Long-term effects of androgen deprivation therapy in prostate cancer patients on metabolic and hematologic parameters

Prostat Kanserinde Androjen Deprivasyon Tedavisinin Metabolik Ve Hematolojik Parametrelere Olan Uzun Dönem Etkileri

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Abstract

Purpose: In this study, we aimed to analyze metabolic and hematologic long term effects in prostate cancer patients receiving andogen deprivation therapy (ADT).

Material and Methods: In last 3 years 50 patients with metastatic prostate cancer treated with LHRH agonists in our department were retrospectively evaluated. The median age was 74.8 years. Serum levels of glucose, total cholesterol, lipoproteins (LDL, HDL) and hemogram parameters, that measured at baseline and first, second and third years after treatment, were compared. The statistical analysis in this study was performed with SPSS for Windows Version 15.0 (Inc., Chicago, IL). $p<0.05$ was accepted as significant.

Results: Even though Glucose (Glu) increased from 111 to 120 mg/dl, it was not statistically significant ($p>0,05$). Serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) levels increased significantly, $p<0,001$, $p=0,005$ and $p=0,04$ respectively. There was no significant changes in high-density lipoprotein (HDL) ($p>0,05$). When hematologic parameters were eveluated, LHRH agonists significantly decreased hemoglobin levels, median decrease was about 1 gr/dl ($p<0,001$). There were no significant changes were found in other parameters.

Conclusions: Although in metastatic pros-

Özet

Amaç: Bu çalışmada amacımız androjen deprivasyon tedavisi(ADT) alan prostat kanserli hastalardaki hematolojik ve metabolik uzun dönem etkileri analiz etmektir.

Gereç ve Yöntemler: Kliniğimizde son 3 yılda metastatik prostat kanseri tanısıyla LHRH agonisti ile androjen deprivasyon tedavisi alan 50 hasta retrospektif olarak değerlendirildi. Hastaların ortalama yaşı 74.8 yıldı. Hastaların tedavi başlangıcındaki ve sonraki 1., 2., ve 3. yıl serum glukoz , total kolesterol , trigliserid , serum lipoproteinleri (LDL, HDL) ve tam kan sayımı parametreleri karşılaştırıldı. Bu çalışmada istatistiksel analiz SPSS for Windows Version 15.0 paket programıyla yapıldı. $p<0.05$ düzeyi istatistiksel olarak anlamlı kabul edildi.

Bulgular: Serum ortalama glukoz seviyesi 111'den 120'ye yükselmesine rağmen istatistiksel olarak anlamlı bulunmadı ($p>0.05$). Serum total kolesterol, trigliserid ve low-densiy lipoprotein (LDL) seviyelerinde istatistiksel olarak anlamlı artış izlendi, sırasıyla $p<0.001$, $p<0.002$ ve $p<0.02$. Serum HDL seviyelerinde farklılık saptanmadı ($p>0.05$). Hematolojik parametreler değerlendirildiğinde LHRH agonistleri hemoglobin seviyelerinde anlamlı düşüşe sebep oldu ($p<0.001$) . Hemoglobin değerlerinde ortalama 1 gr/dl düşme gözlendi. Diğer parametrelerde ise anlamlı farklılık bulunmadı.

Sonuç: LHRH agonistleri metastatik pros-

tate cancer LHRH agonists are used effectively, serious metabolic and hematologic adverse effects may be occured. So close follow-up of patients to adverse metabolic and hematologic effects should be considered and treatment strategy is modified.

Key Words: prostate cancer, andogen deprivation therapy, metabolic changes, hematologic changes

tat kanserinde etkin bir şekilde kullanılmasına rağmen ciddi metabolik ve hematolojik yan etkiler ortaya çıkabilmektedir. Bu açıdan hastaların yakın takibi yapılmalı ve tedavi stratejileri belirlenmelidir.

Anahtar Kelimeler: prostat kanseri, andojen deprivasyon tedavisi (ADT), metabolik yan etkiler, hematolojik yan etkiler

Introduction

Prostate cancer (PCa) is the most common malignancy in men and the second most common cause of mortality among cancers in men. The median age at diagnosis of prostate cancer is 68 years (1). The 5-year relative survival for all stages in men with prostate cancer combined is 98.8% (1). Improvements in cancer spesific survival , treatment related morbidity has become more important.

In 1941 Huggins et al. described the relationship between androgens and prostate cancer (2). Andogen deprivation therapy (ADT) is accomplished with surgical (bilateral orchiectomy) or medical castration (GnRH agonists). Because of a variety of reasons LHRH agonists have largely replaced bilateral orchiectomy. LHRH agonists therapy is an effective treatment for prostate cancer in a variety of clinical settings. ADT is the primary systemic treatment for metastatic or recurrent prostate cancer. Using of LHRH agonists in combination with primary radiotherapy for locally advanced or high risk disease (3,4) and adjuvant therapy for pN1 disease after prostatectomy (5) improved disease-free or overall survival.

In the last two decades using the LHRH agonists has increased steadily (6,7). Men who are undergoing ADT have severe hypogonadism and they are likely to develop complications of hypogonadism. The wellknown adverse effects are hot flashes, gynaecomastia, erectile dysfunction, decreased lipido, osteoporosis, increase in body mass index, decrease in lean body mass and increase in fat mass (8,9). Addition to the benefits of LHRH agonists in survival, the resulting hypogonadism causes detrimental metabolic and hematologic changes in men with prostate cancer. GnRH agonists are also associated with risk of diabetes and cardiovascular disease (10). The aim of this study is to analyze metabolic and hematologic long term effects in prostate cancer patients receiving andogen deprivation therapy (ADT).

Material and Methods

In this study between January 2009 and December 2012, 50 patients with metastatic prostate cancer who had been treated with LHRH agonist were retrospectively evaluated. None of them had a history of anabolic steroid use, hyperthyroidism, Cushing's disease, hyperprolactinemia, chronic liver disease or chronic renal failure. The patients who had normal serum testosterone level (220-800 ng/dl) included in the study. All the patients received LHRH agonist leuprolide acetate (LeuA) 22.5 mg per 3 months. Fasting blood samples were collected and serum levels of testosterone, PSA, glucose, total cholesterol, triglycerides, lipoproteins (LDL, HDL) and hemogram parameters were measured at baseline and at 1, 2 and 3 years. Changes in serum concentrations of testosterone, PSA, glucose, lipids and hemogram parameters were compared between baseline and other time points.

Serum concentrations of testosterone and PSA were measured by an electrochemiluminescence method and chemiluminescence enzyme immunoassay, respectively.

The statistical analysis in this study was performed with SPSS for Windows Version 15.0 (Inc. Chicago, IL). P values <0.05 were accepted as significant.

Results

The median age was 74.8 years. In all patients serum testosterone levels were within normal and the PSA value was 43.8±16.4 ng/ml. LeuA decreased PSA markedly and lowered serum testosterone to castration level in all patients 3 months after the initial treatment (Table 1-2).

Table 1. Patients characteristics

Before treatment			
No.of patients n=50	Age (year) 74.8±9.2	PSA (ng/ml) 43.8±16.4	Testosterone (ng/dl) 428±82,9

Table 2. Treatment process for prostate cancer

Years of treatment			
	1	2	3
PSA (ng/ml)	0.64±0.21	0.59±0.18	0.51±0.11
Testosterone (ng/dl)	22.8±8.5	16.2±5.1	12.4±3.9

Even though Glu levels increased from 111 to 120 mg/dl, it was not statistically significant. Serum TC, TG, LDL levels increased significantly, p<0,001, p=0,005 and p=0,004 respectively and there was no significant changes in HDL. When hematologic parameters were eveluated, LHRH agonists significantly decreased hemoglobin levels, median decrease was about 1 gr/dl (p<0,001). There were no significant changes in other hemogram parameters (Table 2).

Table 2. Variation in serum glucose, lipid profile and hemoglobin level

	Years of treatment			
	0	1	2	3
Total Cholesterol (mg/dl)	180,52±37,88	191,1±40,65*	192,1±37,13*	204,7±43,86*
Triglyceride(mg/dl)	121,21±57,52	144,24±48,42	165,20±77,14*	192,25±108,7*
LDL Cholesterol(mg/dl)	115,45±27,24	120,38±29,30	124,23±36,49*	135,85±47,26*
HDL Cholesterol(mg/dl)	46,33±13,10	46,16±12,24	46,14±13,07	46,21±14,12
Glucose (mg/dl)	111,33±44,34	116,71±47,36	120,02±44,52	120,67±49,24
Hemoglobin(mg/dl)	13,77±1,47	13,37±1,58	13,32±1,50	12,77±1,62*

*p<0,05

Discussion

LHRH agonists cause different changes in serum lipids. Several studies reported a correlation between hypogonadism and dyslipidaemia. Also studies shown that tetosterone replacement therapy in hypogonnodal men results in a significant improvement in lipid profile (11,12). Some clinical trials have shown that ADT increases total cholesterol, triglyceride, HDL levels and these changes have been seen after just 3 months of therapy (13,14,15). In another study of patients receiving leuprolide acetate for a period of 24 months for benign prostatic hyperplasia showed increases in TC (approximately 10%), TG (approximately 27%) and HDL (approximately 8%), LDL did not change significantly (16). In a prospective clinical trial of men with prostate cancer receiving androgen deprivation therapy with leuprolide demostrated that serum levels of TC, LDL and HDL increased significantly, also serum TG levels increased (p=0,39) (17). In contrast, there are contoversial analyses, one of which, a recent study, reported that TC and LDL increased markedly (p < 0.05) at 6 months, but there were no significant changes in HDL or TG levels (18). In an other prospective trial demonstrated that men undergoing long-term ADT have higher total and LDL cholesterol than controls but no significant difference were seen other lipoproteins (19).

Our study demonstrated that the application of LeuA changed serum lipid profile markedly of patients with prostate cancer. During the treatment process serum concentration of total cholesterol, triglyceride, LDL increases significantly, but no change was seen serum HDL level.

An important complication of hypogonadism is to cause the development of insulin resistance and type 2 diabetes. Keating et al. reported, the records of approximately 73,000 men using SEER and Medicare databases, decrease in insulin sensitivity is associated with diabetes in men with prostate cancer receiving ADT (20). Similiarly a population-based study of 19,079 Canadian men treated for prostate cancer found that ADT use was associated with an increased risk of diabetes (21). The relationship was found between ADT and the new diagnosis of diabetes (22). Although ADT effect insulin sensitivity American Diabetes Association does not spesifically list hypogonadism as a risk factor for diabetes (22). In our study fasting serum glucose levels increased but it was not statistically significant. In our study, although it was not significant increase in fasting serum glucose. In our study, having of abnormal fasting glucose levels of patients prior to treatment may be caused by lack of significant change in rising of the level of glucose. But we recommend that new diabetes or diabetic agrevation can be seen in patients, so patients should be screened.

These metabolic alterations and changes in body composition can cause serious cardiovascular morbidity or mortality. The association between ADT and new cardiovascular disease were also evaluated by a large population-based study by Keating at al (20). A retrospective population-based study of men with prostate cancer demonstrated that ADT caused approximately 20% increase in the risk of cardiovascular disease at 1 year (23). But not all studies confirmed same association between ADT and cardiovascular morbidity. Analysis of Canadian da-

tabase showed no increase in the risk of acute myocardial infarction (19). Similiarly EORTC trial 30891 demonstrated no significant difference in cardivascular mortality in men with prostate cancer receiving ADT (24). Similarly, during the LeuA therapy cardiovascular death was not seen in our study.

Androgens increase erythropoetin production and activate directly erytrocyte progenitors (25). Hemoglobin concentrations decreased about 1 g/dl in patients during the therapy by ADT (26) but treatment for anemia is rarely necessary. It is characteristically normochromic and normocytic. In our study similiarly the median decrease in hemoglobin concentrations was approximately 1g/dl and normochromic normocytic anemia was seen. Also none of the patients had required treatment for anemia.

We consider that this study is important because of demostrates long-term effects of ADT on serum lipid profile and hemogram parameters but has some limitations. First of all it is a retrospective study and it does not have a control group. Some changes in body composition and lipid profile may be resulted from normal aging rather than ADT.

Conclusion

In conclusion,our study showed that ADT changed serum lipid profile markedly of patients with prostate cancer, fasting serum glucose levels increased but it was not statistically significant. Lastly, hemoglobin concentrations decreased approximately 1g/dl and none of the patients had required treatment.

Although in prostate cancer LHRH agonists are used effectively and widely, men who undergo long-term ADT are at great risk of insulin resistance, hyperglycemia, dyslipidaemia, metabolic syndrome and cardiovascular morbidity and mortality. Although optimal managment strategies have not yet been defined, there is important the screening and management of patients to adverse metabolic and hematologic effects of ADT. Patients should be informed about the benefits and risks of ADT. Lifestyle modifications and multidisciplinary approach can be applied by physicians.

Furthermore there is a need for a large long-term prospective studies on metabolic and cardiovascular adverse effects of ADT and also there is a need to investigate the reversibility of adverse effects of ADT.

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