Androgen deprivation therapy and morbid obesity: Do they share cardiovascular risk through metabolic syndrome?

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Abstract
Background: Although the use of androgen deprivation therapy (ADT) has resulted in improved survival in men with advanced prostate cancer, the resulting hypogonadism is associated with profound adverse effects comparable to those found in morbid obesity, being cardiovascular risk among the most lethal.
Objectives: Evaluate metabolic syndrome, metabolic abnormalities and cardiovascular risk in patients with prostate cancer under ADT, not under ADT and morbid obese men.
Methods: This is a cross-sectional study that involves 79 men presenting prostate cancer, of whom 54 under ADT and 25 not under ADT and 91 morbidly obese patients paired by sex and age. To define metabolic syndrome, we used the International Diabetes Federation (IDF) criteria. Metabolic abnormalities, metabolic markers and Framingham score to predict the ten year coronary heart disease risk were compared among patients under ADT, not under ADT and morbid obese.
Results: Patients under ADT presented significantly greater occurrence of diabetes and central obesity and higher levels of total cholesterol and low density lipoprotein (LDL) compared to eugonadal men. The mean cardiovascular risk was significantly higher in patients under ADT (39.97 ± 12.53% vs. 26.09 ± 14.80%; p = 0.021). Morbidly obese subjects had increased ten year coronary heart disease risk; comparable to patients under ADT (p = 0.054).
Introduction

Prostate cancer (PCa) is the second most common cancer among men, surpassed only by non-melanoma skin cancer. The preferred treatment of locally confined PCa can be local surgery, radiotherapy or active surveillance.

In 1941 Huggins et al. described the androgen dependence of prostate cancer in their Noble-prize winning work. Androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) agonist or bilateral orchiectomy has since become the main treatment for metastatic or advanced prostate cancer.

Furthermore, the use of ADT is increasing with the advocacy of adjuvant ADT in otherwise asymptomatic patients with locally advanced prostate cancer, and the inclusion of adjuvant temporary ADT in the multimodal treatment of high risk localized prostate cancer.

Similarly to the increase in ADT, figures for the rise in morbid obesity around the world are startling, especially the increase among men. This is a situation that calls for measures to encourage the adoption of healthy lifestyles and preventive approaches once both processes have in common increased cardiovascular morbidity.

Less well-known adverse effects of ADT and consequences of morbid obesity are increased peripheral insulin resistance, dyslipidemia and the development of metabolic syndrome that might contribute to an increased risk of diabetes and cardiovascular disease, resulting in decreased survival in such patients.

There are high rates of metabolic syndrome (MS), diabetes, endothelial dysfunction and hypertension in the morbidly obese, and these co-morbidities have been clearly associated with hypogonadism. While hypogonadism could be an independent factor of MS in ADT, the components predisposing MS in morbid obesity potentiates hypogonadism. Metabolic syndrome (MS) was first proposed as a clinical entity by Reaven in 1988 and has been popularized by numerous health organizations as a way of identifying patients at an increased risk for coronary heart disease or type II diabetes.

Recently MS has been highlighted as an important way to increase cardiovascular morbidity in morbid obesity and ADT; however comparison of both conditions as well as how they join the same progression is to be better explored.

Metabolic abnormalities, metabolic markers and cardiovascular risk were analyzed and compared among prostrate
cancer patients under ADT, not undergoing ADT and morbidly obese subjects in a cross-sectional study.

Methods

Seventy nine consecutive male patients presenting high-risk prostate cancer (stage T2c or PSA level >20 ng/mL or Gleason score ≥8),

9 no other co-morbidity apart from metabolic syndrome defined by the International Diabetes Federation (IDF) criteria and no previous therapy for prostate cancer, 54 undergoing ADT and 25 not undergoing ADT and no chronic use of medications like corticosteroids were considered eligible to participate in this study. Exclusion criteria: did not consent to participate and failed to contemplate inclusion criteria.

These patients were compared with a cohort of 91 morbidly obese patients from bariatric surgery program in their first evaluation before intervention, paired by sex and age, with no co-morbidity apart from metabolic syndrome (IDF criteria), not presenting any history of prostate cancer or hormonal manipulation. Morbid obesity was defined as body mass index (BMI) > 40 kg/m².

Blood samples were taken after a minimum fasting period of 8 h. BMI was defined as the individual’s body weight divided by height squared. To define metabolic syndrome, we used the International Diabetes Federation (IDF) criteria: waist circumference ≥94 cm in women, ≥80 cm in men or BMI ≥30 kg/m²; triglycerides levels ≥150 mg/dL (1.7 mmol/L) and/or specific treatment; HDL levels <40 mg/dL (1 mmol/L) in men, <50 mg/dL (1.3 mmol/L) in women and/or specific treatment; fasting glucose ≥100 mg/dL (5.6 mmol/L) and/or type 2 diabetes; systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg and/or specific treatment.

Patients must present at least three of the five risk factors to be diagnosed with MS. We used the Framingham score to predict the ten-year coronary heart disease risk.

Data were analyzed using the Statistical Package for the Social Science (SPSS v16.0). Quantitative variables were compared using Student's t-test and the qualitative variables using Fisher's Exact Test. The power of association between the quantitative variables was determined using Pearson’s linear correlation. Two-sided p-values < 0.05 were considered significant.

The study was conducted with the approval of the local Research Ethics Committee and all patients consented to participate.

Results

The mean age of the participants was 73.28 ± 7.71 years, Table 1; it was 69.31 ± 6.33 years for morbidly obese patients, p < 0.05. The incidence of metabolic abnormalities and the level of metabolic markers between men with prostate cancer under and not undergoing androgen deprivation therapy are shown in Table 1. Patients undergoing ADT (mean time of 15.37 ± 2.48 months) presented significantly greater occurrence of type 2 diabetes and central obesity, p < 0.05. There was also a tendency towards higher frequency of metabolic syndrome in patients undergoing ADT, but it did not reach statistical significance (p = 0.052).

Cholesterol and low density lipoprotein (LDL) levels and the

<table>
<thead>
<tr>
<th>Metabolic abnormalities</th>
<th>Under ADT (n = 54)</th>
<th>Not under ADT (n = 25)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensiona</td>
<td>39 (72.2%)</td>
<td>16 (64.0%)</td>
<td>0.335</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (25.9%)</td>
<td>3 (12.0%)</td>
<td>0.043</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>29 (53.7%)</td>
<td>6 (24.0%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>17 (31.4%)</td>
<td>7 (28.0%)</td>
<td>0.782</td>
</tr>
<tr>
<td>Central obesityc</td>
<td>38 (70.3%)</td>
<td>9 (36.0%)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic markers</th>
<th>Under ADT (n = 54)</th>
<th>Not under ADT (n = 25)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.06 ± 5.75</td>
<td>73.76 ± 8.16</td>
<td>0.742</td>
</tr>
<tr>
<td>Gleason score</td>
<td>7.25 ± 1.27</td>
<td>6.60 ± 0.54</td>
<td>0.064</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.55 ± 4.27</td>
<td>24.79 ± 3.08</td>
<td>0.490</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>216.37 ± 47.24</td>
<td>193.57 ± 51.43</td>
<td>0.049</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>124.58 ± 34.26</td>
<td>105.92 ± 37.07</td>
<td>0.038</td>
</tr>
<tr>
<td>VLDL (mg/dL)</td>
<td>30.50 ± 16.68</td>
<td>25.76 ± 11.62</td>
<td>0.073</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>61.81 ± 21.24</td>
<td>56.78 ± 12.78</td>
<td>0.295</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>159.86 ± 97.17</td>
<td>179.64 ± 195.59</td>
<td>0.562</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>101.76 ± 23.40</td>
<td>103.78 ± 18.97</td>
<td>0.747</td>
</tr>
<tr>
<td>Abdominal waist (cm)</td>
<td>97.48 ± 8.39</td>
<td>91.23 ± 21.40</td>
<td>0.031</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>130.18 ± 13.93</td>
<td>131.20 ± 15.36</td>
<td>0.773</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>83.98 ± 14.45</td>
<td>88.00 ± 9.12</td>
<td>0.139</td>
</tr>
</tbody>
</table>

a Defined as systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg.

b Defined as triglycerides ≥ 150 mg/dL.

c Defined as abdominal waist ≥ 94 cm.
abdominal waist were higher in the group undergoing ADT. The prevalence of metabolic syndrome in prostate cancer patients in our study was 44.3%.

The mean ten year coronary heart disease risk for the participants was 27.29 ± 13.97%. When stratified by the use or not of ADT we found 39.97 ± 12.53% in patients undergoing ADT and 26.09 ± 14.80% in patients not undergoing ADT (p = 0.021). Morbidly obese subjects had a ten-year coronary heart disease risk of 46.23 ± 10.98%, which was higher than patients not undergoing ADT (p = 0.001) but it was comparable to that found in patients undergoing ADT (p = 0.054).

In Fig. 1 we show the prevalence of metabolic abnormalities between patients undergoing and not undergoing ADT and the cohort of morbidly obese subjects. The prevalence of central obesity showed difference among all the groups and was progressively greater in men not undergoing ADT, men undergoing ADT and morbidly obese subjects.

The prevalence of low HDL and high triglycerides was higher in the morbidly obese subjects and the prevalence of high fasting glucose and hypertension was similar for the three groups. In Fig. 2, we show the biochemical parameters of the three groups. The BMI was higher in morbidly obese subjects (p = 0.001), LDL and cholesterol were higher and HDL was lower in the morbidly obese when compared with patients not undergoing ADT (p = 0.021, p = 0.030 and p = 0.002, respectively).

Discussion

Although the use of ADT has resulted in improved survival in men with advanced prostate cancer, the resulting hypogonadism is associated with profound adverse effects including hot flashes, gynecomastia, bone loss, decreased libido, MS, diabetes, erectile dysfunction, changes in body composition, such as increase in body mass index (BMI), decrease in lean body mass and increase in fat mass.12,13

On the other hand, morbid obesity is related to gynecomastia, osteoporosis, decreased libido, MS, diabetes, erectile dysfunction and hypogonadism. Although hypogonadism is less intense in morbid obesity compared to ADT (mild hypogonadism vs. castrated levels), the cardiovascular risk seems to be equivalent as demonstrated in this study. However, to the best of our knowledge, there is no study comparing cardiovascular risk or mortality between men undergoing ADT and the morbidly obese.

The underlying mechanism of increased cardiovascular risk is likely multifactorial in ADT and obesity and both processes present similarities on outcomes such as high rates of MS, diabetes, and hypogonadism. These co-morbidities have been clearly associated with endothelial dysfunction. Saigal et al.14 found a 20% higher risk of a serious cardiovascular event in men who received ADT for at least 1 year compared with those who did not. These men are reportedly 1.4 times more likely to develop diabetes; 21–37% more likely to develop bone fractures and to have worsening frailty, especially in the oldest cohorts.15

In glycemic control spectrum, men receiving ADT are at greater risk of developing insulin resistance and hyperglycemia. In a small cross-sectional study, men receiving ADT had significantly higher fasting glucose and insulin levels after adjustment for age and BMI.16 Furthermore, in a 12-week prospective study of 25 non-diabetic men with prostate cancer initiated on ADT, the mean insulin sensitivity decreased by 12.8% from baseline. At the same time, fasting plasma insulin levels increased by 25.9% with a small increase of HbA1c.17

In a cross-sectional study comparing 16 men undergoing ADT for ≥1 year, 14 age-matched eugonadal men with localized prostate cancer who had local therapy, and 14 age-controlled eugonadal men with no previous history of...
cancer, diabetes or dyslipidemia; men undergoing ADT had significantly higher levels of total cholesterol than the other groups.\textsuperscript{18} Additionally, in a prospective clinical trial of 1102 men, after a period of ADT, there were significant increases in total cholesterol and triglyceride, with a decrease in HDL.\textsuperscript{19} These changes in lipid profile increase the cardiovascular risk of patients with PCa undergoing ADT. In an observational study men with prostate cancer undergoing ADT showed an increased risk of coronary heart disease (1.16), myocardial infarction (1.11) and sudden cardiac death (1.16).\textsuperscript{20}

This study shows that patients undergoing ADT present higher cardiovascular risk, lipid and glycemic profiles. These parameters were similar to those found in morbidly obese subjects, while different from those presented by patients not undergoing ADT.

Patients undergoing ADT had a greater waist circumference compared with those not undergoing ADT. However, BMI was similar in both groups, which supports the occurrence of visceral obesity in the ADT group, which gives an even greater cardiovascular risk.

On the other hand, despite the increased cardiovascular risk found in patients undergoing ADT, HDL levels, which constitute a major component in the cascade of atherogenesis, does not change with the use of hormonal therapy. This is room for future studies.

From a pathophysiological point of view, the relationship among androgen deficiency, endothelial dysfunction, and cardiovascular disease is very complex. Insulin resistance, which is exacerbated by androgen deficiency, might mediate endothelial dysfunction and cardiovascular disease.\textsuperscript{21} Mechanisms underlying lipotoxicity, which include oxidative stress and pro-inflammatory signaling, and mechanisms underlying glucotoxicity, which include oxidative stress, advanced glycation and product formation, the hexosamine pathway, and pro-inflammatory signaling are also related with endothelial dysfunction and cardiovascular disease.\textsuperscript{22}

Although beyond the scope of this study, cardiovascular risk is probably the result of different ways evolving dissimilar routes in morbid obesity and ADT; however, both routes share metabolic syndrome as the major underlying process.

In this scenario, androgens play an important role in metabolic regulation such as nitric oxide synthase (NOS) isoforms, as well as in structural balance in the vascular endothelium. The steroid environment, in particular estradiol level, can influence vascular tone through the vascular endothelial growth factor or nitric oxide, impacting cardiovascular risk.\textsuperscript{23}

The pathogenic mechanisms responsible for the reduction of circulating testosterone in obese men remain incompletely defined and understood. Estrogen production rates also increase with increasing obesity, possibly due to the aromatization of androgens by adipocytes.\textsuperscript{24}

In this regard, it has been observed that in obese men, the administration of testolactone (an inhibitor of aromatase activity) increases the levels of circulating testosterone and decreases levels of estradiol. But other data point to the possible involvement of a central mechanism, because the pulsatile secretion of gonadotropins—regulated by hypothalamic centers—is disrupted in severe obesity.\textsuperscript{25}

Moreover, some data suggest that the hypofunction of Leydig cells in obese subjects is related to hyperinsulinemia and insulin resistance and this situation improves when these metabolic alterations are corrected through weight reduction.\textsuperscript{26}

Obesity is a complex psychosocial and endocrine disorder for which gastric bypass surgery is one of the few treatment options that has proved to induce substantial weight loss, increase life expectancy and improve numerous co-morbidities such as type II diabetes, hypertension, hormonal and sexual function and consequently cardiovascular risk.\textsuperscript{27}

In the same manner, hormonal replacement in castrated men or interruption of ADT could restore the protective role
of androgens concerning bone loss, MS, diabetes and cardiovascular events. The reversibility of these documented processes is to be better defined in future studies.

The last 20 years have seen remarkable changes in both the diagnosis and treatment of prostate cancer. Two driving forces have been the development of prostate-specific antigen testing as well as the availability of effective pharmacologic interventions to reduce or eliminate the effects of androgens. Clearly, we now recognize that although we might save lives through the screening and effective treatment of discovered disease, our interventions come at a high cost in terms of morbidity to our patients. There are some limitations to our analysis considering the cross-sectional draw. Data must be reanalyzed in larger prospective trials in which cardiovascular mortality could be accessed and the effect of weight loss and androgen recovery could be considered as well as the amount of time under ADT or the BMI levels necessary to cardiovascular risk increase. Furthermore, while some trends to significance were described, future studies should confirm the data presented. Other factors that contribute to increased cardiovascular risk were not controlled in our analysis, such as diet and lifestyle. Conversely, this study has several strengths, including a detailed metabolic evaluation and presence of a control group (prostate cancer patients not undergoing ADT) offering substrate to methodological refinements of future assessments.

Cardiovascular risk should be monitored in patients undergoing ADT and in morbidity obese men; preventive approaches are warranted in these patients while the underlying conditions are kept and it should be well thought-out when considering ADT as prostate cancer treatment.

Conflict of interests

The authors declare to have no conflict of interests.

References