JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
LETTER TO THE EDITOR

Facilitating screening of Klinefelter syndrome among patients with diabetes

Klinefelter syndrome (KS) is the most common male sex chromosomal aneuploidy. KS is severely underdiagnosed, however, partly due to the lack of a systematic screening method[1]. Here, we present two index cases of KS who were diagnosed at the Center for Diabetes and Endocrinology, Tazuke Kofukai Medical Research Institute Kitano Hospital, Osaka, Japan. Furthermore, to improve the screening efficiency of KS in diabetes clinics, we examined physical and endocrinological data non-elderly adults with diabetes.

CASE 1

A 40-year-old man was admitted to our department for glycemic control. He had a 6-year history of poorly controlled diabetes. He was of tall stature (height 188.4 cm, bodyweight 97.5 kg), and his testes were bilaterally small. We found decreased serum total testosterone (0.76 ng/mL), elevated gonadotropin (luteinizing hormone [LH] 27.8 mIU/mL, follicle-stimulating hormone 22.9 mIU/mL) and low human chorionic gonadotropin-stimulated total testosterone level (0.76 ng/mL). KS was suspected, and G-band karyotyping showed 47, XXY. Testosterone enanthate was initiated, and diabetes was well controlled with insulin degludec and dulaglutide.

CASE 2

A 33-year-old man with newly diagnosed diabetes was admitted to our department for glycemic control. He had been married for 6 years with no children. He had a tall stature (height 188.0 cm, bodyweight 101.6 kg) and small testes. He showed a marked decrease in serum total testosterone (0.91 ng/mL), and elevated gonadotropin (LH 30.0 mIU/mL, follicle-stimulating hormone 25.7 mIU/mL). Human chorionic gonadotropin-stimulated total testosterone level was low (2.18 ng/mL). G-band karyotyping showed 47, XXY, diagnostic of KS. Testosterone enanthate was initiated, and diabetes was treated with metformin and teneligliptin. He was also referred to an infertility clinic for assisted reproduction.

ANALYSIS

To develop an efficient screening method for KS among patients with diabetes, we compared physical and endocrinological data from 39 non-elderly (aged <60 years) Japanese male non-KS patients with diabetes admitted to our center from July 2017 to April 2018 with those of the KS patients. The study was approved by the local ethics committee, and conforms to the principles of the Declaration of Helsinki. KS patients tended to be taller than non-KS patients (Figure 1a). LH and follicle-stimulating hormone were higher in KS patients compared with non-KS patients (Figure 1b,c). Total testosterone was lower in KS patients (Figure 1d). Among several parameters, apparently the LH/total testosterone ratio is the most reliable index for distinguishing KS patients from non-KS patients with diabetes (Figure 1e).

DISCUSSION

KS is the most common male sex chromosomal aneuploidy, with an estimated prevalence of one in 600 births. KS is complicated by diabetes, with the estimated frequency of 10–39% in Western countries[2]. Although there are no large cohort studies in Japan, according to a literature review, the prevalence of diabetes among KS might be lower, at 3.9–4.1%[3]. KS can also be associated with an increased risk of type 1 diabetes[4].

There are several possible explanations for the increased risk of diabetes among KS. First, androgen deficiency is associated with impaired insulin sensitivity among patients with diabetes[5]. Second, in a murine model, ablation of androgen receptor in pancreatic β-cells leads to a decreased glucose-induced insulin secretion[6]. In addition to these direct effects on glucose metabolism, KS patients often have learning disabilities[2], which could affect their glycemic control.

In the present study, we found that the combination of physical (height) and endocrinological (LH/total testosterone ratio) parameters can efficiently differentiate KS patients from non-KS patients with diabetes. To facilitate screening of KS among patients with diabetes, we propose a three-step approach: the first step is careful physical examination of all non-elderly male patients, especially those with poorly controlled diabetes, focusing on the characteristics of KS, including tall stature and small testes. The second step is endocrinological examinations including testosterone and gonadotropins. If the LH/total testosterone ratio is high, then we should carry out a human chorionic gonadotropin test and G-band karyotyping for diagnosis. Although further studies are required, this approach might diminish the number of undiagnosed KS patients in diabetes clinics.

Early diagnosis of KS in diabetes clinics will greatly benefit patients. First, it would offer KS patients access to well-established assisted reproductive techniques[7]. Second, testosterone replacement might improve insulin sensitivity and insulin secretion in androgen-deficient patients and animal models[5,6].

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Received 12 March 2019; revised 25 June 2019; accepted 7 July 2019

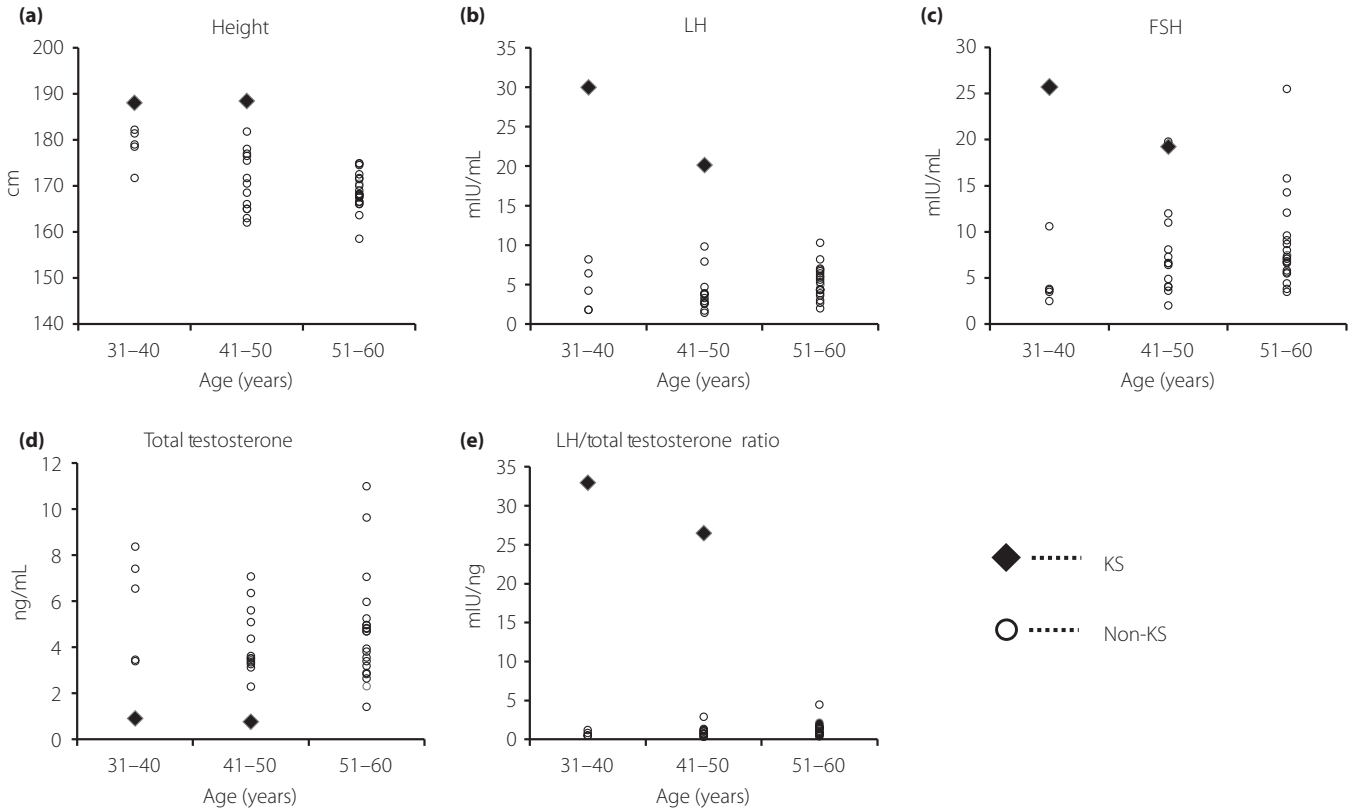

Figure 1 | (a) Physical and (b–e) endocrinological data including height, luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone and the LH/total testosterone ratio obtained from non-elderly diabetes patients with or without Klinefelter syndrome (KS). Open circles represent data of diabetes patients without KS, and closed diamonds represent those of KS patients.

In conclusion, the present data provide an efficient screening strategy to identify undiagnosed KS patients in diabetes clinics.

ACKNOWLEDGMENT

This work was supported by scientific research grants from the Ministry of Education, Culture, Sports and Technology, Japan (JSPS KAKENHI Grant Number 16K09772).

DISCLOSURE

The authors declare no conflict of interest.

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Doi: 10.1111/jdi.13113