesi BMI temelinde PSA, NLR ve CRP kombinasyonu uyulanmalıdır. Biz, biyopsi öncesi BPH ve PCa arasındaki ayırımın öngörülmesinde yeni formülasyonların klinik kullanımının olması ve geliştirilmesi gerektiğini düşünüyoruz.

Anahtar Kelimler: *Prostat; Kanser; PSA; Nötrofil Lenfosit Oranı; BMI*

ABSTRACT

Aim: To describe new prediction tools in differantion of Prostate Cancer from BPH during the diagnosis posedüre.

Material and Methods: BMI was assessed under three categories: BMI-1 (18.5-24.9 kg/m2), BMI-2 (25.0-29.9 kg/m2), and BMI-3 (30.0 kg/m2 or above). New formations, CRP/NLR, CRP/PSA, NLR/PSA, NLR/BMI, (CRP/PSA)/(age/100),NLR/(PSA/age),NLR/(BMI/age),and(CRP*PSA*age)/100, developed on the basis of the above four parameters together with age, waist circumference, neutrophil and lymphocyte counts, were also evaluated. Non-parametric Mann-Whitney U test and Kruskal-Wallis test were used for Statistical analysis p<0.05 was regarded as significant.

Results: When all pathology results (BPH and PCa) were considered together with BMI (BMI-1, -2 and -3), waist circumference exhibited the highest significance in the BPH-BMI-3 (p=0.000) group, NLR in the BPH-BMI-1 (p=0.000) group, and PSA in the PCa-BMI-3 (p=0.000) group. When BMI was analyzed in the PCa groups, age (mean 71.64+1.32) (p=0.003) and CRP/PSA (mean 0.42+0.35) (p=0.048) exhibited the highest values in terms of statistical significance in the BMI-1 group, and PSA (mean 58.85+46.30) (p=0.020) and waist circumference (mean 82.19+9.66) in the BMI-3 group (p=0.009)

Conclusions: The combination of PSA, NLR and CRP based on BMI must be considered before biopsy is performed in the TRUS guideline, which is still valid for patients with PCa. We think that the new formulations we have worked to develop can be of clinical use in the event of uncertainly in differentiating between BPH and PCa.

Keywords: *Prostate; Cancer; PSA; Neutrophil-Lympocyte Rate; BMI*

INTRODUCTION

Benign prostate hyperplasia (BPH) is a benign tumor in males, the incidence of which increases with age (1). BPH is associated with the growth of stromal and epithelial cells in both the transitional and periurethral zones (2,3). Various studies have suggested that inflammation affects prostate growth and the progression of associated symptoms (3-5). Various growth factors and cytokines are involved in inflammation (2). One autopsy study reported signs of chronic inflammation in more than 70% of cases with BPH (6). Chronic prostate inflammation can also lead to an increase in prostate volume and acute urinary retention (7).

Prostate growth and inflammation cause greater secretion of prostate-specific antigen (PSA) from prostatic cells even in the absence of cancer (8). In addition, parameters such as PSA, PSA derivatives and kinetics and the prostate health index (PHI) have to date been used in the prediction of prostate cancer (PCa), but definite diagnosis still relies on pathological examination of tissues obtained with prostate needle biopsy. Various studies have investigated prediction of PCa before biopsy, and cancer positivity rates at first biopsy are 25-30% (5,9).

C-reactive protein (CRP) has long been widely used as a marker of inflammation. CRP plays an important role in both diagnosis and in the management of response to treatment. In the light of the association between BPH and inflammation, anti-inflammatory drugs are sometimes given in addition to conventional treatments, and CRP has become one of the markers used to assess response to treatment (3,4).

The neutrophil/lymphocyte ratio (NLR) is another marker of inflammation, that can be easily calculated from complete blood counts and that can be easily obtained in any environment. The NLR is reported to be capable of use in predicting the progression of BPH (1).

Body mass index (BMI) is one of the factors capable of affecting PSA, CRP, and NLR results. Serum PSA values decrease as BMI increases (10,11). A positive correlation has been reported between total leukocyte, monocyte and neutrophil numbers and obesity (11,12). Obesity accompanies increased systemic inflammation in both human and animal studies.13 Although NLR values and CRP levels are higher in obese subjects than in healthy individuals, no significant correlation has been reported between NLR and BMI (14,15). In contrast, leukocyte, neutrophil and lymphocyte numbers and CRP levels are significantly correlated with BMI (15).

The purpose of this study was to prevent negative biopsies by increasing prediction without biopsy in the differentiation of PCa from BPH. It therefore involved the evaluation of BMI and PSA, CRP, and NLR in combination, rather than assessing these parameters individually. This study was also intended to contribute to the literature by developing new formulations concerning these four parameters.

MATERIALS and METHODS

BMI, CRP, NLR and PSA levels were investigated retrospectively in 361 patients (250 BPH, 101 PCa) aged over 40 presenting to the urology clinic for PSA screening or lower urinary tract symptoms (LUTS). BMI was assessed under three categories: BMI-1 (18.5-24.9 kg/m^2), BMI-2 (25.0-29.9 kg/m^2), and BMI-3 (30.0 kg/m^2 or above). New formations, CRP/NLR, CRP/PSA, NLR/PSA, NLR/BMI, (CRP/PSA)/(age/100), NLR/(PSA/age), NLR/(BMI/age), and (CRP*PSA*age)/100, developed on the basis of the above four parameters together with age, waist circumference, neutrophil and lymphocyte counts, were also evaluated. Mean values for all parameters were analyzed with mean values and BMI in BPH and PCa.

Statistical analysis was performed on SPSS® version 16 software using the non-parametric Mann-Whitney U test and the Kruskal-Wallis test. $p<0.05$ was regarded as significant.

RESULTS

While age ($p=0.000$), waist circumference ($p=0.000$), and PSA ($p=0.000$) differed statistically significantly in male patients presenting to the urology clinic and undergoing PSA screening or with LUTS, no significant difference was determined between CRP, NEU (neutrophil), LYM (lymphocyte), NLR, or BMI ($p>0.05$).

Among formulae involving CRP, NLR, PSA, BMI and age, CRP/PSA (p=0.000), NLR/PSA (p=0.000), (CRP/PSA)/(age/100) (p=0.000), NLR/(PSA/age) (p=0.000), and (CRP*PSA*age)/100 (p=0.000) exhibited statistical significance (Table 1).

When all pathology results (BPH and PCa) were considered together with BMI (BMI-1, -2 and -3), waist circumference exhibited the highest significance in the BPH-BMI-3 (p=0.000) group, NLR in the BPH-BMI-1 (p=0.000) group, and PSA in the PCa-BMI-3 (p=0.000) group (Table 2).

When BMI was analyzed in the PCa groups, age (mean 71.64±1.32) (p=0.003) and CRP/PSA (mean 0.42±0.35) (p=0.048) exhibited the highest values in terms of statistical significance in the BMI-1 group, and PSA (mean 58.85+46.30) (p=0.020) and waist circumference (mean 82.19+9.66) in the BMI-3 group (p=0.009) (Table 2).

Statistical analysis was performed on SPSS® version 16 software using the non-parametric Mann-Whitney U test and the Kruskal-Wallis test. p<0.05 was regarded as significant (Table 2).

Table 1. The Comparison of all parameters between BPH and PCa. p<0.05, Mann-Whitney U Test

BPH – PCa	Total (n)	Total Mean ± SD	BPH (n)	BPH Mean ±SD	PCa (n)	PCa Mean±SD	p
Age	359	63,98±0,47	258	62,82±0,53	101	**66,94±0,91**	**0.000**
Waist Circumference	347	94,09±2,94	251	**101,5±3,65**	96	74,69±4,03	**0.000**
PSA	348	12,37±3,06	257	3,23±0,27	91	**38,19±11,28**	**0.000**
CRP	322	1,52±1,02	232	1,85±1,42	90	0,67±0,14	0.825
NEU	361	4,35±0,18	260	4,41±0,24	101	4,21±0,13	0.394
LYM	361	2,10±0,06	260	2,10±0,07	101	2,09±0,11	0.296
NLR	361	2,53±0,13	260	2,57±0,17	101	2,42±0,13	0.101
BMI	361	27,98±0,39	260	28,11±0,50	101	27,65±0,56	0.624
CRP/NLR	322	0,29±0,07	232	0,29±0,10	90	0,28±0,05	0.848
CRP/PSA	310	0,65±0,29	229	**0,80±0,39**	81	0,22±0,11	**0.000**
NLR/PSA	347	2,05±0,21	256	**2,51±0,28**	91	0,76±0,15	**0.000**
NLR/BMI	361	0,09±0,004	260	0,09±0,006	101	0,09±0,005	0,170
(CRP/PSA)/(Age/100)	308	0,41±0,18	227	**0,51±0,24**	81	0,14±0,007	**0.000**
NLR/(PSA/Age)	345	0,03±0,003	254	**0,04±0,005**	91	0,012±0,002	**0.000**
NLR/(BMI/Age)	359	6,06±0,30	258	6,00±0,38	101	6,20±0,41	0.054
(CRP*PSA*Age)/100	308	11,22±4,23	227	4,89±3,57	81	**28,93±12,4**	**0.000**

BPH – PCa	Total (n)	Total Mean±SD	BPH (n)	BPH Mean±SD	PCa (n)	PCa Mean±SD	p
Age	359	63,98±0,47	258	62,82±0,53	101	**66,94±0,91**	0.000
Waist Circumference	347	94,09±2,94	251	**101,5±3,65**	96	74,69±4,03	0.000
PSA	348	12,37±3,06	257	3,23±0,27	91	**38,19±11,28**	0.000
CRP	322	1,52±1,02	232	1,85±1,42	90	0,67±0,14	0.825
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NLR	361	2,53±0,13	260	2,57±0,17	101	2,42±0,13	0.101
BMI	361	27,98±0,39	260	28,11±0,50	101	27,65±0,56	0.624
CRP/NLR	322	0,29±0,07	232	0,29±0,10	90	0,28±0,05	0.848
CRP/PSA	310	0,65±0,29	229	**0,80±0,39**	81	0,22±0,11	**0.000**
NLR/PSA	347	2,05±0,21	256	**2,51±0,28**	91	0,76±0,15	**0.000**
NLR/BMI	361	0,09±0,004	260	0,09±0,006	101	0,09±0,005	0,170
(CRP/PSA)/(Age/100)	308	0,41±0,18	227	**0,51±0,24**	81	0,14±0,007	**0.000**
NLR/(PSA/Age)	345	0,03±0,003	254	**0,04±0,005**	91	0,012±0,002	**0.000**
NLR/(BMI/Age)	359	6,06±0,30	258	6,00±0,38	101	6,20±0,41	0.054
(CRP*PSA*Age)/100	308	11,22+4,23	227	4,89±3,57	81	**28,93±12,4**	**0.000**

Table 2. The Comparison of All Parameters BPH and PCa together with Body Mass Index. Mean values and Standard Deviation, p<0.05, Kruskal-Wallis Test

DISCUSSION

Diagnosis of PCa has increased in line with advances in the PSA test. However, cancer is determined in approximately one in four first prostate biopsies performed due to PSA elevation. Targeted prostate biopsies have now been developed. Studies on this subject are still ongoing, but promising results are expected. However, increasing the prediction percentage of biochemical tests for identifying patients to undergo biopsy beforehand will benefit both patients and physicians. Research is therefore still continuing. Conditions such as prostatitis, PCa, BPH and acute urinary retention can give rise to PSA elevation. PSA also rises during inflammation (16,17). Patients with elevated serum PSA and indwelling catheter after acute urinary retention: prospective study of 63 patients with 7- year follow up (17).

Obesity is a chronic low-level inflammation resulting from excessive fat tissue deposition (18). Low-degree inflammation is known as metaflammation, and immune cells, particularly macrophages, adipocytes in fatty tissues and factors such as tumor necrosis factor alpha and interleukin 6 are affected in metaflammation (19). Macrophage activation in visceral adipose tissue and cytokine production have been shown to be the main source of pro-inflammatory signals in both animal and human studies (13). Obesity has been reported to significantly increase inflammatory markers and to cause chronic systemic diseases and cancers (12,20-22). Higher leukocyte, monocyte, and neutrophil numbers and CRP levels have been observed in obese adolescents compared to lean subjects (12,13). In one systematic review, Parikesit et al. reported that BPH and PCa increase in line with obesity. The mechanisms probably involved in the relation between BPH and obesity are central obesity leading to systemic inflammation, increased intra-abdominal pressure triggering LUTS, changes in estrogen/androgen ratios, increased sympathetic nerve activity, increased oxidative stress and inflammation processes (23). The mechanisms probably involved in the relation between PCa and obesity include changes in insulin/

insulin-like factor and sex hormones with inflammation and signal changes in adipokines (23). In our study, however, waist circumference was highest and only statistically significant in the BMI-3 group in BPH. In our previously study supported to our present study (24). We determined no significant relation between PCa and waist circumference.

Bahadır et al. showed that NLR is not a good marker of inflammation in obese, non-diabetic patients with metabolic syndrome, but that leukocyte count and CRP may be useful biomarkers (15). Toriola et al. assessed PCa risk and inflammation biomarkers and revealed that while leukocyte counts increased, CRP and fibrinogen were unaffected (25). We used CRP and NLR as inflammation markers in this study. Since PSA, CRP and NLR values change depending on BMI, we considered all the parameters together. We developed new formulae. These parameters were compared by measuring their values in BPH and PCa. Chronic inflammation of the prostate was shown in both BPH and PCa (26). Although findings support the idea that inflammation underlies prostate diseases, no definitive evidence has yet been found.

Poudel et al. showed that PSA levels decrease as BMI increases (10). They also reported an increased incidence of PCa in subjects with low BMI (10). Oh et al. also reported that prostate volume increased with BMI, and that in association with this increase, BMI and enlarged prostate have an adverse effect on the determination of PCa when biopsy is performed (11). In our study, however, there was no difference between BPH and PCa in terms of BMI. PSA, CRP, NLR and BMI have been investigated separately in previous studies, and inconsistent results have been achieved in terms of both BPH and PCa (27-29). Neutrophil-to-lymphocyte and neutrophil-to-lmphocyte rates in the decision for a rebiopsi in patients with a previous benign pathology and consistently 2,5-10 ng/ml PSA value (30-31). The purpose of the present study was to evaluate these four parameters together and to identify a patient group for biopsy by comparing the findings in BPH and PCa. When the newly developed formulae were compared, the CRP/PSA ratio, the NLR/PSA ratio, the (CRP/PSA)/(age/100) ratio and the NLR/(PSA/age) were significantly high in BPH, while only (CRP*PSA*age)/100 was significantly high in PCa. The other formulations were not significant in either BPH or PCa. The above newly identified formulae can be used in addition to routine parameters in predicting both diseases. However, prospective controlled studies with larger patient numbers are now needed. In the event that new studies support these findings, these new formulae should be used to predict the diseases. Among these new formulae, CRP/NLR, CRP/PSA, NLR/PSA, (CRP/PSA)/(age/100), and NLR/(PSA/age) exhibited a significant increase in BMI-3 in BPH patients. These formulae can be used to support the diagnosis of BPH.

Both BPH and PCa emerge and increase with age (32,33). BPH is a chronic lifetime disease, with an incidence of approximately 8% in males aged 31-40, increasing with age to 90% by the age of 90 (32). The incidence of PCa also increases with age (32). We encountered no previous study investigating age together with BMI. When age and BMI were considered together in our study, both BPH and PCa emerged earlier in the BMI-3 group. Although prostate diseases are known to increase with age, our study shows that both diseases increase with higher BMI in the elderly population.
Fujita et al. reported that a high neutrophil count is a good marker for PCa and that biopsy is required in the event of a low neutrophil count and high PSA levels (34). In contrast, Cihan et al. reported no statistical significance despite low neutrophil and leukocyte counts in patients with PCa. However, they reported that neutrophil levels rose in patients with BPH (35). In our study we determined no relation between CRP levels or neutrophil and lymphocyte counts and BMI in either BPH or PCa.

NLR has been reported to be effective in predicting prognosis in PCa and progression in BPH (36,37). Although various studies involving different groups have reported that NLR may be significant or insignificant in patients with PCa (28,35,36), NLR can assist with treatment planning in patients with BPH (1,37). We observed the highest increase in NLR values in the BMI-1 group in BPH patients. NLR values decreased as BMI increased with patients with both BPH and PCa.

CONCLUSION

In conclusion, other parameters, and particularly the newly developed formulae described in this study, were more significant in the BPH/BMI-3 group than in the other groups. The combination of PSA, NLR and CRP based on BMI must be considered before biopsy is performed in the TRUS guideline, which is still valid for patients with PCa. We think that the new formulations we have worked to develop can be of clinical use in the event of uncertainly in differentiating between BPH and PCa. However, further similar studies are now needed in order to confirm this. Additionally our results clinically useful in distinction of Prostate Cancer from BPH especially in obese patients.

Conflict of Interest: No conflict of interest.

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