THIOREDOXIN REDUCTASE AS BIOMARKER FOR DIFFERENTIAL DIAGNOSIS OF PROSTATE CANCER

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ABSTRACT

AIM

This study was aimed to determine whether serum thirodoxine reductase (TR) levels would be a prognostic marker or risk assessment factor in patients with prostate cancer and to investigate whether it could differentiate prostate cancer (PCa) from benign prostate hyperplasia (BPH).

PATIENTS AND METHODS

We enrolled 35 patients with PCa subclassified into 2 groups (group1 PCa: 11 patients with Prostate specific antigen (PSA) less than 10 ng/ml and group2 PCa: 24 patients with PSA more than 10 ng/ml)), 42 patients with BPH, and 27 healthy individuals. Serum TR and PSA levels was measured by ELISA and was compared among all groups. All statistical analyses were calculated using ANOVA software and graph pad prism version 6.

RESULTS

We found statistically significantly increased levels of TR in serum of patients diagnosed with PCa (group 1 and 2 PCa) vs. patients with BPH and healthy subjects at $P \leq 0.0001$ while there was no significant difference in PSA level between group 1 PCa and control (BPH and healthy)

CONCLUSION

The assessment of serum TR in addition to PSA appears to be of great benefit for a more accurate differential diagnosis of BPH and PCa.

KEYWORDS: TR; PSA; biopsy; PCa; BPH

Introduction

Prostate cancer is the fourth cause of death in men worldwide. Due to the magnitude of the impact over public health, strong efforts have been made aiming the prevention, early diagnosis, and treatment of this disease ***(Miotto et al., 2004 and Miyoshi et al., 2014)***.

It has been found that Africa carries an increasing cancer burden, and men of African heritage have been found to have earlier age of diagnosis of the disease and more advanced cases of the disease ***(American Cancer Society, 2013 and Siegel et al., 2014)*** and are almost four times more likely to die of the disease when compared to their Caucasian male counterparts ***(Gomez, 2012)***. Current data from most parts of the country indicate that prostate cancer is the 3rd most common cancer ***(Kolawole, 2011)***. Benign prostate hyperplasia (BPH) is a condition that affects as many as 62% of men aged 50 years and above. Traditionally, the two conditions are considered as two distinct and unrelated diseases, although several issues suggest possible linkages. Specifically, both are hormone dependent, their incidence increases with age, and they often coexist in the same patients and are determined by a complex interaction of endogenous and exogenous factors ***(Alcaraz et al., 2009)***. However, there is no proven causal relationship between BPH and PCa (although both conditions may be associated with certain forms of hyperplasia), and BPH is not considered to be a premalignant lesion or a precursor of prostate carcinoma ***(Bostwick et al., 2004)***. Factors such as cellular senescence, inflammation, and oxidative stress have been described as key players in the process of prostate carcinogenesis ***(Shen and Abate-Shen, 2010)***.

The incidence rates and 5-year survival rates are heavily influenced by the introduction of serum prostate-specific antigen (PSA) and widespread screening ***(Brawley, 2012)***. Although it remains controversial, screening appears to be effective in reducing mortality from PCa, especially if screening and treatment are freely available to all patients ***(Carter et al., 2013)***. The American Cancer Society recommends that beginning at age 50, a PSA blood test and digital rectal examination (DRE) should be offered to men annually ***(Smith et al., 2004)***. Unfortunately, PSA screening cannot distinguish the early stages of PCa from benign prostatic hyperplasia (BPH) effectively, especially when the PSA levels are within 4-10 ng/ml range. Biological evidence suggests that benign prostatic hyperplasia and prostatic carcinoma share common predisposing factors ***(Wu et al., 2014)***.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are not only byproducts of normal cellular metabolism, but also play important roles in cell signaling. Studies have shown that oxidative stress (OS) conditions play an important role in both the initiation and the progression of prostate cancer by regulating molecules such as DNA, enhancers, transcription factors, and cell cycle regulators ***(Gupta-Elera et al., 2012)***. The relevance of OS in prostate carcinogenesis is suggested by associations between prostate cancer and conditions associated with OS as well as medications and nutrients that affect OS level ***(Pathak et al., 2005).*** Several studies have identified a link between OS and PCa using tissue level markers such as 8-hydroxydeoxyguanosine ***(Arsova-Sarafinovska et al., 2009)***.

Redox imbalance has long been recognized to be a factor in the pathology of PCa ***(Chaiswing et al., 2014)***. One of the major redox control systems is the thioredoxin system comprised of thioredoxin (TRX) and TR ***(Lin et al., 2013)***. The mammalian TR are a family of selenium-containing pyridine nucleotide-disulphide oxidoreductases with mechanistic and sequence identity, including a conserved catalytic site to glutathione reductases ***(Mustacich and Powis, 2000)***. TRs catalyse the NADPH-dependent reduction of the redox protein TRX, as well as of other endogenous and exogenous compounds. Secretion of TR under conditions of oxidative stress and inflammation has been observed from many neoplastic cells ***(Lincoln et al., 2002)***. TR over-expression has been reported in several malignancies (colorectal, prostate and hepatocellular carcinomas) and may be associated with aggressive tumor growth and poor outcome ***(Mollbrink et al., 2014)***. The aim of our study was to determine whether TR were detectable in serum, and whether the TR can distinguish PCa from age-matched BPH or healthy controls. Finally, the diagnostic value of TR combined with routine biomarkers such as PSA was also investigated.

Subjects and methods

Subjects

In our study, 35 consecutive patients with PCa and 69 age-matched controls (42 patients with BPH and 27 healthy individuals) recruited from El – Sahel Teaching Hospital, Cairo, Egypt from January 2014 to May 2014.

Patients with PCa and BPH were initial diagnosis without any treatment. Subjects with other conditions, which may alter TR, such as previous concomitant other neoplasms, inflammatory, diabetes, chronic kidney disease, severe burn injury and cardiovascular diseases, were excluded. The diagnosis for each case including BPH and PCa was confirmed by fine needle aspiration biopsy histopathology examination by the urologist using the National Comprehensive Cancer Network guidelines ***(Kawachi et al., 2007)***.

The healthy age-matched men from routine physical exam including DRE, B-mode ultrasound prostate scan, and International Prostate Symptom Score were selected as normal control population. There were no significant differences in demographic or clinicopathological characters of patients with PCa. Ethics Committee-approved protocol and written informed consent was obtained from all participants.

Clinical variables

Demographic and pre-biopsy clinical parameters, including age, history of smoking, height, weight, Body mass index (BMI), family history of PCa, history of previous prostate biopsy, DRE findings and pre-biopsy PSA were obtained using interviewer-administered questionnaires and abstracting data from patients' medical records. The patients with PCa were graded using the Gleason system ***(Gleason, 1988)***.

Laboratory testing

The preoperative serum PSA and TR levels were simultaneously measured in the patients and control using standard methods at admission. Venous blood samples were taken in the morning's fasting state. After at least 30 min, but within 2 h, the tubes were centrifuged at 20°C for 15 min at 1200 g, and the sera were stored frozen in plastic vials at -80°C until the time of consecutive analyses. The controls samples were collected and stored in the same way as the PCa samples. Total PSA concentration was determined using solid phase two-site immunoassay (ELISA) method of ***Stowell et al., 1991*** using AccuDiag—PSA ELISA kits from Diagnostic Automation/Cortez Diagnostics, Inc., USA. Serum levels of TR was measured using a solid-phase sandwich ELISA that uses two highly specific antibodies to human TrxR protein (BioVision Incorporated, Milpitas Boulevard, Milpitas, CA, USA) according to the manufacturer's instruction. For all measurements, levels that were not detectable were considered to have a value equal to the lower limit of detection of the assay.

All data were analyzed by SPSS v.17 (SPSS Inc, Chicago, Illinois, USA) using descriptive statistics. Analytical data were analyzed via one way ANOVA software and graph pad PRISM version 6.

Results

In our study, we recruited 104 participants overall. The mean ages of the PCa groups were 62 (range, 55-69), BPH were 63 (range 55-69) and healthy were 61(range 55-69) years. All participant baseline characteristics (age, smoking, family history of PCa and BMI) were matched. Baseline characteristics of the PCa and control cases were shown in **table 1.**

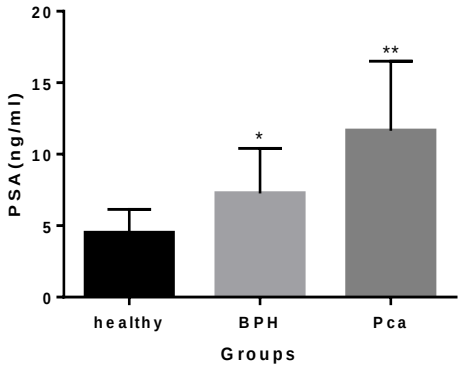
The mean value ± SEM of serum TR in PCa group was 20.3±0.86U/ml, which was significantly higher than that of healthy subjects 4.89±0.25 and patients with BPH 5.83±0.38 ($P < 0.0001$; **Figure 1b**). Although M±SEM of PSA in serum was increased for patients in the PC group compared with that in healthy controls, as expected ($P < 0.001$), but also a significant increases were also seen in patients with BPH ($P < 0.01$; **Table 1** and **Figure 1a**).

Table 1: Baseline characteristics of the PCa and control cases

Characteristics		PCa	Control	
			BPH	Normal
No		35	42	27
Age (Years)	M±SEM	62±1.4	63±1.3	61±1.3
	Range	55-69	55-69	55-69
Smoking	(%)	19 (54%)	26(61%)	14(52%)
Family history	(%)	3(8.5%)	2(4.7%)	2(7.4%)
BMI	M±SEM	25.2±0.5	25.3±0.4	25.2±0.4
	Range	23.4-27.5	23.4-27.5	23.4-27.5
DRE	(+, -)	+	+	_
Lab finding				
Serum PSA (ng/ml)	M±SEM	11.6±0.82**	7.25±0.47*	4.49±0.31
	Range	2.10-19.1	2.10-12.3	2.20-8.10
Serum TR (U/ml)	M±SEM	20.3±0.86**	5.83±0.38	4.89±0.25
	Range	8.50-26.9	2.10-10.3	3.10-7.60

PC = Prostate cancer; PSA = Prostate-specific antigen; DRE = Digital rectal examination; BPH = Benign prostatic hyperplasia; TR = Thioredoxin reductase; BMI = Body mass index; M= mean; SEM= standard error of mean.

1a



1b

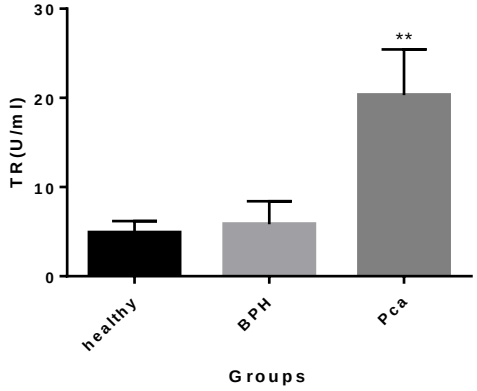


Figure 1: Descriptive statistics of PSA(ng/ml) and TR(U/ml) in studied subjects

* Significant different from healthy group at p≤0.01

** Significant different from control groups at p≤0.0001

Patient with PCa subclassified into two groups according to serum PSA level. **Table 2** shows M±SEM, range and 95% CI of serum PSA (ng/ml) and serum TR (U/ml) in different studied groups.

Table 2: Results for measurement of serum TR, PSA, or both in the diagnosis of PCa

		PCa		Control	
		Serum PSA≤ 10 ng/ml	Serum PSA ≥ 10.1ng/ml	BPH	healthy
Serum PSA (ng/ml)	M±SEM	5.50±0.58	14.4±0.54**	7.25±0.47	4.49±0.31
	Range	2.10-8.10	10.1-19.1	2.10-12.3	2.20-8.10
	95% CI	4.20-6.81	13.3-15.5	6.31-8.21	3.84-5.14
Serum TR (U/ml)	M±SEM	14.3±1.04**	23.0±0.62**	5.83±0.38	4.89±0.25
	Range	8.50-17.3	18.6-26.9	2.10-10.3	3.10-7.60
	95% CI	12.0-16.7	21.7-24.3	5.06-6.67	4.38-5.40

In our study, 11 patients (31.4%) were classified as serum PSA level less than10ng/ml. The mean level± SEM of serum TR in those patients was 14.3±1.04U/ml, which was significantly higher than in BPH 5.83±0.38U/ml and healthy 4.89±0.25U/ml; P < 0.001; **Table 2 and Figure 2**. In contrast, the mean level± SEM of serum PSA in PCa patient with serum PSA less than 10 ng/ml was none significantly different from BPH and healthy subjects.

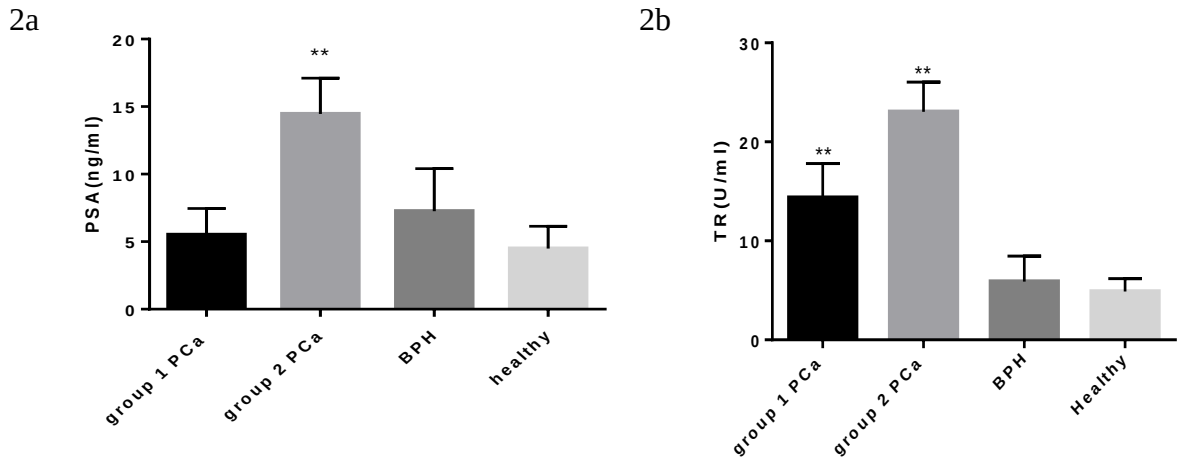


Figure 2: Descriptive statistics of PSA(ng/ml) and TR(U/ml) in studied subjects

** Significant different from control groups at p≤0.001

Dissection

Morphology-based approaches, especially Gleason scoring, combined to clinical parameters of PSA and cancer stage have provided clinicians some important prognostic information about PCa. Recent successes have served to cultivate the growing interest in discovering more molecular-based prognostic factors ***(Chakravarti and Zhai, 2003)***. Such biomarker should be quickly quantifiable in accessible biological fluids without any overlapping to untreated and healthy people; moreover, they should be consistent, cost-effective, readily interpretable by clinicians, prostate-specific, able to differentiate cancerous prostate and its stages from prostatic hyperplasia, evaluate the survival of the patients as well as response to treatment ***(Madu and Lu, 2010)***.

There are several lines of evidence suggesting that OS is linked to the development of PCa ***(Gupta-Elera et al., 2012 and Yang et al., 2015)***. PCa is commonly associated with a shift in the antioxidant-prooxidant balance towards increased OS. Previous studies highlighted the altered prooxidant-antioxidant status in prostatic tissue of man, rat and also in cell lines, where the imbalance between these antagonist played a major role in the initiation of prostate carcinogenesis ***(Ripple et al., 1997)***. Another major component involved in the maintenance of redox balance in the cell is the glutathione oxidation-reduction system. Somatic mutations, causing inactivation of the glutathione S-transferase gene (GSTP1) have been identified in almost all the prostate cancer cases examined by ***Nelson et al., 2004***. Therefore, the sensitive balance between the oxidant and antioxidant components of the cells and their regulatory mechanisms seem to play a major role in developing a malignant state in prostate tissue. In the present study, we first evaluated the different serum levels of TR, an OS biomarker in Egyptian PCa and BPH patients.

In our study, we firstly suggested that serum TR may be a novel marker of PCa in Egyptian sample. Comparing results from patients with BPH and PCA we found that TR was superior to PSA in diagnosing PCa. Importantly, the PCa patients with PSA less

than10ng/ml had a positive TR. In addition, the level of TR tended to increase as PCa disease progressed as seen in PCa patients with PSA level more than 10ng/ml. Similarly, previous studies had suggested that OS markers play importantly role in the PCa diagnose, prevention and treatment. ***Antognelli et al., 2013*** pointed out a significant role for Glyoxalase 1 in PCa progression, providing an additional candidate for risk assessment in PCa patients and an independent prognostic factor for survival. ***Barocas et al., 2011*** reported that F2-isoprostanes may also serve to estimate the efficacy of interventions targeting OS mechanisms in PCa prevention or treatment. ***Kumar et al., 2008*** suggested that therapies aimed at reducing ROS production might offer effective means of combating prostate cancer in particular.

PSA is one of the most widely used biomarkers for PCa. Although PSA is an organ-specific marker, it is not disease-specific and raised serum levels can occur in many benign conditions such as BPH or prostatitis as well as manipulations (bicycling, digital rectal examination, and catheterization) of the prostate can also cause elevated PSA serum concentrations ***(Stephan et al., 2014)***. Currently, early detection of PCa relies primarily on an abnormal DRE and an elevated PSA level leading to a prostate biopsy ***(Lucarelli et al., 2012).*** However, because of the low specificity of PSA, up to 75% of men with PSA levels of 4-10 ng/ml and/or a suspicious DRE have a negative first biopsy ***(Thompson et al., 2004)***. Thus, the vast majority of patients subjected to biopsy have negative results, so there is clearly a need for better means to select whom to biopsy. There have been several modifications to serum PSA assessment to improve the test's performance, including recourse to age-specific PSA levels, PSA density, and free-to-total PSA ratios ***(Shariat et al., 2008)***. Meanwhile, many biomarkers have been developed, such as: free PSA (fPSA) and A [-2] pro PSA ***(Stephan et al., 2009)***. In our study, according to the results of TR, the patients with BPH did not need unnecessary biopsies. This will significantly reduce the rate of over-detection and treatment.

Whether higher circulating level of TR is an accelerator or only is a marker of PCa remains uncertain. It is important to discuss whether TR in PCa patients has pathological roles or just is as indicator of OS or inflammation.

Conclusion

In conclusion, these study report the clinically diagnostic relevance of TR as a serum protein marker for PCa. Nevertheless, our study has demonstrated the additional benefit of TR measurement in the diagnosis of PCa in the Egyptian population. Further studies of the application of TR in this region may be beneficial. Moreover, TR levels were related with disease progressed in this subset of patients, suggesting that this marker may be a further tool not only for diagnosing PCa but also for predicting.

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الثيرودوكسين ريداكتيز كدلالة للتشخيص التفريقي لسرطان البروستاتا

للسادة الدكاترة

هشام محمد جاد – احمد محمد السيسي – احمد عبد الله علي

مـــــــــــــن

قسم الكيمياء الحيوية – كلية الصيدلة (بنين) جامعة الازهر – القاهرة

تهدف الدراسة لتحديد مستوى انزيم الثيرودوكسين ريداكتيز في عينات الدم كدلالة للتوقع الاصابة بسرطان البروستاتا واستخدام هذه النتائج في معرفة اذا كان يمكن التفرقة بين سرطان البروستاتا والتضخم الحميد لتلك الغدة باستخدام انزيم الثيرودوكسين ريداكتيز.

وقد اجريت الدراسة على اجمالى ٩٤ شخص منهم ٣٥ شخص مصاب بسرطان البروستاتا و ٤٢ شخص مصاب بتضخم البروستاتا الحميد و ٢٧ من الاشخاص الطبيعين كمجموعة ضابطة.

وقد بينت الدراسة ارتفاع انزيم الثيرودوكسين ريداكتيز في كل الاشخاص المصابين بسرطان البروستاتا سواء كان هناك ارتفاع ملحوظ في الانتيجين الخاص بالبروستاتا او لا يوجد . ومن هذا يتضح ان الثيرودوكسين ريداكتيز انزيم يمكن استخدامه كدلالة مبكرة على الاصابة بسرطان البروستاتا.