Letter to the Editor

INSULIN RESISTANCE AS AN ADVERSE EFFECT OF LEUPROLIDE AND BICALUTAMIDE TREATMENT

To the Editor:

The use of the gonadotropin-releasing hormone analogue leuprolide and the antiandrogenic bicalutamide in advanced, metastatic prostate cancer (Pca) is well known. However, a correlation between glucose metabolism, insulin resistance, and the use of these drugs to our knowledge has not yet been recognized in this setting. We report a case of a 66-year-old male who received repeated leuprolide and bicalutamide treatment for stage D2 prostate cancer with subsequent hyperglycemia and insulin resistance.

There are a limited number of case reports in the literature illustrating an impairment in glucose metabolism or changes in diabetes glycemic control in female patients on gonadotropin-releasing hormone analogue therapy for endometriosis (1–5). There is no literature regarding this phenomenon as an adverse effect of bicalutamide treatment (6). To our knowledge, this has not been described in male patients, and the potential mechanism of this phenomenon has not been evaluated.

Case Report

A 66-year-old male with a history of stage D2 adenocarcinoma of the prostate with metastatic bone disease presented to his radiation oncologist in January 1994 with complaints of polyuria, polydipsia, and weight loss despite a good appetite. His capillary blood glucose at that time was 431 mg/dL (23.9 mmol). His past medical history was significant for a history of dyslipidemia and degenerative joint disease. He endorsed a family history of type 2 diabetes, and his mother had diabetes in a brother and his mother.

At the time of presentation, he was receiving 7.5 milligrams of intramuscular depot leuprolide therapy, with favorable clinical response, and normal prostate specific antigen. Previously, he had received leuprolide and flutamide therapy in October 1993, followed by two courses of leuprolide and bicalutamide treatments in February and September 1996, respectively. He was subsequently referred to the Diabetes Care Center at the University of Washington Medical Center in June 1996. At that time, his hemoglobin A1c was 13.2% (normal range 4%–6%; see Table 1). He was started on Glucotrol (glipizide extended release) XL at that time, and over the next 9 months saw a significant decline in his hemoglobin A1c.

Discussion

Hyperglycemia and insulin resistance may have been exacerbated or elucidated in our patient being treated by leuprolide and bicalutamide. It is not clear which drug, if not both in concert, was responsible for this phenomenon. However, based on previous reports describing similar phenomenon in women treated with gonadotropin-releasing hormone agonists for endometriosis, it may be postulated that treatment with leuprolide in our patient was the culprit.

Within 3 months of receiving Pca treatment, the patient clearly developed diabetes, and sustained a noticeable degree of insulin resistance and persistent hyperglycemia for the 12 months following his initial treatment, despite long-acting oral glipizide and subsequent subcutaneous insulin therapy (Table 1). Thirteen months after the initial gonadotropin-releasing hormone agonist treatment, the patient’s hemoglobin A1c was normal on the same regimen (Table 1). The same phenomenon was illustrated the following year during the second treatment period (Table 2), where subsequently the patient had a normal hemoglobin A1c and had discontinued all diabetic therapy. Of note, his weight remained stable throughout the evolution and wane of his diabetes, and incidentally, he had a significant weight gain in the period 6 months off therapy (Table 1) despite a normalization of his hemoglobin A1c.

Conclusions

Hormonal treatment is becoming more widely utilized in men with advanced prostate cancer. A decline in serum testosterone levels has been associated with a decrease in lean body mass and muscle mass, and an increase in visceral adiposity (all associated with insulin resistance and an increased risk of type 2 diabetes mellitus). The literature also suggests that testosterone levels are lower in men with type 2 diabetes mellitus, and low levels are associated with a higher risk of developing type 2 diabetes (7,8). Conversely, studies evaluating body composition with regard to testosterone-replacement therapy showed an increase in lean body mass and decrease in visceral fat mass with treatment (7). It stands to reason that this phenomenon may also be reproduced in practice with intentional androgen antagonism for the purposes of prostate cancer treatment. Physicians should be aware of hyperglycemia and diabetes developing as a potential adverse effect of this treatment. Therefore, more rigorous screening of at-risk adults for diabetes should include men receiving hormonal treatment for prostate cancer. Further studies about the incidence of such a phenomenon and its mechanism are needed.

Table 1. First Posttreatment Period

<table>
<thead>
<tr>
<th></th>
<th>June 1996</th>
<th>August 1996</th>
<th>January 1997</th>
<th>March 1997*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A1c</td>
<td>13.2%</td>
<td>9.9%</td>
<td>9.1%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>94.1</td>
<td>94.5</td>
<td>98.6</td>
<td>100.5</td>
</tr>
<tr>
<td>Treatment</td>
<td>Glipizide XL</td>
<td>Glipizide XL</td>
<td>Glipizide XL</td>
<td>Glipizide XL</td>
</tr>
<tr>
<td>NPH qd</td>
<td>NPH qd</td>
<td>NPH qd</td>
<td>NPH qd</td>
<td>NPH qd</td>
</tr>
</tbody>
</table>

Note: Leuprolide, bicalutamide treatment administered in February and September 1996, respectively.

*Six months off Pca treatment.

NPH = insulin human isophane.
Table 2. Second Posttreatment Period

<table>
<thead>
<tr>
<th>November 1997</th>
<th>January 1998</th>
<th>August 1998*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin Alc</td>
<td>8.7%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>96.8</td>
<td>95.9</td>
</tr>
<tr>
<td>Treatment</td>
<td>Glipizide XL and NPH qd</td>
<td>Glipizide XL and NPH qd</td>
</tr>
</tbody>
</table>

Note: Leupron, bicalutamide treatment administered in June and September 1997, respectively.

*Eleven months off Pca treatment.

NPH = insulin human isophane.

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REFERENCES


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