Correlation between Testosterone Hormone Levels and Prostate Cancer: A Case-Control Study

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Abstract:

Background:

Prostate cancer is the most commonly diagnosed male cancer in Sudan. Testosterone, a hormone necessary for the development of the prostate, has been considered for over 70 years as a potential inducer of proliferation in both normal and cancerous cells.

Objectives: This study aims to examine the association between prostate cancer and serum testosterone levels, and to explore the potential of testosterone as a diagnostic biomarker.

Materials and Methods:

This is Case-Control study was conducted in Khartoum, Sudan during 2009-2010. The study included 40 men confirmed prostate cancer patients and 40 volunteers as controls, matched for aged 40-89 years. Serum testosterone levels were measured using a Human ELISA kit, following the manufacturer's

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instructions (leaflet of the ELISA kits, using the principle of ELISA). The study was approved by the University Of Khartoum Faculty Of Science and followed ethical guidelines set forth by the University of Khartoum and Radiation and Isotopes Center of Khartoum (RCIK). Patient samples were provided by RCIK and demographic and clinical data was extracted from their medical records.

Results:

The majority of prostate cancer cases (75%) had below-normal testosterone levels (3.5-8.6 ng/ml), while 15% had elevated levels and 10% were within the normal range. Prostate cancer patients had significantly lower mean testosterone levels (2.772 ng/ml) (95% CI 5.8456-7.9644 compared to controls (6.90 ng/ml) (95% CI 5.8456- 7.9644) P value=0.000 and odd ratio =0.

Conclusion:

This study suggests a strong correlation between low testosterone levels and prostate cancer (P = 0.000). Serum testosterone may have potential as a diagnostic biomarker for prostate cancer, indicating the possibility of future diagnostic applications.

Keywords: Prostate cancer, Testosterone, ELISA

العلاقة بين مستويات هرمون التستوستيرون وسرطان البروستاتا: دراسة الحالات والشواهد

خلاصة:

خلفية:

يعد سرطان البروستاتا من أكثر أنواع السرطان التي يتم تشخيصها عند الذكور في السودان. يعتبر هرمون التستوستيرون، وهو هرمون ضروري لنمو البروستاتا، لأكثر من 70 عامًا كمحفز محتمل للتكاثر في كل من الخلايا الطبيعية والسرطانية.

الأهداف: تهدف هذه الدراسة إلى فحص العلاقة بين سرطان البروستاتا ومستويات هرمون التستوستيرون في الدم، واستكشاف إمكانات هرمون التستوستيرون كمؤشر حيوي تشخيصي.

المواد والطرق:

أجريت هذه الدراسة للحالات والشواهد في الخرطوم، السودان خلال الفترة 2009–2010. شملت الدراسة 40 رجلاً مصابين بسرطان البروستاتا و40 متطوعًا كعناصر تحكم، تتراوح أعمارهم بين 40 و89 عامًا. تم قياس مستويات هرمون التستوستيرون في الدم باستخدام مجموعة ELISA البشرية، باتباع إرشادات الشركة المصنعة (نشرة مجموعاتELISA ، باستخدام مبدأ .(ELISA تمت الموافقة على الدراسة من قبل كلية العلوم بجامعة الخرطوم واتبعت المبادئ التوجيهية الأخلاقية التي وضعتها جامعة الخرطوم ومركز الخرطوم للإشعاع والنظائر (RCIK) تم تقديم عينات من

المرضى بواسطة RCIK وتم استخراج البيانات الديموغرافية والسريرية من سجلاتهم الطبية.

نتائج:

كانت غالبية حالات سرطان البروستاتا (75٪) لديها مستويات هرمون تستوستيرون أقل من الطبيعي (3.5–8.6 نانوغرام / مل)، في حين أن 15٪ كانت لديها مستويات مرتفعة و10٪ كانت ضمن المعدل الطبيعي. كان لدى مرضى سرطان البروستاتا انخفاض ملحوظ في متوسط مستويات هرمون التستوستيرون (2.772 نانوغرام/مل) (95–5.8456 % CI 7.9644مقارنة بالضوابط (6.90 نانوغرام/مل) (95–5.8456 % CI 7.9644)قيمة P = 0.000 ونسبة غريبة OR= 0.

خاتمة:

تشير هذه الدراسة إلى وجود علاقة قوية بين انخفاض مستويات هرمون تستوستيرون وسرطان البروستاتا .(P = 0.000) قد يكون لهرمون التستوستيرون في الدم إمكانات كمؤشر حيوي لتشخيص سرطان البروستاتا، مما يشير إلى إمكانية تطبيقات التشخيص المستقبلية.

الكلمات المفتاحية: سرطان البروستاتا، التستوستيرون، إليزا

Introduction:

Prostate cancer is the most common cancer in men. It carries a high morbidity and mortality rate, especially when not diagnosed early. In resource-limited countries, patients tend to be diagnosed late, resulting in delayed surgery for benign prostate hypertrophy (BPH). The incidence rates of prostate cancer are increasing, particularly in limited-resource countries like South Sudan. A pooled study from the African Cancer Registry Network showed a significant rise in prostate cancer incidence in sub-Saharan Africa (Seraphin et al., 2021). Globally, prostate cancer, an adenocarcinoma, is an increasingly important health burden. It is estimated that 0.9 million cases and 0.26 million deaths from prostate cancer occur annually. It is the second-leading cancer in men and the fifth-leading cause of malignancy worldwide (Samtal et al., 2022). However, there is a wide variation in prostate cancer occurrence in developed countries, with the highest number of new cases (180,890) and deaths (26,120) recorded in the USA in 2016 (Aguer et al., 2023). In Sudan, prostate cancer is the most common cancer in men, according to data from the Sudanese Radiation and Isotopes Center of Khartoum (RICK) (Abdullah et al., 2015). The incidence of prostate cancer has increased in Sudan in the past two decades (Abuelgasim, 2018), resulting in a mortality

rate of 8.7 per 100,000 people. It has also been found that cases of prostate cancer in Sudan are related to age and sexual activity rather than race (Elamin et al., 2015). The reasons for this disparity have been attributed to differences in social, environmental, and genetic influences (Abdalla, A., 2015). The prostate gland remains relatively small throughout childhood and begins to grow at puberty under the influence of testosterone. It reaches its maximum size by the age of 20 and remains at this size until around the age of 50 (Hall, 2016). Serum testosterone levels decrease with age, and men over 40 years old tend to have low testosterone levels (Costanzo, 2010). Prostate cancer is primarily a disease of older men and is rare before the age of 45. The prostate-specific antigen (PSA) test is the most important laboratory test used in the diagnosis of prostate cancer. Other specific tests have led to increased interest in the development and research of other markers, such as serum human kallikrein-2 (KLK-2) and free prostate-specific antigen (fPSA) (Yousif et al., 2023). Epithelia cells of the prostate express androgen receptors, which are necessary for the normal development and physiological control of the prostate from embryonic differentiation to pubertal maturation and beyond. Androgens also help maintain the normal metabolic and secretory functions of the prostate. However, androgens do not

act alone, and other hormones and growth factors are being investigated. Once prostate cancer occurs, the cancerous cells are usually stimulated to grow more rapidly by testosterone. They can be inhibited by the removal of both testes, preventing the formation of testosterone. A benign prostatic fibroadenoma frequently develops in the prostate in many older men and can cause urinary obstruction. This hypertrophy is caused by abnormal overgrowth of prostate tissue, not by testosterone (Hall, 2016). Sex hormones have been linked to prostate cancer, but the evidence remains inconclusive. Steroid hormone receptors are found to be increased in prostate cancer, and estrogen therapy has been found to be effective in treating prostate cancer, suggesting that hormones may play a role. Higher levels of testosterone and dihydrotestosterone are found in cancerous prostatic tissue than in the normal prostate gland. Other hormones, such as estrogen and prolactin, may also influence the growth of the prostate gland, either directly or indirectly, through negative feedback inhibition (Selly et al., 1997). Androgen is the generic term for any natural or synthetic compound, usually a steroid hormone that stimulates or controls the development and maintenance of masculine characteristics in vertebrates by binding to androgen receptors (ARs). Androgens play a role in the development and differentiation of

male reproductive organs, with testosterone being the main androgen present throughout the body. In the prostate, testosterone is locally converted to dihydrotestosterone, which binds to the androgen receptor with ≈ 10-fold higher affinity. This conversion is catalyzed by 5α-reductase. The androgen receptor is present in mesenchymalstroma cells, which are stimulated by the androgen receptor. These are stimulated by testosterone and dihydrotestosterone to produce FGF and IGF growth factors that regulate the proliferation and survival of the epithelium, particularly of those basal cells, which lack an active androgen receptor (Schulz, 2007).

Testosterone was found to be positively associated with human prostate cancer (Signorello et al., 1997), and several epidemiologic studies propose that the racial differences in the susceptibility and occurrence of prostate cancer are moderately related to hormonal influences (Montie, 1996). Another study shows that androgen withdrawal is a practical approach in prostate cancer therapy (Dearnaley, 1994; Ganesan, 1995).

Prostate cancer is notably absent in castrated men. Laboratory studies show that the administration of testosterone induces prostate cancer in rats and that androgens encourage cell proliferation and slow down prostate cell death. However, epidemiologic data supporting the role of androgens are

inconclusive. Over 17 prospective studies have investigated the role of circulating androgens, and only one observed a significantly higher risk of prostate cancer among men with higher serum testosterone levels (Hsing et al., 2006). The goal of this study is to assess the correlation between serum testosterone hormone levels and prostate cancer among Sudanese patients and use it as a biomarker for prostate cancer diagnosis and prognosis.

Materials and methods:

Study duration: 2009-2010

Study area: Khartoum- Sudan

Ethical issue:

Ethical permission was obtained from the director and manager of RCIK to collect serum samples of prostate cancer patients from the hormone lab. Control samples were collected from volunteers.

The study was approved by the University of Khartoum Faculty of Science and followed ethical guidelines set forth by the University of Khartoum and the Radiation and Isotopes Center of Khartoum (RCIK). Patient samples were provided by RCIK, and demographic and clinical data was extracted from their medical records.

Subjects:

This study was carried out on men who were confirmed by biopsy and PSA as prostate cancer patients. 40 serum samples of prostate cancer cases were collected from the Radiation and Isotopes Center of Khartoum (RCIK), and 40 men normal controls in the same age group were selected randomly from the general community. Cases and controls are all aged between 40-89 years. Blood samples (5 ml) were collected in a vacutainer serum separating vial, and serum was separated within one hour of collection for the analysis of serum testosterone until further analysis.

ELISA:

The testosterone levels of 40 prostate cancer cases and 40 controls were determined using a Human ELISA kit according to the manufacturer's instructions from the human company based on ELISA principles.

Statistical analysis:

The data were analyzed with the help of SPSS software version 16. The analysis of continuous data was done using a T-test, and the results were found to be statistically significant (P =0.00).

Results:

Testosterone measurement: The samples (cases and controls) were distributed into five groups according to their age: group I (≤50 years), group II (51-60 years), group III (61-70 years), group IV (71-80), and group V (≥81years).

In prostate cancer patients about 75% are below the normal range (3.5-8.6 ng/ml), about 15% above the normal range and 10% in the normal range. The data were analyzed using SPSS, the mean of control age was (61.8250±12.62453years) (95%CI 57.7875-65.8625) and the mean of testosterone levels was (6.9050±3.31252ng/ml) (95%CI 5.8456-7.9644). T-test of controls and cases was 0.000, odd ratio= 0 and, the P value=0.000(highly significant).

Table (1) Correlation between testosterone levels and age groups among cases:

No.	Age- groups	Normal	Abnormal		Total	P
			Below	Above		
I	≤50	0	2	1	3	0.011
II	51……60	1	9	3	13	0.035
III	61……70	0	13	0	13	0.031
IV	71……80	3	5	1	9	0.036
V	≥81	0	1	1	2	0.500
Total		**4 (10%)**	**30(75%)**	**6(15%)**	**40**	

Table (2): Correlation between testosterone levels and age-groups within normal controls

No.	Age- groups	Normal	Abnormal		Total	P value
			Below	Above		
I	≤50	3	1	4	8	0.000
II	51……60	10	0	3	13	0.000
III	61……70	6	1	4	11	0.000
IV	71……80	2	1	1	4	0.069
V	≥81	3	1	0	4	0.023
Total		24(60%)	4(10%)	12(30%)	40	

Table (3): Odd ratio, P value and 95%CI of cases and controls

	Case	Control	Total	Odd ratio	P value	95%CI	
						Lower	Upper
Normal	4	24	28	0.000	0.000	5.1118	6.2025
Abnormal	36	16	52	0.000	0.000	4.0069	7.3731
Total	40	40	80				

Discussion:

Studies from the 1940s seemed to indicate a association between higher testosterone levels and prostate cancer growth, research in recent years has been refuting this link. Some studies are even finding that there seems to be a greater risk of prostate cancer in men with low testosterone levels. The goal of

this study is to use serum testosterone levels as a marker for prostate cancer diagnosis and prognosis. The cases in this study showed low levels of testosterone, since the levels of testosterone decreased in older men. But most of the controls had normal levels. Although 60% of controls possessed normal testosterone levels (3.5–8.6 ng/ml) 30% were above the normal range and 10% were under the normal range. Moreover, the mean (2.7725±4.18269ng/ml) of testosterone levels in cases was below the normal range while controls mean represent the normal range (6.9050±3.3152ng/ml) P=0.000(highly significance). There is a correlation between prostate cancer and testosterone levels.

Men in the lowest tenth of free testosterone concentration had a lower risk of overall prostate cancer (OR = 0.77, 95% confidence interval [CI] 0.69–0.86; p < 0.001) compared with men with higher concentrations (2nd–10th tenths of the distribution). Heterogeneity was present by tumor grade (p= 0.01), with a lower risk of low-grade disease (OR = 0.76, 95% CI 0.67–0.88) and a non-significantly higher risk of high-grade disease (OR = 1.56, 95% CI 0.95–2.57). There was no evidence of heterogeneity by tumor stage (Watts et al., 2018).

Low levels of Testosterone might be related to the carcinogenesis of higher grade prostate cancer and is a

potential marker of a prognosis of prostate cancer (Albuquerque etal ., 2017).

Experimental and clinical evidence implicates testosterone is in the etiology of prostate cancer. Nearly all metastatic prostate tumors overexpress the androgen receptor, and androgen deprivation therapy is the mainstay treatment approach for many prostate tumors (Taylor, 2010).

Some studies noted an increased prostate cancer risk with low testosterone levels (Morgentaler, 2006).

Several studies have measured plasma androgen levels among men with prostate cancer and age-matched controls. Some studies found elevated testosterone and DHT levels among those with cancer, whereas others either did not detect any differences or actually found lower testosterone levels (Gabriel *et al*., 1997).

Many longitudinal studies have established a correlation between elevated testosterone and subsequent development of prostate cancer. men in the highest level of serum testosterone were more likely to develop Prostate cancer [odds ratio (OR) 2.6, 95% confidence interval (CI) 1.34–5.02, p = 0.004] (Gann et al. 1996).

Another longitudinal study examined the relationship between prostate cancer, serum testosterone, SHBG and free

testosterone index (FTI), calculated as total serum testosterone divided by sex hormone- binding globulin (SHBG). They found that high risk PrCa was associated with both FTI [hazard ratio (HR) 1.91, 95% CI 1.10–3.32, p = 0.02] and calculated free testosterone (HR 1.61, 95% CI 1.18–2.20, p = 0.003) (Pierorazio et al. 2010).

Controlling for testosterone, SHBG , estradiol, body mass index (BMI) and age, they demonstrated an increase in Prostate cancer for men in the highest quartile of serum testosterone (OR 2.34, 95% CI 1.3–4.2), but no association of Prostate Cancer with estradiol or DHT (Shaneyfelt et al. 2000).

Various longitudinal studies have demonstrated increased risk of prostate cancer with elevations in testosterone, smaller, well-designed studies have demonstrated the opposite, that is, increased Prostate Cancer risk in patients with lower testosterone levels. A numerous study of untreated hypogonadal men with prostate-specific antigen (PSA) <4.0 ng/ml revealed a association between low testosterone and prostate Cancer (OR 2.02, 95% CI 1.10–3.72) (Morgentaler and Rhoden, 2006).

Reduction of testosterone by castration or hormonal therapy (estrogen) causes metastatic prostate cancer to regress and introduced exogenous testosterone causes prostate cancer to grow. Prostate cancer is never seen during the peak of

testosterone late teens and early 20s and becomes prevalent in older men when testosterone levels have declined (Moretaler, 2006; Tubaro, 2007).

Another prospective cohort study of Korean men undergoing prostate biopsy for suspected Prostate Cancer compared biopsy results among men with low testosterone, defined as total testosterone levels below the median of 13.3 nmol/l (385 ng/dl). On multivariate analysis, low testosterone was associated with Prostate Cancer risk (OR 1.99, 95% CI 1.25–3.16, p = 0.003), but not Prostate cancer grade (Shin et al. 2010).

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