Hypogonadism Makes Dyslipidemia in Klinefelter’s Syndrome

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INTRODUCTION

Hypogonadism is one of the most common endocrine disorders. Clinical characteristics of patients demonstrating hypogonadism include elevated gonadotropin levels and other hormonal and physical abnormalities. Testosterone deficiency, a hormonal abnormality observed in patients diagnosed with hypogonadism, is associated with central obesity, dyslipidemia, osteoporosis, muscle weakness, and fatigue (1). Recent studies have found that testosterone deficiency occurs as a possible complication in men with type II diabetes and may contribute to impaired performance, mood, and libido (2,3).

Klinefelter’s syndrome (KS) is the most common sex chromosome disorder showing a prevalence of 1 in 660 newborn males (4,5). Clinical characteristics of KS include elevated gonadotropin levels and hypogonadism, and it can be associated with various physical states such as a tall stature, slender figure with small testes, gynecomastia, narrow shoulders, and sparse body hair. Recent studies have examined the epidemiology of morbidity and mortality associated with KS and found that both are increased due to a variety of factors in KS patients. Increased morbidity and mortality may be caused by hormonal and genetic imbalances (6). KS patients show decreased bone mineral density (BMD) (7), increased glucose intolerance, (8) and an increased risk of cerebrovascular disease (9).

Body composition of KS patients was significantly different compared to normal males. Although their body mass index (BMI) was not different, truncal fat, and waist circumference were significantly increased compared to normal males (4). Unfavorable body composition changes, increased truncal obesity, and decreased body muscle mass may decrease insulin sensitivity (10), which can increase the prevalence of metabolic syndrome. Therefore, we aimed to determine the association between KS and dyslipidemia, which is an important component of metabolic syndrome.

MATERIALS AND METHODS

The KS group included patients who visited the infertility clinic for an infertility evaluation and were confirmed as having a diagnosis of KS and no other chromosomal abnormality, based on chromosome analysis. Patients who visited the clinic for health screening between January 2011 and December 2011 and related no relevant medical and/or surgical history were enrolled in
the control group. We retrospectively reviewed medical records of all patients. Clinical history, physical examination, as well as height and weight were evaluated in all enrolled patients, in addition to measurement of serum testosterone, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) levels. All blood samples were obtained before 10:00 am after overnight fasting.

Patient characteristics are reported as mean ± standard deviation unless otherwise indicated. Statistical analysis was performed using a paired t-test for normally distributed data and a Mann-Whitney U test for skewed data to evaluate baseline characteristics. A value of $P < 0.05$ was considered statistically significant. IBM SPSS ver. 18.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Ethics statement
The present study protocol was reviewed and approved by the Institutional Review Board of Cheil General Hospital and Women’s Healthcare Center (IRB number: CGH-IRB-2013-40). Because ours was a retrospective medical review, the requirement to obtain informed consent was waived.

RESULTS
Our study included 55 KS patients and 120 controls. The mean age of patients was 35 years (range, 27–44 years). Mean ages of patients belonging to the KS and control groups did not significantly differ. KS patients were heavier and taller compared to controls; however, BMI values did not significantly differ between the groups (Table 1). Serum testosterone levels were lower in those belonging to the KS group. Evaluation of the lipid profile indicated that TG levels were found to be higher in KS patients while HDL cholesterol was higher in the control group. Serum cholesterol and LDL cholesterol levels were higher in patients belonging to the KS group, but these levels were not significantly different when compared to control levels (Table 2).

DISCUSSION
During adolescence and after puberty, clinical characteristics of KS include small testes and varying symptoms of androgen deficiency (11). After 25 years of age, 70% of KS patients complain of decreasing libido and erectile dysfunction. The most commonly reported sexual problem in KS patients is hypoactive sexual desire (12), which is seen to improve following testosterone replacement therapy (13). General characteristics observed in KS patients include small testes, gynecomastia, hypogonadism, azoospermia, and low BMD (14). Early diagnosis and treatment of KS significantly improves the patient’s quality of life. Testosterone replacement therapy results in increased strength, and virility, as well as improvement in libido, and BMD (1,15).

Most clinicians examining patients in outpatient departments routinely perform karyotyping and measure hormone levels in those presenting with small testes, hypergonadotrophic hypogonadism, and azoospermia. When testosterone levels are low in symptomatic KS patients, lifelong therapy is planned and initiated to avoid symptoms and sequelae of androgen deficiency.

Life expectancy in patients diagnosed with KS is found to be reduced by 1.5–2 years (8). An important factor associated with the increased mortality risk could be a smaller diameter of arteries that has been recently identified in patients with KS, which can lead to reduced organ perfusion (16). Cardiovascular disease accounts for a significant number of deaths in individuals with low testosterone levels. Testosterone deficiency is also associated with central obesity, hypertension, muscle weakness, reduced insulin sensitivity, and fatigue.

When treating KS patients, physicians should consider multifactorial aspects of patient physiology. Early testosterone replacement improves strength, libido, BMD, and body hair (17). Recently, it has been reported that testosterone demonstrates beneficial effects in men diagnosed with chronic heart failure. Exercise capacity and symptoms were seen to significantly improve following restoration of testosterone levels in men diagnosed with chronic heart failure (18). Testosterone replacement also reduces fatigue and produces a positive effect on mood and behavior (19). However, testosterone replacement does not bring about a positive effect on patient fertility (20).

In Korea, the age-standardized prevalence of metabolic syndrome was noted to be 26.6% in men and 21.3% in women (21). In Northern Europe, the incidence of metabolic syndrome that met the National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP) III criteria in KS patients was approximately 50% (4,22). Currently, no published reports have discussed...
the incidence of metabolic syndrome in Korean KS patients. In Japan, however, some studies have reported that the incidence of metabolic syndrome in KS patients was 33% in a study that included 60 patients (23). Several studies have explained the correlation between testosterone and metabolic syndrome. Testosterone deficiency in elderly men is associated with various conditions such as reduced insulin sensitivity, central obesity, hypertension, muscle weakness, fatigue, and sexual dysfunction (1,15). Metabolic syndrome in KS patients is associated with abdominal obesity, reduced insulin resistance, and hypogonadism.

Compared to a placebo group, a significant reduction in visceral adiposity has been observed in middle-aged obese men who were administered testosterone therapy over 8 months (24). Additionally, studies involving a large population of elderly men, and several placebo-controlled studies have concurrently shown that testosterone replacement treatment can increase lean body mass and decrease body fat mass (25-27). However, to date, no controlled study has assessed the association between dyslipidemia and KS. Ours was the first observational study that examined dyslipidemia in KS patients compared to controls.

The limitations of our study are that ours was a retrospective study based on medical chart reviews. Most patients enrolled in this study were followed-up regularly and consistently, although all patients could not be followed-up.

Dyslipidemia indices in KS patients were found to be abnormal compared to those in patients belonging to the control group. All patients could not be followed-up.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Seo JT. Data curation: Lee JS, Park CW. Investigation: Lee JS, Park CW. Writing - original draft: Lee HS.

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REFERENCES

1. Stanworth RD, Jones TH. Testosterone for the aging male; current evidence and recommended practice. Clin Interv Aging 2008; 3: 25-44.
2. Dhand S, Prabhakar S, Sethi M, Bandypadhyay A, Chaudhuri A, Dan dona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 2004; 89: 5462-8.
3. Kapoor D, Aldred H, Clark S, Chanher KS, Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes Care 2007; 30: 911-7.
4. Bojesen A, Hest C, Gravholt CH. Klinefelter’s syndrome type 2 diabetes and the metabolic syndrome: the impact of body composition. Mol Hum Reprod 2010; 16: 386-401.
5. Jo DG, Seo JT, Lee JS, Park SY, Kim JW. Klinefelter syndrome diagnosed by prenatal screening tests in high-risk groups. Korean J Urol 2013; 54: 263-5.
6. Bojesen A, Gravholt CH. Morbidity and mortality in Klinefelter syndrome (47,XXY). Acta Paediatr 2011; 100: 807-13.
7. van den Bergh JP, Hermus AR, Spruyt AI, Smeets J, Smals AG. Bone mineral density and quantitative ultrasound parameters in patients with Klinefelter’s syndrome after long-term testosterone substitution. Osteoporos Int 2001; 12: 55-62.
8. Bojesen A, Juel S, Birkebaek N, Gravholt CH. Increased mortality in Klinefelter syndrome. J Clin Endocrinol Metab 2004; 89: 3830-4.
9. Swerdlow AJ, Higgins CD, 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: 6516-22.
10. Bojesen A, Kristensen K, Birkebaek NH, Fedder J, Moskilde L, Bennett P, Laurberg P, Frystyk J, Flyvbjerg A, Christiansen JS, et al. The metabolic syndrome is frequent in Klinefelter’s syndrome and is associated with abdominal obesity and hypogonadism. Diabetes Care 2006; 29: 1591-8.
11. Lanfranco F, Kamischke A, Zitzmann M, Niesslach E, Klinefelter’s syndrome. Lancet 2004; 364: 273-83.
12. Corona G, Petrone L, Paggi F, Longi F, Oddi V, Fisher A, Vignozzi L, Balercia G, Sforza A, Forti G, et al. Sexual dysfunction in subjects with Klinefelter’s syndrome. Int J Androl 2010; 33: 574-80.
13. Isidori AM, Giannetta E, Gianfrilli D, Greco EA, Aversa A, Isidori A, Fabbrini A, Lenzi A. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol (Oxf) 2005; 63: 381-94.
14. Seo JT, Lee JS, Oh TH, Joo KJ. The clinical significance of bone mineral density and testosterone levels in Korean men with non-mosaic Klinefelter’s syndrome. BJU Int 2007; 99: 141-6.
15. Rao PM, Kelly DM, Jones TH. Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. Nat Rev Endocrinol 2013; 9: 479-93.
16. Forresta C, Carena N, Palego P, Ferlin A, Zuccarello D, Lenzi A, Selice R. Reduced artery diameters in Klinefelter syndrome. Int J Androl 2012; 35: 720-5.
17. Jo DG, Lee HS, Joo YM, Seo JT. Effect of testosterone replacement therapy on bone mineral density in patients with Klinefelter syndrome. Yonsei Med J 2013; 54: 1331-5.
18. Pugh PJ, Jones RD, West JN, Jones TH, Channer KS. Testosterone treatment for men with chronic heart failure. Heart 2004; 90: 446-7.
19. Khalifa MM, Struthers JL. Klinefelter syndrome is a common cause for mental retardation of unknown etiology among prepubertal males. Clin Genet 2002; 61: 49-53.
20. Matsumoto AM. Hormonal therapy of male hypogonadism. *Endocrinol
Metab Clin North Am* 1994;23: 857-75.

21. Yang JJ, Yoon HS, Lee SA, Choi JY, Song M, Han S, Lee JK, Kang D. Meta-
bolic syndrome and sex-specific socio-economic disparities in childhood
and adulthood: the Korea National Health and Nutrition Examination
Surveys. *Diabet Med* 2014; 31: 1399–409.

22. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cho-
lesterol in Adults. Executive summary of the third report of The National
Cholesterol Education Program (NCEP) Expert Panel on Detection, Eval-
uation, and Treatment of High Blood Cholesterol in Adults (Adult Treat-
ment Panel III). *JAMA* 2001; 285: 2486-97.

23. Ishikawa T, Yamaguchi K, Kondo Y, Takenaka A, Fujisawa M. Metabolic
syndrome in men with Klinefelter’s syndrome. *Urology* 2008; 71: 1109-13.

24. Mårin P, Holmång S, Jönsson L, Sjöström L, Kvist H, Holm G, Lindstedt G,
Björntorp P: The effects of testosterone treatment on body composition
and metabolism in middle-aged obese men. *Int J Obes Relat Metab Dis-
ord* 1992;16: 991-7.

25. Page ST, Plymate SR, Bremner WJ, Matsumoto AM, Hess DL, Lin DW, Amo-
ry JK, Nelson PS, Wu JD: Effect of medical castration on CD4+ CD25+ T
cells, CD8+ T cell IFN-gamma expression, and NK cells: a physiological
role for testosterone and/or its metabolites. *Am J Physiol Endocrinol Metab*
2006; 290: E856-63.

26. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R; North Amer-
ican AA2500 T Gel Study Group. AA2500 testosterone gel normalizes an-
drogen levels in aging males with improvements in body composition
and sexual function. *J Clin Endocrinol Metab* 2003; 88: 2673-81.

27. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE.
Oral testosterone supplementation increases muscle and decreases fat
mass in healthy elderly males with low-normal gonadal status. *J Gerontol
A Biol Sci Med Sci* 2003; 58: 618-25.