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RESEARCH

THE EFFECT OF ORAL GLUCOSE TOLERANCE TEST ON INSULIN AND SOME RELATED INDICATORS IN ELDERY MALE PATIENTS WITH PROSTATE CANCER AND BENIGN PROSTAT HYPERPLASIA

ABSTRACT

Introduction: Insulin, insulin like growth factor-1 and insulin like growth factor binding protein-3 were associated with prostate cancer. The aim of our study was to define the relationship between insulin like growth factor-1 and insulin like growth factor binding protein-3 serum levels, and correlate these proteins with the oral glucose tolerance test.

Materials and Method: Eighty-four male patients who had undergone prostate biopsy were included in the retrospective study. Oral GlucoseToleranceTest was done. Fasting, 1-hour and 2-hour plasma samples were used to measure serum levels of insulin, insulin like growth factor-1 and insulin like growth factor binding protein-3. The patients were divided into two groups: Benign and Malign.

Results: The mean age was 64.5±0.91 years. There was a significant difference between benign and malign groups in prostate specific antigen levels—6.14±0.7 ng/ml, and 11.6±2.2 ng/ml (p=0.001). The mean insulin level for 2 hour in malign group was significantly lower than that of benign group (81.9±12 µIU/ml and 57.4±17.2 µIU/ml (p=0.033) . Insuline like growth factor binding protein-3 levels after glucose tolerance test were 4725.9±504.4 ng/ml and 3929.4±346.5 ng/ml for 1 hour and 2 hours, respectively, and significantly lower in benign group (p=0.046).

Conclusion: Insulin, insulin like growth factor-1 and insulin like growth factor binding protein-3 remain far away as being defined as tumor markers for prostate cancer since findings are still inconclusive and unclear. Future studies on the their axis and its genetics are obviously needed to understand if there is any role of these substances in the development of prostate cancer.

Key Words: Prostatic Hyperplasia; Prostatic Neoplasms; Insulin; Insulin-Like Growth Factor I; Insulin-Like Growth Factor Binding Protein 3.

ARAŞTIRMA

PROSTAT KANSERİ VE BENİGN PROSTAT HİPERPLAZİSİ OLAN YAŞLI ERKEK HASTALARDA ORAL GLUKOZ TOLERANS TESTİNİN İNSÜLİN VE İLGİLİ BAZI BELİRTEÇLERE ETKİSİ

ÖZ

Giriş: İnsülin, insülin benzeri büyüme faktörü-1 ve insülin benzeri büyüme faktörü bağlayıcı protein-3'ün prostat kanseri ile ilişkisi bildirilmiştir. Çalışmamızın amacı, insülin benzeri büyüme faktörü-1 ve insülin benzeri büyüme faktörü bağlayıcı protein-3 serum miktarlarının benign ve malign prostat hastalıklarında oral glukoz tolerans testi ile etkileşimini incelemektir.

Gereç ve Yöntem: Prostat biyopsisi yapılan 84 hasta çalışmaya dahil edildi ve retrospektif olarak incelendi. Tüm hastalardan alınan açlık, glukoz tolerans testi sonrası birinci ve ikinci saat serum kan örneklerinden, insülin, insülin benzeri büyüme faktörü-1 ve insulin benzeri büyüme faktörü bağlayıcı protein-3 düzeyleri ölçüldü. Hastalar, patoloji sonuçlarına göre benign ve malign olarak ayrıldı.

Bulgular: Hastaların yaş ortalaması 64,5±0,91 yıl olarak bulundu. Prostat kanserli grupta prostat spesifik antijen düzeyleri 11,6±2,2 ng/ml ile ortalaması 6,14±0,7 ng/ml olan benign gruptan anlamlı yüksekti (p=0,001). Serum insülin düzeyleri prostat kanserli grupta glukoz tolerans testi sonrası ikinci saatte benign gruptan anlamlı düşük bulundu (57,4±17,2 µIU/ml, 81,9±12 µIU/ml sırasıyla, p=0,033). Glukoz tolerans testi sonrası 1 ve 2. saatlerdeki insülin benzeri büyüme faktörü bağlayıcı protein-3 düzeyleri benign grupta anlamlı düşük bulundu (4725±504,4 ng/ml, 3929,4±346,5 ng/ml, sırasıyla, p=0,046).

Sonuç: İnsülin, insülin benzeri büyüme faktörü-1 ve insülin benzeri büyüme faktörü bağlayıcı protein-3 serum düzeyleri prostat kanseri için tümör belirteci olmaktan uzaktır, sonuçlar şüphelidir ve açık değildir. Gelecekte büyüme faktör yolakları ve genetiği üzerine yapılacak çalışmalar, bu proteinlerin prostat kanserinin gelişiminde eğer varsa rollerinin anlaşılması için gereklidir.

Anahtar Sözcükler: Benign Prostat Hiperplazisi; Prostat Kanseri; İnsülin, IGF-1, IGFBP-3.

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Introduction

Prostate related problems are quite common in men over age 50 (1). Prostate specific antigen (PSA) is the most common tumor marker for prostate cancer; in addition, PSA levels may be afflicted by several other conditions like benign prostatic hyperplasia (BPH), prostatitis, prostate biopsy, androgen deprivation therapy. Therefore, PSA can be defined as an organ-specific marker, instead of being defined as a disease specific marker, and PSA use in daily practice should be carefully considered (2).

The mitogenic effects of insulin and insulin-like growth factor-1 (IGF-1) on cells are well known (3,4). Insulin and IGF-1 were also reported as potential markers for prostate cancer by some authors (3,5,6). Correlated with IGF is the insulin-like growth factor binding protein-3 (IGFBP-3), a protein that transports more than 90% of IGF-1 (7). IGFBP-3 was reported to have a protective role against prostate cancer (8). Serum IGF-1 levels may change with age and nutrition like insulin, which is the most powerful regulator for glucose metabolism (7,9,10). The production of IGFs, although mainly dependent on growth hormone, can be manipulated by other factors. Their circulation levels are dependent on both production and degradation of their binding proteins. The circulation levels of all of them vary throughout life, increasing from birth to their peak at puberty and decreasing steadily after the third decade (11). Also, their serum levels may changes in the systemic inflammatory response (12). IGF-1 is synthesized primarily in the liver in a 1:2 molar ratio, along with most other viscera, including the prostate (11).

The aim of our study was to define the relationship between total PSA levels, as well as those of IGF-1 and IGF-BP3 levels, and correlate these with an oral glucose tolerance test (OGTT).

Materials and Method

After approval by the ethic committee, we performed a retrospective study between 2007 and 2011 at Numune Training and Research Hospital, Ankara and Atatürk Training and Research Hospital, Ankara and Kafkas University Medicine Faculty, Kars. Patients were selected from a study that evaluate the transrectal ultrasound guided prostate biopsy complications and these patients were with suspicious of diabetes mellitus and were selected to perform OGTT. Eighty-four male patients, who underwent transrectal ultrasound guided prostate biopsy for abnormal digital rectal examination findings or increased PSA levels, were included in the study. Urine analyses and routine biochemical tests were also done on all patients. Patients with diabetes mellitus, liver disease, cachexia, obesity, active infection, and metastatic prostate cancer were excluded from the study. (Patients were defined as obese or cachectic based on body mass index). All patients were instructed to fast for 8 hours prior to the glucose tolerance test. A baseline 5 cc blood sample was taken from antecubital vein initially. The patients were then given 75 grams oral dose of glucose solution to drink within 5 minutes. Afterwards, 1 hour and 2 hour blood samples were taken. Plasma samples were preserved at -80 ºC after 20 minutes of centrifuge at 1500 g. PSA, insulin levels were measured. IGF-1 and IGF-BP3 levels were also measured from the samples that were preserved at at -80 ºC. Chemiluminescence, radio immunoassay and immunoradiometric assay (IRMA) were used for determination of PSA, insulin, IGF-1 and IGFBP-3 levels, respectively. Fasting, 1-hour and 2-hour plasma samples were used to measure insulin, IGF-1 and IGFBP-3 levels. All patients underwent transrectal ultrasound guided prostate biopsies (10 cores). The patients were divided into two groups according to biopsy pathology: BPH (group 1) and Pca (group 2). SPSS software, version 21 (SPSS Inc, Chicago, IL) Mann-Whitney *U*-test and Wilcoxon Signed Test was used to compare differences in age, PSA, insulin, IGF-1 and IGFBP-3 levels between groups. Statistically significant levels were set at a P value of < 0.05.

Results

Thirty-nine patients with Pca and 45 patients with BPH were included in the study. The mean age was 64.5±0.91 years, for all patients; 65.09±1.1 years for group 1, and 63.86±1.4 years for group 2 (p=0.134). There was a significant difference between two groups in PSA levels 6.14±0.7 ng/ml, and 11.6±2.2 ng/ml (p=0.001), as well as insulin levels in 2-hour plasma samples 81.9±12 µIU/ml and 57.4±17.2 µIU/ml (p=0.033) in groups 1 and 2, respectively. The mean insulin level in group 2 was significantly lower than that of Group 1. The comparison of two groups is presented in Table 1.

One-hour and 2-hour plasma insulin levels after OGTT were found to be significantly higher than fasting levels as usual. There was only a significant difference after OGTT in IGFBP-3 levels for group 1. IGFBP-3 levels after OGTT were 4725.9±504,4 ng/ml and 3929.4±346.5 ng/ml for 1 hour and 2 hours, respectively and this was significantly lower

Table 1— Comparison of The Two Groups.

	BPH (n=45)	PCA (n=39)	p
PSA	6.14±0.7	11.6±2.2	0.001
Insulin (0 time)	12.7±1.1	17.6±7	0.301
Insulin (1 hour)	95.9±12.4	86.9±18.3	0.542
Insulin (2 hours)	81.9±12	57.4±17.2	0.033
IGF-1 (0 time)	215.3±14.7	203.4±19.7	0.319
IGF-1 (1 hour)	233.2±17.7	214.3±21.5	0.277
IGF-1 (2 hour)	210.6±20.1	198.8±22.1	0.801
IGFBP-3 (0 time)	4064.9±353.1	4460.7±466.6	0.608
IGFBP-3 (1 hour)	4725.9±504.4	3880.5±436	0.184
IGFBP-3 (2 hours)	3929.4±346.5	4084.7±4.9.8	0.686

(p=0.046). There was not a significant difference both before and after the OGTT in IGF-1 serum levels.

Discussion

Prostate cancer is the most common form of non-cutaneous cancer in elderly men and insulin-like growth factors (IGFs) have been proposed as important growth factors in the development of this tumor and its progression to androgen independence (1,13). The IGF network is composed of two peptid growth factors (IGFI-II), two transmembrane receptors (type I and II), IGF binding proteins (IGFBPs) number of which are yet unclear, and IGFBP proteases (PSA, cathepsin D) (9,14).

The IGF ligands are structurally similar and share a 70% homology with each other and 40% homology with pro-insulin. IGF-1 is mainly bound to IGFBP-3 and the principal functions of the IGFBPs are the transport and modulation of IGFs and their activities (11). IGFBP-3 is mainly known as an inhibitor of IGF-1, however, it has been demonstrated to both prevent cell growth and induce apoptosis by way of novel pathway independent of either p 53 or the IGF/IGF receptor-mediated systems (14). IGFs exert an acute anabolic action on protein and carbohydrate metabolisms and regulate cell proliferation, differentiation and apoptosis. IGF is required for the normal growth cell and development of the prostate gland. In vitro, it has been shown to stimulate androgen receptors in the prostate cancer cells, resulting in PSA production (15).

Chan at al. examined serum IGF-1 levels in patients who later went on to develop prostate cancer. They found that those with higher IGF-1 levels were at greater risk of later being diagnosed as having prostate cancer than those with lower IGF-1 levels (6). The study by Wolk et al. demonstrated an association between the serum levels of IGF-1 and the risk of prostate cancer (16). These studies showed that there was a two- to threefold increase in the risk of cancers when serum IGF-1 was in the higher quartiles. Chan et al. proposed a protective effect of increased serum IGFBP-3 levels, a finding which was not supported by Wolk et al. Recently, in another study, high levels of IGF-1 were found to elevate the risk of prostate cancer (17). In our study, there was not a significant difference either before or after OGTT in IGF-1 levels between groups. Our results were similar with that published by Latif and Cutting's study (12,18). The only significant difference after OGTT was in the IGFBP-3 levels in group 1. IGFBP-3 levels were not decreased in group 2. This result didn't support the idea that IGFBP-3 has a protective role against to prostate cancer, but the correlation was not strong. Tricoli et al. demonstrated that African Americans, who have the highest incidence of prostate cancer, did not have elevated serum IGF-1 levels but instead had lower IGFBP-3 levels. They concluded that the IGF-1/IGFBP-3 ratio, which is higher in African Americans, high-risk people for the developing prostate cancer, may be more significant (19). Kurek et al. found no association between IGF-1 and prostate cancer as well (20). Hazem et al. didn't determine IGF-1 and IGFBP-3 as tumor markers, in a similar study without using OGTT (21). Finally, we did not find a strong correlation between Pca and the IGF axis, like many authors. Studies on the IGF axis and nuclear polymorphism are being compromised due to a lack of relationship between cancer and the IGF axis (10,14).

Normal glucose homeostasis is characterized by appropriate insulin secretion and low HbA1c (10). Higher insulin le-

vels are associated with increased risk of prostate cancer. Moreover, prostate cancer cells need insulin for their growth in the culture (22). One large epidemiologic study proposed an equivocal relationship between diabetes mellitus and Pca. Association of diabetes mellitus with Pca was explored during a 13-year follow up among men. After adjustment for factors associated with prostate cancer in previous studies, little association was found between diabetes mellitus at baseline and prostate cancer incidence (23). Sara et al. suggest that abdominal obesity and increasing serum insulin levels are associated with a higher risk of BPH (24). However, the European Prospective Investigation into Cancer and Nutrition (EPIC) proposed that there was an inverse association between self-reported diabetes mellitus and subsequent risk of prostate cancer recently (25).

In our study, insulin serum levels after OGTT were higher than their basal levels; however, there was no significant difference between 1-hour and 2-hour insulin serum levels. Late plasma insulin levels "2 hour samples after OGTT) were found to be significantly lower in patients with prostate cancer compared to BPH patients (p=0.033), compatible with the literature.

In conclusion, insulin, IGF-1 and IGFBP-3 remain far away as being defined as tumor markers for prostate cancer since findings are still inconclusive and unclear. Future studies on the IGF axis and its genetics are obviously needed to understand if these substances play any role of in the development of prostate cancer.

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