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Effects of Maximal Androgen Blockade Therapy on Hematological, Biochemical and Bone Density Parameters in Locally Advanced Prostate

Lokal İleri Evre Prostat Kanserinde Maksimal Androjen Blokaj Tedavisinin Hematolojik, Biyokimyasal Ve Kemik Yoğunluğu Parametreleri Üzerine Etkileri

Erhan Demirelli[1*], Ahmet Hakan Haliloğlu[2], Ömer Gülpınar[3], Mehmet Giray Sönmez[4], Yaşar Bedük[3], Sadettin Küpeli[2]

1.Giresun University Faculty of Medicine, Department of Urology, Giresun, Turkey
2.Ufuk University Faculty of Medicine, Department of Urology, Ankara, Turkey
3.Ankara University Faculty of Medicine, Department of Urology, Ankara, Turkey

ABSTRACT

Aim: In the present study we aimed to check the impact of maximal androgen deprivation therapy (MADT) on cellular blood components such as hemoglobin (Hb) and hematocrit (Htc) fasting blood glucose (FBG), serum lipid values and bone mineral density (BMD) in locally advanced prostate cancer.

Patients and Methods: Having been treated with maximal androgen blockade therapy, thirty-nine patients' initial values and at the twelfth month values of hemoglobin (Hb), hematocrit (Htc), FBG, total cholesterol (tChol), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) and spine BMD were recorded. Statistical comparisons of initial and at the twelfth month values were performed.

Results: A statistically significant decrease was recorded in Hb and BMD values after one year MADT. On the other hand, TG, tChol, LDL, HDL and FBG values showed a statistically significant increase. Although Hb levels were significantly reduced, none of our patients developed symptoms of anemia. Fourteen of 37 patients whose FBG levels were under 110 mg/dl before treatment, increased over 110 mg/dl at the twelfth month of treatment. Seven patients developed diabetes mellitus (DM) after treatment. Moreover, T score evaluation revealed newly developed osteoporosis in 4 patients. All of the patients with developed osteoporosis had osteopenic T score values before treatment. No bone fractures occurred in any of our patients.

Conclusion: Our study points out the increase of FBG related to the treatment of MADT. Decrease in BMD is higher in previously osteopenic patients. The lack of bone fracture and anemia symptoms might be considered as a result of evaluation of the early data on MADT.

Key words: Prostate cancer, Lipid profile, Maximal androgen blockage, Bone mineral density.

ÖZ

Amaç: Bu çalışmanın amacı, lokal olarak ilerlemiş prostat kanserinde maksimal androjen blokajı tedavisinin (MABT) hemoglobin (Hb) ve hematokrit (Htc) değerleri ile açlık kan şekeri (AKŞ), serum lipid değerleri ve kemik mineral yoğunluğu (KMD) üzerindeki etkisini kontrol etmektir.

Hastalar ve Yöntemler: MABT ile tedavi edilen 39 hastanın başlangıç ve onikinci aydaki hemoglobin, hematokrit, açlık kan şekeri, total kolesterol (tChol), trigliserit (TG), yüksek yoğunluklu lipoprotein (HDL), düşük yoğunluklu lipoprotein (LDL) ve omurga KMD değerleri kaydedildi. İlk ve onikinci aydaki değerlerin istatistiksel karşılaştırmaları yapıldı.

Bulgular: Bir yıllık MABT sonrası Hb ve KMD değerlerinde istatistiksel olarak anlamlı azalma kaydedildi. Öte yandan, TG, tChol, LDL, HDL ve AKŞ değerleri istatistiksel olarak anlamlı bir artış gösterdi. Hb düzeyleri önemli ölçüde azalmış olmasına rağmen, hastalarımızın hiçbirinde anemi belirtileri gelişmedi. Tedaviden önce FBG seviyeleri 110 mg / dl'nin altında olan 37 hastanın 14'ü tedavinin onikinci ayında 110 mg / dl'nin üzerine çıktı. Yedi hastada tedaviden sonra diyabetes mellitus (DM) gelişti. Dahası, T skoru değerlendirmesi 4 hastada yeni gelişen osteoporozu ortaya koymuştur. Osteoporoz gelişen tüm hastaların tedaviden önce osteopenik T skoru değerleri vardı. Hiç bir hastamızda kemik kırığı oluşmadı.

Sonuç: Çalışmamız MABT bağlı AKŞ artışını göstermektedir. KMD değerindeki azalma, daha önce osteopenik olan hastalarda daha yüksektir. Kemik kırığı ve anemi semptomlarının olmaması, MABT ile ilgili erken verilerin değerlendirilmesinin bir sonucu olarak düşünülebilir.

Anahtar kelimeler: Prostat kanseri, Lipit profili, Maksimal Androjen Blokajı, Kemik mineral dansitesi.

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*Corresponding Author:Erhan Demirelli, MD., Giresun University, School of Medicine, Department of Urology, Giresun,Turkey
e-mail: erhandemirelli@yahoo.com Tel: 05053393039 Fax: 04543101696

Androgens are essential for the maintenance of male sexual differentiation, virilization and reproductive functions. Androgen receptors are expressed more or less in almost all tissues of the body. For this reason, androgens are involved in many physiological events such as bone formation, skeletal development, laryngeal growth, hair growth, growth of sebaceous glands, and fat cell production. They also stimulate erythropoiesis, serum lipids and insulin regulation, sexual activity, behavior [1]. Androgens are absolutely necessary for the formation and growth of prostate tissue. Testiculer testosterone is the main effective androgen on the prostate tissue. The effects of serum testosterone on prostate tissue may lead to diseases such as benign prostatic hyperplasia (BPH) and pCa .[2]

Prostate cancer (PCa), the most frequently diagnosed cancer type, is the third leading cause of death due to cancer among men. Huggins et al. in 1941 demonstrated that castration generate improvements in the symptoms of PCa. Castration therapy is applied in two forms as either medical or surgical. MADT is the most commonly used method of medical castration. Luteinizing hormone releasing hormone (LHRH) agonist is used in combination with androgen receptor blockers in MADT. MABT lowers the testosteron level to castrated level. The decrease in the testosterone level, however, leads to androgen deficiency which have some adverse effects such as anemia, loss of BMD and an increased risk of metabolic syndrome. Metabolic syndrome is associated with the increased risk of both DM and coronary artery disease and also elevated serum lipid value [3-5]. Several other adverse effects of androgen deficiency are the loss of libido, hot flushes, gynecomastia, muscle mass loss, cognitive impairment [6-7]. The aim of the present study was to investigate the effects of MADT on Hb value, FBG, serum lipid values andBMD after a year long therapy.

Material and Methods

After approval from Ufuk University ethics committee, thirty nine patients with PCa diagnosed by prostate biopsy and were applied MADT included in the study. All biopsies were performed transrectally via a rectal ultrasound probe by usinga 18 gauge biopsy needle. All of the patients were taken twelve core samplings with six cores from each prostate lobes. Solid organ metastasis were investigated by abdominopelvic computed tomography (CT) while bone metastasis were investigated by whole-body bone scintigraphy in our out-patient clinic. Patients with bone and distant metastasis were excluded from the study. On the other hand, after the written approval of patients for study patients with locally advanced prostate cancer and those with high risk factors acording to D'Amico risk categories without radiological evidence of metastasis were included. Patients who were decided to have radiotherapy had neoadjuvant ADT with an androgen receptor blocker (bicalutamide 50 mg per day) and a LHRH agonist (Goserelin acetate 10.8 mg or leuprolide acetate 11.25 mg in the form of subcutaneous injection). The Hb, Htc, FBG, serum lipids, prostate specific antigen (PSA), free prostate specific antigen (fPSA), total testosterone, free testosterone and BMD of spine preliminary values of all patients before and after a year long treatment were recorded (Table 1). T-scores of the patients were also recorded. T-score is a difference between the patient's mean BMD and the mean of the population with the same gender.The patients' BMD values are normal, osteopenic or osteoporotic formation is determined according to T-score [8]. However, patients with osteoporosis, DM, having medication for dislipidemia or anemia were also excluded.

Table 1: The mean values and the changes of parameters of all patients initial and after a year long treatment.

	MeanValues			P value
	Initial	12th month	Change	
Hb	13.96 g/dl	12.93 g/dl	-1.03 g/dl	p<0.001
Htc	41.52	38.46	-3.06	p<0.001
tChol	176.28 mg/dl	213.78 mg/dl	+37.50 mg/dl	p<0.001
TG	120.34 mg/dl	133.85 mg/dl	+13.51 mg/dl	p<0.001
HDL	47.24 mg/dl	50.18 mg/dl	+2.93 mg/dl	p<0.001
FBG	96.54 mg/dl	111.53 mg/dl	+14.99 mg/dl	p<0.001
BMD	1.1202 g/cm^2	1.0817 g/cm^2	-0.0384 g/cm^2	p<0.001
PSA	70.23 ng/ml	0.18 ng/ml	-70.05 ng/dl	p<0.001
fPSA	13.80 ng/ml	0.55 ng/ml	-13.25 ng/dl	p<0.001
	MedianValues			
	Initial	12th month	Change	
LDL	110.30 mg/dl	130.79 mg/dl	+20.49 mg/dl	p<0.001

Statistical Analysis

Statistical analysis was performed with SPSS for Windows Version 15.0 statistic software package. Quantitative variables are expressed as mean ± Standard deviation or median (min-max) values. Qualifications variables were summarized by number and percentage. T-test was used in cases where the treatment related changes were associated with parametric paired case. Wilcoxon test was used to compare non parametric two paired samples. The significance level was determined as $p<0.05$.

Results

The mean age of the patient was 73.26 years with the range of 47 to 88 years. The dramatic decrease has seen in the PSA and fPSA levels with the treatment. The mean PSA level was decreased from 70.23 ng/ml (0.89-568) to 0.18 ng/ml (0.02-0.62) and the mean fPSA level was decreased from 13.8 ng/ml (7.16-19.17) to 0.55 ng/ml (0.01-11.8) after a year long treatment. Likewise, the mean Hb levels of the patients at diagnosis were 13.96 g/dl (10.5-17.2) and decreased to 12.93 g/dl (10.1-16.4) after treatment with the change of 7.37% which was found statistically significant ($p<0.001$). Besides the mean Htc levels of the patients decreased from 41.52 (32.72-54.30) to 38.46 (30.7-50.2) which was also found statistically significant ($p<0.001$).

The mean FBG value at diagnosis was 96.54 mg/dl (66.45- 114) and increased to 111.53 mg/dl (80- 168) after the treatment with the change of 15.8% which was found statistically significant ($p<0.001$). While only two patients had FBG values above 110 mg/dl before the treatment 17 patients had FBG values above 110 mg/dl at the end of a year long treatment. In fact, 7 patients among them had FBG levels ofeven above 126 mg/dl. This dramatic increase was also found statistically significant ($p<0.05$) (Table 2). The rate of patients diagnosed with DM was 17.95% after a year long MADT. At diagnosis, the mean tChol and TG values were 176.28 mg/dl (126.44-226.98) and 120.34 mg/dl (48.97-213.24), respectively. At the end of a year long treatment, the mean tChol and TG values increased to 213.78 mg/dl (155.34 to 309.07) and 133.85 mg/dl (50.63 to 295.01), respectively. The mean increase rates of tChol and TG were 22.58% or 37.49 mg/dl and 14.86% or 13.50 mg/dl, respectively and both increases were found statiscally significant ($p<0.001$).

The change in LDL value was calculated according to the median value. The median LDL value was 110.3 mg/dl at thediagnosis and increased to 130.79 mg/dl after a year long treatment. The increase of 18.28% or 21.04 mg/dl in the median value of LDL was also found statistically significant ($p<0.001$).

The mean value of HDL was measured as 47.24 mg/dl (19.6-82.49) and 50.18 mg/dl (28.9-78.67) at the diagnosis and after a year long treatment, respectively. The increase in mean HDL value was 2.93 mg/dl or %8.81 which found statistically significant ($p<0.001$)

The mean BMD values at diagnosis and after a year long treatment were 1.1202 g/cm^2 and 1.0817 g/cm^2, respectively. The decrease in mean BMD values was 0.0384 g/cm^2 or 3.5% which also found statistically significant ($p<0.001$). At the diagnosis, 23 patients were found in the normal range, 16 patients were found in osteopenic range and there were no patients in the osteoporotic range according to T-score values. After a year long treatment, T-score values of 4 patients have changed to osteopenic range from the normal range. None of the patients' T-score values have changed to osteoporotic range from normal range. However, T-scores of 4 patients were in the osteopenic range at diagnosis have changed to osteoporotic range after a year long treatment. All the changes in the T-score values were found statistically significant ($p<0.05$) (Table 3).

Table-2: Changes on FBG with the treatment of MADT

	First Year FBG			
Initial FBG		<110	110-126	>126
	<110	22 (56.41 %)	10 (25.64 %)	5 (12.82 %)
	110-126	0 (0 %)	0 (0 %)	2 (5.13 %)

Table-3: Changes of T-Score on bone mineral densitometry with the treatment of MADT

	First Year T-Score			
Initial T-Score		NORMAL	OSTEOPENIC	OSTEOPOROTIC
	NORMAL	19 (82.6 %)	4 (17.4 %)	0 (0 %)
	OSTEOPENIC	0 (0 %)	12 (75 %)	4 (25 %)

Testosterone levels decreased to castrated level (50 ng/ml) in all patients. No patients had biochemical recurrens or distant metastasis. Furthermore, no patients required neither anemia nor hyperlipidemia treatment during the study. However, 4 patients whose T-score values have changed to osteoporotic range after a year

long treatment were medicated with 1500 mg calcium carbonate tablets and 4 mg (400 IU of vitamin D3 equivalent) cholecalciferol tablets once a day. Bone fracture has not observed in any of the patients.

Discussion

The basics of the endocrine (hormonal) therapy in the treatment of locally advanced PCa were introduced by Huggins et al. in 1941 whose studies showed the relationship between hypothalamic-pituitary-gonad axis. These researchers demonstrated that castration generate improvements in the symptoms of PCa [4]. Castration therapy is traditionally applied in two ways as either medical or surgical. The method of surgical castration is bilateral orchiectomy. Recently, medical castration is more preferable and MADT is the most common method used as medical castration. In MADT, LHRH agonist and androgen receptor blockers are used together in combination. The steroidal deficiency caused by castration after MADT have some adverse effects such as anemia, loss of bone mineral density and an increased risk of metabolic syndrome. Metabolic syndrome is associated with the increased risk of DM, elevated serum lipid values and the risk of coronary artery disease [5].

In a study, 142 patients, treated with MADT, had been investigated and their initial mean Hb level was reported as 14.9 g/dl, and decreased to 13.9 g/dl, 13.2 g/dl and 13.1 g/dl in the first, second and third month of the treatment, respectively [9]. In another study, the mean decrease in hemoglobin level was reported as 0.54 g/dl after 3-month follow-up [10]. Bogdanos et al. showed that the mean Hb levels reduced from baseline of 14.2 g/dl to 14.0 g/dl, 13.5 g/dl, 13.2 g/dl and 12.7 g/dl at 1st, 2nd, 3th and 6th months after the initiation of treatment, respectively. The decreases in Hb level of all months were found statistically significant ($p<0.05$) [11].

The decline in Hb level was associated with higher baseline Hb level, flutamide treatment, increased age, and radiation therapy [10]. Strum et al. [9] showed that flutamide causes a higher decline in Hb value than bicalutamide. A decrease of 1.03 g/dl (7.37%) in average Hb values in our study was recorded between baseline and a year long of MADT values, which was statistically significant ($p<0.001$). Decrease in the value of Hb in our study is lower when compared with the previous studies that probably might be associated with the use of bicalutamide as androgen receptor blocker instead of flutamide in all of our patients. Besides, the mean patients' age was lower and the mean baseline Hb value was higher in our study comparing to previous studies.

Recent studies show that MADT causes an increase in serum glucose values, insulin resistance and the risk of DM. On the other hand, serum glucose level is not affected in the early stages of MADT [12-15]. Another study, carried out on 50 PCa patients, reported that FBG values of patients undergoing MADT was greater than that of control group after the 45 months follow-up. In the same study, the risk of developing DM in patients undergoing MADT was reported as higher comparing with control group [12]. In a large series of study, DM was diagnosed 38.9 % of patients treated with LHRH analogue after the average follow-up of 54 months [11]. Our rate of patients diagnosed with DM was 17.95% and the short follow-up time might be associated with this low rate of DM.

In several studies, it was reported that low serum testosterone levels have a negative effect on the lipid profile especially, on the values of tChol, LDL and TG [14,16,17]. No changes in serum lipid values were reported in a study, run with 22 PCa men treated with oral cyproterone acetate (300 mg/day), followed by long-acting LHRH analog therapy (leuprorelin acetate, 3.75 mg), administered by monthly intramuscular (IM) injection [18]. In another prospective study, carried out on 16 patients with PCa, significant increase in HDL level was reported while no significant change was found in both the LDL and TG levels after three months follow-up [15]. Changes in tChol and TG in patients receiving MADT was associated with age however it was not statistically significant in patients older than 80 years [19]. In our study, the change ratio of the lipid profile was higher than the previous studies which might be the result of our longer average follow-up period as well as not given diet and exercise education for dislipidemia. In a study, 66 patients were divided into two groups randomly and after 12 months follow-up; FBG, tChol, LDL and TG values increased ($P=0.009$, 0.000, 0.000 and 0.000) while HDL value decreased significantly ($P=0.000$) [20]. In our study, the avarage age and mean follow-up time were similar with the study of Saglam et al. The change in lipid profile was also similar, with the exception of the change in HDL value. Even the greater initial HDL level, we found an increase in final HDL value, which was similar with the previous studies. Saglam

et al, however, showed a decrease in final HDL values conflicting with all other studies [20].

Androgens play a vital role on bone biology for sure while their role in bone regeneration is not clear in men [21]. Despite MADT has been used ever since early 1940's, the relationship between androgen deficiency and BMD has been firstly reported by Stefan et al. in 1989 [22]. MABT results a decrease in androgen, changes bone remodeling and resorption in a direction to reduce BMD which cause osteopenia, osteoporosis and increased risk of fractures [23]. BMD changes according to various locations such as total hip, ultra-distal radius, spine, femoral neck and one third of radius was recorded in a study after12 months follow-up and only total hip and ultra distal radius BMD values decreased significantly by 3.3% and 5.3%, respectively [24]. Sertac et al. declared that L1-L4 lumbar spine BMD decreased significantly by 3.57% after six months of LHRH therapy ($p<0.05$) [25]. Similarly, Smith et al. reported a decrease in BMD value as % 2.5 and % 1.4 in spine and total hip, respectively [26]. In another study, there was an average decrease on BMD after orchiectomy as 2.4% and 7.6%, after first and second years, respectively. In the same study, the average BMD continued to decrease by 1.4% and 2.6% per year after 3th and 8th years [27]. Likewise, spine vertebra BMD value showed a decrease of 3.5% in our study. Diamond et al. determined a decrease level of BMD in femoral neck by 6.5% and in the lumbar spine by 6.6% after six months treatment with goserelin acetate and flutamide. Before the treatment, osteoporosis of the lumbar spine and femoral neck was presented in 9 (75%) and 4 (33%) patients, respectively [28]. The decrease in BMD, stated by Diamond et al., was greater twice comparing with our study. This difference might be the consequence of the absence of osteoporotic patients and lower average age in our study. A significant correlation was identified between the duration of androgen suppression and risk of skeletal fracture [29]. The relative risk of any fracture was significant among those receiving 9 or more doses of gonadotropin-releasing hormone agonist [23]. In another study, median time of bone fracture in patients to whom underwent MADT was reported as 22 months [30]. No bone fractures were observed in our study which might be the result of our limited follow-up period only with12 months, and our relatively high average initial BMD values. Only 4 of our patients developed osteoporosis.

Conclusions: The mean values of Hb, BMD and serum lipid except HDL were decreased, while FBG and HDL values were increased significantly with MADT in the present study. The most important limitation of our study was the limited number of patients, and short follow-up period of the patients. Despite of these shortcomings, the present study is important to point out the side effects of MADT, which is one of the most important reasons for lowering quality of life in patients with PCa. Indeed, it might be valuable to evaluate FBG, lipid profile, Hb and BMD values during the follow-up of PCa patients to increase quality of life. Larger series with longer follow-up studies are still necessary to clarify MADT side effects.

Conflict of Interest: The authors declare that they have no conflict of interest.

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