Glucose Metabolic Disorder in Klinefelter Syndrome: A Retrospective Analysis in a Single Chinese Hospital and Literature Review

Tao Yuan
Peking Union Medical College Hospital
Shixuan Liu
Peking Union Medical College Hospital
Shuoning Song
Peking Union Medical College Hospital
Shi Chen
Peking Union Medical College Hospital
Linjie Wang
Peking Union Medical College Hospital
Yong Fu
Peking Union Medical College Hospital
Yingyue Dong
Peking Union Medical College Hospital
Yan Tang
Peking Union Medical College Hospital
Weigang Zhao (xiehezhaoweigang@163.com)
Peking Union Medical College Hospital

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Abstract

Background

We aimed to investigate the clinical characteristics and islet β-cell function in patients with Klinefelter syndrome (KS) and hyperglycemia.

Methods

This is a retrospective study. There were 22 patients diagnosed of KS identified from electronic medical record system including 9 patients with hyperglycemia (THG-KS group). There were 5 hyperglycemic KS patients with oral glucose tolerance test (OGTT) results (HG-KS group), other 5 subjects with hyperglycemia and 5 euglycemic subjects matched in body mass index were included as HG group and NGT group, respectively. Clinical data and laboratory examinations were collected. We further performed a systematic literature review of KS and hyperglycemia.

Results

We found KS patients developed abnormal glucose metabolism earlier in life than those without KS. There were 35.3% patients diagnosed of DM and 17.6% patients diagnosed of prediabetes. Among 10 patients had both fasting blood glucose and insulin levels drawn, there were 47.1% patients with KS and insulin resistance. The incidence of hypertension and dyslipidemia were higher in patients with hyperglycemia and KS than euglycemic KS patients. Comparing with HG group, the level of insulin sensitivity was lower in HG-KS group, while the value of HOMA-β ($p = 0.030$) was significantly increased which indicated higher insulin secretion level in HG-KS group.

Conclusions

KS patients with hyperglycemia are more likely to combine other metabolic diseases. Compared with hyperglycemic patients without KS, they present lower insulin sensitivity and higher insulin secretion.

Background

Klinefelter syndrome (KS) is the most frequent sex chromosome disorder of the male population[1] with an estimated prevalence ranging from 1 in 500 to 1 in 1000 in males[2]. It is characterized by hypergonadotropic hypogonadism with decreased level of androgens causing a feedback-mediated increased secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH)[3], other classical phenotypes including aspermatogenesis[4], tall and slender body with narrow shoulders, long arms and legs, small testes and sparse body hair[5]. The genetic background of KS is the presence on one or more extra X chromosomes, the most universe karyotype is 47 XXY, accounting for almost 80–90% patients[1], other karyotypes including 47 XXY/46 XY chimera, 48 XXXY, 48 XXYY or 49 XXXXY have also been detected in remaining KS patients[6].

Previous studies have observed KS was associated with the development of diabetes mellitus (DM), insulin resistance, hyperinsulinemia, hyperlipidemia, obesity and other metabolic diseases[7]. The prevalence of overt DM in KS is estimated to be above 10% depending on the population[8], and the abnormal oral glucose tolerance test (OGTT) can be detected in nearly more than one-third of KS patients[9], those subjects are characterized by earlier age and lower body mass index (BMI) than the general population at onset of glucose metabolic disorder[10]. Epidemiological studies of both morbidity and mortality have found occurrence of DM in KS to be more than threefold increased[11, 12]. However, most of previous studies focused on either the prevalence of DM or metabolic syndrome among KS patients, or different features between KS patients with and without DM, just a few studies discovered the different characteristics of islet β-cell function between hyperglycemic patients with and without KS.

In this study, we retrospectively summarized characteristics of patients with hyperglycemia and KS from a single Chinese hospital database, compared clinical features, insulin sensitivity and islet β-cell secretion function between hyperglycemic subjects with and without KS, and further performed a literature review. We aimed to study the characteristics of patients with hyperglycemia and KS and guide the hypoglycemic therapy.

Materials And Methods

Subjects

This was a retrospective study. An electronic medical record system in Peking Union Medical College Hospital (PUMCH) was used to identify patients with final diagnosis of KS from January 2000 to December 2019 by searching the clinical notes. KS was diagnosed according to the medical records of diagnosis of KS in other hospitals or karyotyping records, and there were 22 KS patients identified. After excluding 5 patients without electronic records of laboratory tests, there remained 8 KS patients with normal glucose tolerance (NGT-KS group, n = 8), and 9 KS patients with hyperglycemia (THG-KS group, n = 9). Among those 9 patients, 4 patients diagnosed of DM but without records of OGTT were excluded, and the remaining 5 patients were enrolled in KS and hyperglycemia group (HG-KS group, n = 5), including 2 DM patients and 3 prediabetes patients. All patients did not start testosterone treatment at the time of collecting the clinical data. Other 10 subjects matched in BMI with patients in HG-KS group were included, including 5 subjects with hyperglycemia but without KS (HG group, n = 5) and 5 euglycemic subjects (NGT group, n = 5).

The diagnosis of DM was based on the diagnostic criteria of American Diabetes Association[13]. Prediabetes was defined as fasting blood glucose (FBG) between 6.1mmol/L and 6.9mmol/L or hemoglobin A1c (HbA1c) from 5.7–6.4% or 2-hour postprandial blood glucose (PBG) between 7.8mmol/L and 11.1mmol/L and no diagnosis of DM. Hyperglycemia included the states of DM and prediabetes. Obesity was defined as BMI ≥ 25 kg/m^2 according to diagnostic criteria for Asian population[14]. Hypertension was diagnosed if a systolic blood pressure (SBP) ≥ 130 mmHg, diastolic blood pressure (DBP) ≥ 85 mmHg, or the use of antihypertensive medications. Dyslipidemia was diagnosed with elevated serum triglyceride (TG) (> 1.7mmol/L), low serum high density lipoprotein cholesterol level (HDL-c) (< 1.04mmol/L), or the use of lipid-lowering agents[15].

This study was approved by the PUMCH Ethics Committee and followed the ethical standards of the responsible committee on human experimentation (institution and national) and with the Helsinki Declaration of 1964, as revised in 2013. All participants have given written consent to the inclusion of material pertaining to themselves, that they acknowledge that they cannot be identified via the paper; and they have been fully anonymized.

Clinical Data And Oral Glucose Tolerance Test

Clinical history, results of physical examination and laboratory examination were collected from the medical database during the period of admission. BMI was calculated as weight (kg) divided by the square of the height in meters (m^2). Blood pressure was measured three times after five minutes' rest and was recorded as the mean value of three times measurements.

Blood samples were collected for assays of serum glucose, insulin and C-peptide at fasting (0-minute), 30-minute, 60-minute, 120-minute and 180-minute after 75g anhydrous glucose load by oral after fasting for 8 to 12 hours. Quantitative Insulin Sensitivity Check Index (QUICKI)[16], insulin sensitivity index proposed by Matsuda et al. (ISImatsuda) [17], the reciprocal of the product of fasting serum insulin and blood glucose which named insulin action index (IAI), the ratio of area under curve of glucose and insulin (AUC_{Glu}/AUC_{Ins}) [18] and homeostasis model assessment of insulin resistance (HOMA-IR) [19] were calculated to reflect insulin resistance, homeostasis model assessment of β-cell function (HOMA-β)[19] and area under curve of insulin (AUC_{Ins}) were calculated to reflect islet β-cell secretion function.

Literature review

We searched PubMed for manuscripts with full text in English published prior to February 2020 using key words "Klinefelter syndrome" AND "diabetes mellitus" OR "insulin resistance" OR "hyperglycemia" OR "impaired glucose tolerance" OR "impaired fasting glucose" OR "metabolic syndrome". Two co-authors extracted the medical information of the enrolled patients and the literatures using standardized forms, there were 12 studies[9, 11, 20–29]and 10 case reports[30–39] of Klinefelter syndrome combined with DM or prediabetes selected.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Students' t test was used to compare differences between continuous variables of each group, and the continuous variables that failed the normality test were logarithmically transformed before analysis. P-value less than 0.05 was considered significant. All statistical analyses were carried out using the statistical program SPSS (version 25, SPSS, Chicago, IL).

Results

Characteristics of our patients

Among 17 KS patients recruited in this study, there were 35.3% (6/17) patients diagnosed of DM and 17.6% (3/17) patients diagnosed of prediabetes, 47.1% (8/17) patients presented insulin resistance diagnosed of HOMA-IR≥ 2.5. The clinical data of patients with KS in our center was summarized in **Table 1**. There were 10 patients with recording of karyotype results, and all presented classical 47 XXY karyotype. The incidence of hypertension and dyslipidemia were both higher in THG-KS group (57.1% and 85.7% for hypertension and dyslipidemia, separately) than NGT-KS group (12.5% and 40.0% for hypertension and dyslipidemia, separately). Compared with NGT-KS group, the incidence of cryptorchidism (14.3% in THG-KS group vs 60.0% in NGT-KS group) was much lower in THG-KS group, while the ratio of gynecomastia was much higher (75.0% in THG-KS group vs 50.0% in NGT-KS group).

Characteristics of islet β-cell function in KS and hyperglycemia patients

KS patients developed abnormal glucose metabolism earlier in life than those without KS (p 0.01) (**Table 2**). There was no significant difference in BMI between subjects in HG group and HG-KS group because we matched BMI when enrolling subjects. Between the two groups with hyperglycemia, the level of FINS and HOMA-IR were higher in HG-KS group, ISImatsuda, QUICKI, IAI and AUC_{Glu}/AUC_{Ins} were lower in HG-KS group, however without significant differences. The value of HOMA-β (p=0.030) was significantly increased in HG-KS group compared with those with hyperglycemia only, AUC_{Ins} was also increased in HG-KS group but showing no statistical difference.

Between HG-KS group and NGT group, HOMA-IR (p=0.036) was significantly increased in HG-KS group and $ISI_{matsuda}$ (p=0.013), QUICKI (p=0.028) and IAI (p=0.015) were significantly decreased, whereas HOMA-β (p=0.044) was higher in HG-KS group. **Figure. 1** showed the increment curves of serum insulin and glucose based on OGTT in HG-KS group, HG group and NGT group. **Figure. 2** showed the characteristics of insulin sensitivity and islet β-cell secretion function related parameters of these three groups.

Literature review

In the literature review, previous studies showed that the prevalence of DM in KS patients was from 6.8% to 39%, and the prevalence of insulin resistance in KS patients was from 24.0% to 38.5% (**Table 3**). By summarizing the characteristics of 12 patients in previous case reports (with the details of clinical data) and 9 patients in THG-KS group (**Table 4**), we found the average age of onset of hyperglycemia was 27.75±11.8 years. Among 16 patients with data of sex hormone records, 15 presented hypergonadotropic hypogonadism and the one left only presented decreased testosterone level. The most common clinical feature related to KS was decreased testosterone levels (100.0%), followed by increased gonadotropin levels (93.8%), decreased pubic hair (88.9% in adults), small testicles (83.3% in adults), delayed secondary sexual characteristics (63.6%), behavioral and intelligence problems (31.3%), gynecomastia (28.6%) and cryptorchidism (20.0%). All patients with infertility plan complained of infertility. Of karyotypes, 71.4% patients were 47 XXY, 14.3% were 46 XY/47 XXY and 14.3% were 49 XXXXY.

The specific clinical data of patients with hyperglycemia in both PUMCH center and previous literatures were summarized in **Supplementary Table 1**.

Discussion

In this study, we summarized clinical features of KS patients in a single Chinese hospital center and evaluated characteristics of islet β-cell function in KS and hyperglycemia patients, compared with hyperglycemia patients without KS and euglycemic subjects. The incidence of DM in PUMCH center was 35.3%, that was much higher than the prevalence of DM in the general population, which was 10.4% in China according to the guidelines of Chinese Diabetes Society published in 2017 and 14.3% in the United States[40]. KS was considered as a state of "pre-diabetes"[41], the associations between KS and impaired glucose tolerance and DM have been reported, several possible mechanisms of DM have been proposed. Low level of testosterone is proposed to correlate with the increased incidence of insulin resistance and DM in males[42, 43]. In several studies in KS patients, testosterone deficiency was identified as an independent predictor for insulin resistance and metabolic syndrome [10, 20], and the effects of testosterone replacement therapy (TRT) on ameliorating glycemic disorder and insulin resistance[44] were observed. The gene dosage effect from the extra copies of X chromosomes was speculated to be another factor[6], since the close relationship between karyotypes and DM [6, 9], and the level of insulin resistance[45] have been reported. Autoimmune abnormity may also involve, the incidence of type 1 diabetes mellitus (T1DM) and the presence of DM related auto-antibodies can be detected in some patients with KS[10, 46]. Other mechanisms, such as changes in body composition, inflammation status[11], socioeconomic factors[2], high triglyceride level, fatty liver and acute pancreatitis[6] might

play important roles in the development of DM in KS patients as well. However, up to now the specific pathogenesis remains to be elucidated, further large, long-term, prospective, randomized, controlled studies are needed to clarify whether and how much above factors may affect the glycemic metabolism in KS patients.

We found KS patients develop hyperglycemia earlier in life than those without KS which was consistent with previous observations. Insulin sensitivity was lower in hyperglycemic KS patients compared with hyperglycemic patients without KS, whereas HOMA-β was significantly higher which indicated better competence of insulin compensatory secretion. Insulin resistance was considered as the major characteristic in KS patients with DM. Bojesen et al.[11] calculated insulin sensitivity by the HOMA model and showed a significant decreased insulin sensitivity but a significant increased islet β-cell secretion function in KS patients. Pei et al.[47] confirmed that insulin resistance was elevated in KS patients by area under the curve of serum insulin after a 75g oral glucose load and insulin suppression test. Using the gold standard, hyperinsulinemic euglycemic clamp test, Lee et al.[48] demonstrated impaired peripheral insulin resistance as the underlying mechanism of impaired glucose tolerance in Korean patients with KS, whereas Yesilova et al.[21] discovered that plasma insulin levels of KS patients were significantly elevated but without reduced insulin-mediated glucose disposal values compared with the controls, they concluded that hyperinsulinemia may be the primary metabolic abnormality rather than insulin resistance. Our results found that insulin resistance and compensatory increase in insulin secretion did exist in KS patients, and the increased islet β-cell secretion function was statistical significance compared to those of impaired glucose metabolism but without KS.

As for hypoglycemic therapy in hyperglycemic KS patients, best practices were still not established. The effects of TRT on the improvement of glucose control remained controversial, some clinical trials observed improvement of HbA1c level after TRT[44, 49], while others reported no improvement[50–52]. Especially, improvements of TRT in insulin sensitivity was observed in obese hypogonadal patients but not lean patients [53]. According to previous evidences, populations with lower level of testosterone tend to have higher proportion of body fat, which resulted in impaired insulin sensitivity. After TRT, improvement of ratio of fat and muscle composition could benefit glucose and lipid metabolism rather than the direct effects of TRT. Insulin therapy was a common strategy in KS patients with DM, in the cases review in Japanese, among 895 Japanese KS patients reported in literatures up to 2001, 61 patients was diagnosed of DM, and at least 20 patients were treated with insulin preparations but the glycemic control was poor with HbA1c level of 10.6%[23] which reflected less effective in glycemic control of insulin therapy among KS and DM patients. From the results of the changes of insulin sensitivity and islet β-cell secretion function in our study, we found those KS patients with hyperglycemia presented with similar insulin resistance level but better islet β-cell secretion function compared with those without KS, which suggested insulin preparations might not be the best choice for those KS patients with hyperinsulinemia, since hyperinsulinemia and insulin resistance would result in the increased dosage of insulin preparations and reduce the curative effects, further weight gain following the increased insulin dosage would aggravate insulin resistance. From this point of view, oral hypoglycemic drugs that target to improve insulin resistance might be considered first for those still with existed islet β-cell secretion function. For those KS patients with hyperglycemia, we recommended individualized hypoglycemia drugs choice after evaluating islet β-cell function rather than taking insulin therapy at first.

From the results of clinical features associated with KS, those patients with hyperglycemia were more likely to present gynecomastia, which accorded with the lower testosterone level than those with NGT. The incidence of cryptorchidism was lower in hyperglycemia patients, while the incidence of behavioral and intelligence problems was higher. We also found the higher frequency of development of other metabolic diseases in hyperglycemia and KS patients, including hypertension and dyslipidemia, which confirmed other metabolic factors including blood pressure and serum lipid levels may have effects on glycemic metabolism in KS patients.

This study has some limitations. First, KS is a rare disease and this is a retrospective study in a single Chinese center, so the sample size was small. Second, the clinical information was limited with missing data in some clinical features. Third, the age of patients in HG-KS group did not match with those in HG group because adolescents with type 2 diabetes mellitus were mostly obese which could not match BMI with KS patients.

Conclusions

In conclusion, the results of this study indicate patients with KS and hyperglycemia are more likely to combine other metabolic diseases, and may have different frequencies in developing KS-related symptoms comparing with those euglycemic KS patients. KS patients with glucose metabolic disorder present decreased insulin sensitivity and hyperinsulinemia, also increased insulin secretion compared with hyperglycemia patients without KS. According to the characteristics of glucose metabolism of KS patients, we recommend evaluating islet β-cell function before hypoglycemic treatment, considering oral hypoglycemic drugs may be the first choice for those still with islet β-cell secretion function rather than insulin preparations, because the decreased insulin sensitivity may result in the poor hypoglycemic effect.

List Of Abbreviations

KS, Klinefelter syndrome; FSH, follicle stimulating hormone; LH, luteinizing hormone; DM, diabetes mellitus; OGTT, oral glucose tolerance test; BMI, body mass index; PUMCH, Peking Union Medical College Hospital; NGT, normal glucose tolerance; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; PBG, postprandial blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; high density lipoprotein cholesterol level, HDL-c; QUICKI, Quantitative Insulin Sensitivity Check Index; ISImatsuda, insulin sensitivity index proposed by Matsuda et al.; IAI, the reciprocal of the product of fasting serum insulin and blood glucose which named insulin action index; $AUC_{Glu}/AUC_{Ins,}$ the ratio of area under curve of glucose and insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; TRT, testosterone replacement therapy; T1DM, type 1 diabetes mellitus

Declarations

Ethics approval and consent to participate

This study was approved by the Peking Union Medical College Hospital (PUMCH) Ethics Committee and followed the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. All participants signed written informed consent and provided consent for publication if any identifying information is included in the manuscript.

For all minors involved in the study, their legally authorized representatives provide informed consent.

Consent for publication

The authors affirm that all individual participants provided informed consent for publication of the data. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

The informed consent of minors were also provided by their legally authorized representatives provide.

Availability of data and materials

The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

Conceptualization: TY and SL; Investigation: YD, YT and YF; Methodology: TY and WZ; Clinical data collection: SL, SS, SC and LW; Writing - original draft: TY and SL; Writing - review editing: TY and WZ; Supervision: WZ.

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All authors follow the ICMJE requirements on privacy, and all participants have given written consent to the inclusion of material pertaining to themselves, that they acknowledge that they cannot be identified via the paper; and they have been fully anonymized.

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Tables

Table 1. Clinical data of patients with Klinefelter Syndrome in PUMCH center

Characteristics	KS (n=17)	THG-KS (n=9)	NGT-KS (n=8)
Age (y)	18.6±5.4	19.6±6.9	17.5±2.7
Height (cm)	176.9±11.4	180.7±11.4	172.5±9.5
Body weight (kg)	72.2±19.8	76.2±19.3	67.6±19.3
BMI (kg/m^2)	22.76±4.48	23.00±3.77	22.49±5.17
SBP (mmHg)	128.9±22.4	144.7±22.45	115.1±13.3
DBP (mmHg)	78.5±20.0	89.9±21.7	68.5±11.1
Testes size (ml)	2.9±1.6	1.5±1.5	2.4±1.5
T (ng/ml)	1.84±1.22	2.24±1.52	1.43±0.57
FSH (IU/L)	25.88±16.84	23.30±12.13	29.32±25.71
LH (IU/L)	29.23±19.72	30.37±13.48	27.72±25.71
TC (mmol/L)	4.95±2.00	5.39±2.30	4.34±1.22
TG (mmol/L)	2.22±1.26	2.57±1.41	1.73±0.77
LDL-c (mmol/L)	2.79±1.09	2.94±1.27	2.61±0.79
HDL-c (mmol/L)	1.02±0.21	1.05±0.22	0.99±0.19
Clinical features			
Decreased testosterone levels	14/14 (100.0%)	7/7 (100.0%)	7/7 (100.0%)
Increased gonadotropin levels	11/13 (84.6%)	4/6 (66.7%)	7/7 (100.0%)
Infertility	4, others were not considering fertility when collecting the data	4	0
Small testicles (adults)	4/7 (57.1%)	1/3 (33.3%)	3/4 (75.0%)
Decreased pubic hair (adults)	7/8 (87.5%)	3/4 (75.0%)	4/4 (100.0%)
Gynecomastia	5/11 (45.5%)	3/7 (75.0%)	2/4 (50.0%)
Behavioral and intelligence problems	2/13 (15.4%)	1/8 (12.5%)	1/5 (20.0%)
Delayed secondary sexual characteristics	10/13 (76.9%)	4/7 (57.1%)	6/6 (100.0%)
Cryptorchidism	4/12 (33.3%)	1/7 (14.3%)	3/5 (60.0%)
Obesity	4/13 (30.8%)	1/7 (14.3%)	3/6 (50.0%)
Hypertension	5/17 (29.4%)	4/7 (57.1%)	1/8 (12.5%)
Dyslipidemia	8/12 (66.7%)	6/7 (85.7%)	2/5 (40.0%)
Kayotype	10/10 (100%) 47 XXY		
Insulin resistance	8/17 (47.1%)		

Abbreviations: PUMCH, Peking Union Medical College Hospital; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T, testosterone; FSH, follicle stimulating hormone; LH, luteinizing hormone. TC, total cholesterol; TG, triglyceride; LDL-c, low density lipoprotein cholesterol level; HDL-c, high density lipoprotein cholesterol level. Insulin resistance was defined as HOMA ≥ 2.5. HOMA was calculated as a measure of insulin resistance as follows: [fasting blood glucose (mmol/L) × fasting insulin (μIU/mL)]/22.5.

Table 2. Characteristics of patients in three groups

	HG-KS (n=5)	HG (n=5)	NGT (n=5)	p value	
				HG-KS vs HG	HG-KS vs NGT
Age (y)	16.2±3.3	41.2±2.1	34.0±6.2	0.01*	0.001*
BMI (kg/m^2)	22.68±2.97	24.82±2.00	22.08±2.50	0.265	0.765
FBG (mmol/L)	5.90±2.04	7.54±3.21	5.22±0.37	0.414	0.529
FINS (μIU/ml)	29.22±26.00	12.66±7.01	8.89±2.62	0.254	0.158
HOMA-IR	7.47±7.05	5.22±5.47	2.10±0.75	0.443	0.036*
HOMA-β	346.24±202.59	76.64±28.69	103.56±20.07	0.030*	0.044*
ISImatsuda	35.98±13.87	61.17±23.05	88.29±29.67	0.098	0.013*
QUICKI	0.30±0.03	0.32±0.03	0.35±0.02	0.411	0.028*
IAI	0.01±0.005	0.02±0.008	0.02±0.008	0.236	0.015*
AUC_{Ins}	423.89±254.66	146.06±62.23	179.62±69.83	0.067	0.101
AUC_{Glu}/AUC_{Ins}	0.17±0.25	0.31±0.17	0.14±0.05	0.381	0.786

* represents significant difference between two groups.

Abbreviations: KS, Klinefelter syndrome; HG, hyperglycemia; NGT, normal glucose tolerance; BMI, body mass index; FBG, fasting blood glucose; FINS, fasting serum insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; $ISI_{matsuda}$, insulin sensitivity index proposed by Matsuda et al.; QUICKI, quantitative insulin sensitivity check index; IAI, insulin action index; AUC_{Ins}, area under curve of insulin; AUC_{Glu}/AUC_{Ins}, ratio of area under curve of glucose and insulin.

Table 3. Literature review of studies evaluating diabetes mellitus or insulin resistance in Klinefelter syndrome

Author, year (ref.)	Number of patients	Age (year)	BMI (kg/m^2)	DM (%)	IFG (%)	IR (%)	Diagnosed criteria of IR	Karyotype
Han, 2016 (19)	376	32	24.7±3.9	28 (12.8%)	57 (26.0%)	—	—	47 XXY, 354; 48 XXXY, 2; 48 XXYY, 1; 46 XY/47 XXY, 13; 47 XXY/ 48 XXXY/ 46 XY, 3; 47 XXY/46 XY/46 XX, 1; 47 XXY/48 XXXY, 1; 47 XX, inv (Y), 1
Yesilova, 2005 (20)	13	22	23.7 ± 4.9	—	—	38.5%	Glucose disposal rates < 4.53 mg/kg/min in hyperinsulinemic euglycemic clamp	All 47 XXY
Bojesen, 2006 (11)	70 (35 without TRT/35 with treatment)	35/39	27.3/25.1	3 (8.5%)/4 (11.4%)	6 (17.1%);7 (20.0%)	—	—	—
Falhammar,2018 (21)	224	22	26.1±5.3	9.10%	—	—	—	47 XXY, 204; 47 XXY/46 XY, 6; 47 XXY/46 XX, 3; Others and unknown, 5; 46 XX testicular males, 6.
Ota, 2002 (22)	895	43	21.5±4.44	61 (6.8%)	—	—	—	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.
Bardsley, 2011	89 Prepubertal Boys	8	—	0	0	20 (24%)	HOMA ≥ 2.5	47 XXY, 84; 48 XXYY, 1; 47 XXY/46 XY, 2; 46 XX translocation, 1.
Jackson, 1966 (23)	8	—	—	—	1 (12.5%)	—	—	47 XXY, 2; others unknown.
Becker, 1966 (24)	50	38	—	5 (10.0%)	—	—	—	—
Pasquali, 2013 (25)	69	31	27.5	3	16	—	—	—
Nielsen, 1969 (9)	31	—	—	12 (39%); especially 47 XXY/46XY, 4; 47 XXY, 5; 48 XXXY, 3.	—	—	—	47 XXY/46 XY, 4; 47 XXY, 24; 48 XXXY, 3.

Davis, 2016 (26)	96 Prepubertal Boys	—	—	0	0	9 (33.3%), only 27 patients calculated for HOMA	HOMA ≥ 2.5	47 XXY, 88; 46 XY/47XXY, 2; 48 XXXY, 1; 48 XXYY, 1; 46 XX+SRYtrans, 1.
Davis, 2017 (27)	93 Prepubertal Boys	—	—	—	1	—	—	47 XXY, 89; 46 XY/47 XXY, 2; 48 XXXY or 48 XXYY, 3.

Abbreviations: TRT, testosterone replacement therapy; T, testosterone; FSH, follicle stimulating hormone; LH, luteinizing hormone; BMI, body mass index; DM, diabetes mellitus; IFG, impaired fasting glucose; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA homeostatic model assessment; IR insulin resistance. Continuous variables were expressed as mean or mean ± standard deviation (SD). HOMA was calculated as a measure of insulin resistance as follows: [fasting blood glucose (mmol/L) × fasting insulin (μIU/mL)]/22.5.

Table 4. Abnormalities associated with KS and hyperglycemia combined our center and previous case reports

Characteristics	Patients (n=21)
Age	27.75±11.8
Clinical features	
Decreased testosterone levels	16/16 (100.0%)
Increased gonadotropin levels	15/16 (93.8%)
Infertility	7 adults with recording
Small testicles (adults)	10/12 (83.3%)
Decreased pubic hair （adults）	8/9 (88.9%)
Gynecomastia	4/14 (28.6%)
Behavioral and intelligence problems	5/16 (31.3%)
Delayed secondary sexual characteristics	7/11 (63.6%)
Cryptorchidism	3/15 (20.0%)
Obesity	9/18 (50.0%)
Hypertention	8/15 (53.3%)
Hyperglycemia	9/13 (69.2%)
Karyotype	10/14 (71.4%), 47 XXY; 2/14 (14.3%), 46 XY/47 XXY; 2/14 (14.3%), 49 XXXXY
Prediabetes	3/21 (14.3%)
Diabetes mellitus	18/21 (85.7%)
Insulin resistance	8/10 (80.0%)

Insulin resistance was defined as HOMA≥ 2.5. HOMA was calculated as a measure of insulin resistance as follows: [fasting blood glucose (mmol/L) × fasting insulin (μIU/mL)]/22.5.

Figures

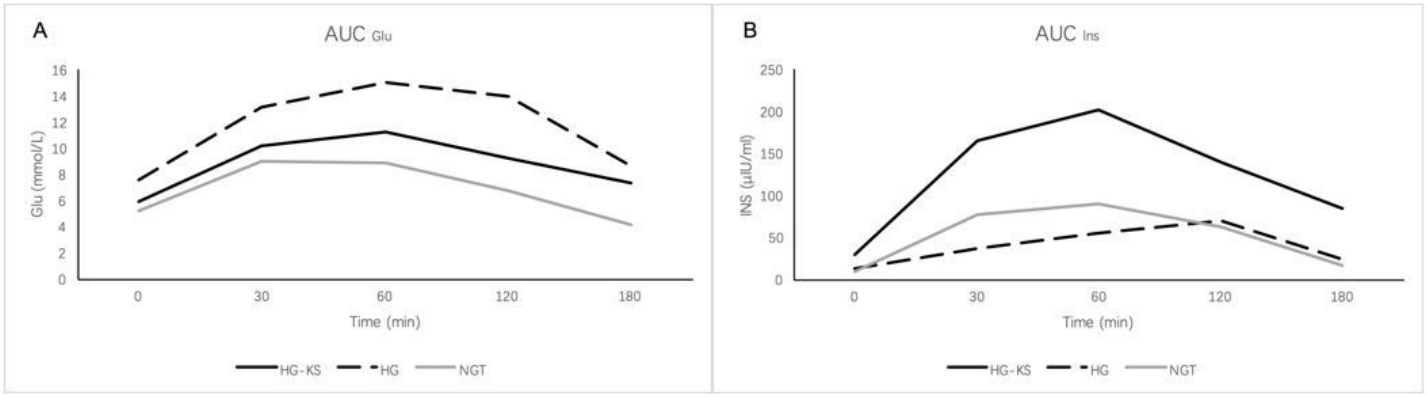

Figure 1

The increment curves of serum glucose (A) and insulin (B) during OGTT in HG-KS group, HG group and NGT group Abbreviations: OGTT, Oral glucose tolerance test; KS, Klinefelter syndrome; HG, hyperglycemia; NGT, normal glucose tolerance; AUC, area under curve; Glu, glucose; Ins, insulin.

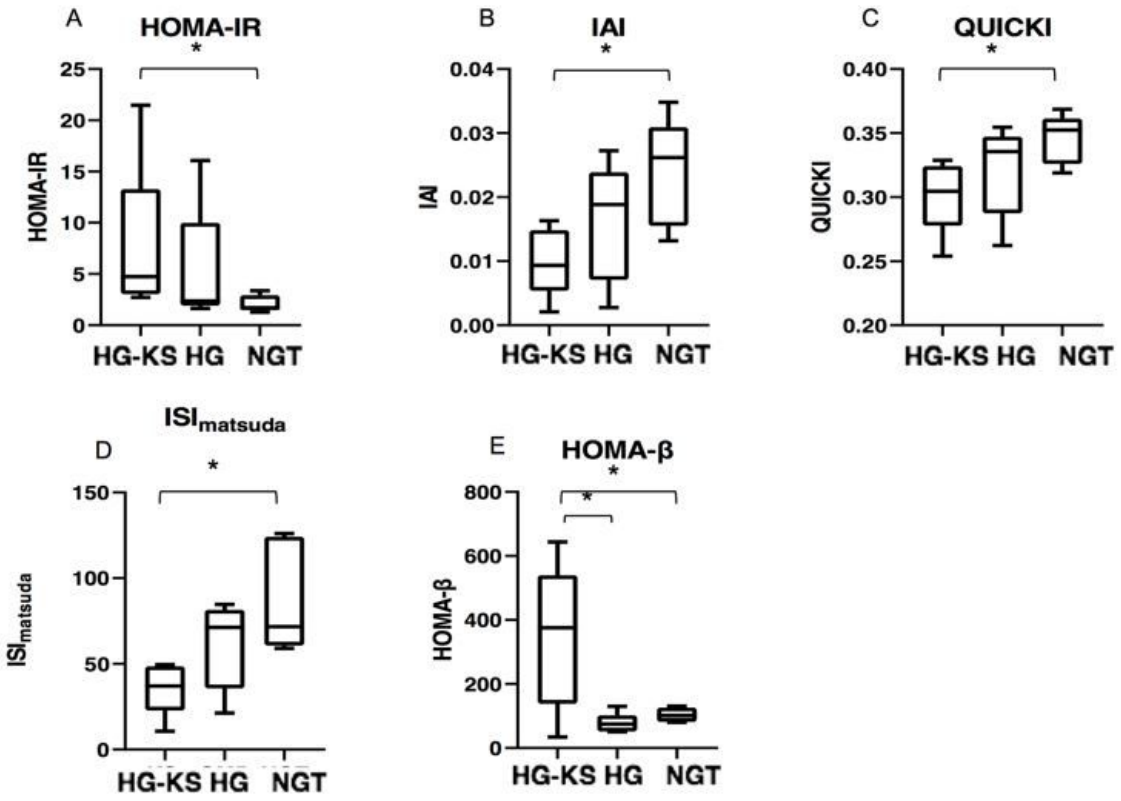

Figure 2

Boxplots of HOMA-IR (A), IAI (B), QUICKI (C), ISImatsuda (D) and HOMA-β (E) in HG-KS group, HG group and NGT group * represented significant difference (p□0.05) between two groups. HOMA-IR (A) (p=0.036) was significantly increased in HG-KS group compared to NGT group, IAI (B) (p=0.015), QUICKI (C) (p=0.028) and ISImatsuda (D) (p=0.013) was significantly decreased in HG-KS group compared to NGT. HOMA-β (E) was significantly increased in HG-KS group compared to both HG (p=0.030) and NGT (p=0.044) groups. Abbreviations: KS, Klinefelter syndrome; HG, hyperglycemia; NGT, normal glucose tolerance; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β -cell function; ISImatsuda, insulin sensitivity index proposed by Matsuda et al.; QUICKI, quantitative insulin sensitivity check index; IAI, insulin action index.

Supplementary Files

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- SupplementaryTable1.xlsx