ORIGINAL ARTICLE

Metabolic syndrome in patients with prostate cancer undergoing androgen suppression

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KEYWORDS
Metabolic syndrome; Androgen suppression; Prostate cancer

Abstract
Objectives: Cardiovascular mortality is the leading cause of death in patients with prostate cancer (PC), metabolic syndrome (MS) being related to it. The main objective of this study was to determine the prevalence of MS in patients with PC undergoing androgen suppression (AS).

Materials and methods: We performed a retrospective study of cases and controls that included 159 patients. The study group was made up of 53 patients with PC undergoing AS for a period exceeding 12 months. The control group had 53 patients with PC at the time of diagnosis and 53 patients with negative prostate biopsy. All the patients were evaluated for presence of MS according to NCEP-ATPIII criteria.

Results: Prevalence of MS in patients without PC was 32.1% and in those with non-treated PC 35.8%, P = .324. In patients with PC undergoing AS, prevalence of MS was 50.9%, P < .001. When AS duration was less than 36 months, prevalence of MS was 44.0% and when greater than 36 months 57.1%, P < .001. Waist circumference and hyperglycemia were the two MS components that significantly increased. AS and its duration were independent predictors factors for the development of MS.

Conclusions: Continuous AS therapy increases the prevalence of MS and especially waist circumference and hyperglycemia. Development of MS increases according to AS duration.

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PALABRAS CLAVE
Síndrome metabólico; Supresión androgénica; Cáncer de próstata

Resumen
Objetivos: La mortalidad cardiovascular es la primera causa de muerte en pacientes con cáncer de próstata (CP) y el síndrome metabólico (SM) está relacionado con ella. El objetivo principal


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de este estudio fue conocer la prevalencia del SM en pacientes con CP sometidos a supresión androgénica (SA).

Material y métodos: Se realizó un estudio retrospectivo de casos y controles que incluyó 159 pacientes. Cincuenta y tres pacientes con CP sometidos a SA durante un periodo superior a 12 meses formaron el grupo de casos; 53 pacientes con CP en el momento de su diagnóstico y 53 pacientes con biopsia prostática negativa formaron el grupo control. En todos los pacientes se evaluó la existencia de SM según los criterios del NCEP-ATPIII.

Resultados: La prevalencia de SM en pacientes sin CP fue del 32,1% y en pacientes con CP no tratados fue del 35,8%; p = 0,324. En pacientes con CP sometidos a SA la prevalencia de SM fue del 50,9%; p < 0,001. Cuando la SA fue inferior a 36 meses se observó una prevalencia del 44,0% y cuando fue superior o igual a 36 meses del 57,1%; p < 0,001. El perímetro abdominal (> 102 cm) y la hiperuglicemia (> 110 mg/dl) fueron los 2 componentes del SM que se incrementaron significativamente. La SA y su duración fueron factores predictores independientes del desarrollo de SM.

 Conclusiones: La SA continuada incrementa la prevalencia de SM y especialmente el perímetro abdominal y la hiperuglicemia. Su desarrollo aumenta con la duración de la SA.

Background

Prostate cancer (PC) is the most commonly diagnosed solid neoplasm in men from industrialized countries. Nevertheless, cardiovascular mortality is the primary cause of death in patients with PC.

Metabolic syndrome (MS) is a condition characterized by the presence of clinical and serological disorders (obesity, hypertension, insulin resistance and dyslipidemia), which identifies patients at high risk of cardiovascular morbidity and mortality. In recent years, there has been an increase in the prevalence of MS worldwide, and its growth is directly associated with age, obesity and hypogonadism.

Studies that have analyzed the influence of MS on prostate carcinogenesis have not been conclusive. However, a number of studies suggest an association between MS and increased tumor aggressiveness. More conclusive are the studies that have analyzed the influence of androgenic suppression (AS) on the development of MS. Therefore, a consistent hypothesis that explains the high cardiovascular mortality in patients with PC would be based, not only on the age of the patients, but also on the influence of AS in the development of MS. AS is the treatment of choice in patients with disseminated and locally advanced PC. It is estimated that 1 of every 6 patients with PC will receive this treatment over the course of its natural history.

The primary objective of this study was to analyze the influence of AS and its duration in the development of MS.

Materials and methods

We conducted a retrospective, case-control study that included 159 patients distributed as follows: (1) a case group, composed of 53 patients who underwent AS for a period longer than 12 months and (2) a control group, composed of 106 patients selected randomly from men with age ranges and PSA levels similar to those of the case group, in a cohort of 2408 patients who underwent prostate biopsies (53 with PC and 53 with no PC). The indication for AS in the control group patients was (a) the presence of disseminated disease at the time of diagnosis (16 cases, 30.2%); (b) locally advanced PC with serum PSA levels higher than 50 ng/mL and doubling time less than 12 months (20 cases, 37.7%); and (c) biochemical recurrence following radical prostatectomy with high-risk dissemination criteria (time from surgery less than 24 months, Gleason score for surgical specimen ≥8, involvement of seminal vesicles and/or lymphatic nerve ganglia) (17 cases, 32.1%). All patients were treated with LHRH analogues, and the mean treatment duration at the time of inclusion in the study was 29 months, ranging between 12 and 64 (25 patients between 12 and 36 months and 28 with more than 36 months). None of the patients with PC in the control group had been treated. Table 1 lists the ages, PSA levels, body mass indexes and testosterone levels of the groups included in the study.

The components of MS were assessed in all patients according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII). Patients with 3 or more of the following factors were diagnosed with MS: abdominal circumference >102 cm; triglyceride levels ≥150 mg/dL; HDL ≤40 mg/dL; fasting glycemia levels ≥110 mg/dL and blood pressure (BP) ≥130/85 mm Hg. Positivity for the corresponding factor was also considered for undergoing specific medical treatment with lipid-lowering, hypoglycemic or antihypertensive agents.

The quantitative variables were defined with the statistical median and semi-interquartile range, and the qualitative variables were defined as percentages. To compare the quantitative variables, we used the nonparametric Mann–Whitney U and Wallis tests. To compare the proportions, we used the chi-squared test. We calculated the hazard ratios (HR) and their 95% confidence intervals. Finally, we performed a multivariate analysis using binary logistic regression to define the independent predictors of MS development. The statistical analysis was performed using the SPSS V.20 program.

Results

The ages and serum PSA levels were similar among all the groups included in this study. In fact, the selection of
patients who comprised the control group, with or without PC, was performed based on ranges for these variables that were similar to those observed in the case group. Nevertheless, we detected a significantly greater body mass index in the group of patients with PC who underwent AS (30 kg/m²) than in the control group patients with or without PC (27 kg/m²). Serum testosterone levels were also significantly lower in the group of patients with PC who underwent AS (17 ng/dL) than in the control group, which had a trend towards lower levels in the patients with untreated PC (416 ng/dL) when compared with the levels observed in patients without PC (430 ng/dL) (Table 1).

Seventeen of the 53 patients with no PC (32.1%) and 19 of the 53 patients with untreated PC (35.8%) (p = 0.429) met the criteria for MS. In the group of 53 patients with PC who underwent AS, MS was diagnosed in 27 (50.9%), confirming a significant increase when compared to the groups of patients without PC and with untreated PC in the control group (p = .001). We also observed that 11 of the 25 patients (44.0%) who had undergone AS between 12 and 36 months met the criteria of MS, with this prevalence increasing to 57.1% (16/28) in patients with AS sustained for more than 36 months; p = .001 (Fig. 1). When considering the various components of MS, we observed that the percentage of patients with abdominal circumferences greater than 102 cm was significantly higher in the patients who underwent AS than in the control group patients (69.7% vs. 40.6%); p = 0.016. The percentage of patients with fasting glycemia levels >110 mg/dL was also significantly greater in the group of patients who underwent AS (41.5% vs. 28.6%; p = 0.043). In contrast, there were no significant differences among the proportions observed in the remaining components that define MS (triglyceride levels >150 mg/dL, HDL levels <40 mg/dL and BP >130/85) (Table 2).

A multivariate analysis performed using binary logistic regression revealed that treatment with AS and its duration, along with the testosterone serum levels and body mass index, were independent predictors of the development of MS (Fig. 1). Undergoing treatment with AS represented a HR of 2.312 (95% CI: 1.620–6.532) compared with patients not treated with AS. Additionally undergoing treatment with AS for longer than 36 months represented a HR of 1.609 (95% CI: 1.121–3.281) compared with undergoing treatment with AS for a shorter period (Table 3).

Discussion

Epidemiological evidence suggest that low testosterone levels are associated with an increased probability of developing MS. In such cases, patients with PC undergoing AS represent a group at high risk of developing MS, thereby contributing to the high cardiovascular morbidity and mortality observed in patients with PC. Profound hypogonadism secondary to AS is responsible for severe changes in body composition including an increase in fat mass and a reduction in lean mass. The increase in fat mass, both subcutaneous and visceral, results in abdominal obesity and increased adipokine levels, which is ultimately responsible for insulin resistance. Testosterone deficiency has also been related to the rest of the components of MS, as it has adverse lipid profiles and the development of high blood pressure. Few studies have prospectively evaluated the metabolic abnormalities that result from AS in patients with PC. Nevertheless, 2 small studies performed with 22 and 16 patients, respectively, demonstrated that at 3 months of AS, there was an increase in insulin levels, without any changes in fasting glucose levels. These observations suggest that insulin resistance develops a few months after starting AS, and that approximately a year after treatment there is a significant development of marked hyperglycemia.

To date, only 2 studies have analyzed the overall development of MS in patients who underwent AS, while the other studies have analyzed only some of its components. Both studies had a cross-sectional design and included 20 and 53 patients who underwent AS, with a mean period of 45 and 15 months, respectively. The prevalence of MS in the 2 studies was 53% and 55%, which was significantly greater than that detected in its respective control groups. One of the problems with comparing the results of these 2 studies is that
they used different criteria to evaluate MS: NCEP-ATPIII and  
IDF. Our study detected a prevalence of MS approaching  
51%, comparable to the 53% detected in the study by Braga-  
Basaria, which also used the NCEP-ATP III criteria. As a  
new observation, we can report that the development of MS  
is also related to the duration of the AS. Our study detected  
MS in 44% of the patients who underwent AS for a period of  
between 12 and 36 months, and this rate increased to 57%  
in patients who underwent AS during a period longer than  
36 months.

Another issue to consider is the different involvement of  
the 5 components of MS with AS. The Braga-Basaria  
series detected a significant increase in the proportion of  
patients with abdominal circumferences greater than  
102 cm and glycemia levels higher than 110 mg/dL. However,  
they did not observe a significant increase in the percentage  
of patients with triglyceride levels ≥150 mg/dL, HDL levels  
<40 mg/dL or hypertension. Even with different evaluation  
criteria, the series by Ceffi et al. found that abdominal  
circumference and hyperglycemia were also affected  
significantly. Similar to our study, the abdominal circumference  
and fasting glycemia were the 2 components that  
were significantly affected. Consequently, we can suggest  
that the involvement of the various components of MS is  
not equal in patients who undergo AS. Smith et al. suggested  
that metabolic disorders induced by AS differ from  
those of classical MS. AS induces a greater accumulation of  
subcutaneous fat than visceral fat, increases adiponectin  
levels and does not change C-reactive protein levels, in  
contrast to what is produced with classical MS. Therefore,  
these authors suggest adhering to the recommendations of  
the American Diabetes Association (ADA), which advocates  
the evaluation and treatment of all cardiovascular risk factors,  
regardless of whether the patient meets the diagnostic  
criteria of MS or not. The limitations inherent in cross-sectional studies, the  
reduced group sizes and the different methods for evaluating MS suggest that there is a need for prospective studies with follow-ups of not less than 3 years that evaluate the development of the various components of MS and other cardiovascular risk factors in patients with PC who undergo AS. The preventive role that a proper diet, routine physical exercise and early treatment of cardiovascular risk factors can have should also be assessed and of concern to urologists who treat patients with PC with AS.

**Conclusions**

AS causes metabolic changes and a significant increase in the  
prevalence of MS, which increases with the duration of AS.  
Given that many of these changes are cardiovascular risk factors, it is worth recommending a lifestyle and diet  
that favors their prevention, as well as early detection to  
establish specific treatments for each change.

**Conflicts of interest**

The authors declare that they have no conflicts of interest.

**References**


