□ CASE REPORT □

Diabetes Mellitus Associated with Klinefelter's Syndrome: A Case Report and Review in Japan

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Abstract

We report a case of Klinefelter's syndrome in a 48-year-old man who had diabetes mellitus associated with severe insulin resistance. We diagnosed him with Klinefelter's syndrome from his atrophic testicles, primary hypogonadism in hormonal examination, and a chromosomal aberration of 47,XXY. He showed severe decreased insulin sensitivity in a hyper-insulinemic euglycemic clamp test. He had injected over 100 units of insulin per day, however, testosterone replacement and administration of pioglitazone improved his glycemic control, which resulted in a decrease of insulin dose to less than 50 units per day. Here, we discuss the characteristics of diabetes mellitus associated with Klinefelter's syndrome in Japanese patients including this case.
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Key words: Klinefelter's syndrome, diabetes mellitus, insulin resistance

Introduction

In aberrations of the sex chromosomes, the 47, XXY karyotype is found in patients with Klinefelter's syndrome who are phenotypic males and have testicular dysgenesis, gynecomastia and infertility (1, 2). It was reported that patients with Klinefelter's syndrome tended to have diabetes mellitus or autoimmune diseases (3–5). It has not been clarified why diabetes mellitus develops in patients with Klinefelter's syndrome, and what the characteristics of diabetes in the syndrome are. We report a case with Klinefelter's syndrome who had diabetes mellitus associated with severe insulin resistance, and discuss Japanese cases of Klinefelter's syndrome with diabetes mellitus.

Case Report

A 48-year-old man had history of type 2 diabetes for more than 18 years and required insulin therapy from 42 years old. Since then, he self-injected over 60 units of insulin everyday, while his blood glucose levels were uncontrolled. At 45 years old, he suffered arthralgia in several joints and was diagnosed with rheumatoid arthritis. Although he was treated with disease modified antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoid, his rheumatic symptoms of arthralgia and joint swelling gradually worsened. Simultaneously, his blood glucose levels were not controlled despite injection of over 100 units of insulin every day. He was admitted to a hospital for management of his rheumatoid arthritis and diabetic control in January 2001, however, his symptoms and blood glucose control did not improve. Therefore, he was transferred to our department in May 2001.

The patient was single and had not been married. His paternal cousin and paternal uncle had diabetes mellitus. He had normal intelligence, and was mildly obese (height, 163 cm; weight, 66.4 kg; BMI, 25.5 kg/m^2). He had also moon face and gynecomastia (Fig. 1). His blood pressure was normal (138/70 mmHg while sitting). His body hair was thin and his pubic hair was female-like. His penis was slightly small, and both testicles were markedly atrophic (each volume was approximately 2 ml), which he had recognized since 20 years of age. There was tenderness in his elbows and knees, and rheumatoid nodules were recognized at both forearms. Pateral tendon reflex and vibration sense in his foot were decreased due to diabetic neuropathy. His fundus occuli showed the class B2 of diabetic retinopathy in Fukuda's classification.

His laboratory examinations are shown in Table 1. ESR was increased. Hematological examinations revealed mild anemia and leukocytosis. Blood chemistry examinations showed normal liver functions and normal plasma lipid profiles on medication of statin. Fasting plasma glucose was as high as 200 mg/dl and HbA1c was 9.7%. Urinary C-peptide reactivity (CPR) was 9.8 μg/day, extremely low. Serological examina-

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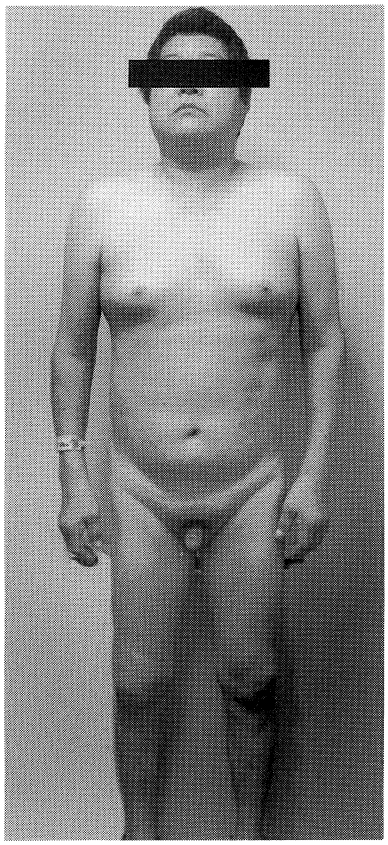

Figure 1. Photograph of the patient.

tions showed high C-reactive protein (CRP), a strongly positive RA test, and positive antinuclear factor (ANF). Anti-glutamic acid decarboxylase (GAD) antibody and anti-islet cell antibody were negative. In hormonal examinations (Table 2), both leuteinizing hormone (LH) and follicule stimulating hormone (FSH) levels were high, while the testosterone level was very low. Dehydroepiandrosterone sulfate (DHEA-S) and estradiol levels were also decreased. LH releasing hormone (LH-RH) loading test showed high baseline levels and a normal response of LH and FSH, however, the testosterone response was low in the human chorionic gonadotropin (hCG) loading test. These hormonal findings revealed that he had primary hypogonadism. His lumbar bone mineral density was slightly low at 0.878 g/cm^2. His chromosome analysis revealed an aberration of 47,XXY. Klinefelter's syndrome was diagnosed from his physical characteristics, hormonal findings and his chromosomal aberration.

Clinical course (Fig. 2)

After admission, we studied his insulin sensitivity using the glucose clamp test (high insulinemic normal glycemic clamp study). At an insulin infusion rate of 2.25 mU/min and steady glucose level of 90 mg/dl, his glucose infusion rate (GIR) was extremely low at 2.48 mg/kg/min [normal rate in controls; 7.4±2.4 (mean±SD), n=20]. He injected a mix of rapid and NPH insulin twice daily (24 units of rapid and 54 units of NPH in the morning and 30 units of rapid in the evening) before his admission. We changed his insulin therapy to an intense insulin therapy (rapid insulin before every meal and NPH before sleep). For his rheumatoid arthritis, we increased the glucocorticoid dose (prednisolone 10 mg/day) and administered D-penicillamine and methotrexate, although his symptoms and CRP level were not improved. For his hypogonadism, he was intramuscularly injected with 125 mg of testosterone enanthate every 2 weeks, and we added pioglitazone for his diabetes treatment. From that time, his diabetic control gradually improved and he could decrease the insulin dose even after 3 months, and his serum glycoalbumin levels were kept low. A second examination of his insulin sensitivity revealed 5.8 mg/kg/min of GIR, which showed a marked improvement. He could decrease his total dose of insulin from 110 units to 50 units. His rheumatoid arthritis was better after controlling his diabetes, although the steroid dose was the same. His insulin injection method was changed to rapid insulin before breakfast and lunch, and a mix of rapid and NPH insulin before supper, without injection before sleep. He was discharged in December 2001 and returned to an ordinary life.

Study of Klinefelter's syndrome in Japan

We investigated 895 Japanese cases of Klinefelter's syndrome that had been reported in the literatures up to 2001. Among those cases, 61 patients (6.8%) were described as having diabetes mellitus (Table 3) (5–29). The true frequency of diabetes may be higher because there were many incomplete reports regarding glucose intolerance. The characteristics of those Japanese patients with Klinefelter's syndrome accompanied with diabetes were as follows. The frequency of the 47,XXY karyotype was 66% and that of 46,XY/47,XXY was 15%. Half of the patients had a family history of diabetes mellitus. The diabetic controls were generally poor and the mean HbA1c was 10.6%. The frequency of obesity (BMI ≥25) was only 7 in 29 patients, and the mean BMI was 21.5 (15.2–37.0). The secretion of insulin was decreased in half of the patients, and 20 in 26 patients were treated with insulin. Most patients had diabetic complications of microangiopathy. Some of them had diabetic ketoacidosis or hyperosmolar non-ketotic diabetic coma. In seven of 8 patients, the glucose clamp test showed decreased insulin sensitivity.

Discussion

Klinefelter's syndrome was first reported as hypogonadism in a male by Klinefelter et al in 1942 (1), and it has since been identified that those patients had sex chromosomal aberration of not only 47,XXY karyotype but also 46,XY/47,XXY (mosaic), 48,XXXY, 48,XXYY, or 49,XXXXY karyotype. The 47,XXY karyotype is the most frequent (90%) (2). This syndrome is most common in sex chromosomal aberrations of newborn infants, and the prevalence is about 0.2% in males

Table 1. Laboratory Findings on Admission

ESR	119 mm/h	Blood biochemistry	
Urine analysis		Total protein	7.0 g/dl
Glucose	17 g/day	Albumin	3.6 g/dl
Protein	200 mg/day	AST	11 IU/l
Ketone body	(–)	ALT	17 IU/l
		ALP	308 IU/l
Complete blood cell count		LDH	237 IU/l
RBC	435×10^4/μl	CPK	11 IU/l
Hb	11.2 g/dl	BUN	19 mg/dl
Ht	35.5%	Creatinine	0.6 mg/dl
WBC	14,800/μl	Uric acid	4.6 mg/dl
Platelet	42.2/μl	T-cho	199 mg/dl
		Triglyceride	120 mg/dl
Serological test		HDL-c	33 mg/dl
IgG	1,360 mg/dl	Na	139 mEq/l
IgA	169 mg/dl	K	4.3 mEq/l
IgM	348 mg/dl	Cl	103 mEq/l
CRP	12.2 mg/dl	Ca	4.7 mEq/l
RF	1,772 IU/l	P	1.8 mEq/l
ANF	(+)	FPG	200 mg/dl
	diffuse type	HbA1c	9.7%
Anti-GAD antibody	(–)	Urinary CPR	9.5 μg/day
ICA	(–)		
		24 h Ccr	82.4 ml/min

RF: rheumatoid factor, ANF: anti-nuclear factor, GAD: glutamic acid decarboxylase, ICA: islet cell antibody, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, FPG: fasting plasma glucose, CPR: C-peptide immunoreactivity.

(30).

It was reported that patients with Klinefelter's syndrome tend to have various degrees of glucose intolerance in both Western countries (3, 31) and Japan (6, 7). The relative risk of death in patients with Klinefelter's syndrome (1.63: 1.40–1.91, CI 95%) is higher than that in the normal population, which may in part arise from the complication of diabetes (32). The frequency of diabetes mellitus in patients with Klinefelter's syndrome has been reported as 15%–50% in Western countries (3, 33, 34), while, in Japan it was lower at 3.9%–4.1% (6, 7). Sagara et al suggested that the low prevalence of diabetes in Japanese with Klinefelter's syndrome might be caused by insufficient examinations for glucose tolerance (6).

The present patient had severe diabetes with diabetic retinopathy, nephropathy and neuropathy upon admission to our department. His diabetes was characterized by the simultaneous existence of insufficient insulin secretion and severe insulin resistance. His insulin deficiency did not improve after glycemic control, suggesting that the deficiency was not simply due to glucose toxicity. His diabetes was not slowly progressive insulin-dependent diabetes mellitus (SPIDDM) because of his clinical course. His blood glucose levels gradually decreased after testosterone replacement and administration of pioglitazone. Four months after testosterone replacement, facial hair appeared and his gynecomastia tended to be improved. At that time, his diabetic control was still getting better and the insulin dose required was decreased from more than 100 units to 50 units per day. This suggested that not only pioglitazone but also testosterone replacement contributed to his improved glycemic control. Prednisolone administered for rheumatoid arthritis might, in part, have influenced his insulin resistance. However, his glycemic control was better despite the increase in prednisolone dose, suggesting that prednisolone was not the main cause of his insulin resistance. His control for rheumatoid arthritis was insufficient and inflammatory reactions such as CRP did not change compared with those immediately before testosterone replacement therapy.

The pathogenesis of development of diabetes mellitus in Klinefelter's syndrome has been suggested to be genetic factors, autoimmune mechanisms or endocrinal abnormalities. The type and severity of diabetes in the syndrome is not identical, therefore, multiple factors may be involved in the diabetic development. Insulin resistance may be an important characteristic of diabetes in this syndrome. Obesity, which is one symptom of this syndrome, may be involved in the insulin resistance. In addition, Breyer et al showed that insulin binding to erythrocytes was decreased in non-diabetic patients with the syndrome (35). Jackson et al suggested that sex chromosome aberrations alone caused abnormalities in the glucose metabolism because of the existence of some enzyme gene related to

Table 2. Endocrinological Examinations

LH	13.7 mIU/*l*	(1.71–8.59)*
FSH	32 mIU/*l*	(1.5–12.4)
ACTH	21 pg/ml	(<60)
PRL	20 ng/ml	(3.1–20.5)
GH	0.3 ng/ml	(<0.42)
TSH	4.05 μU/ml	(0.47–4.33)
Free T3	2.87 pg/ml	(2.0–4.2)
Free T4	1.36 ng/dl	(1.0–1.8)
Serum cortisol	6.28 μg/dl	(4.64–24.56)
Urinaly 17-OHCS	4.8 mg/day	(3.4–12.0)
Urinaly 17-KS	5.3 mg/day	(4.6–18.0)
Serum testosterone	78 ng/dl	(320–1030)
Serum free testosterone	1.1 pg/ml	(18.0–42.0)
Serum DHEA-S	177 ng/ml	(1,300–5,600)
Estradiol	<10 pg/ml	(12–49)

*( ): normal ranges

LH-RH loading test

	before	15 min	30 min	60 min	90 min
LH (mIU/*l*)	32.8	46.3	54.0	55.8	16.8
FSH (mIU/*l*)	37.2	41.7	44.8	49.4	33.5

hCG loading test

	before	4 day	5 day
Testosterone (ng/dl)	51	141	167

the glucose metabolism (36). Tada and Hayashi also reported an involvement of glucose-6-phosphate dehydrogenase whose gene was in the chromosome, in the glucose metabolic dysfunction (8). Some Klinefelter's syndrome patients with diabetes revealed positive islet cell surface antibody and a clinical course of SPIDDM (9), and autoimmune diseases such as systemic lupus erythematodes were reported to frequently accompany Klinefelter's syndrome (5, 10, 37). Therefore, an autoimmune mechanism may be involved in the development of diabetes in the syndrome. It was reported that testosterone replacement did not improve the glycemic control, which did not support an endocrinological mechanism for the development of diabetes in the syndrome. On the other hand, Pei et al reported that insulin resistance was consistently noted in patients with the syndrome and the plasma testosterone concentration was inversely related to insulin resistance (38). Testosterone deficiency may directly or indirectly be involved in the abnormality of glucose metabolism in Klinefelter's syndrome.

Studies in Western countries reported that diabetes conditions in patients with Klinefelter's syndrome were usually mild, and showed a hyperinsulinemic hyperglycemic pattern, and that their relatives also frequently had diabetes mellitus (3). In Japanese patients with Klinefelter's syndrome, the frequencies of normal body weight, decreased secretion of insulin and the necessity for insulin therapy are high as compared with those in Western countries, and in addition, there are frequent insulin resistances.

In conclusion, we reported a case of Klinefelter's syndrome with diabetes mellitus, which was associated with severe insu-

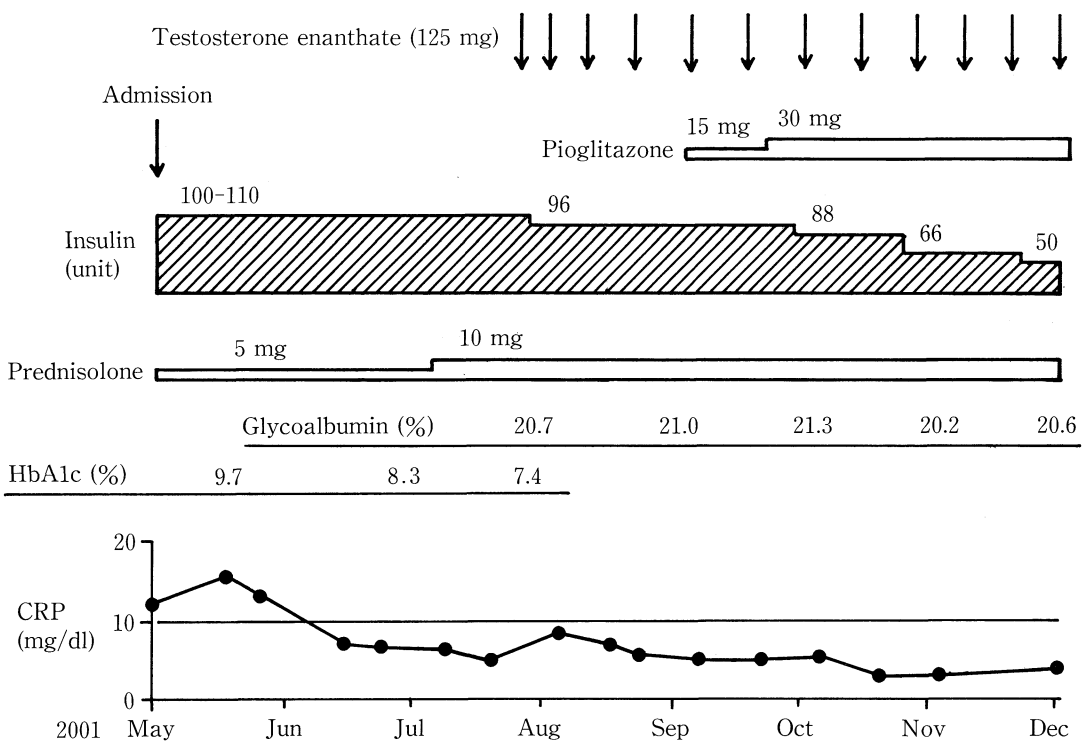

Figure 2. Clinical course.

Table 3. Characteristics of 61 Cases with Diabetes Mellitus Among 895 Japanese

Patients with Klinefelter's syndrome

Reported age	42.9±11.8	(15–70)
Body mass index (BMI) (kg/m^2)	21.5±4.44	(15.2–37)
Fasting plasma glucose (mg/dl)	313±145	(82–1,118)
HbA1c (%)	10.6±2.28	(4.7–16.5)
Karyotypes	Number	
47, XXY	40	
46, XY/ 47, XXY	9	
48, XXYY	2	
47, XXY/ 48, XXXY/ 46, XY	1	
47, XXY/ 46, XY/ 46, XX	1	
Unknown	8	
Family history of diabetes mellitus		
(+)	15	
(–)	14	
Unknown	32	
Secretion of insulin		
Decrease	11	
Normal	12	
Unknown	38	
BMI <25.0	22	
≧ 25.0	7	
Unknown	32	
Therapy Diet only	3	
Per os	3	
Insulin	18	
Insulin and per os	2	
Unknown	35	

Diabetic complications (numbers): triopathy (8), retinopathy + neuropathy (1), retinopathy + nephropathy (2), neuropathy (1), hyperlipidemia (7), diabetic ketoacidosis (3), hyperosmolar non-ketotic coma (2), leg ulcer (3), renal failure (2).

lin resistance, and we discussed the relation between the syndrome and diabetes mellitus reported in the literature. The present case showed characteristics of the simultaneous existence of insulin deficiency and resistance, and suggested that his insulin resistance was partially associated with testosterone deficiency. The characteristics of diabetes in Klinefelter's syndrome are varied, therefore, we should manage patients case by case. It is also important that insulin secretion and insulin resistance (receptor number and post-receptor signaling) in patients with Klinefelter's syndrome should be investigated before diabetic onset.

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