Metabolic syndrome in patients with prostate cancer being treated with androgen deprivation therapy


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Abstract

Background: Prostate cancer is the most frequent tumor in men. In Mexico it is diagnosed at late stages of the disease. Androgen deprivation therapy is widely used as treatment in the different stages of prostate cancer. Metabolic syndrome is estimated to present in approximately 50% of the patients that undergo androgen blockade.

Methods: A cross-sectional, retrospective, observational, and descriptive study was conducted on patients diagnosed with prostate cancer that were seen at the Urology Outpatient Service within the time frame of August 2012 to January 2013. General variables were analyzed, together with waist circumference, fasting glucose, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, testosterone, prostate specific antigen (PSA), and the type and duration of androgen deprivation therapy.

Results: A total of 43% of the patients were identified as having locally advanced cancer and 57% with metastatic disease. Defining metabolic syndrome as 3 or more Adult Treatment Panel (ATP) III criteria, 5 patients (7%) presented with none of the criteria and 48% met 3 or more of the criteria consistent with metabolic syndrome diagnosis.

Conclusions: No statistical association was found between the duration of androgen deprivation therapy and metabolic syndrome ($X^2=1.749, p>0.05$).
Introduction

Prostate cancer is the most frequently diagnosed neoplasia in men. In 2011, 222,000 new cases and 32,000 deaths were reported in the United States.\(^1\)

Eighty-six percent of the cases are diagnosed as localized or locally advanced disease, but this figure is lower in Mexico and the rest of the Latin American countries where the majority of cases are diagnosed as metastatic disease.\(^2\)

An age-adjusted general prevalence of 23.7% has recently been reported in the United States; this prevalence is higher in Mexican-American subjects, at 31.9%.\(^3\)

Androgen deprivation therapy (ADT) is widely used in treating prostate cancer in its different stages, whether in association with brachytherapy, radiotherapy, radical prostatectomy, or sole management in metastatic disease.\(^4\)

Different studies have recently reported the identification of an association between androgen suppression and increased risk for presenting with cardiovascular events. These results have heightened the interest in and discussion of the effects of ADT and their possible association with greater risk for cardiovascular disease.\(^5\)

Likewise, observational studies have concluded that there is an independent association between hypogonadism (under 350 ng/dL) caused by androgen suppression and the development of type 2 diabetes mellitus and metabolic syndrome.\(^6\)\(^7\)

Metabolic syndrome is estimated to present in close to 50% of the patients that undergo ADT.\(^8\)

Among the metabolic effects of ADT that have been reported are: increased body fat and its accumulation mainly at the subcutaneous cell level, elevated triglycerides, increased LDL cholesterol, an increase in fasting insulin, and a decrease in insulin sensitivity.\(^9\)\(^10\)

It has been observed that the development of metabolic syndrome in patients with ADT is associated with a 3-fold increase in the risk for developing cardiovascular disease (mainly ischemic cardiopathy), which is the principal cause of death in patients with prostate cancer, exceeding the cancer-specific mortality.\(^11\)\(^12\)

Since its description in 1999, different definitions of metabolic syndrome have been proposed. The most important are those of the Adult Treatment Panel III criteria (ATP III) and the International Diabetes Federation (IDF).\(^13\)

The ATP III (2001) criteria define metabolic syndrome as the presence of 3 of the following 5 criteria:

1. Fasting glucose in plasma equal to or greater than 110 mg/dL.
2. An increase in triglycerides equal to or greater than 150 mg/dL.
3. Reduction of HDL cholesterol lower than 40 mg/dL.
4. Waist circumference measurement above 102 cm.
5. An increase in systolic pressure equal to or greater than 85 mmHg.\(^14\)\(^15\)

The aim of this study was to determine the proportion of patients that were diagnosed with metabolic syndrome within the time frame of August 2012 and January 2013, and its relation to the type of androgen deprivation therapy they received and their treatment duration.

Methods

A descriptive, retrospective, observational, cross-sectional study was conducted. The study universe was made up of the medical records of patients diagnosed with prostate cancer that were seen at the Urology Outpatient Service within the time frame of August 2012 and January 2013. A conventional sample was made up of those medical records that fit the selection criteria.

Medical records that had insufficient data for the purposes of the study were eliminated. The patients gave their informed consent.

The variables studied were: age, staging, treatment, weight, height, body mass index, blood pressure, waist circumference, fasting glucose, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, testosterone, prostate-specific antigen (PSA), and type and duration of ADT. Based on the analysis of these variables, the existence of metabolic syndrome was determined in accordance with the ATP III criteria.
Results

The data of 75 medical records that met the selection criteria were analyzed. The patients were staged as: locally advanced cancer 43% and metastatic disease 57%. In relation to the treatment received, pure hormone was the most frequently used (77%), followed by trimodal therapy (radical prostatectomy + radiotherapy + ADT). Bimodal treatment (radiotherapy + ADT) was used the least, in only 3% of the patients. Biochemical control of the patients that was observed from PSA levels indicated that 87% of the patients had figures below 4 ng/mL; only 10 patients had higher figures that could be explained by their hormonal resistance.

Maximum androgen blockade was used in 69% of the patients and was the type of ADT used the most. Simple bilateral orchiectomy was used in the remaining 31%.

The mean duration of ADT was 24.5 months, with a range of one to 120 months. The chi-square test was used, with the cut-off point of 24 months of treatment, to determine whether the duration of ADT was associated or not with the presence of metabolic syndrome; no such association was found ($X^2=1.749; \text{gl}=1; p>0.05$).

Seven percent of the patients were in intermittent treatment, and because theoretically the “off” period is related to a lower number of adverse effects, the relation of intermittence to the presence of metabolic syndrome was looked for through the chi-square test; no association was found between the two ($X^2=0.137; \text{gl}=1; p>0.05$).

Given that the ATP III guidelines define metabolic syndrome with 3 or more criteria, 5 of the patients in the present study had none of the criteria (7%). Forty-eight percent had 3 or more of the criteria and so were consistent with metabolic syndrome diagnosis.

Hypertriglyceridemia was the most frequent criterion and was present in 71% of the patients, followed by high blood pressure and the reduction of HDL cholesterol figures in 50% of the patients, respectively. The least frequent criterion was central obesity, and was present in only 27% of the patients (fig. 1).

In regard to testosterone levels, considering 50 ng/mL as the castration cut-off point, 84% of the patients presented with figures below that amount. However, when the cut-off point was changed to 20 ng/mL, 65% of the patients had figures below that amount.

Observational studies have concluded that there is an independent association between hypogonadism (less than 350 ng/dL) caused by androgen suppression and metabolic syndrome. In the present study we found that 93% of the patients presented with figures consistent with hypogonadism. Therefore a possible association between these 2 entities was explored, finding no statistically significant association between them ($X^2=0.309; p>0.05$) (fig. 2).

Discussion

ADT is widely used as treatment for prostate cancer in its different stages, whether in association with brachytherapy, radiotherapy, radical prostatectomy, or as the sole management in metastatic disease. Eighty-six percent of the cases are diagnosed as localized or locally advanced disease. However, this figure is lower in Mexico and Latin America, where the majority of cases are metastatic disease.

We found a high number of patients with metastatic disease (57%), results coinciding with those of the Mexican Department of Health in its “Action Against Prostate Cancer” program and with Jemal et al. in relation to the number of cases of metastatic disease in Mexico and Latin America.

Theoretically, the withdrawal of ADT should be related to a reduction in the frequency of metabolic syndrome, but we found no mention of this in the bibliographic literature; an important contribution of the present study is having found that 7% of the patients had intermittence, without finding a statistically significant relation between the 2 variables.

In their article reporting ATP III criteria frequency, published in the Journal of Clinical Oncology in 2006, Braga-Basaria et al. found that the most frequent criterion was central obesity, present in 75% of the cases. In our study it was the least frequent criterion, present in only 27% of the patients. Hypertriglyceridemia was found in only 55% of the cases of that report, whereas in our study it was the most frequent criterion at 71%.

The use of gonadotropin-releasing hormone (GnRH) agonists has been reported to be associated with a greater risk for diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death.\textsuperscript{16-20} Men treated with simple bilateral orchietomy have more probability of developing diabetes, but not coronary heart disease, myocardial infarction, or sudden cardiac death.\textsuperscript{17,21}

At present there are no reports in the literature on the association between the type of ADT and its duration and the presence of metabolic syndrome, and therefore these could be analyzed in future studies. It would also be of interest to carry out a comparative study between patients with and without ADT and their relation to metabolic syndrome.

Another very relevant study would be the determination of metabolic syndrome due to causes other than hormone therapy in patients, before ADT, so that the true value of ADT as a risk factor for metabolic syndrome could be precisely established.
Conclusions

Based on the abovementioned results we can make the following conclusions:

1. In the patients studied, 57% were in a metastatic stage, and 43% had locally advanced disease.
2. Biochemical control was under 4 ng/ml in 87% of the patients.
3. Only 2 types of ADT were used: maximum androgen blockade (69%) and simple bilateral orchiectomy (31%).
4. The mean duration of ADT of the patients studied was 24.5 months, with a range of one to 120 months. No statistically significant association between ADT duration and metabolic syndrome was found ($X^2=1.749; gl=1; p>0.05$).
5. Only 7% of the patients were in intermittence, and there was no statistically significant relation between that status and metabolic syndrome ($X^2=0.137; gl=1; p>0.05$).
6. The most frequent ATP III criteria were, in first place, hypertriglyceridemia at 71%, followed by reduced HDL cholesterol and high blood pressure at 50%, respectively; the least frequent was central obesity at 27%.
7. Eighty-four percent of the patients presented with testosterone levels under 50 ng/mL, and there was no association of these levels with metabolic syndrome ($X^2=0.309; gl=1; p>0.05$).

Conflict of interest

The authors declare that there is no conflict of interest.

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