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Original Article

Neutrophil gelatinase- associated lipocalin as a screening test in prostate cancer

Prostat kanserinde tarama testi olarak nötrofil jelatinaz ilişkili lipokalin

Necati Muşlu[1], Bahadır Ercan[2], Serin Akbayır[3], Şenay Balcı[1], H. Didem Ovla[4], Murat Bozlu[5]

ABSTRACT

Objective: Prostate specific antigen (PSA) with digital rectal examination is used for diagnosis of prostate cancer (PCa), where definite diagnosis can only be made by prostate biopsy. Recently neutrophil gelatinase-associated lipocalin (NGAL), a lipocalin family member glycoprotein, come into prominence as a cancer biomarker. This study is aimed to test serum NGAL as a diagnostic biomarker for PCa and discriminate PCa from benign prostatic hyperplasia (BPH).

Material and methods: In this prospective study, 90 patients who underwent transrectal ultrasound-guided 12-core prostate biopsy between May 2015 and September 2015, were evaluated. Histopathologically diagnosed 45 PCa and 45 BPH patients were enrolled in this study. Serum NGAL and PSA levels of all participants were measured, then these data were evaluated by statistical programs.

Results: When sensitivity fixed to 80% specificity of NGAL was better than PSA (49%, 31% respectively). Receiver operating characteristic (ROC) curve analysis showed that NGAL alone or its combined use with PSA have better area under curve (AUC) results than PSA alone (0.662, 0.693, and 0.623 respectively).

Conclusion: In conclusion NGAL gave promising results such as increased sensitivity and a better AUC values in order to distinguish PCa from BPH. NGAL showed a potential to be a non-invasive biomarker which may decrease the number of unnecessary biopsies.

Keywords: Biomarker; cancer; hypertrophy; NGAL; prostate; PSA.

ÖZ

Amaç: Kesin tanısı ancak prostat biyopsisi ile yapılabilen prostat kanseri (PCa) tanısında parmakla rektal muayene ile prostat spesifik antijen (PSA) kullanılmaktadır. Son zamanlarda lipokalin aile üyesi bir glikoprotein olan nötrofil jelatinaz ilişkili lipokalin (NGAL) bir kanser belirteci olarak ön plana çıkmaktadır. Bu çalışma, PCa için bir tanı belirteci olarak serum NGAL'nin benign prostat hiperplazisi (BPH) ve PCa'yı ayırt edebilmesini test etmeyi amaçlamıştır.

Gereç ve yöntemler: Bu prospektif çalışmada, Mayıs 2015 ve Eylül 2015 tarihleri arasında transrektal ultrasonografi kılavuzluğunda 12 kor prostat biyopsisi yapılan 90 hasta değerlendirilmiştir. Histopatolojik olarak tanısı konmuş 45 PCa ve 45 BPH hastası çalışmaya alındı. Tüm hastaların serum NGAL ve PSA düzeyleri ölçüldü, daha sonra bu veriler istatistiksel programlar ile değerlendirildi.

Bulgular: Duyarlılıkları %80'e sabitlendiği zaman NGAL'in özgüllüğü PSA'dan daha iyiydi (sırasıyla; %49, %31). Alıcı işletim karakteristiği (Receiver Operating Characteristic - ROC) eğrisi analizi, NGAL'nin tek başına veya PSA ile birlikte kullanımının tek başına PSA'ya göre daha iyi eğri altında alan sonuçlarına sahip olduğunu göstermiştir (sırasıyla; 0,662, 0,693 ve 0,623).

Sonuç: Sonuç olarak, NGAL daha yüksek duyarlılık ve PCa'yı BPH'dan ayırt etmede daha iyi eğri altında alan gibi umut verici sonuçlar vermiştir. Bulgularımız NGAL'nin gereksiz biyopsi sayısını azaltabilecek non-invaziv bir biyobelirteç olma potansiyeli olduğunu göstermektedir.

Anahtar Kelimeler: Biyobelirteç; kanser; hipertrofi; NGAL; prostat; PSA.

This study was presented as a poster at the 27th National Biochemistry Congress in Antalya, on 03-06 November 2015.

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[1]Department of Biochemistry, Mersin University School of Medicine, Mersin, Turkey

[2]Department of Biochemistry, Dicle University School of Medicine, Diyarbakır, Turkey

[3]Karaman State Hospital, Biochemistry Laboratory, Karaman, Turkey

[4]Department of Biostatistics Mersin University School of Medicine, Mersin, Turkey

[5]Department of Urology, Mersin University School of Medicine, Mersin, Turkey

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Correspondence: Serin Akbayır
E-mail: serinakbayir@hotmail.com

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Introduction

Prostate cancer (PCa) is one of the most frequent solid cancer seen among men.[1,2] Its prevalence increases with increasing average lifespan. Similarly benign prostatic hyperplasia (BPH) is a condition related to aging and consists of prostate tissue enlargement that gives rise to lower urinary tract syndromes. In recent years, with the use of PCa screening tests, PCa can be detected earlier which increases the life quality and decreases rates of mortality caused by PCa. For this purpose annual prostate specific antigen (PSA) screening test is advised to

men over the age of 50. Presence of high PSA level together with detection of a suspicious mass during digital rectal examination (DRE), biopsy and histopathological examination is used as the gold standard method for the diagnosis of PCa.[1-4]

Although there are many biomarkers tested for PCa such as human kallikrein- 2, prostate specific membrane antigen, prostatic acid phosphatase, neuroendocrine biomarkers, none of them is a widely used biomarker as PSA. [5,6] However serum PSA has its own controversies as it reflects malignant character of the prostate as well as the prostate volume. Low specificity of PSA, which is a prostate specific not a cancer specific marker, is the cause of many unnecessary biopsies. Therefore, researchers are still looking for a better biomarker with a higher specificity and sensitivity for PCa.[5-9]

Recently a lipocalin family member glycoprotein neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2, come into prominence as a cancer biomarker.[10-12] It is 25-kDa biomarker, and associated with cellular iron absorption, antibacterial activity and epithelial cell differentiation. NGAL was first discovered in neutrophils, and subsequently shown to be expressed in many tissues and cells. There are numerous studies on NGAL which indicate that it could be used as a tool for the diagnosis and monitoring of many diseases.[10-12] Higher expression levels and release of NGAL have been shown in acute and chronic inflammatory states as is the case with an acute phase reactant, and also in different cancer types (ovarian, colorectal, breast, esophageal, endometrial and prostate cancers). These studies have argued that NGAL and matrix metalloproteinases (MMP) are involved in extracellular matrix degradation by forming a complex, and NGAL can play an important role in the development, progress, and invasion of cancer.[13-17]

The aim of this study is to test serum NGAL levels as a biomarker for distinguishing PCa from BPH. To achieve this goal serum NGAL levels with and without serum PSA levels were compared with serum PSA levels alone in terms of their specificity, sensitivity and area under curve (AUC) values.

Material and methods

This prospective study performed on 45 PCa and 45 BPH patients was approved by Ethics Comittee of Mersin University Clinical Research Institute. All patients were referred to Urology Clinics with lower urinary tract symptoms (LUTS) and/or elevated serum PSA levels between May 2015 and September 2015. Their medical history including age, tobacco and alcohol consumption, hypertension, diabetes and family history of PCa and BPH were recorded. All participants gave written informed consent at the time of recruitment.

Study population

Patients referred to Urology Clinics with LUTS, and/or for a PCa screening with elevated serum PSA levels were subjected to DRE. The indications for transrectal ultrasound-guided 12-core prostate biopsy were abnormal DRE findings and/or an elevated serum total PSA.

Serum PSA and NGAL analysis

Venous blood of all participants were sampled in standart serum separation tubes and transported to a reference laboratory. After a 10 min centrifugation at 4000 rpm, 500 μL of serum aliquoted and stored at -80°C for NGAL analysis. PSA levels were measured immediately after sampling via Advia Centaur XP (Siemens Healthcare Diagnostics Inc, Tarrytown, NY, 10591-5097, USA) autoanalyser. NGAL levels were measured with a rapid ELISA kit (KIT 037, BioPorto Diagnostics, Gentofte, Denmark).

Statistical analysis

Continuous measurements were tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk test. Continuous variables were presented as mean ± standard deviation (mean±SD) and categorical variables were expressed as numbers. Continuous variables were compared across the groups using independent samples t test, and categorical variables with the *chi*-square test. A P value less than 0.05 was considered statistically significant. Diagnostic accuracy of individual biomarkers was measured by receiver operating characteristic (ROC) curve analysis. AUC, sensitivity and specificity values were calculated. Probabilities were calculated for common effect of biomarkers and evaluated by combined ROC analysis.

Results

Forty-five cases with histopathologically diagnosed PCa and 45 patients with BPH were enrolled in this study. Their demographic data including age, family history, alcohol and tobacco consumption, diabetes mellitus and hypertension were given in Table 1. No difference was observed between groups as for their demographic parameters.

Both serum PSA and NGAL levels were statistically higher (p=0.044 for PSA and 0.008 for NGAL) in PCa patients when compared with BPH patients (Table 2). In order to distinguish PCa from BPH, ROC analysis were performed separately for both PSA, NGAL as well as PSA and NGAL in combination (Figure 1). Area under curve (AUC) values for PSA, NGAL and both biomarkers combined were 0.623 (p=0.0369), 0.662 (p=0.0046) and 0.693 (p=0.0005), respectively (Table 3).

When sensitivity levels were fixed to 80% for both tests to see which test has a better specificity to distinguish PCa from BPH,

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Table 1. Demographic variables of the study population

		BPH (n=45)	PCa (n=45)	p
Age (mean±SD) yrs		64.60±9.02	61.98±8.39	0.164
Family history	+	16	9	0.069
	-	29	36	
Alcohol consumption	+	8	6	0.606
	-	37	39	
Tobacco consumption	+	14	6	0.134
	-	31	39	
Diabetes mellitus	+	9	7	0.821
	-	36	38	
Hypertension	+	27	15	0.662
	-	18	30	

BPH: benign prostatic hyperplasia; PCa: prostate cancer; SD: standard deviation

Table 2. Serum PSA and NGAL levels in BPH and PCa patients

	BPH Median (range)	PCa Median (range)	p
PSA (ng/mL)	6.66 (2.39-18.69)	7.75 (3.15-59.47)	0.044
NGAL (pg/mL)	57.1 (23.0-225.7)	78.1 (28.0-197.3)	0.008

BPH: benign prostatic hyperplasia; PCa: prostate cancer; PSA: prostate specific antigen; NGAL: neutrophil gelatinase-associated lipocalin

Table 3. Area under curve with respective 95% confidence intervals and p values of PSA, NGAL, and their combination

	AUC (95% CI)	p
PSA	0.623 (0.52-0.72)	0.0369
NGAL	0.662 (0.56-0.76)	0.0046
PSA + NGAL	0.693 (0.59-0.79)	0.0005

AUC: area under curve; PSA: prostate specific antigen; NGAL: neutrophil gelatinase-associated lipocalin

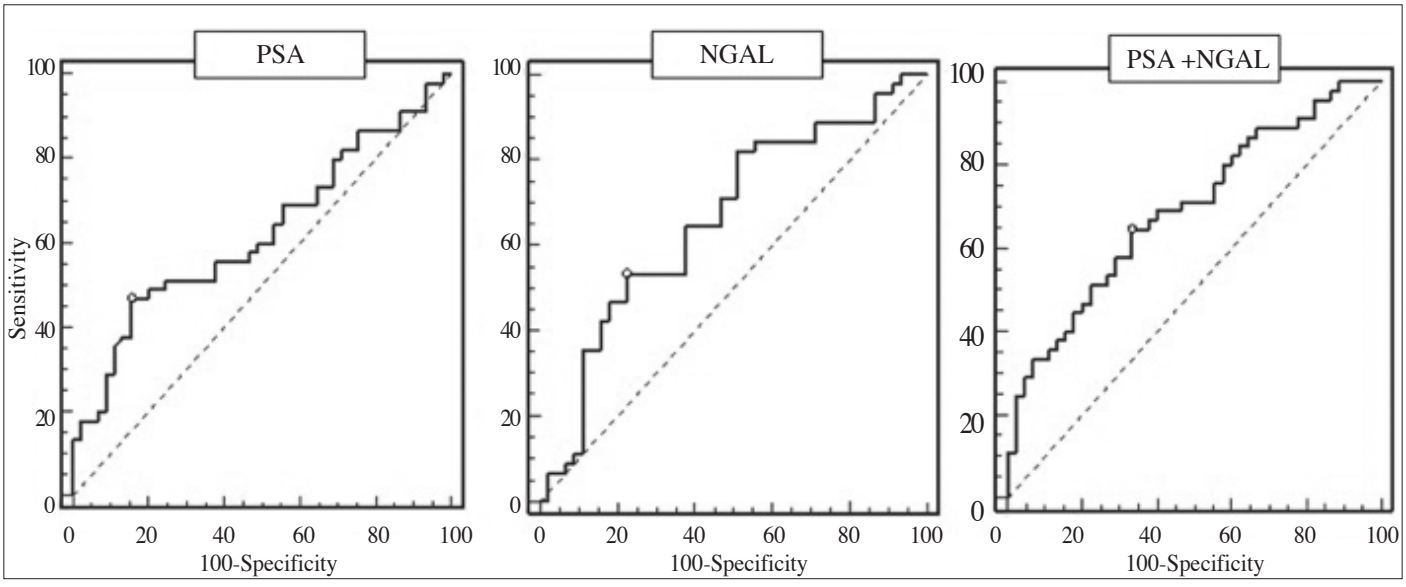


Figure 1. Receiver operating characteristic curves of serum total PSA, NGAL and PSA and NGAL combination

it can easily be seen that NGAL has a better specificity than PSA (49 and 31 %, respectively) (Table 4).

When the sensitivities of PSA, NGAL and their combination were fixed to 64%, specificities rose up to 46%, 62% and 66%, respectively with the cut-off levels shown in Table 5. ROC analysis of both PSA, and NGAL in combination had a better efficiency than both PSA and NGAL alone to distinguish PCa from BPH (Table 5).

Discussion

There is a need for statistically powerful PCa screening tests as in all other cancer types to diagnose the cancer in early stages and to diffentiate it from BPH with an increasing incidence rates within 50-60 years. Typical diagnostic procedure starts with the detection of an increased serum PSA level and a positive DRE and ends up with prostate biopsy. In clinical use PSA is the most important biomarker for PCa. In order to overcome the weak-

Table 4. Specificity values of PSA and NGAL when the sensitivity set to 80% with the relevant cut-off values

Cut-off	Sensitivity (%)	Specificity (%)
PSA >5.1 ng/mL	80	31
NGAL >52.9 pg/mL	80	49

PSA: prostate specific antigen; NGAL: neutrophil gelatinase-associated lipocalin

Table 5. Specificities of PSA, NGAL alone and combined tests when sensitivity set to 64% with the relevant cut-off levels

Cut-off	Sensitivity (%)	Specificity (%)
PSA >6.21 ng/mL	64	46
NGAL >63.1 pg/mL	64	62
PSA >4.94 ng/mL NGAL >84.8 pg/mL	64	66

PSA: prostate specific antigen; NGAL: neutrophil gelatinase-associated lipocalin

ness of the test, particularly its low specificity and sensitivity, age specific PSA levels, PSA increasing rate, PSA density and serum PSA derivatives (free and bound form) were performed but none of them was accepted as a routine laboratory test.[18-22]

When PCa patients compared with healthy people, sensitivity and specificity values of serum PSA levels are about 75% and 55%, respectively. Many of the patients subjected to a biopsy procedure after a screening test received BPH rather than a PCa diagnosis and people were faced complications and costs of unnecessary biopsies.[23,24]

As in this study when PSA levels are used to distinguish PCa from BPH at a fixed sensitivity level of 80%, specificity of PSA decreases down to 30 percent. Actually PSA levels with a cut-off value of 4 ng/mL is generally used for biopsy decision rather than a cancer marker. Diagnostic power of PSA is reasonable for distinguishing cancer patients from healthy people but it is insufficient to discriminate between BPH, and PCa. For this reason, there is a need for a biomarker with a higher specificity and sensitivity that will help to reduce the number of unnecessary biopsies and enable early diagnosis of PCa.

Neutrophil gelatinase-associated lipocalin which is a member of lipocalin family is involved in many events such as immune response, iron transport, cellular growth and regulation of metabolism.[10,11] It has a role in apoptosis, carcinogenesis, growth and differentiation of normal and neoplastic tissues, invasion and metastasis of cancer cells. Increased serum NGAL concentrations have been accepted as a prognosis- related independent variable in different types of cancer.[13,16,17,25-28]

Although there are studies showing that increased serum NGAL levels indicate a relation with PCa diagnosis and poor prognosis, there is no study investigating possible role of NGAL in discrimination between benign, and malign diseases of the prostate.[29-31] In this study, potential role of NGAL in minimizing unnecessary biopsies as a biomarker was investigated and NGAL levels were found to be significant higher than PSA in PCa patients relative to BPH patients.

Receiver operating characteristic curve analysis is a good tool to manifest the characteristics of a biomarker.[32] In our study when we compared AUC values of PSA and NGAL both separately or in combination, we observed that AUCs of NGAL alone and NGAL-PSA combination have statistically significant higher values than those of PSA alone.

When determining a cut-off value for ROC curve analysis data that represents a better trade off between sensitivity and specificity, at a fixed and high sensitivity level, selecting the screening test with higher specificity is the main strategy for achieving improved outcomes. Using this strategy, at a similar and higher sensitivity value we set for both NGAL and PSA, we observed that despite NGAL and PSA demonstrated lower specificities, NGAL had a much better specificity than PSA (49, and 31%, respectively). The importance of this finding is that NGAL is a tissue non-specific marker which is known to be under influence of many benign conditions, and had a better specificity than a tissue specific marker, PSA. This result also gives rise to thought a cancer specific marker.[22,23]

In combined PSA and NGAL analysis, when a cut-off value with high sensitivity for PSA and a cut-off value with high specificity for NGAL were set, we observed that this combination discriminated PCa from BPH more efficiently. However more studies are needed to define more accurate cut-off values for both NGAL alone and PSA-NGAL combination.

Our results suggest that as a screening test serum NGAL concentrations have better specificity than serum PSA levels when discriminating PCa from BPH in patients with abnormal DRE findings. Although NGAL showed a potential to be a non-invasive biomarker which may decrease the number of unnecessary biopsies, more accurate results can be achieved by increasing the number of cases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Mersin University School of Medicine (2015/154).

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Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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