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Marked hyperglycemia after androgen-deprivation therapy for prostate cancer and usefulness of pioglitazone for its treatment

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Abstract

Here we demonstrate 2 patients who showed marked hyperglycemia after androgen-deprivation therapy for prostate cancer and the efficacy of the thiazolidinedione pioglitazone on their glycemic control. Case 1 was a 61-year-old man diagnosed with prostate cancer who had type 2 diabetes mellitus for 7 years. His glycemic control had been good for the previous 5 years because of diet therapy and acarbose administration. He was given the gonadotropin-releasing hormone agonist leuprolide acetate and the androgen receptor antagonist flutamide for the treatment of prostate cancer. After the second injection of leuprolide acetate, fasting glucose and hemoglobin A1c (HbA1c) levels were found to be markedly elevated (22.8 mmol/L and 10.5%, respectively). Case 2 was an 81-year-old man whose fasting glucose and HbA1c had been normal 10 months ago. He was injected with leuprolide acetate for the treatment of prostate cancer. Six months after starting the leuprolide treatment, the patient complained of thirst and weight loss and was diagnosed with diabetes mellitus with a fasting glucose of 19.4 mmol/L and HbA1c of 9.9%. The correct homeostasis model assessment evaluation indexes for pancreatic β-cell function (HOMA-%β) and for insulin sensitivity (HOMA-%S) were reduced in these 2 patients compared with control men. Their serum testosterone and 17β-estradiol concentrations were depressed. After improvement of hyperglycemia by insulin treatment, their glycemic control remained good after treatment with pioglitazone without use of insulin. The values of HOMA-%β and HOMA-%S increased to control ranges. Insulin resistance after the androgen-deprivation therapy might lead to marked hyperglycemia in these patients.

1. Introduction

A gonadotropin-releasing hormone (GnRH) agonist/antagonist alone or in combination with an antiandrogen often leads to either partial or full remission of prostate cancer [1]. GnRH agonists cause an initial surge in luteinizing hormone (LH) along with a rise in testosterone that is followed by down-regulation of the LH receptors in the pituitary, inhibition of LH release, and decrease of sex hormones secretion from the testes. Because the initial rise in testosterone may exacerbate the disease, an antiandrogen is sometimes coadministered to block the flare. The combined use of an antiandrogen has the additional potential to block the effects of adrenal androgens. Although these medical therapies are shown to be associated with hot flashes, decrease of libido, bone loss, and fatigue [2,3], their effects on glucose metabolism are not well defined. Here we report 2 cases with prostate cancer who showed marked hyperglycemia after treatments with combined GnRH agonist and an androgen receptor antagonist or with a GnRH agonist alone. The analysis by homeostasis model assessment (HOMA) indicated that both insulin sensitivity and insulin secretion were impaired in these patients. The thiazolidinedione drug pioglitazone was effective in maintaining good glycemic control in these patients.

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2. Subjects and methods

2.1. Patients

2.1.1. Case 1

A 61-year-old Japanese man was diagnosed with prostate cancer (stage T3b N_0 M_1) in August 2002. At age of 54 years, he was diagnosed with type 2 diabetes mellitus and advised by a dietitian to take a diet consisting of 1800 kcal/d: the percentages of each nutrient in the total calories were 50% to 60% of carbohydrates, 25% to 30% of fat, and 15% to 20% of protein. At that time, he was started on a α-glucosidase inhibitor acarbose (300 mg/d). Fasting plasma glucose levels remained 6.1 to 7.4 mmol/L and hemoglobin A1c (HbA1c) levels 5.3% to 6.4% (normal range, 4.3%-5.8%) during the previous 5 years, and thus, his glycemic control had been good. His height was 175.3 cm and body weight was 71.1 kg (body mass index 23.0 kg/m^2). For the treatment of prostate cancer, subcutaneous injection of leuprolide acetate (3.75 mg/mo) and oral administration of flutamide (250 mg/d) were started in September 2002. He did not change his dietary habits and his body weight did not change after the diagnosis of prostate cancer. He continued to work as usual and had no event that appeared to worsen his glycemic control, such as physiological or psychological stress, infections, and other medications. At 3 weeks after the second injection of leuprolide acetate, his glycemic control was found worse: fasting glucose and HbA1c levels were 18.2 mmol/L and 8.0%, respectively. He was administered nateglinide (270 mg/d), but fasting glucose and HbA1c reached 22.8 mmol/L and 10.5%, respectively, in December 2002 (Fig. 1). Serum testosterone and 17β-estradiol levels decreased to 0.45 nmol/L (control range in men, 10-35 nmol/L) and 40 pmol/L (control range in men, 70-110 pmol/L), respectively. After ceasing the administration of flutamide, we started injection of insulin lispro before each meal on admission. Plasma glucose levels declined on a maximal dose of 40 U/d at day 7 after insulin treatment, when we coadministered pioglitazone (15 mg/d). Thereafter, we could reduce the doses of insulin lispro. In February 2003, we stopped the insulin injection and increased the dosage of pioglitazone to 30 mg/d. We readministered flutamide and continued the injection of leuprolide acetate (11.25 mg per 3 months). In December 2003, fasting glucose levels remained below 7 mmol/L and HbA1c declined to 5.2% (Fig. 1).

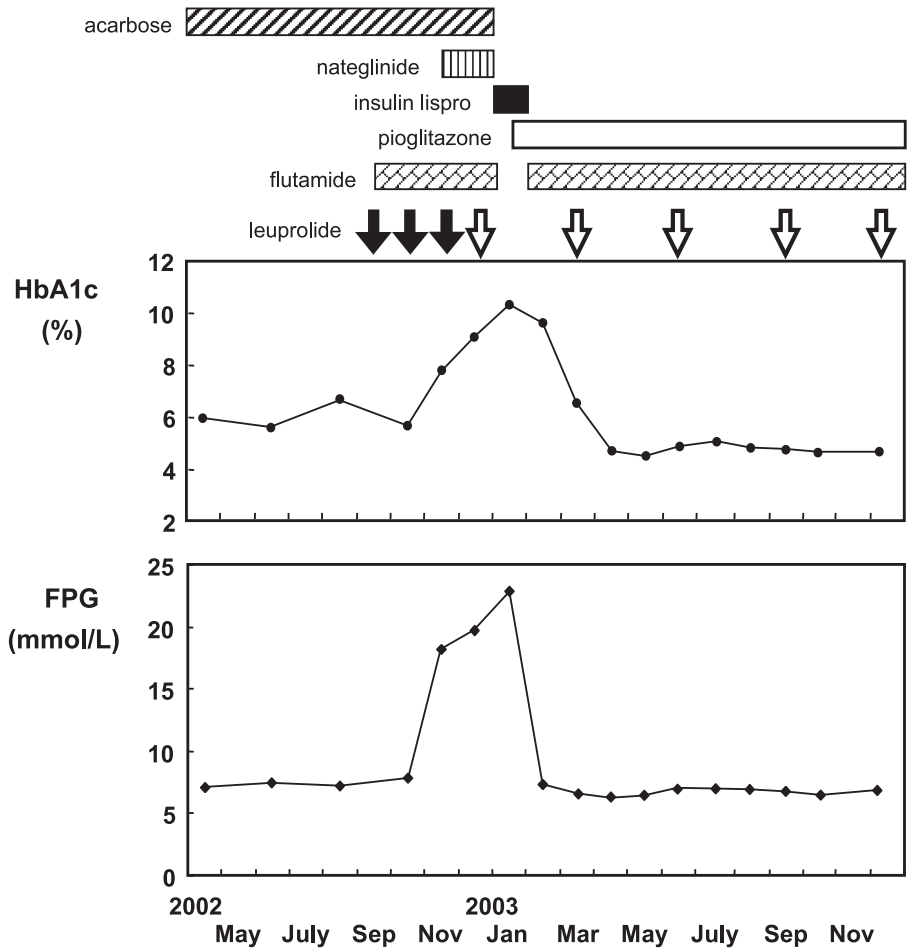

Fig. 1. Longitudinal changes of fasting plasma glucose (FPG) and HbA1c levels in case 1. Black arrows indicate subcutaneous injection of 3.75 mg leuprolide acetate; white arrows, 11.25 mg leuprolide acetate.

2.1.2. Case 2

An 81-year-old Japanese man was diagnosed with prostate cancer (stage T3a N_0 M_0) in June 2003. He has never been diagnosed with diabetes mellitus. Fasting glucose and HbA1c levels were 6.1 mmol/L and 5.1%, respectively, in April 2003. His height was 161.5 cm and body weight was 47.0 kg (body mass index 18.0 kg/m^2). The patient was started on subcutaneous injections of leuprolide acetate (3.75 mg/mo) for the treatment of prostate cancer in August 2003. After the third injection, the dose of leuprolide acetate was changed to 11.25 mg each 3 months. In March 2004, he complained of thirst and weight loss (−3.0 kg during 6 months); laboratory tests revealed marked hyperglycemia (19.4 mmol/L) and elevated HbA1c (9.9%) levels. Both serum testosterone and 17β-estradiol were undetectable (<0.42 nmol/L and <37 pmol/L, respectively). He was admitted to Osaka University Hospital and was given injections of insulin lispro before each meal. Plasma glucose concentration gradually decreased at a maximal dose of 24 U/d of insulin lispro (Fig. 2). By coadministration of pioglitazone (15 mg/d), we were able to reduce the dose of insulin lispro and thereafter stop the insulin treatment, followed by coadministration of the α-glucosidase inhibitor voglibose. The injection of leuprolide acetate (11.25 mg every 3 months) was continued. His glycemic control remained good in June 2004: fasting glucose was 6.7 mmol/L and HbA1c was 7.0%.

2.2. Control subjects

One hundred and forty-four Japanese men aged 58 to 68 years (60 ± 2 years, mean ± SD), who were confirmed to have normal glucose tolerance by the 75-g oral glucose tolerance test, were studied as control subjects. Their body mass index was 23.4 ± 2.5 kg/m^2.

2.3. Determination of pancreatic β-cell function and insulin sensitivity

Pancreatic β-cell function and insulin sensitivity were estimated by calculation from fasting plasma glucose and serum insulin levels using the HOMA method [4]. The

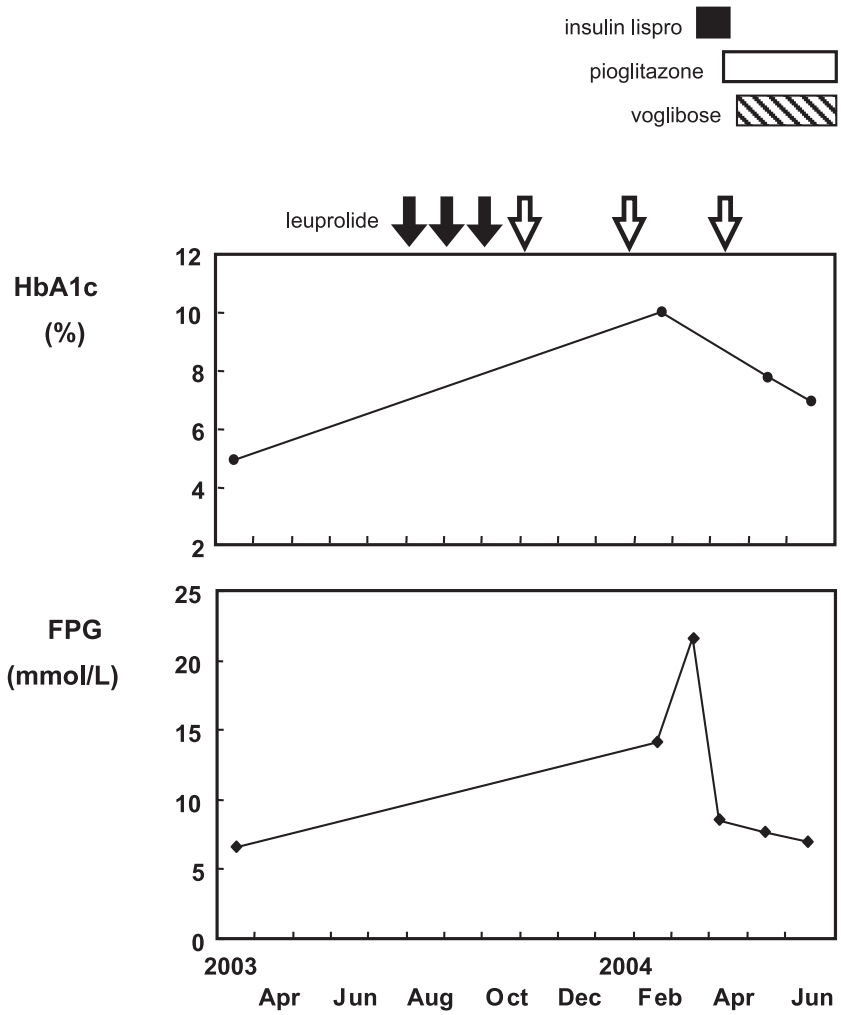

Fig. 2. Longitudinal changes of fasting plasma glucose (FPG) and HbA1c levels in case 2. Black arrows indicate subcutaneous injection of 3.75 mg leuprolide acetate; white arrows, 11.25 mg leuprolide acetate.

Table 1
Clinical and biochemical parameters of study subjects

	Fasting plasma glucose (mmol/L)	Fasting serum insulin (pmol/L)	HOMA-%β (%)	HOMA-%S (%)
Case 1				
December 2002	22.8	79	13	11
March 2003	6.3	43	58	100
June 2003	6.9	57	59	74
December 2003	7.1	50	51	84
Case 2				
March 2004	21.9	129	22	9
June 2004	6.7	34	43	125
Control subjects	5.5 ± 0.4	46 ± 17	78 ± 23	117 ± 52
Range	4.5-6.1	16-101	37-139	44-294

Control subjects are 144 Japanese men aged 58 to 68 years (60 ± 2 years) who have normal glucose tolerance. HOMA-%β and HOMA-%S were determined by the correct HOMA evaluation.

estimates of β-cell function and insulin sensitivity have been shown to correlate with estimates obtained by hyperglycemic and euglycemic clamp techniques, respectively [4]. The values for β-cell function (HOMA-%β) and insulin sensitivity (HOMA-%S) were assessed by the correct HOMA evaluation using a computer program reported by Levy et al [5].

3. Results

HOMA-%β and HOMA-%S were determined by the correct HOMA evaluation [5] in control subjects. Their HOMA-%β was 78% ± 23% (range, 37%-139%) and HOMA-%S was 117% ± 52% (range, 44%-294%).

Table 1 shows fasting glucose, fasting insulin, HOMA-%β, and HOMA-%S in 2 cases before and after treatments for diabetes mellitus. HOMA-%β and HOMA-%S in case 1 were 13% and 11%, respectively, before starting insulin treatment. Both estimates were below the ranges in the control subjects. After treatment with insulin followed by pioglitazone alone, HOMA-%β increased to 58% at 3 months, 59% at 6 months, and 51% at 12 months, which were within the control ranges (Table 1). HOMA-%S also increased to the ranges in the control subjects (100% at 3 months, 74% at 6 months, and 84% at 12 months). In case 2, HOMA-%β and HOMA-%S were 22% and 9% before treatment of insulin, both of which were below the control ranges. Both parameters increased to the control ranges (HOMA-%β 43%; HOMA-%S 125%) at 3 months after treatments with insulin followed by administration of pioglitazone and voglibose (Table 1).

4. Discussion

There is growing evidence indicating that sex hormones influence risk factors for diabetes mellitus. It has been shown that serum testosterone concentrations are inversely related to insulin resistance in men [6-8]. In addition, low levels of testosterone had been shown to predict the development of type 2 diabetes mellitus in men [9]. The effects of postmenopausal hormone replacement therapy are lower fasting glucose and insulin levels in nondiabetic women [10] and improved glycemic control in type 2 diabetic women [11], although disparate results had been reported [12,13]. Recently, the Heart and Estrogen/progestin Replacement Study (HERS) has shown that the postmenopausal hormone therapy reduced the incidence of diabetes mellitus [14]. Thus, androgens and estrogens may have favorable effects on glucose metabolism in men and in postmenopausal women, respectively.

The 2 male patients presented here demonstrated marked hyperglycemia after androgen-deprivation therapy for prostate cancer. Both cases had reduced pancreatic β-cell function as well as reduced insulin sensitivity, as determined by the correct HOMA evaluation. In case 1, a patient with type 2 diabetes mellitus whose glycemic control has been good using acarbose treatment alone was administered the GnRH agonist leuprolide acetate and the androgen receptor antagonist flutamide. Case 2, who had never been diagnosed with diabetes mellitus, was given leuprolide acetate but not antiandrogens. Leuprolide acetate causes a decrease in serum levels of androgens and estrogens. Thus, reduction of serum androgens and/or serum estrogens may contribute to marked hyperglycemia in these patients. The thiazolidinedione pioglitazone, an insulin-sensitizing drug, was very effective in maintaining good glycemic control after lowering of blood glucose levels by insulin therapy. These observations suggest that insulin resistance occurred in our patients with reduced β-cell function after androgen-deprivation therapy and it resulted in the exacerbation of hyperglycemia.

Coddington et al [15] reported a type 1 diabetic female patient who showed deterioration in glucose control after leuprolide treatment of endometriosis. This suggests the involvement of a decrease in serum estrogens in worsening of glycemic control. Furthermore, a male patient with aromatase deficiency, who had decreased serum estrogens but not androgens, has been shown to have insulin resistance [16]. In addition, androgens had been shown to impair insulin action in women [17]. Taken together, the reduction of serum estrogen levels rather than serum androgen levels may have lead to the reduction of insulin sensitivity, causing marked hyperglycemia in our cases.

At present, we have no information on the prevalence of alterations of glucose metabolism in prostate cancer patients who are given androgen-deprivation therapy, and this needs to be studied in the future. The onset of overt diabetes may depend on β-cell function as well as insulin sensitivity of the patients. Because androgen-deprivation therapy has become the mainstay of prostate cancer treatment, physicians should pay attention to carbohydrate metabolism in patients receiving androgen-deprivation therapy.

References

[1] Scher HI. Prostate carcinoma: defining therapeutic objectives and improving overall outcomes. Cancer 2003;97(3 Suppl):758-71.

[2] Maillefert JF, Sibilia J, Michel F, Saussine C, Javier RM, Tavernier C. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostate carcinoma. J Urol 1999;161: 1219-22.

[3] Stone P, Hardy J, Huddart R, A'Hern R, Richards M. Fatigue in patients with prostate cancer receiving hormone therapy. Eur J Cancer 2000;36: 1134-41.

[4] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetolgia 1985;28:412-9.

[5] Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 1998;21:2191-2.

[6] Pasquali R, Casimirri F, Cantobelli S, et al. Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism 1991;40:101-4.

[7] Simon D, Preziosi P, Barrett-Connor E, et al. Interrelation between plasma testosterone and plasma insulin in healthy adult men. Diabetologia 1992;35:173-7.

[8] Haffner SM, Valdez RA, Mykkänen L, Stern MP, Katz MS. Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men. Metabolism 1994;43:599-603.

[9] Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. Am J Epidemiol 1996;143:889-97.

[10] Barret-Connor E, Laakso M. Ischemic heart disease risk in postmenopausal women. Effects of estrogen use on glucose and insulin levels. Arteriosclerosis 1990;10:531-4.

[11] Friday KE, Dong C, Fontenot RU. Conjugated equine estrogen improves glycemic control and blood lipoproteins in postmenopausal women with type 2 diabetes. J Clin Endocrinol Metab 2001;86:48-52.

[12] Kimmerle R, Heinemann L, Heise T, Bender R, Weyer C, Hirschberger S, et al. Influence of continuous combined estradiol-norethisterone acetate preparations on insulin sensitivity in postmenopausal nondiabetic women. Menopause 1999;6:36-42.

[13] Vehkavaara S, Westerbacka J, Hakala-Ala-Pietilä T, Virkamäki A, Hovatta O, Yki-Järvinen H. Effect of estrogen replacement therapy on insulin sensitivity of glucose metabolism and preresistance and resistance vessel function in healthy postmenopausal women. J Clin Endocrinol Metab 2000;85:4663-70.

[14] Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2003;138:1-9.

[15] Coddington CC, Hassiakos DK, Harrison HC, Brzyski RG, Jones GS. Effect of a gonadotropin-releasing hormone analogue on the glucose metabolism in a diabetic patient. Gynecol Obstet Invest 1990;30: 246-8.

[16] Bilezikian JP, Morishima A, Bell J, Grumbach MM. Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency. N Engl J Med 1998;339:559-603.

[17] Moghetti P, Tosi F, Castello R, et al. The insulin resistance in women with hyperandrogenism is partially reversed by antiandrogen treatment: evidence that androgens impair insulin action in women. J Clin Endocrinol Metab 1996;81:952-60.