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

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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/m² 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 (m²). 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 AUCGlu/AUCins 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, AUCins 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 ISImatsuda (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 abnormality 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 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; HDL-c, high density lipoprotein cholesterol level; 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\textsubscript{Glu}/AUC\textsubscript{Ins}, the ratio of area under curve of glucose and insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-\beta, homeostasis model assessment of \beta-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.

References

1. Kanakis, G.A. and E. Nieschlag, *Klinefelter syndrome: more than hypogonadism*. Metabolism, 2018. 86: p. 135–144. doi: https://doi.org/10.1016/j.metabol.2017.09.017.
2. O'Connor, M.J., E.A. Snyder, and F.J. Hayes, Klinefelter Syndrome and Diabetes. Curr Diab Rep, 2019. 19(9): p. 71. doi: https://doi.org/10.1007/s11892-019-1197-3.

3. Herlihy AS, M.R., Screening for Klinefelter syndrome. Curr Opin Endocrinol Diabetes Obes, 2015. 22: p. 224–229. doi: https://doi.org/10.1097/med.0000000000000154.

4. Ishikawa, T., YAMAGUCHI, K., KONDO, Y., et al., Metabolic syndrome in men with Klinefelter's syndrome. Urology, 2008. 71(6): p. 1109–13. doi: https://doi.org/10.1016/j.urology.2008.01.051.

5. Gravholt, C.H., JENSEN, et al., Body composition, metabolic syndrome and type 2 diabetes in Klinefelter Syndrome. Acta Paediatr, 2011. 100(6): p. 871–7. doi: https://doi.org/10.1111/j.1651-2227.2011.02233.x.

6. Jiang-Feng, M., HONG-LI, X., XUE-YAN, et al., Prevalence and risk factors of diabetes in patients with Klinefelter syndrome: a longitudinal observational study. Fertil Steril, 2012. 98(5): p. 1331–5. doi: https://doi.org/10.1016/j.fertnstert.2012.07.1122.

7. Calogero, A.E., GIAGULLI, V. A., MONGIOI, L. M., et al., Klinefelter syndrome: cardiovascular abnormalities and metabolic disorders. J Endocrinol Invest, 2017. 40(7): p. 705–712. doi: https://doi.org/10.1007/s40618-017-0619-9.

8. Gravholt CH, C.S., Wallentin M, Fedder J, Moore P, Skakkebaek A, Klinefelter syndrome: integrating genetics, neuropsychology, and endocrinology. Endocr Rev, 2018. 39: p. 389–423. doi: https://doi.org/10.1210/er.2017-00212.

9. J. Nielsen, K.J., H. Yde, Frequency of diabetes mellitus in patients with Klinefelter's syndrome of different chromosome constitutions and the XXY syndrome. Plasma insulin and growth hormone level after a glucose load. J Clin Endocrinol Metab, 1969. 29(8): p. 1062–1073. doi: https://doi.org/10.1210/jcem-29-8-1062.

10. Salzano A, D.A.R., Heaney LM, Monaco F, Rengo G, Valente P, et al, Klinefelter syndrome, insulin resistance, metabolic syndrome, and diabetes: review of literature and clinical perspectives. Endocrine, 2018. 61: p. 194–203. doi: https://doi.org/10.1007/s12020-018-1584-6.

11. Bojesen A, J.S., Birkebaek NH, Gravholt CH, Morbidity in Klinefelter syndrome: a Danish register study based on hospital discharge diagnoses. J Clin Endocrinol Metab, 2006. 91(4): p. 1254–1260. doi: https://doi.org/10.1210/jcem.2005-0697.

12. Swerdlow AJ, H.C., Schoemaker MJ, Wright AF, Jacobs PA, United Kingdom Clinical Cytogenetics Group. Mortality in patients with Klinefelter syndrome in Britain: a cohort study. J Clin Endocrinol Metab, 2005. 90(12): p. 6516–6522. doi: https://doi.org/10.2215/CJN.10981114.

13. Association, A.D., American Diabetes Association Standards of Medical Care in Diabetes-2019. Diabetes Care, 2019. 42(Suppl 1). doi: https://doi.org/10.2337/dc19-S002.

14. Region, W.W.P., The Asia-Pacific perspective: redefining obesity and its treatment.. 2000.

15. Grundy, S.M., BREWER, H. B., et al., Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation, 2004. 109(3): p. 433-8. doi: https://doi.org/10.1161/01.CIR.000011245.75752.C6.

16. Katz A, N.S., Mather K, et al, Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab, 2000. 85(7): p. 2402–2410. doi: https://doi.org/10.1210/jcem.85.7.6661.

17. Matsuda M, DEFRONZO, R., Insulin Sensitivity Indices Obtained From Oral Glucose Tolerance Testing: Comparison with the euglycemic insulin clamp. Diabetes Care, 1999. 22(9): p. 1462–1470. doi: https://doi.org/10.2337/diabcare.22.9.1462.

18. Antuna-Puente, B., DISSE, E., RABASA-LHORET, R., et al., How can we measure insulin sensitivity/resistance? Diabetes & Metabolism, 2011. 37(3): p. 179–188. doi: https://doi.org/10.1016/j.diabet.2011.01.002.

19. Matthews DR, H.J., Rudenski AS, et al, Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 1985. 28: p. 412–419. doi: https://doi.org/10.1007/bf00280883.

20. Han SJ, K.K., Kim W, et al., Obesity and hyperglycemia in Korean men with Klinefelter syndrome: the Korean Endocrine Society Registry. Endocrinol Metab (Seoul), 2016. 31: p. 598–603. doi: https://doi.org/10.3803/EnM.2016.31.4.598.

21. Yesilova Z, O.C., Sanisoglu SY, Musabak U, Cakir E, Ozata M, et al., Evaluation of insulin sensitivity in patients with Klinefelter's syndrome: a hyperinsulinemic euglycemic clamp study. Endocrine, 2005. 27: p. 11–5. doi: https://doi.org/10.1385/ENDO:27:1:011.

22. Falhammar, H., CLAAHSEN-VAN DER GRINTEN, H., REISCH, N., et al., Health status in 1040 adults with disorders of sex development (DSD): a European multicenter study. Endocr Connect, 2018. 7(3): p. 466–478. doi: https://doi.org/10.1530/EC-18-0031.

23. Ota K, S.T., Ikeda Y, Arii K, Kumon Y, Hashimoto K, Diabetes mellitus associated with Klinefelter's syndrome: a case report and review in Japan. Intern Med, 2002. 41(10): p. 842–7. doi: https://doi.org/10.2169/internalmedicine.41.842.
24. I. M. D. JACKSON, K. D. B., M. T. McKIDDIE and C. R. M. PRENTICE, CARBOHYDRATE METABOLISM IN KLINEFELTER’S SYNDROME. J Endocrin, 1966. 35: p. 169–172. doi: https://doi.org/10.1677/joe.0.0350169.

25. Becker KL, H. D., Underdahl LO, Mason HL., Klinefelter’s syndrome. Clinical and laboratory findings in 50 patients. Arch Intern Med, 1966. 118(4): p. 314–21. doi: https://doi.org/10.1001/archinte.118.4.314.

26. DANIELA, P., MICHELE, A., ANDREA, R., et al., Cardiovascular abnormalities in Klinefelter Syndrome. International Journal of Cardiology, 2013. 168(2): p. 754–759. doi: https://doi.org/10.1016/j.ijcard.2012.09.215.

27. Davis, S., LAHLOU, N., BARDSELY, M., et al., Gonadal function is associated with cardiometabolic health in pre-pubertal boys with Klinefelter syndrome. Andrology, 2016. 4(6): p. 1169–1177. doi: https://doi.org/10.10111/andn.12275.

28. Davis SM, C.-M.M., Bardsley MZ, Kowal K, Zeitler PS, Ross JL, Effects of Oxandrolone on Cardiometabolic Health in Boys With Klinefelter Syndrome: A Randomized Controlled Trial. J Clin Endocrinol Metab, 2017. 102(1): p. 176–184. doi: https://doi.org/10.1210/jc.2016-2904.

29. Bardsley, M.Z., FALKNER, B., KOWAL, K., et al., Insulin resistance and metabolic syndrome in prepubertal boys with Klinefelter syndrome. Acta Paediatri, 2011. 100(6): p. 866–70. doi: https://doi.org/10.1111/j.1651-2227.2011.02161.x.

30. Wei, L., LIU, Y., SUN, S., et al., Case report of 49,XXXXY syndrome with cleft palate, diabetes, hypothyroidism, and cataracts. Medicine (Baltimore), 2019. 98(39): p. e17342. doi: https://doi.org/10.1097/MD.0000000000017342.

31. Hara S, A.R., Bland W, Crump EP, Simultaneous occurrence of diabetes mellitus and Klinefelter's syndrome in two patients. J Natl Med Assoc, 1970. 62(1): p. 42 – 5. PMID: 5445444.

32. Yoshiuchi, I., ITOH, N., NAKANO, M., et al., Case report of Klinefelter's syndrome with severe diabetes, dyslipidemia, and stroke: The effect of pioglitazone and other anti-inflammatory agents on interleukin-6 and – 8, tumor necrosis factor-alpha, and C-reactive protein. Diabetes Care, 2006. 29(8): p. 1981. doi: https://doi.org/10.2337/dc05-2375.

33. Gotto M, N.J., Midorikawa S, Niimura S, Ono Y, Mizuno K, Multiple endocrine disorders and Rathke's cleft cyst with Klinefelter's syndrome: a case report. Endocr J, 2002. 49(4): p. 523–9. doi: https://doi.org/10.1507/endocrj.49.523.

34. Yamaguchi AV, C.P., Peuchot VA, Testosterone Replacement Therapy and the Risk of Hypoglycemia. Case Rep Endocrinol, 2019. doi: https://doi.org/10.1155/2015/9616125.

35. Kim, H.J., KIM, D., SHIN, J. M., et al., 49,XXXXY syndrome with diabetes mellitus. Horr Res, 2006. 65(1): p. 14–7. doi: https://doi.org/10.1159/000090327.

36. Seno Y, I.Y., Aizawa-Abe M, et al., Facilitating screening of Klinefelter syndrome among patients with diabetes. J Diabetes Investig, 2019. doi: https://doi.org/10.1111/jdi.13113.

37. Isobe K1, N.T., Ohkubo M, Ohba M, Shikano M, Watanabe Y, Klinefelter’s syndrome accompanied by diabetes mellitus and diabetes insipidus. Intern Med, 1992. 31(7): p. 917–21. doi: https://doi.org/10.2169/internalmedicine.31.917.

38. TOJO, K., KAGUCHI, Y., TOKUDOME, G., et al., 47 XXY/46 XY mosaic Klinefelter's syndrome presenting with multiple endocrine abnormalities. Intern Med, 1996. 35(5): p. 396–402. doi: https://doi.org/10.2169/internalmedicine.35.396.

39. Ayli, M. and S. Ertek, Serious Venous Thromboembolism, Heterozygous Factor V Leiden and Prothrombin G20210A Mutations in a Patient with Klinefelter Syndrome and Type 2 Diabetes. Internal Medicine, 2009. 48(18): p. 1681–1685. doi: https://doi.org/10.2169/internalmedicine.48.1985.

40. Menke, A., CASAGRANDE, S., GEISS, L., et al., Prevalence of and Trends in Diabetes Among Adults in the United States, 1988–2012. Jama, 2015. 314(10): p. 1021. doi: https://doi.org/10.1001/jama.2015.10029.

41. J. Mirozue, C.C., J. Bernard, E. Cartry, The prediabetes of Klinefelter’s syndrome. Diabe, 1966. 14(2): p. 57–59.

42. Wu FC, T.A., Beynon JM, et al., Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med, 2010. 363: p. 123–35. doi: https://doi.org/10.1056/nejmoa0911101.

43. Wang C, J.G., Jones TH, et al, Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. Diabetes Care, 2011. 34: p. 1669–75. doi: https://doi.org/10.2337/dc10-2339.

44. Corona G, M.M., Rastrelli G, Aversa A, Tishova Y, Saad F, et al., Testosterone and metabolic syndrome: a meta-analysis study. J Sex Med, 2011. 8: p. 272–83. doi: https://doi.org/10.1111/j.1743-6109.2010.01991.x.

45. Zitzmann M1, B.R., Werler S, et al., Gene expression patterns in relation to the clinical phenotype in Klinefelter syndrome. J Clin Endocrinol Metab, 2015. 100(3): p. E518-23. doi: https://doi.org/10.1210/jc.2014-2780.
46. Panimolle F, T.C., Granato S, Semeraro A, Gianfrilli D, Anzuini A, Lenzi A, Radicioni A, Screening of endocrine organ-specific humoral autoimmunity in 47,XXY Klinefelter's syndrome reveals a significant increase in diabetes-specific immunoreactivity in comparison with healthy control men. Endocrine, 2016. 52(1): p. 157–64. doi: https://doi.org/10.1007/s12020-015-0613-y.

47. Pei D, S.W., Jeng CY, Liao WK, Fuh MM, Insulin resistance in patients with Klinefelter's syndrome and idiopathic gonadotropin deficiency. J Formos Med Assoc, 1998. 97: p. 534 – 540. doi: https://doi.org/10.1021/jp0313472.

48. Lee KW, C.C., Uhm C, Kwon OY, Lee SK, Chung YS, et al., Impaired glucose tolerance associated with klinefelter syndrome. J Korean Soc Endocrinol 1998. 13: p. 495–500.

49. Kapoor D, G.E., Channer KS, Jones TH, Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol, 2006. 154: p. 899–906. doi: https://doi.org/https://doi.org/10.1530/eje.1.02166.

50. Tan WS, L.W., Ng CJ, Tan WK, Tong SF, Ho C, et al, Efficacy and safety of long-acting intramuscular testosterone undecanoate in aging men: a randomised controlled study. BJU Int, 2013. 111: p. 1130–40. doi: https://doi.org/10.1111/bju.12037.

51. Gianatti EJ, D.P., Hoermann R, et al, Effect of testosterone treatment on glucose metabolism in men with type 2 diabetes: a randomized controlled trial. Diabetes Care, 2014. 37(8): p. 2098–107. doi: https://doi.org/10.2337/dc13-2845.

52. Grossmann M, H.R., Wittert G, Yeap BB, Effects of testosterone treatment on glucose metabolism and symptoms in men with type 2 diabetes and the metabolic syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. Clin Endocrinol (Oxf), 2015. 83(3): p. 344–51. doi: https://doi.org/10.1111/cen.12664.

53. Groth, K.A., et al., Clinical review: Klinefelter syndrome—a clinical update. J Clin Endocrinol Metab, 2013. 98(1): p. 20–30. doi: https://doi.org/10.1210/jc.2012-2382.

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       |              |

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 $\geq$ 2.5. HOMA was calculated as a measure of insulin resistance as follows: [fasting blood glucose (mmol/L) × fasting insulin (μIU/mL)]/22.5.
|                      | 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/m²)          | 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*     |
| ISI_matsuda          | 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 XXXY, 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%) | --     | --                      | 47 XXY, 204; 47 XXY/46 XY, 6; 47 XXY/46 XX, 3; Others and unknown, 5; 46 XX testicular males, 6. |
| Falhammar, 2018 (21)| 224                | 22         | 26.1±5.3     | 9.10%  | --      | --     | --                      | 47 XXY, 40; 46 XY/47 XXY, 9; 48 XXY/48 XXXY/46 XY, 1; 47 XXY/46 XY/46 XX, 1; unknown, 8. |
| Ota, 2002 (22)      | 895                | 43         | 21.5±4.44    | 61 (6.8%) | --     | --     | --                      | 47 XXY, 40; 46 XX translocation, 1. |
| Bardsley, 2011      | 89 Prepubertal Boys | 8         | --           | 0      | 0       | 20 (24%) | HOMA ≥ 2.5              | 47 XXY, 84; 48 XXXY, 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/46 XY, 4; 47 XXY, 5; 48 XXXY, 3. | -- | -- | -- | 47 XXY/46 XY, 4; 47 XXY, 24; 48 XXXY, 3. |
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%)
- Hypertension: 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: \[\frac{\text{fasting blood glucose (mmol/L)} \times \text{fasting insulin (μIU/mL)}}{22.5}.\]
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
This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.xlsx