The Effects of Androgen Deprivation Therapy on Lipid Metabolism and Body Composition in Japanese Patients with Prostate Cancer

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Objective: In Japan, androgen deprivation therapy is employed as the primary therapy for prostate cancer in more than 50% of patients, which is a percentage larger than that in the USA. The adverse effects of androgen deprivation therapy on body composition and lipid profile associated with metabolic syndrome have been reported mainly in Caucasian populations, and few studies have been performed in East Asian populations, including Japanese.

Methods: This study enrolled 39 Japanese patients who were starting to receive androgen deprivation therapy for prostate cancer. Subjects were evaluated at baseline and at 3, 6, 9 and 12 months. Body composition and lipid profiles were measured by bioelectrical impedance analysis and using blood samples, respectively.

Results: The volume of fat and visceral fat was significantly increased 6 months after the treatment and continued to increase until 12 months. On the other hand, skeletal muscle was significantly decreased during the same period. The serum concentration of total cholesterol and low-density lipoprotein cholesterol increased significantly over the same period.

Conclusions: Androgen deprivation therapy changed the body composition and lipid profile of men with prostate cancer. It was demonstrated that even Japanese patients with prostate cancer who are treated with androgen deprivation therapy have the risk of developing metabolic syndrome.

Key words: gonadotropin-releasing hormone – prostatic neoplasms – lipid metabolism – body composition – electric impedance

INTRODUCTION

The CaPSURE data in the USA showed that, between 2000 and 2002, regarding the primary therapy for prostate cancer, ~40% of patients underwent radical prostatectomy and 20% of patients received androgen deprivation therapy (ADT) according to the report of the Veterans Affairs health care system (1). In Japan, the trends in primary therapy for prostate cancer are different from those in the USA. As primary therapy, 51% of patients received ADT and 30% underwent radical prostatectomy. The higher rate of primary ADT is characteristic for Japanese patients (2). Reports have been published concerning the risks of adverse effects with ADT in Caucasian populations. It was described that ADT increases the rates of myocardial infarction, diabetes, etc., but these findings are still controversial (3–7). In East Asian countries, such as China, Japan and Korea, prevalence rates of metabolic syndrome have generally varied from 8 to 13% in men and 2 to 18% in women, depending on ethnic group and definition used, and are consistently lower than most Western Caucasian populations (8). In the Japanese population, ADT may be a safer treatment for prostate cancer because the risk of adverse effects with ADT may be lower. Therefore, we investigated the effects of
ADT on lipid metabolism and body composition, associated with metabolic syndrome, in order to infer the risks of ADT in Japanese population.

**PATIENTS AND METHODS**

**SUBJECTS**

Thirty-nine Japanese patients were enrolled who were starting to receive ADT for prostate cancer at Nara Prefectural Nara Hospital between August 2006 and April 2008. All the patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. None of them had a history of hypogonadism, history of growth hormone or anabolic steroid use, hyperthyroidism, Cushing’s disease, hyperprolactinemia, chronic liver disease or serum creatinine concentration $<2.0$ mg/dl. Neither had any of the patients received glucocorticoid or thyroxine. Twenty-five received both a luteinizing-hormone-releasing hormone (LH-RH) analog depot and goserelin 3.6 mg per month or leuprorelin 3.75 mg per month subcutaneously, and oral bicalutamide 80 mg daily for 12 months. Fourteen received an LH-RH analog alone for 12 months.

**STUDY DESIGN**

Subjects were evaluated at baseline and at 3, 6, 9 and 12 months. A serum sample was obtained at each visit. Body composition was also measured at each visit by bioelectrical impedance analysis (BIA), using an InBody S20® (Biospace Co., Ltd, Korea). We investigated the following parameters: body weight, waist circumference, skeletal muscle, fat, visceral fat area (VFA) and lipid profile [total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides]. LDL cholesterol was calculated by the formula $\text{LDL cholesterol} = \left(\frac{\text{total cholesterol}}{\text{HDL cholesterol}} - \frac{\text{triglyceride}}{5}\right)$. The subjects fasted for at least 12 h before taking blood samples. The institutional review board of Nara Prefectural Nara Hospital approved the study. All the subjects gave written informed consent.

**MEASUREMENTS**

Waist circumference was measured using a manual tape measure at umbilical level in a standing position to the nearest 0.1 cm by a technician just before BIA when the subjects were in a morning fasting state. Height was measured using a wall-mounted stadiometer to the nearest 0.1 cm. Body weight, wearing light indoor clothing without shoes, was measured using a BF-035® (TANITA Corporation, Tokyo, Japan) to the nearest 0.1 kg. A correlation factor of $-1$ kg was used to adjust for the weight of clothes.

Skeletal muscle, fat and VFA were measured by BIA, using an InBody S20®. Resistance of the arms, trunk and legs was measured in fasting patients at a frequency of 1, 5, 50, 250, 500 and 1000 kHz. This instrument makes use of eight tactile electrodes: two in contact with the thumb and middle finger of each hand, and two with the bilateral aspects of the ankle joint of each foot. The patient lies supine, and body weight and height are input into the analyzer. As controlled by a microprocessor, the sequence of measurements then proceeds. An alternating current of $<100 \mu A$ at 1 kHz or $<500 \mu A$ at another frequencies is applied between two electrodes to measure the impedance each part (arms, trunk and legs), as previously described by Bedogni et al. (9). The InBody S20 measures the volume of fat and skeletal muscle using the difference in resistance of the body depending on the amount of water. The accuracy of BIA measurements has been demonstrated in previous studies (9,10). Patients were instructed to keep their stomach and bladder empty, avoid exercise and lie down for at least 5 min before BIA measurements, and to lie quietly during BIA in order to make the measurement more precise.

We measured VFA in other subjects using both BIA and a PC software-based method (Fat Scan® V5.0, East Japan Institute Technology Co., Ltd, Japan), which can calculate VFA at computed tomography (CT) to demonstrate the accuracy of BIA. VFA measured by BIA significantly correlated with VFA measured at CT in 20 patients with urolithiasis who underwent CT and BIA for a study of our institute ($r^2 = 0.6782, P < 0.001$) (Fig. 1).

Serum concentrations of testosterone and prostate-specific antigen (PSA) were measured by an electrochemiluminescence method and chemiluminescence enzyme immunoassay, respectively. The lower limits of detection for serum testosterone and PSA were 0.05 ng/dl and 0.008 ng/ml, respectively.

**STATISTICAL ANALYSIS**

Changes in body composition and serum concentrations of testosterone, PSA and lipids were compared between baseline and other time points by one-way ANOVA and Dunn’s
multiple comparison test. Statistical analyses were performed using Prism 5 (version 5.03, GraphPad Software, Inc., CA, USA). Values are reported as mean ± SE. All P values are two-sided and values <0.05 are considered significant.

RESULTS

CHARACTERISTICS OF THE SUBJECTS

The clinical stages of prostate cancer were as follows: 1 patient was classified as Stage A, 18 as Stage B, 17 as Stage C and 3 as Stage D2. Their mean age was 74.0 ± 1.3 (54–91) years. Serum testosterone levels before treatment were within normal in all patients (Table 1).

TESTOSTERONE AND PSA

LH-RH analog with or without bicalutamide lowered serum testosterone to castration level in all of the patients 3 months after the start of treatment. They also lowered PSA markedly (Table 1).

BODY COMPOSITION

Body weight gradually increased after the initiation of treatment. Waist circumference also increased, which reflected the increase in visceral fat. The volume of fat increased significantly at 6 months after the start of treatment and continued to increase until 12 months. On the other hand, the volume of skeletal muscle decreased significantly by 6 months after the start of treatment, but the volume stabilized after 9 months (Table 3). VFA increased significantly in the same manner as fat and abdominal circumference. The increase in VFA correlated significantly with those of fat and abdominal circumference ($r^2 = 0.8267$, $P < 0.0001$ and $r^2 = 0.7175$, $P < 0.0001$, respectively) (Fig. 2).

LIPID PROFILE

Triglyceride and HDL cholesterol did not change during treatment. Total cholesterol and LDL cholesterol increased significantly at 3 months after the initiation of treatment (Table 3).

DISCUSSION

This study demonstrated that the administration of LH-RH analog with or without bicalutamide changed the body composition and lipid profile of Japanese men with prostate cancer. The patient’s weight and fat increased significantly and their skeletal muscle decreased significantly over the course of the 12 months treatment. The patients also experienced significant increases in serum concentration of total cholesterol and LDL cholesterol over the same period. These changes in body composition and lipid profile may contribute to the adverse effects of ADT on not only patients’ quality of life (11,12) but also their health.

Obesity is a risk factor for cardiovascular disease, adult-onset diabetes mellitus, hypertension, stroke, osteoarthritis and some cancers (13). As serious adverse effects, cardiovascular and endocrine complications have been described recently. Some papers reported increased risk of myocardial infarction, diabetes and sudden death with ADT (3–5). In contrast, there are controversial analyses, one of which reported that LH-RH agonists do not seem to increase cardiovascular mortality in men with locally advanced prostate cancer (6). A very recent study showed that continuous ADT use for at least 6 months in older men is associated with an increased risk of diabetes and fragility fracture but not acute myocardial infarction or sudden cardiac death (7). Although each possibility of adverse effects has not been demonstrated completely, the change of body composition with ADT must be highly associated with any adverse

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Age (y.o.)</th>
<th>Before treatment</th>
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<tr>
<td></td>
<td></td>
<td>PSA (ng/ml)</td>
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<tr>
<td>Stage A</td>
<td>1</td>
<td>75</td>
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<tr>
<td>Stage B</td>
<td>18</td>
<td>72.7 ± 9.6</td>
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<tr>
<td>Stage C</td>
<td>17</td>
<td>70.5 ± 9.3</td>
</tr>
<tr>
<td>Stage D2</td>
<td>3</td>
<td>72.0 ± 11.3</td>
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PSA, prostate-specific antigen.

Table 2. Treatment process for prostate cancer

<table>
<thead>
<tr>
<th>Months of treatment</th>
<th>Testosterone (ng/dl)</th>
<th>PSA (ng/ml)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>4.65 ± 0.46</td>
<td>46.35 ± 18.25</td>
</tr>
<tr>
<td>3</td>
<td>0.09 ± 0.02***</td>
<td>1.91 ± 0.69***</td>
</tr>
<tr>
<td>6</td>
<td>0.08 ± 0.02***</td>
<td>0.87 ± 0.39***</td>
</tr>
<tr>
<td>9</td>
<td>0.08 ± 0.02***</td>
<td>0.69 ± 0.29***</td>
</tr>
<tr>
<td>12</td>
<td>0.08 ± 0.02***</td>
<td>0.61 ± 0.28***</td>
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***$P < 0.001$ compared with values before treatment.
events. In the present study, neither cardiovascular events nor appearance/aggravation of diabetes were found. The findings reported here indicate that ADT increased fat mass, especially visceral fat. In the healthy male population, testosterone concentrations are negatively correlated with the degree of central abdominal obesity (14), but the underlying mechanisms are not well known. Androgen receptors are known to be present on visceral adipocytes, and it is likely that testosterone is directly involved in the mobilization of free fatty acids (15). Another study reported that testosterone deficiency results in reduced lipolysis in visceral adipose tissue (14), and, therefore, the accumulation of abdominal fat stores. Increases in fat mass were positively correlated with rising insulin concentrationssupporting the concept that central abdominal adiposity is closely associated with disturbances in insulin and glucose metabolism in hypogonadal males (16).

There are contradictory reports on changes in the distribution of abdominal fat. Smith et al. (17) reported that lowering serum gonadal steroid concentrations to castrate levels with an LH-RH agonist increased the abdominal subcutaneous fat area without significantly changing intra-abdominal fat area. Testosterone therapy given to adult men with acquired hypogonadism decreased subcutaneous fat and increased lean muscle mass (18).

We measured the segmental water volume in the body using direct segmental multi-frequency BIA (DSM-BIA) with an InBody S20. BIA is not invasive and can measure the segmental body composition of each limb and body water quickly and repeatedly. DSM-BIA uses eight polar tactile electrodes and various electrical voltage and current are sent through the inner body, resulting in five different impedance readings for the trunk and the four limbs. This makes DSM-BIA accurate in comparison with the conventional BIA using single impedance. However, the accuracy of measurements of VFA is debatable. Therefore, we measured VFA in other subjects by two methods, DSM-BIA and calculation with CT to demonstrate the accuracy of DSM-BIA. We used PC software, Fat Scan® V3.0 for the calculation with CT, which is the standard software to study metabolic syndrome in Japan. The data gathered by both methods significantly correlated with each other. In addition, the analyses of data should be more reliable than the comparison analyses between the data of each subject because we compared the change in parameters before and after treatment in the same subjects.

The present study had limitations. First, the study did not have a control group. Part of the observed changes may have resulted from normal aging rather than ADT. In a prospective study of healthy older men, lean body mass and fat mass did not change significantly after 3 years (19), suggesting that aging alone cannot account for the marked body composition changes observed in our study. Secondly, this was a 1-year study, but

<table>
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<th>Table 3. Variation in body components and lipid profile</th>
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<tr>
<td>Months of treatment</td>
</tr>
<tr>
<td>△Body weight (kg)</td>
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<tr>
<td>△Fat (kg)</td>
</tr>
<tr>
<td>△Skeletal muscle (kg)</td>
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<tr>
<td>△VFA (cm²)</td>
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<tr>
<td>△Waist circumference (cm)</td>
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<tr>
<td>Triglyceride (mg/dl)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
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<tr>
<td>HDL cholesterol (mg/dl)</td>
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<td>LDL cholesterol (mg/dl)</td>
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VFA, visceral fat area; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*P < 0.05, **P < 0.01, ***P < 0.001 compared with values after 3 months of treatment.
#P < 0.05, ##P < 0.01 compared with values before treatment.

Figure 2. The increase in VFA correlated significantly with those of fat ($r^2 = 0.8267, P < 0.0001$).
additional studies are needed to assess the long-term effects of ADT on lipid metabolism and body composition. Energy intake and activity were not controlled, and differences in diet or exercise may have influenced body composition outcomes. Some of the subjects, who had originally had lean bodies and a healthy diet, did not gain weight, although this was not analyzed statistically. In others, who gained weight during ADT, body composition and lipid profiles changed little after 1 year, which implied that ADT may not influence them for a long time.

In conclusion, ADT changed the body composition and lipid profile of men with prostate cancer. Their weight and fat increased significantly and their skeletal muscle decreased significantly during 12 months' treatment. The serum concentration of total cholesterol and LDL cholesterol decreased significantly during 12 months' treatment. The fat increased significantly and their skeletal muscle composition and lipid profiles changed little after 1 year, which implied that ADT may not influence them for a long time.

Conflict of interest statement
None declared.

References