

Original Research Article

Is serum glutathione level in combination with serum PSA useful for early detection of prostatic carcinoma? A local study of Iraq

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ABSTRACT

Background: Prostate cancer is the most common cancer and the second leading cause of cancer-related death among men of western countries. The aim of this study is to develop non-invasive diagnostic tools for the early detection of prostate cancer (PCa) through detection of low level of Serum reduced Glutathione (GSH).

Methods: Serum samples from men being evaluated for PCa were analyzed for reduced Glutathione (GSH) level. The results were compared with the prostate needle biopsy findings and (PSA) level combined with Digital Rectal Examination (DRE). Samples were obtained from 59 cases including 18 controls.

Results: The maximum sensitivity of the test was observed in the first category of confirmed cases with 93.33% true positive detected with low GSH. Among those highly suspected Ca prostate there was 87.5% true positive test and 12.5% false negative results. Among those in grey zone where PSA between is 4 and 10, and DRE is suggestive, the proportion of true positive was 50%.

Conclusions: These results demonstrate that serum reduced Glutathione (GSH) level is helpful in patient with definite carcinoma. This test could be useful in augmenting current PCa diagnostic procedures. For example, the examination test for reduced Glutathione (GSH) level with an elevated prostate- specific antigen level might be used in predicting which patients will have negative biopsies and may be used as treatment modality for PCa.

Keywords: Glutathione, Molecular marker, Prostate cancer

INTRODUCTION

Carcinoma of the prostate is the second leading cause of male cancer-related death on the United States, and it is estimated that in 2003 there were approximately 220,900 new cases and 28,900 death from this disease.¹ Since the introduction of serum prostate-specific antigen (PSA) screening of asymptomatic population, prostate cancer incidence rates have increased dramatically, as has the number of men undergoing radical prostatectomy and radiation therapy for this disease.² However, false positives for PSA continue to be a significant problem resulting in unnecessary biopsies and the value of broad-based PSA testing with regard to predicting surgical cures has recently come into question.³ Currently, there are no

markers that differentiate clinically relevant from clinically benign disease. Better indicators of prostate cancer presence and progression are needed to avoid unnecessary treatment, predict disease course, and develop more effective therapy.⁴ A variety of putative prostate cancer markers have been described in human serum, urine, seminal fluid, and histological specimens. These markers exhibit varying capacities to detect prostate cancer and to predict disease course. Prostate cancer rarely causes symptoms early in the course of the disease because the majority of adenocarcinomas arise in the periphery of the gland distant from the urethra.⁵ The presence of periphery of the gland distant from the urethra. The presence of symptoms as a result of prostate cancer suggests locally advanced or metastatic disease.

Growth of prostate cancer into the urethra or bladder neck can result in obstructive (e.g., hesitancy, decreased, force of stream, intermittency) and irritative (e.g., frequency, nocturia, urgency, urge incontinence) voiding symptoms. Local progression of disease and obstruction of the ejaculatory ducts can result in hematospermia and the finding of decreased ejaculate volume. Impotence can be a manifestation of prostate cancer that has spread outside the prostatic capsule to involve the branches of the pelvic plexus (neurovascular bundle) responsible for innervation of the corpora cavernosa.⁶

Oxidative stress has been associated with prostate cancer development and progression due to an increase of reactive oxygen species (ROS).⁷ However, the mechanisms whereby ROS and the antioxidant system participate in cancer progression remain unclear. Alteration in oxidative and nitrosative stress as well as antioxidant status is known to occur in carcinogenesis and during treatment of cancer with chemotherapeutic drugs.^{8,9} The current method of detection and screening of prostate cancer rely mainly on serum PSA level and biopsy. However, these two procedures come with limitation in terms of cost and false positive results. In order to find a compliment for this test we undertook this study to assess the accuracy of Serum reduced Glutathione (GSH) in detection of prostate cancer.

METHODS

Study subjects were recruited from the al AL-Yarmouk teaching hospital, Baghdad, and AL-Ramadi teaching hospital, Anbar from January 2015 to February 2018.

Fifty-nine patients with adenocarcinomas of the prostate (cases) were recruited from the Urology Units of these hospitals. Eligibility criteria for cases were: age 45 or more, histologically proven adenocarcinomas of the

prostate and ability to give informed consent. Eligibility for controls was age 45 or more, male gender, and lack of any malignancy, with normal liver function test.

After giving informed consent, studied group (patients and control) were asked through a questionnaire regarding age, occupation, past medical and surgical history, and family history of cancer. Five ml of peripheral blood were taken from each subject, centrifuged, and freezed down to (-10to20) to be analyzed.

Serum GSH was determined by using a modified procedure using Elman's reagent (DTNB).⁹ Tubes are mixed in vortex intermittently for 10-5 minute, and centrifuged for 15 minutes at 3000xg, then pipetted to test tubes. Tubes are mixed in vortex mixture. The spectrophotometer is adjusted with reagent blank to read zero absorbance (A) at 412nm. All patients underwent serum PSA level assay, biopsy and DRE and were grouped into 6 categories according to the diagnosis.

RESULTS

The GSH concentration in sera of healthy adult male ranged 17.87 to 38.23uM. Ninety-five samples were analyzed of whom 18 were normal controls. In category I with true cut biopsy proved CaP with mean age 68.54 years there was 15 patients. Out of those, 14 case result had reduced level of GSH i.e. 93.33% of this category result a positive test. This results in 6.66% false negative test.

In category II with true cut biopsy proved CaP, and are on Anti androgen therapy (AAT), there was 3 cases with mean age of 71.33 years. Out of those, 2 cases result normal level of GSH. i.e.66.67% of this category result a false negative test.

Table 1: Characteristics of the study sample.

Category	n	Mean age years	Diagnosis	Biopsy	% of + ve GSH test	% of - ve GSH test	PSA	DRE
I	15	68.54	CaP	+ ve	93.33	6.66	>20	+ ve
II	3	71.33	CaP + AAT	+ ve	33.33	66.67	>20	+ ve
III	8	67.87	High sus. CaP	Repeated - ve	87.5	12.5	>15	+ ve
IV	6	64.36	Grey area	No Bx.	50	50	4 <10	+/-
V	9	66.01	BPH	No Bx.	88.88	11.11	<4	-ve
VI	18	58.76	Healthy control	No Bx.	0	100	Not done	Not done

In category III, there was 8 patients with mean age 67.87 years who are highly suspected CaP i.e. PSA more than 15, and highly suspected DRE, but with repeated negative biopsies. Of those, 7 cases result reduced level of GSH yielding 87.5% true positive test and 12.5% false negative results. In category IV, there was 6 cases with

mean age 64.36 years in grey zone i.e. PSA between 4 and 10, and DRE is suggestive. Out of the 6 patients, 3 cases result reduced level of GSH i.e. 50% of this category was true positive test. the other 3 cases result normal level of GSH i.e. 50% of this category result a negative test. In category V, there were 9 cases with

mean age 66.01 years had BPH without any evidence of any malignancy, normal PSA. Out of total, 8 cases result normal level of GSH i.e. 88.88% of this category result a negative test while 11.11% of this category result a positive test (Table 1).

DISCUSSION

Prostatic cancer is rarely symptomatic early in its course, as the majority of malignancies arise in the peripheral portion of the gland away from the prostatic urethra. Symptomatic presentation often implies local extension or even metastatic disease.¹⁰

In this clinical biochemical study, we tried to measure the level of Glutathione in the sera of patients of different presentation combined with PSA and DRE in correlation with normal healthy subjects, or Benign Prostatic Hypertrophy (BPH) patients without evidence of malignancy. Such approach would provide an insight about the utility of the newly used marker.¹¹

We used double blind method for analysis, in which neither the investigator nor the biochemist knows cases to avoid bias testing.¹² We found that level of GSH is significantly reduced in patients with proved CaP, as well as it significantly reduced the third category group with insignificant reduction in the fourth category; the grey zone. Also, the level of GSH is normal in both the BPH and healthy control categories.

Despite the elevated GSH level apparently confusing in the second category i.e. CaP and on antiandrogen therapy, this elevated GSH level carries a very significant value, putting in mind that physiologic levels of androgens are capable of increasing oxidative stress in androgen-responsive LNCaP prostate carcinoma cells.¹³

The evidence suggests that this result is due in part to increased mitochondrial activity. Androgens also alter intracellular glutathione levels and activity of certain detoxification enzymes, such as gamma-glutamyl transpeptidase, that are important for maintenance of the cellular prooxidant- antioxidant balance.^{14,15} In addition, the antiandrogen therapy may abolish this oxidative stress leading to elevation of GSH level.

CONCLUSION

From this study we conclude that determination of GSH level easy, non-invasive to the patient, and carries a significant value in differentiation between benign and malignant or potentially malignant prostatic condition especially if adjunct with the triad of DRE, serum PSA, and TRUS-directed prostatic biopsy. Furthermore; it carries significant value in predicting the response to the antiandrogen therapy as it reflects reversal of androgen induced oxidative stress, and this may lead us to study its potential value as a therapeutic agent in treatment of CaP and other hormone dependent malignancies. We

recommend using the level of GSH as a marker or indicator for predicting, diagnosing, following up, and responding to treatment of patients with prostatic carcinoma.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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