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Klinefelter Syndrome and Metabolic Disorder

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Hypogonadism is reported to be an independent risk factor for the development of central obesity in men, and epidemiologic studies indicate an inverse relation between serum testosterone and obesity [1]. In patients with prostate cancer, androgen deprivation therapies increased body fat mass [2], whereas it is known that androgen can prevent the differentiation of pluripotent cells into an adipogenic lineage [3]. Hypogonadism is also associated with metabolic syndrome and type 2 diabetes. Type 2 diabetes and metabolic syndrome are frequent in hypogonadal patients [1,4]. Cross-sectional studies have consistently reported an inverse relationship between plasma testosterone and insulin resistance in normal males [1,5]. Cessation of testosterone replacement therapy in patients with hypogonadism for 2 weeks reduced insulin sensitivity, indicating that testosterone itself has direct effects on insulin sensitivity [6]. Hypogonadism may lead to central obesity, increasing the risk of metabolic syndrome and the development of type 2 diabetes.

Hypergonadotropic hypogonadism is a key finding in Klinefelter syndrome, which is the most common sex chromosomal disorder in males [4]. Klinefelter syndrome patients have an unfavorable muscle/fat ratio with decreased muscle mass and increased total body and truncal fat accompanied by lower aerobic capacity and muscle strength [4,7]. Both epidemiological and clinical studies show clear evidence of a dramatically increased risk of diabetes and metabolic syndrome in Klinefelter syndrome [4]. Studies on Klinefelter syndrome have shown an increased risk of death due to diabetes or admission to a hospital with a metabolic disorder [8,9]. Hypogonadism in Klinefelter syndrome may cause an unfavorable change in body composition, increasing the risk of metabolic disorder [7].

In this issue of *Endocrinology and Metabolism*, Han et al. [10] found that the prevalence of obesity (defined by body mass index [BMI] ≥25 kg/m^2) in Korean men with Klinefelter syndrome was 42.6% (160 of 376 patients). Based on the data acquired from the Korea National Health and Nutrition Examination Survey (KNHANES) in 2011, the prevalence of obesity (defined by BMI ≥25 kg/m^2) in the Korean general population was 32.0% [11]. Considering this KNHANES data from the general population, prevalence of obesity in Korean patients with Klinefelter syndrome is greatly increased, as found in previous studies [4,10]. Additionally, in the current study, testosterone levels were negatively correlated with BMI and fasting glucose, which agrees with previous findings [1,4,10]. Epidemiological studies on Klinefelter syndrome have been conducted mostly in Western cohorts, particularly in the British and the Danish populations [4]. The present study by Han et al. [10] with a large sample size was conducted in Asian patients, which make the findings in this study more valuable.

There is a close relationship between testosterone and insulin sensitivity or body composition [4]. Evidence from several studies has demonstrated that testosterone replacement therapy in hypogonadal men with obesity reduced body fat mass and increased insulin sensitivity [1]. However, available evidence does not support testosterone replacement therapy for Klinefelter syndrome patients for improving metabolic disorder. It is uncertain whether hypogonadal males and Klinefelter syndrome

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patients are comparable. Genetic factors related to Klinefelter syndrome might add another layer of complexity [4]. Thus, it is necessary to conduct a prospective study in hypogonadal obese insulin resistant patients with Klinefelter syndrome to clarify these issues.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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