ORIGINAL ARTICLE

Impact of androgen deprivation on the lipid profile and atherogenic risk in prostate cancer patients


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Available online 9 August 2012

Abstract

Objective: This study has aimed to analyze the changes observed in the lipid profile and atherogenic risk in prostate cancer patients subjected to androgen deprivation.

Material and methods: Between 2001 and 2008, serum lipoproteins (total cholesterol, HDL, LDL and triglycerides) were determined in 636 patients. Of these, 129 were treated with maximum androgen blockade and 177 patients were only treated with LHRH analogue. The control group was formed by 339 subjects treated for prostate cancer. The atherogenic risk was calculated using the Castelli formula.

Results: Mean atherogenic risk was 4.2 in the control group and 4 in the group of patients subjected to androgen deprivation. The mean atherogenic risk in those subjects that were treated with LHRH analogues was 4.1 while it was 3.9 in patients subjected to maximal androgen blockade. We did not find significant differences for atherogenic risk according to length of treatment. The multivariate analysis confirmed that the treatment modality was the only significant variable influencing atherogenic risk.

Conclusions: This study demonstrates that continuous androgen deprivation does not increase atherogenic risk in patients with prostate cancer. This risk did not increase during the treatment either. The association of bicalutamide to the LHRH analogue seems to have a protective effect on atherogenic risk.

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Impacto de la supresión androgenica sobre el perfil lipídico y el riesgo aterogénico en pacientes con cáncer de próstata

Resumen

Objetivo: Analizar los cambios observados en el perfil lipídico y el riesgo aterogénico en pacientes con cáncer de próstata sometidos a supresión androgenica.

Material y métodos: Los niveles séricos de lipoproteínas (colesterol total, colesterol HDL, colesterol LDL y triglicéridos) fueron determinados en 636 pacientes entre 2001 y 2008. De estos, 129 fueron tratados con bloqueo androgénico máximo y 177 fueron tratados únicamente con análogo de LHRH. El grupo control estaba formado por 339 pacientes sometidos a biopsia


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prostática (212 con cáncer de próstata y 127 sin cáncer de próstata). El riesgo aterogénico fue calculado según la fórmula de Castelli (colesterol total/HDL).

Resultados: El riesgo aterogénico medio en el grupo control fue de 4,2 y de 4 en el grupo sometido a supresión androgénica (p > 0,05). El riesgo aterogénico medio en los pacientes sometidos a monoterapia con análogos de LHRH fue de 4,1, mientras que en los pacientes en tratamiento con bloqueo androgénico máximo fue de 3,9 (p = 0,02). No se observaron diferencias significativas del valor del riesgo aterogénico en función de la duración del tratamiento. El análisis multivariante confirmó que la modalidad de tratamiento fue la única variable significativa respecto al riesgo aterogénico.

Conclusiones: Este estudio demuestra que la supresión androgénica no incrementa el riesgo aterogénico en pacientes con cáncer de próstata. Este riesgo tampoco se incrementa a lo largo del tratamiento. La asociación de la bicalutamida al análogo de LHRH parece ejercer un efecto protector sobre el riesgo aterogénico.

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Introduction

Prostate cancer (PCa) is one of the most common neoplasias in men. Relative survival at 5 years for all PCa tumor stages is 98%. It is for this reason that considerations regarding the morbidity and mortality of the treatments used have increased in importance.

In recent years, the use of androgen deprivation (AD) has been extended in patients with PCa, even in circumstances not covered in the guidelines. AD is the treatment of choice in metastatic patients, although it is also used in patients with high risk disease in association with radiotherapy. 

Despite the improvement in the survival objective in different studies, AD associates a number of side effects among which are: decreased sexual desire, gynecomastia, hot flashes, redistribution of body fat, depression, loss of bone mineral mass, or changes in the lipid profile.

Cardiovascular mortality is the second cause of death in patients with PCa. This fact has been related with the use of AD due to the increased incidence of diabetes, metabolic syndrome, and arterial stiffness among the patients with PCa undergoing AD. These changes can explain the increased cardiovascular morbidity observed in the patients with PCa undergoing AD.

Recent studies have shown significant changes in the lipid profile of patients undergoing hormonal therapy. An unfavorable lipid profile might, therefore, increase the cardiovascular risk in this patient population. In this regard, several epidemiological studies have shown that the total cholesterol/HDL, cholesterol (TC/HDL) ratio, or Castelli index is a powerful predictor of ischemic heart disease. High levels of the ratio TC/HDL are associated with a significant increase of obstructive coronary disease and atherogenic risk at this level.

A review paper prepared by a panel of experts which recommends an initial assessment of every patient that should undergo treatment with AD has recently been published. This assessment should include measurement of blood pressure values, levels of blood glucose, and lipid profile.

The aim of this paper is to analyze the changes observed in the lipid profile and the atherogenic risk (calculated by the ratio TC/HDL) in patients with prostate cancer undergoing androgen deprivation.

Materials and methods

We conducted a retrospective study that included 636 patients. Of all the patients, 127 (20%) had no PCa at the time of the study because they were patients with negative prostate biopsy and which formed the control group. Forty-six (7.2%) patients had PCa and initially underwent radical prostatectomy. Ninety-two (14.5%) patients were diagnosed with PCa and were initially treated with radical prostatectomy and then with AD for seminal involvement or biochemical progression after initial surgical treatment with curative intent. Two hundred and five (32.2%) underwent AD as an initial treatment of their prostate cancer pathology. Of the total of 297 patients undergoing AD, 120 (18%) received maximum androgen blockade (MAB) with three-monthly LHRH analog and 50 mg/day bicalutamide. The other 177 (27.8%) received only monotherapy with LHRH analogs (Fig. 1).

The levels of total cholesterol (TC), LDL cholesterol (LDL), HDL cholesterol (HDL), and triglycerides (TG) were determined systematically. Lipid levels were measured by enzymatic colorimetric method using the AUS400 Olympus Diagnostic Analyser. The LDL levels were calculated using the Friedewald equation when TG ≤ 300 mg/dl.

Atherogenic risk or Castelli index were defined as the result of dividing the TC by the HDL, both expressed in mg/dl.

Figure 1 Patient distribution scheme.
The Mann–Whitney U-test was used to compare the means between two groups. In order to compare more than two means, we used the nonparametric test of Kruskall–Wallis. For the analysis of the predictors of atherogenic risk, we conducted a multiple linear regression analysis, incorporating the variables in a qualitative and quantitative way.

*p* values lower than 0.05 were considered as statistically significant. The statistical analysis was carried out with the software package SPSSv15.0 (Statistical Package for Social Sciences).

**Results**

When comparing the group of patients who underwent AD with the group of patients without AD there were no significant differences in lipid profile and atherogenic risk (Table 1).

When comparing the group of patients diagnosed with PCa, but not undergoing AD, with the group of patients with PCa undergoing AD, we only found significant differences in HDL levels. All other parameters, including atherogenic risk, showed no significant differences (Table 2). Regarding the analysis in line with the method of AD, we objectified that the atherogenic risk was significantly lower in the group undergoing MAB with respect to the group undergoing monotherapy with LHRH analogs, while the HDL levels were significantly higher in the group under MAB (Table 3).

The atherogenic risk did not show significant differences according to the patients grouped based on the time under androgen deprivation (Table 4).

In the linear regression analysis, the AD modality was the only atherogenic risk predictor (*p* = 0.02).

**Table 1** Analysis of lipid profile and atherogenic risk of patients with androgen deprivation (AD) and without AD.

<table>
<thead>
<tr>
<th></th>
<th>Without AD (n = 339)</th>
<th>With AD (n = 297)</th>
<th><em>p</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dl)</td>
<td>212.7 ± 37.2</td>
<td>217.2 ± 44.8</td>
<td>0.287</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>52.8 ± 11.1</td>
<td>54.8 ± 12.6</td>
<td>0.078</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>135.5 ± 31.7</td>
<td>136 ± 38.1</td>
<td>0.956</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>125.2 ± 75.1</td>
<td>130.1 ± 72.7</td>
<td>0.069</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>4.1 ± 0.9</td>
<td>4 ± 0.8</td>
<td>0.599</td>
</tr>
</tbody>
</table>

**Table 2** Analysis of lipid profile and atherogenic risk in patients with PCa without androgen deprivation (AD) and PCa undergoing AD.

<table>
<thead>
<tr>
<th></th>
<th>PCa without AD (n = 212)</th>
<th>PCa with AD (n = 297)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dl)</td>
<td>212.2 ± 36.7</td>
<td>217.2 ± 44</td>
<td>0.221</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>52 ± 11.3</td>
<td>54.8 ± 12.6</td>
<td>0.014</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>134.5 ± 31.7</td>
<td>136.3 ± 38.1</td>
<td>0.653</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>134.2 ± 82.9</td>
<td>130.1 ± 72.7</td>
<td>0.963</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>4.2 ± 0.9</td>
<td>4 ± 0.8</td>
<td>0.173</td>
</tr>
</tbody>
</table>

**Table 3** Analysis of lipid profile and atherogenic risk for the group undergoing maximum androgen blockade (MAB) and the group undergoing monotherapy with LHRH analogs.

<table>
<thead>
<tr>
<th></th>
<th>LHRH analogs</th>
<th>MAB (n = 177)</th>
<th><em>p</em> value (n = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dl)</td>
<td>215.8 ± 45.3</td>
<td>219.3 ± 44.1</td>
<td>0.409</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>52.9 ± 11.4</td>
<td>57.5 ± 13.7</td>
<td>0.004</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>136.9 ± 39.2</td>
<td>135.4 ± 36.5</td>
<td>0.807</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>129.7 ± 54.4</td>
<td>130.7 ± 93.7</td>
<td>0.173</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>4.1 ± 0.9</td>
<td>3.9 ± 0.7</td>
<td>0.022</td>
</tr>
</tbody>
</table>

**Discussion**

The side effects associated with the AD have been well-known for years. Most of them have a direct effect on the quality of life of the patient and other health issues. Recent studies show that patients undergoing AD had a higher cardiovascular morbidity.4-12

Alterations in lipid profile are a well-documented risk factor in atherosclerotic processes. Low testosterone levels have been associated with dyslipidemia.13

At the end of the 80s, different studies objectified alterations in the lipid profile of patients with PCa under hormonal treatment.14,15

On the other hand, it has always been thought that the MAB associated a greater presence of adverse effects than monotherapy with LHRH analogs. In our study, we tried to characterize the possible differences between both treatment modalities. Only Moorjani et al., in a prospective study, analyzed the changes on the lipid profile experienced by a number of PCa patients undergoing different treatments including orchiectomy, estrogen therapy, and the combination of an LHRH analog with an antiandrogen.

Estrogen is associated with hypertriglyceridemia and elevated serum levels of HDL, while orchiectomized patients had elevated TC without appreciating changes in levels of TG, LDL, or HDL. The patients receiving MAB developed a significant elevation of serum levels of HDL.14 In our study, the patients undergoing MAB also showed serum HDL levels higher than those of the patients undergoing monotherapy with LHRH analogs.

In a prospective study with 22 patients undergoing AD for three months (a period of two weeks of pre-treatment with cyproterone acetate followed by leuprolide acetate) Smith et al. observed no significant changes in lipid profile compared to the baseline serum levels.16 In another prospective study with 16 patients, and after three months, performed by Dockery et al., the authors showed a significant increase in TC and HDL levels. There were no significant changes in TG and LDL levels.4 It should be noted that both studies have the limitation of a short follow-up period and a small sample size. In our study, significantly lower levels of TG are objectified in patients undergoing AD for over 36 months, although this finding does not appear to be significant from a clinical point of view.

In 2002, Smith et al. published the prospective study with the longest follow-up (48 weeks). In that study, 40 patients were treated with bicalutamide for 4 weeks before starting the treatment with leuprolide. The authors observed a
significant increase in serum TC, HDL, LDL, and TG levels (9, 11.3, 7.3, and 26.5%), respectively. In turn, Braga-Basaria, in a cross-sectional case-control study, showed that the patients undergoing AD had higher levels of TC than those in the control group. No differences, however, were observed in LDL, HDL, and TG levels. Nevertheless, in our work, we did not objectify any differences between the patients undergoing AD and the control group (patients not undergoing AD).

In another cross-sectional case-control study recently published by Cleffi et al., we observed a significant increase in TC and LDL in the group undergoing AD. In this same study, a calculation of the average risk of coronary heart disease at 10 years was also carried out, showing a greater cardiovascular risk for the group undergoing AD.

As for the analysis conducted in our study with respect to atherogenic risk, it should be noted that we did not find statistically significant differences between the different groups under study, except when comparing the subgroup of patients under monotherapy with respect to the subgroup of patients undergoing MAB. They had a significantly lower atherogenic risk than the patients under monotherapy with analogs.

These findings are consistent with the results obtained by Braga-Basaria in the only study of the literature that analyzed the differences between a group of patients undergoing AD and a control group in terms of atherogenic risk (TC/HDL). The TC/HDL ratio had a mean value of 4.7 in the group undergoing castration, whereas in the control group the mean value of the TC/HDL ratio was 4.4. When analyzing the data, no statistically significant differences were found with regard to atherogenic risk between both groups.

Our study has several limitations; first, it is a retrospective study consisting of a control group and a treatment group, so the conclusions we have reached have a 3b level of evidence. For this reason, we think it would be necessary to develop further prospective studies to assess the variation in serum levels for the same patient throughout the treatment and determine the incidence of cardiovascular events.

Secondly, despite having 636 patients, the sample size of some of the subgroups analyzed was not large enough to have found statistically significant differences with regard to some of the variables analyzed.

Finally, this being a retrospective study, the patients who were taking lipid-lowering therapy were not excluded. Other variables related to lifestyle such as exercise, diet, and smoking habits of the patients under study were not controlled either.

Conclusions

The results of our study show, first, that there are no significant differences in lipid profile and atherogenic risk in patients undergoing AD and patients without AD. Secondly, that the association of an antiandrogen with treatment with LHRH analogs seems to exert a ‘protective’ role with respect to atherogenic risk.

With our results, we cannot attribute the increase in cardiovascular morbidity observed in the patients undergoing AD to the changes induced in lipid profile. Therefore, the etiology of cardiovascular disease in this type of patients is multifactorial.

As pointed out in the work by Levine et al., those patients diagnosed with PCA and candidates for treatment of AD should be monitored before and during hormone treatment regarding the levels of TA, lipid profile, and serum glucose.

Conflict of interest

The authors declare that they have no conflict of interest.

References