

The effect of androgen deprivation therapy in arterial stiffness of the aorta and the endothelial function of peripheral arteries

Abstract

Objective: To study the effect of androgen deprivation therapy (ADT) is using an LHRH agonist in arterial stiffness and endothelial function of peripheral arteries as a possible mechanism increasing their cardiovascular risk.

Material and methods: This pilot study is a prospective analysis of 32 patients with metastatic prostate cancer who received androgen deprivation therapy (ADT) using an LHRH agonist. We evaluated the endothelial function of brachial artery through ultrasound and measurement of Flow Mediated Dilatation (FMD) and we assessed the central arterial stiffness of the aorta by measuring Augmentation index (AIX) and velocity of the aortic pulse wave (PWV). The measurements were performed one day before starting treatment and then three months and six months after the initiation of treatment.

Results: PWV increased significantly by 8.26% from three to six months of follow up ($p=0.037$). FMD was found slightly elevated from baseline to 6months of follow up by 7.18% ($p>0.99$), but AI was increased significantly (15.53%, $p=0.007$) at six months as compared with baseline measures. Glucose, LDL, Triglycerides were increased by 15.23% ($p=0.002$) 14.34% ($p<0.001$), and 13.46% ($p<0.001$) respectively at 6months follow up and these values increased significantly between all other time points. HDL was decreased statistically significantly by 14.56% ($p<0.001$) during the follow up of 6months.

Conclusion: We found that these agents cause changes in arterial stiffness of the aorta and the endothelial function of peripheral arteries and we proposed them as a possible mechanism of increasing their cardiovascular risk.

Keywords: prostate cancer, ADT, cardiovascular, FMD, AIX

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Abbreviations: PCa, prostate cancer; MAB, maximal androgen blockade; ADT, androgen deprivation therapy; FMD, flow mediated dilatation; AIX, augmentation index; NSA, non-steroid antiandrogen; SD, standard deviation; ANOVA, analysis of variance

Introduction

Prostate Cancer (PCa) is one of the most important medical problems that male population is facing. The incidence rate is 214 cases per 1000 men in Europe.¹ PCa is the most common malignancy in males, accounting for 37% of all new cases of cancer in 2004 in Sweden.² Hormonal therapy is a well documented therapy for the metastatic PCa since 1941 when Huggins and Hodges assessed the effect of surgical castration and estrogen administration and demonstrated its responsiveness to androgen deprivation.^{3,4} More recently there has been a move towards the increasing use of hormonal therapy in younger men with earlier disease⁵ and also as an adjuvant treatment in non-metastatic disease and this fact force us to study more intensively the possible side effects of this treatment.

There is large number of different hormonal manipulations in the disposal of the clinical urologist in order to manage PCa. One of the most widely used so far is the use of LHRH agonist which has been used in advanced PCa for more than 15years.⁵ The combination of this LHRH agonist with an antiandrogen called Maximal Androgen Blockade (MAB) can be continued for a large period of time

increasing its side effects. The impact of the use of LHRH analogue in the cardiovascular system has been the objective of many studies but most of them didn't end up in the liable mechanism. Many factors were been held responsible for this increased cardiovascular risk such as insulin resistance, metabolic syndrome, changes of body mass, dyslipidemias, lower levels of high density lipoprotein and higher levels of triglycerides, total cholesterol and low density lipoprotein concentrations. The objective of the paper is to study the effect of androgen deprivation therapy (ADT) using an LHRH agonist in arterial stiffness and the endothelial function in those patients receiving hormonal therapy for prostate cancer. These changes if proven would suggest a part of the morbidity and mortality from cardiovascular events in patients receiving hormonal treatment with an LHRH analog.

Material and methods

This pilot study is a prospective analysis of 32 patients with metastatic prostate cancer who were planned to receive androgen deprivation therapy (ADT) using an LHRH agonist and a non-steroid antiandrogen (NSA) for prevention of the flare up phenomenon. The LHRH agonist that patients received was goserelin, leuprolide or triptorelin 11.25mg and the NSA was bicalutamide 50mg. The patients received and injection of an LHRH agonist every 3months and started bicalutamide 50mg the same day of the injection which lasted for 4 weeks. All 32 patients had no cardiac comorbidities other

than hypertension. 12 patients had a history of hypertension under medication and 7 had diabetes mellitus controlled only with diet. We evaluated the endothelial function of brachial artery through ultrasound and measurement of Flow Mediated Dilatation (FMD) and we assessed the central arterial stiffness of the aorta by measuring Augmentation index (AIX) and velocity of the aortic pulse wave (PWV) using Sphygmocor® (Atcor Medical, Australia). The overall performance status of the patients was assessed by measuring their biochemical profile and by documenting their comorbidities. The measurements of FMD, PWV and AI along with the blood tests were performed in the same manner and with the same procedures one day before starting treatment and then three months and six months after the initiation of treatment.

Assessment of endothelial function

The assessment of endothelium-dependent vasodilatation is widely used to evaluate endothelial function. FMD is a marker that results from the measurement of the diameter of brachial artery before and after increases in shear stress which is due to reactive hyperemia. This measurement was done with high frequency ultrasound recording of the brachial artery and the placement of a tourniquet lead to the hyperemia. Each patient was subjected to measurement of endothelial-dependent vascular response in the right brachial artery. Once, placed supine on examination table, in a room controlled for temperature (24-26°C) and after resting for 10minutes, a portion of the brachial artery in the absence of branching and above the height of the elbow was identified and analyzed in longitudinal section. When settings and determination were clear, we measured the diameter of the brachial artery for 1minute (baseline measurement). A cuff was used for 5minutes on the forearm by exerting pressure 200mmHg and the portion of the humeral artery recorded continuously for another 5minutes. Thereafter, we took recordings at the end of the diastolic phase of cardiac contraction, throughout the length thereof and for intervals of 3seconds. The diameter of the brachial artery was determined by an automatic detection system, and was expressed as the percent change from baseline diameter. Also, there was a continuous measurement system with Doppler, while increasing blood flow after cuff solution was expressed as a percentage of the base flow.

Estimation of the elastic properties of the aorta

Measurements included calculating the velocity of the aortic pulse wave and evaluating of the reflected wave. Each contraction of the left ventricle produces a pulse wave, which is transmitted rapidly through the arterial tree to the rest of the vascular system. The basic principle of fluid mechanics is that the waves travel through a hard line faster than in an elastic one. By placing sensitive tonometer over the common

carotid artery and then the femoral artery, we received signals of pressure and measured the time delay between the appearances of two signals with simultaneous ECG recording. The difference in the distance between these two positions of the aortic arch as measured transdermally, divided by the time taken to travel this distance gives another marker called PWV. The evaluation of the reflected wave was again measured noninvasively with the apparatus SphygmoCor®, (PWV Medical). A sensitive tonometer (Millar Instruments) placed over the radial artery measures the pressure waveform of the radial artery. The machine software analyzed the harmonics of the waveform, and then reconstructed the waveform of the pressure of the ascending aorta. From the waveform of the pressure in the aorta the contribution of the reflected pressure wave was estimated and then augmentation index (AIX) was calculated as the ratio between the pressures contributing the reflected wave in the aortic pressure to the pressure pulse.

Statistical analysis

Continuous variables are presented with mean and standard deviation (SD). Quantitative variables are presented with absolute and relative frequencies. For the comparison of proportions chi-square tests were used. Differences in changes of cardiac and biochemical parameters during the follow up period were evaluated using repeated measurements analysis of variance (ANOVA). Bonferroni correction was used in order to control for type I error in multiple comparisons. All p values reported are two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (version 19.0).

Results

Sample consisted of 32 patients with mean age 75.6years (SD=6.9years). Changes in cardiac parameters during the follow up period are shown in Table 1. PWV increased significantly by 8.26% from three to six months of follow up (p=0.037). FMD was found slightly elevated from baseline to 6months of follow up by 7.18% (p>0.99), but AI was increased significantly (15.53%, p=0.007) at six months as compared with baseline measures. Table 2 shows mean values in biochemical parameters during all time points. Glucose, LDL, Triglycerides were increased by 15.23% (p=0.002) 14.34% (p<0.001), and 13.46 % (p<0.001) respectively at 6months follow up and these values increased significantly between all other time points. HDL was decreased statistically significantly by 14.56 % (p<0.001) during the follow up of 6months. When Glucose, HDL and Triglycerides were categorized according to metabolic syndrome criteria⁶ (Table 3), no significant changes in the proportion of patients with elevated levels were found during the follow up period.

Table 1 Changes in cardiac parameters during the follow up period

	Pre 1	3 months after 2	6 Months after 3	P 1 vs 2	P 1 vs 3	P 2 vs 3
	Mean (SD)	Mean (SD)	Mean (SD)			
PWV	10.9 (3.2)	10.6 (3.1)	11.5 (2.9)	>0.999	0.272	0.037
FMD	5.43 (3.14)	5.04 (2.25)	5.82 (6.11)	>0.999	>0.999	>0.999
AI	26.4 (5.9)	28 (7.3)	30.5 (5.8)	0.57	0.007	0.067

Table 2 Changes in biochemical parameters during the follow up period

	Pre 1	3 Months after 2	6 Months after 3	P	P	P
	Mean (SD)	Mean (SD)	Mean (SD)	1 vs 2	1 vs 3	2 vs 3
Glucose	98.5 (24.3)	108.5 (31.4)	113.5 (60.5)	0.016	0.002	0.016
HDL	52.9 (10.8)	49 (9.8)	45.2 (8.8)	0.002	<0.001	<0.001
LDL	103.2 (18.7)	111.6 (19.6)	118 (19.5)	<0.001	<0.001	0.007
Triglycerides	140.4 (44)	154.2 (50.9)	159.3 (54.2)	<0.001	<0.001	<0.001

Table 3 Changes in biochemical parameters as categorized with metabolic syndrome criteria during the follow up period

	Pre 1	3 Months after 2	6 Months after 3	P	P	P
	N (%)	N (%)	N (%)	1 vs 2	1 vs 3	2 vs 3
Triglycerides						
<150	18 (56.3)	16 (50)	13 (40.6)	0.616	0.211	0.451
≥150	14 (43.8)	16 (50)	19 (59.4)			
Glucose						
<100	20 (62.5)	16 (50)	13 (40.6)	0.313	0.08	0.451
>100	12 (37.5)	16 (50)	19 (59.4)			
HDL						
≥40	27 (84.4)	26 (81.3)	24 (75)	0.545	0.351	0.74
<40	5 (15.6)	6 (18.8)	8 (25)			

Discussion

Androgen deprivation therapy (ADT) is an established therapy for metastatic PCa and some cases of locally advanced and/or localized PC.⁷ However, concerns have been raised about the cardiovascular side effects of ADT and their impact on the survival of elderly patients with PCa. Firstly studies in animals demonstrated that after castration, the percentage of arteriosclerosis was increased, and this observation was inhibited by testosterone.^{8,9} In a study on 1015 patients that received ADT (mean duration: 4.1months), the use of ADT statistically significantly increased the risk of death from cardiovascular causes (HR=2.6, P=0.002).¹⁰ In another study on 22816 patients with PC,¹¹ multivariate analysis revealed that ADT significantly increased cardiovascular morbidity (HR 1.20 p<0.001). Several studies have demonstrated an increased incidence of coronary artery disease, heart failure and acute myocardial infarction in patients on ADT without been able to justify the potential mechanism. Testosterone supplementation has been found to reduce exercise-induced ischemia during treadmill testing.^{12,13} Keating et al found that the use of a GnRH agonist use was associated with increased risk of incident diabetes (adjusted hazard ratio [HR], 1.44; P<.001), coronary heart disease (adjusted HR, 1.16; P<.001), myocardial infarction (adjusted HR, 1.11; P=.03), and sudden cardiac death (adjusted HR, 1.16; P=.004).¹⁴ Another study proposes that increased cardiovascular risk is due to a correlation between many different mechanisms which are interconnected with arterial stiffness as an independent factor.¹⁵

Many factors were held responsible for increasing cardiovascular risk in patients receiving ADT. ADT changes the body mass composition as it leads to muscular atrophy and increase in subcutaneous fat, a situation characterized as “sarcopenic obesity”.¹⁶ Furthermore ADT increases insulin concentration despite unchanged plasma glucose, which is suggestive of insulin resistance.¹⁷ Peripheral resistance to

insulin can induce or precipitate type 2 diabetes mellitus (DM) and metabolic syndrome.¹⁸ Moreover, studies have demonstrated that ADT is associated with dyslipidemias, lower levels of high density lipoprotein and higher levels of triglycerides, total cholesterol and low density lipoprotein concentrations. Furthermore, Chen et al.,¹⁹ revealed that long-term ADT (mean duration: 2.5years) significantly decreased the levels of apolipoproteins I and II. Lastly, Nishiyama et al.,²⁰ demonstrated that after 6months of ADT, body weight, levels of fasting blood sugar, serum total cholesterol, blood urea nitrogen, compensated calcium, inorganic phosphorus, bone-specific alkaline phosphatase, and compensated urinary deoxyypyridinoline increased significantly. A study in patients on ADT (mean duration: 3months) has shown a 4.3% increase in fat mass and a 1.4% decrease in lean body mass. In our study all the studied parameters were changed and the results were all statistically significant result that agrees with the existing literature. The levels of glucose, LDL and triglycerides were all increased in 6months and the levels of HDL in contrast was decreased in the same follow up period. Finally when these values were categorized with metabolic syndrome criteria the results didn't show any statistically significant change which may imply that since no metabolic syndrome occurred in the follow up period, changes in elasticity and endothelium of larger vessels may have a much larger role in cardiovascular events occurring in a shorter period of time.

There are several sparse data in the literature implying the role of arterial stiffness in increasing cardiovascular risk in patients receiving ADT. In a relevant study, arterial stiffness was assessed with pulse wave analysis.²¹ After 3months of ADT, the augmentation index increased from 24% to 29% (P=0.003), while the timing of wave reflection was reduced from 137 to 129msec (P=0.003). In a subgroup of patients whose treatment was discontinued after 3months, the augmentation index decreased from 31% at month to 29% at month

6, in contrast to patients receiving continuous ADT, where the augmentation index remained elevated at month 6 ($P=0.043$). In another study the researchers measured systemic arterial compliance (SAC) and found it significantly lower in the androgen-depleted men compared to controls (0.81 ± 0.53 vs. 1.18 ± 0.43 arbitrary compliance units, $p=0.01$).²² In our study the (AIX) increased from 26.4% to 30.5% ($p=0.007$) in 6 months follow up and it even increased in 3 months period without this result reaching statistical significance. We also evaluated another factor indicating change in arterial stiffness which is PWV. We found that there has been a change from 10, 9 to 11, 5 in 6 months after the therapy initiation but these results have not reached statistical significance. Same results in the evaluation of endothelial function of brachial artery through FMD. There has been an overall increase from 5.43 to 5.82 in 6 months that indicates a possible effect of androgen deprivation therapy to the endothelial function of the major blood vessels even if these results are not statistically significant ($p=0.272$).

Our study has some limitations. Firstly since it is a pilot study the number of patients involved is small. This small number may have influenced our results. Secondly our study has no control group and finally the follow up period is relatively short (6 months).

Conclusion

The use of ADT with an LHRH agonist especially in younger men with earlier disease has raised concerns about their cardiovascular side effects. We found that these agents cause changes in arterial stiffness of the aorta and the endothelial function of peripheral arteries and we proposed them as a possible mechanism of these effects. In our knowledge this is the first paper that used these three parameters (FMD, AIX, and PWV) alongside with biochemical indicators and found a correlation between them and the use of androgen deprivation therapy. Larger randomized trials with bigger follow up periods are needed in order to exclude safer results.

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None.

Conflict of interest

The author declares no conflict of interest.

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