The Effects of Androgen Replacement Therapy on Glycemic Control in a Case with Klinefelter Syndrome and Poorly Controlled Diabetes

Klinefelter Syndrome and Poorly Controlled Diabetes

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Summary

Klinefelter syndrome (KS) is the most common sex chromosome anomaly among men. It is usually characterized by hypergonadotropic hypogonadism, eunuchoid body structure, and most often, 47,XXY karyotype. Studies have shown that KS patients have high risk of developing autoimmune diseases and diabetes, and the hypogonadism that accompanies the syndrome makes regulation of diabetes more difficult. A 39-year-old man with KS was admitted to Endocrinology and Metabolic Diseases Polyclinic because of increased blood glucose level: His glycated hemoglobin (HbA1c) value was 14.9%. He had diabetes for approximately 5 years and was using 80 IU insulin daily at time of admission, but after testosterone replacement therapy, his insulin requirement decreased to 60 units. Follow-up HbA1c was 7.7% after 2 months of androgen replacement therapy. Hypoandrogenemia may contribute to development of newly diagnosed diabetes or deterioration of pre-existing diabetes. Testosterone replacement therapy can improve glycemic control in these patients.

Keywords: Androgen replacement therapy; diabetes mellitus; Klinefelter’s syndrome.

Introduction

Klinefelter syndrome (KS) was first defined by Dr. Harry Klinefelter in 1942, and it is characterized by hypergonadotropic hypogonadism and eunuchoid body structure.

Great majority of cases are diagnosed as result of infertility. Chromosome structure...
may have different patterns (47,XXY/48,XXXY/48,XXYY/49,XXXXY or mosaicism); most frequently (90%), 47,XXY karyotype is seen.[2] This syndrome is the most frequently encountered sex chromosome anomaly in male newborns, with an average incidence of nearly 0.2 percent.[3] Among general characteristics of the syndrome are greater than average height, eunuchoid body structure, long arm span, scarce facial and pubic hair, small testicular volume, gynecomastia, learning disability, and personality and behavioral problems. Increase in incidence of diabetes and metabolic syndrome as result of hypogonadism have been reported in cases of KS.[4]

In this report, case of a patient who presented at outpatient clinic with complaints of polyuria and polydipsia is described. Although he was receiving intensive insulin therapy from time of diagnosis with diabetes, glycemic control had not been achieved. Investigation upon detection of regression of secondary sex characteristics revealed presence of hypergonadotropic hypogonadism. Finding of 47,XXY karyotype on cytogenetic analysis established diagnosis of KS, and evaluation of clinical and biochemical responses following administration of androgen replacement therapy are presented.

**Case Report**

Despite extreme attention to diet, as well as treatment that included intensive insulin (3x20 IU insulin aspart plus 1x20 IU insulin detemir) since determination of type 2 diabetes diagnosis 5 years earlier, a 39-year-old male patient presented at outpatient clinic due to persistence of high glycemic levels. Patient was taking daily dose of 80 IU (1.35 IU/kg) insulin and had serious symptoms of polyuria and polydipsia. His father and 2 siblings also had type 2 diabetes mellitus. Patient had been married and trying to conceive for 14 years, but was childless. He had previously sought medical care for infertility, but had not attended follow-up visits.

Patient was 169 cm tall and weighed 59 kg. Physical examination findings included: body mass index: 21 kg/m², body temperature: 36.8°C, arterial blood pressure: 130/70 mmHg, heart rate: 72 beats/min, rhythmic. Eunuchoid body proportions (arm span: 176 cm, distance from vertex of the head to the pubis: 80 cm, from pubis to floor: 89 cm), and regression of secondary sex characteristics (absence of facial and chest hair, Tanner stage 3–4 axillary and pubic hair, 8 cm-long penis, below normal muscle mass, and feminine-type fat distribution) were also detected (Figure 1).

**Figure 1.** Patient with 47,XXY karyotype was 169 cm tall, weighed 59 kg, and was 39 years old. Body proportions were arm span of 176 cm, distance from crown of the head to the pubis of 80 cm, and from pubis to floor of 89 cm. Regression of secondary sex characteristics (absence of facial and chest hair, Tanner stage 3–4 axillary and pubic hair, 8 cm-long penis, below normal muscle mass, and feminine-type fat distribution) was also present. Colored images can be seen in online issue of the journal (www.keahdergi.com).
Laboratory values as follows are provided in Table 1: Fasting blood sugar: 421 mg/dL (range: 74–106 mg/dL), glycated hemoglobin (HbA1c): 14.9% (range: 4.2–6.5%), and erythrocyte sedimentation rate (ESR): 7 mm/h were determined; there were no symptoms of infection. Karyotype analysis was consistent with 47,XXY KS. Scrotal ultrasound revealed presence of intrascrotal testes smaller than physiological limits for normal [right testis: 13x7x15 mm (0.7 cc) and left testis 12x7x19 mm (0.8 cc)]. 

Serum analysis disclosed presence of azoospermia. Thyroid function test results were within normal limits as follows: thyroid-stimulating hormone (TSH): 0.77 uIU/mL (range: 0.35–4.5 uIU/mL), free T3 (FT3): 3.06 pg/mL (range: 2.3–4.2 pg/mL), free T4 (FT4): 1.05 ng/dL (range: 0.76–1.4 ng/dL), and anti-thyroid peroxidase (anti-TPO): <10 IU/mL (≤10 IU/mL), and anti-tiroglobulin (anti-TG): <20 IU/mL (≤20 IU/mL). Patient was evaluated for microvascular complications of diabetes. Renal function test results were within reference ranges [urea: 37 mg/dL (range: 17–43 mg/dL), creatinine (Cr): 0.89 mg/dL (range: 0.84–1.25 mg/dL), and microalbumin/creatinine ratio (f/t PSA) ratio (0.52) was not pathological.

Testosterone replacement therapy (50 mg gel 2x1) was initiated. At follow-up visits, insulin requirement decreased (1 U/kg; 60 U/d), and glycemic control was achieved. Eight weeks later, HbA1c was 7.7% (Figure 2).
Written, informed consent was obtained from the patient.

Discussion

KS is the most frequently encountered sex chromosome disorder in men, with a prevalence of 1/660. Hypogonadism is the most widespread cause of male infertility and is often accompanied by learning disabilities. Classic features of men with KS included tall height, narrow shoulders, wide hips, and disproportional body parts (eunuchoid habitus), minimal facial and pubic hair, small and hard testes, micropenis, gynecomastia, mild to moderate levels of cognitive disorders, and hypergonadotropic hypogonadism.[5] Now, however, incompleteness of this classic definition has been recognized, and it is known that patients with KS demonstrate a wide spectrum of phenotypical manifestations. Syndrome also occurs across all of society.[6] Therefore, in many male patient diagnosis of KS is overlooked. In a study performed in Denmark, authors demonstrated that nearly 25% of the patients with KS could be diagnosed.[7] Adult KS patients really share only a few characteristics of the syndrome, such as elevated LH and FSH, azoospermia, and small testes.[8] In Western countries, incidence of diabetes in patients with KS has been reported as 15% to 50%.[9–11] In this syndrome, type and severity of diabetes may differ, and many factors may contribute to development of diabetes. Insulin resistance is an important component of diabetes in this syndrome. Genetic factors, autoimmune mechanisms, and hormonal disorders have been suggested in pathogenesis of diabetes seen in KS. Incidence of leg ulcers, osteopenia, osteoporosis, and some tumors (e.g., breast, germ cell tumors) increases in patients with this syndrome.[12,13] Men with KS are also at risk for autoimmune diseases, such as systemic lupus erythematosus.[14,15]

One of the components of KS, hypogonadism, can lead to development of abdominal obesity, which may then have well-known consequences of development of metabolic syndrome and insulin resistance. Abdominal obesity may also lead to lower testosterone levels.[5] In other words, hypogonadism can contribute to development of metabolic syndrome and diabetes by inducing changes in distribution of body fat. However, diabetes, and metabolic syndrome per se, can trigger development of hypogonadism secondary to increased body weight, decreased SHBG level, and suppression of gonadotropin release and testosterone production.[16] Diabetes and metabolic syndrome are associated with increased levels of some cytokines, including interleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor-alpha, which can depress steroidogenesis and production of testosterone.[17–19] Both of these scenarios can contribute partially or completely to this vicious cycle.

Hormonal disorders, such as hyperestrogenism, increase in estrogen/testosterone ratio (responsible for gynecomastia), and delay in increase in testosterone level during puberty, are responsible for characteristic body habitus of KS.[20] It is not known whether morbidities associated with syndrome are consequences of hypogonadism and hyperestrogenism, or if they manifest as a result of dysfunction of genes related to X chromosome.

In men with KS and those with normal karyotype, hypogonadism is an independent risk factor for abdominal adiposity.[21] In cross-sectional studies, increased incidence of hypogonadism has been reported in diabetic men.[16,22,23] In a study performed in the USA, prevalence of hypotestosteronemia (<300 ng/dL) was 38.7% in 2162 men aged ≥45 years who presented at primary healthcare clinics. Increased incidence of hypogonadism has been demonstrated both in obese (2.4-fold) and diabetic (2.1-fold) men.[24]

Hypergonadotropic or hypogonadotropic hypogonadism induces insulin resistance in men irrespective of etiology.[25] Testosterone levels are inversely correlated with Hba1c levels. In other words, Hba1c levels are markedly elevated at lowest testosterone levels.[26]

Despite close relationship between hypogonadism and diabetes, very few studies have investigated effects of androgen replacement treatment on diabetes. One is a double-blind, placebo-controlled study conducted by Kapoor et al. In this study of 24 men with type 2 diabetes and hypogonadism, testosterone replacement therapy increased insulin sensitivity and induced marked reductions in Hba1c (0.37±0.17%), fasting blood glucose level, waist circumference, and waist/hip ratio.[27]

In placebo-controlled meta-analysis of 5 studies performed by Cai et al. in 2014, which included the study of Kapoor et al., effects of testosterone replacement treatment on patients with diagnosis of hypogonadism and type 2 diabetes were evaluated in 351 partici-
In summary, incidence of diabetes increases in KS. Hypoandrogenemia associated with syndrome contributes to development of de novo diabetes and worsening of pre-existing diabetes. However, whether or not any chromosomal anomaly is present in diabetic patients, generally, treatment of hypogonadism, which can be associated with diabetes, has been overlooked. This case report has demonstrated very important role of testosterone replacement in achievement of glycemic control.

**Conflict of interest**

None declared.

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