Tumor necrosis factor alpha as a potential marker for prostate cancer

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Abstract:

Background: Prostate cancer is currently the most common cause of cancer death in men. The exact cause of developing prostate cancer is not known though inflammation, ageing, ethnicity and heredity are important factors involved in the initiation and development of this cancer.

Aim of study : The aim of this study to determine the levels of prostate specific antigen (PSA), tumor necrosis factor alpha (TNF-α), testosterone (T) and dihydrotestosterone (DHT) in sera of thirty patients with prostate cancer (PCa), thirty patients with benign prostate hyperplasia (BPH) and in thirty health volunteers, T/DHT ratio was also calculated.

Result: There was a significant increase in the levels of PSA, TNF-α, T and T/DHT ratio in PCa as well as BPH patients compared to the controls. There was a significant decrease in DHT levels in both PCa and BPH compared to the controls.

Conclusion: TNF-α could serve as a potential marker for the diagnosis of PCa.

Keywords: prostate cancer, benign prostate hyperplasia, TNF-α, testosterone, dihydrotestosterone.

Introduction:

PCa remains one of the most universal malignant tumors and the major cause of cancer-associated death in the male worldwide (1). The incidence of PCa may vary among different ethnic groups and countries. BPH is a common symptom of the urinary system in old age (2,3). BPH is characterized by a non-malignant enlargement of the prostate gland due to the uncontrolled proliferation of smooth muscle and epithelial cells located in the periurethral transition zone of the prostate gland surrounding the urethra (4,5). Chronic inflammation has been implicated in the development of complex human diseases including PCa and BPH. Cytokines are important inflammatory markers secreted in response to tumors and often by tumor cells. Also, the initial stages of the disease have been linked to hormonal stimuli, notably the anabolic steroid, T. T molecules enter the prostatic cell by diffusion; after that, about 90% of T molecules are converted by the enzyme 5-alpha-reductase (5α-R) to DHT which is the main tissue androgen involved in the growth of the adult prostate (6). DHT and remaining T molecules bind to the androgen receptor, which is activated and translocated to the nucleus   which binds to androgen-response elements in the DNA of prostate cells, ultimately inducing proliferation (7). TNF-α, a proinflammatory cytokine can activate the oncogenic transcription factors like NF-jB and AP-1 in cells. These factors further accelerate proliferation, anti-apoptotic activity, and inflammation reaction. Epidemiologic and molecular evidence has supported the key role of TNF-α in both inflammatory and cancer-promoting pathway in various cancer like oral, breast (8,9) and prostate (10). This study aims to investigate the hormonal profile in the pathogenesis of PCa and the possibility of using TNF-α as a marker for the diagnosis of PCa.

Materials &Methods:

Study subjects

A case-control study was conducted on sixty male patients, were enrolled from Ghazi Al-Hariri hospital/Medical City/Baghdad, Iraq. Thirty of which were diagnosed with PCa and thirty with BPH with ages ranged (45-86) and (46-91) years respectively. Besides, thirty apparently healthy volunteers their ages ranged between (41-86) years were selected and served as control. The study was done during the period from February 2018 to January 2019, in Baghdad, Iraq.

Exclusion criteria

These include the followings; Patients under chemo or radiotherapy, Patient who underwent prostatectomy, Patients with different cancers, Patients with any type of inflammation and Diabetic patients.

Sample collection

Ten ml of venous blood samples were collected from thirty PCa patients, thirty patients with BPH and from thirty controls. Serum samples were separated and stored at -20 °C until assayed.

Measurement of PSA serum levels

PSA serum levels were measured using the ARCHITECT i1000 SR PSA kit (Abbott/Ireland) according to the manufacturer's instructions.

Measurement of TNF-α serum levels

TNF-α serum levels were measured using TNF-α ELISA Kit (Invitrogen/USA) according to the manufacturer's instructions.

Measurement of testosterone serum levels

Testosterone serum levels were measured using Testosterone ELISA Kit (VEDALAB/France) according to the manufacturer's instructions.

Measurement of dihydrotestosterone serum levels

Dihydrotestosterone serum levels were measured using the dihydrotestosterone ELISA Kit (Demeditec /Germany) according to the manufacturer's instructions.

Statistical analysis

The statistical package for social sciences (SPSS V. 25) was used to analyze the biochemical data.

Results and discussion

Serum levels of PSA, TNF-α, T and T/DHT ratio measured in PCa, BPH and controls are shown in Table (1).

Table (1): serum levels of PSA, TNF-α, T and T/DHT ratio measured in PCa, BPH and controls

parameters	PCa (mean±SD)	BPH (mean±SD)	Control (mean±SD)	p-value		
	A	**B**	**C**	**A vs C**	**B vs C**	**A vs B**
PSA (ng/mL)	47.419 ± 28.495	10.079 ± 5.501	0.488 ± 0.461	0.000*	0.029*	0.000*
TNF-α (pg/mL)	44.468 ± 20.187	23.513 ± 0.865	20.806 ± 0.719	0.000*	NS	0.000*
T (ng/mL)	13.222 ± 3.615	9.657 ± 1.614	5.620± 2.711	0.000*	0.000*	0.000*
DHT (pg/mL)	176.86 ± 88.622	228.98 ± 74.807	306.73± 185.44	0.000*	0.019*	NS
T/DHT	87.110 ± 38.028	46.379 ± 17.406	22.431± 13.916	0.000*	0.000*	0.000*

* Significant at P<0.05, NS: Non-significant at p>0.05, PCa: prostate cancer, BPH: benign prostate hyperplasia.

These results showed a highly significant increased in PSA serum levels (47.41 ± 28.49) and (10.07 ± 5.50) for PCa and BPH patients groups respectively as compared to control group (0.48 ± 0.46). The results also showed a highly significant increased in TNF-α serum levels (44.468 ± 20.187) for PCa and no significant increased (23.513 ± 0.865) for BPH patients groups respectively as compared to control group (20.806 ± 0.719). These results revealed a highly significant increased in T serum levels (13.222 ± 3.615) and (9.657 ± 1.614) for PCa and BPH patients groups respectively as compared to control group (5.620± 2.711). The results also revealed a significant increased in DHT serum levels (176.86 ± 88.622) and (228.98 ± 74.807) for PCa and BPH patients groups respectively as compared to control group (306.73± 185.44). The results also showed a highly significant increased (P=0.000) in T/DHT ratio (87.110 ± 38.028) and (46.379 ± 17.406) for PCa and BPH patients groups respectively as compared to control group (22.431± 13.916).

Various examinations have demonstrated that patients with prostate malignant growth have in general raised serum PSA levels concerning men without the prostate disease. In any case, the risk of malignancy is relative to the serum PSA level even at concentrations less than 4 ng/mL. With a serum PSA level under 2 ng/mL, the likelihood of malignant growth is under 2%, it is increased to about 18% when the PSA serum level is 2.5 to 4.0 ng/mL. Several trial studies showed that significant cancers in patients with serum PSA levels of 2.5 to 4.0 ng/mL, a few specialists have proposed bringing down the PSA cutoff to 2.5 ng/mL to

improve the early discovery of the disease in younger men (11). Because of benign prostate tissue secrete PSA, therefore, the serum level of PSA is not considered a diagnostic for prostate cancer. Different factors, for example, prostatitis, infarct and instrumentation of the prostate elevate serum PSA levels (12,13).

Inflammation has now been recognized to contribute to proliferation, malignancy, angiogenesis, metastasis, modulation of adaptive immunity, and unresponsiveness to hormones and chemotherapeutic agents (14). TNF-α is a proinflammatory cytokine, that is associated with cancer progression. There has been a study by (15), where TNF-α is associated with prostate cancer progression. Serum TNF-α activity was positive in 76% of the patients with relapsed disease who had a significantly higher mortality rate than those with undetectable serum TNF-α levels. The expression and action of TNF-α and its receptors has been reported in several tumors such as esophageal (16), prostate (17), follicular thyroid (18), ovarian (19) and breast (20) cancers. A study reported elevated serum levels of the TNF-α in patients with prostate cancer as compared with controls. Their results showed that there was a strong association between the serum levels of the cytokine, disease stage and the presence of metastatic disease (21). TNF-α was significantly elevated in patients with metastatic cancer compared with the two groups of patients with localized disease and controls and was correlated with increasing PSA. In patients with progressive disease, TNF-α levels were elevated at the point of biochemical progression and further raised at symptomatic progression. Michalaki *et al*. concluded that TNF-α may, therefore, provide an additional marker to PSA that reflect the activity of prostate cancer, they postulated that serum TNF-α levels might be useful prognostic markers concerning progression to biochemical or symptomatic relapse based on the results of serial measurements.

In the adult human, serum T level is 10 times higher than serum DHT level. In contrast, the level of intraprostatic DHT is at least five times higher than the level of intraprostatic T (22). The most important source of DHT in the human body is the prostate, particularly prostatic stroma, which produces 10 times more DHT than epithelium (23,24). The development of benign prostate hyperplasia (BPH) depends on the interaction between stromal and epithelial cells. This process includes the progressive production of DHT and the synthesis of growth factors (GFs) and survival factors (SFs) in fibroblasts and their influence on the proliferation and protein synthesis in the epithelial cells (25). From the clinical point of view, a prostate is considered enlarged when its volume exceeds 31 mL (26). The current literature lacks definite data on the intraprostatic levels of T and DHT, due to different methods of tissue retrieval and chemical analyses. However, the current opinion is that intraprostatic DHT concentrations are maintained but not elevated in BPH, while there is an absence in similar data concerning intraprostatic T concentrations (27,28), The results of the present research are in accordance to some of the results mentioned in the literature stating that increased levels of testosterone are associated with increased risk of prostate cancer. In the retrospective Physicians' Health Study (612 cases) a strong trend of increasing PCa risk was observed with increasing total T when hormones and Sex hormone-binding globulin were adjusted simultaneously (29). In a previous study, 420 patients who underwent prostate biopsy and had a PSA<10ng/ml, pretreatment total T was significantly higher in patients diagnosed with PCa (p=0.007) (30). A meta-analysis restricted to only two studies that performed mutual adjustment for all measured serum hormones, age, and body mass index indicated that men whose total T was in the highest quartile were 2.34 times more likely to develop PCa (31). Surprisingly, in a cohort of 724 patients who underwent radical prostatectomy, high-risk of recurrent PCa (tumors stage>T3a; Gleason score (32) or PSA>20ng/ml) was significantly more frequent both for the lowest and the highest-circulating T (p=0.03), depicting a nonlinear U-shaped risk behavior (33).

Conclusions

TNF-α in addition to PSA may serve as a potential marker for the diagnosis of PCa in cases where PSA is not significantly correlated with PCa. Decreased DHT along with increased T levels as well as T/DHT ratio could be associated with increased risk of PCa.

Acknowledgement

Conflict of interests

The authors declare that they have no conflict of interests.

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