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OTHER FORMS OF DIABETES AND ITS COMPLICATIONS (JJ NOLAN AND H THABIT, SECTION EDITORS)

Klinefelter Syndrome and Diabetes

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Abstract

Purpose of Review Klinefelter syndrome (KS) is associated with increased insulin resistance and high rates of type 2 diabetes (T2DM). Our aim was to review what is known about the prevalence of diabetes in men with KS, potential mechanisms underlying the observed metabolic phenotype, and the data that are available to guide treatment decisions.

Recent Findings The increased prevalence of T2DM seen in men with KS appears to be the result of multiple mechanisms including increased truncal adiposity and socioeconomic disadvantages, but it is likely not a direct consequence of hypogonadism alone. No randomized trials have been conducted to evaluate the impact of testosterone replacement therapy on T2DM in men with KS, but observational data suggest that testosterone replacement is not associated with lower rates of diabetes or improved glycemic control.

Summary Metabolic derangements are common in KS, but treatment strategies specific to this population are lacking. Early lifestyle and dietary interventions are likely important. Additional research is needed to dissect the complex interaction between genotype and metabolic phenotype. Collaboration between academic centers caring for men with KS is needed to facilitate the development of evidence-based clinical practice guidelines, which would inform optimal screening and treatment strategies for this patient population.

Keywords Klinefelter syndrome · Sex chromosome aneuploidy · Type 2 diabetes · Insulin resistance · Testosterone replacement therapy

Introduction

Klinefelter syndrome (KS) was first described by Drs. Harry Klinefelter and Fuller Albright in 1942. Working at Massachusetts General Hospital, they described a novel clinical phenotype characterized by gynecomastia, azoospermia, and increased concentrations of follicle-stimulating hormone [1]. The etiology of the syndrome remained unclear for more than a decade after the initial publication of the case series. In fact, it was not until 1956 that investigators including Murray Barr noticed the presence of inactivated X chromosomes, now known as Barr bodies, in the cells of affected men [2–4]. A few years later in 1959, advances in karyotyping revealed that the classic karyotype for men with KS is 47,XXY [5]. It is now known that the overall prevalence of KS in the male population is relatively high, with estimates ranging from 1 in 500 to 1 in 1000 [6], making it the most common sex chromosome aneuploidy. Recent data suggest that the prevalence may be increasing [7]. There is a striking discrepancy between prenatal and postnatal prevalence, which indicates that many cases, particularly those with milder phenotypes, go undiagnosed [8].

The defining feature of the syndrome, the supernumerary X chromosome, is the result of meiotic non-disjunction, which can occur in either parent during gametogenesis [9]. More than one extra copy of the X chromosome may be present, although these variants are rarer, and mosaicism is also

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possible. Most genes on the redundant X chromosome(s) are subject to X inactivation, but there is a pseudoautosomal region containing multiple genes that escape inactivation. Some of the phenotypic features observed in men with KS are thought to be related to genes in this pseudoautosomal region. The short stature homeobox-containing gene (SHOX), for example, seems to be responsible, in a dose-dependent manner, for the increased stature often seen in KS [10]. The functions of many other genes in the pseudoautosomal region, however, remain unclear. Further complicating matters, KS is associated with DNA methylation changes across the entire genome [11••]. Indeed, a recent study found that the majority of the 363 significantly deregulated genes in men with KS were not, in fact, located on the X chromosome [12]. Increasingly, the genetic basis of complex traits such as type 2 diabetes (T2DM) is thought to have less to do with single genes on the supernumerary X chromosome and more to do with subtle changes to the epigenome and transcriptome.

While testicular abnormalities and hypogonadism are hallmark features of KS, the prevalence of metabolic derangements including dyslipidemia, metabolic syndrome, and diabetes is significantly higher than in the general population [11••]. European cohort studies have shown that men with KS are at higher risk for all-cause mortality [13, 14], and a significant portion of this excess risk is attributable to cardiovascular and endocrine complications [11••]. In this review, we will focus on what is known about how KS leads to a higher risk of diabetes and what management options are available for affected men.

Scope of the Problem

Over the past 50 years, multiple studies have examined the prevalence of diabetes in men with KS. Most of the literature involves T2DM, which is significantly more common than type 1 diabetes (T1DM) in this patient population, as in the general population. Estimates of the prevalence of T2DM in men with KS vary, ranging from 10 to 39% depending on the population studied [11••]. One small study of 31 men with KS found that 17% of those under age 50 years and 62% of those over 50 failed an oral glucose tolerance test as compared to 1.6% and 16%, respectively, of the general population [15]. This study, however, had a strong ascertainment bias in that the subjects with KS were recruited from medical wards and psychiatric hospitals, and were thus not representative of the general KS population. More recent studies have found a lower rate of diabetes, averaging 13%, for example, in a population of men with a mean age of 32 years [16], but this rate is still higher than in the general population. Indeed, a Danish registry study from 2006 found that the risk of T2DM in men with KS is almost four times as high as that in age-matched controls [17]. In addition, some studies suggest men with KS develop T2DM not only at an earlier age than the general population, but also at a lower body mass index (BMI) [18].

While the bulk of excess diabetes found in men with KS is attributable to T2DM, the risk of T1DM also appears to be increased. The Danish registry study referenced above found that KS confers a risk for T1DM that is more than double that of men with a 46,XY karyotype [17]. In addition, autoantibodies associated with T1DM including GAD65 and IA2 are present in 8% of men with KS, compared to less than 1% of controls [19].

As one would expect based on its increased prevalence, mortality from diabetes is increased in men with KS, although the exact magnitude of this risk is unclear. A 2004 Danish registry study of 781 men with KS found that the hazard ratio for death from diabetes was 1.64 [13]. Shortly thereafter, a larger British registry study of 3,518 men with KS found a standardized mortality rate for diabetes of 5.8 [14]. The problem posed by this excessive risk is likely to increase in the future as the global diabetes epidemic progresses. Based on data from the World Health Organization, the prevalence of diabetes in the general population has doubled since 1980 [20], and it seems unlikely that men with KS will be immune to this trend.

Potential Mechanisms

The pathogenesis of the metabolic changes associated with KS remains incompletely understood. In the general population, it is known that hypogonadism and insulin resistance have a bidirectional relationship [18, 21]. Men with prostate cancer treated with androgen deprivation therapy become much more insulin resistant than eugonadal controls, including those with prostate cancer treated by prostatectomy alone [22], and are 1.4 times more likely to develop diabetes during follow-up [23]. This suggestion that hypogonadism causes insulin resistance is corroborated by the fact that male mice lacking the androgen receptor display marked insulin resistance [24]. At the same time, physiologic experiments in male volunteers have shown that insulin resistance is associated with decreased responsiveness of the Leydig cell to human chorionic gonadotropin, an analog of luteinizing hormone [25].

The body composition changes associated with KS appear to play a significant role in the development of the metabolic phenotype. For any given BMI, men with KS have higher percentages of body fat than 46,XY peers, and when men with KS are compared to controls, truncal adiposity is the strongest predictor of decreased insulin sensitivity [26]. It is tempting to think that the decreased muscle mass and increased fat mass seen in KS are consequences of hypogonadism, but in fact, the changes in body composition start before puberty, indicating the importance of non-hormonal factors. One study of boys 4

to 12 years of age found that while BMI was similar in those with and without KS, the prevalence of waist circumference greater than the 90% percentile tended to be more common in the boys with KS [27]. Similarly, a more recent study showed that 80% of prepubertal boys with KS had at least one feature of metabolic syndrome, defined as abnormal waist circumference, lipids, glucose, or blood pressure [28].

An inflammatory milieu associated with KS could also explain the observed tendency towards insulin resistance. Higher C-reactive protein levels have been observed in men with KS compared to controls [26]. Levels of the C-C motif chemokine ligand 2 (CCL2), a cytokine that is released by monocytes and macrophages and is associated with insulin resistance, are also increased in men with KS [29]. Intriguingly, men with KS lacking features of metabolic syndrome still had elevated CCL2 levels, suggesting that CCL2 could be more than a downstream marker of metabolic derangements [29].

Several studies to date have separated "classic" KS (47,XXY) from atypical forms, which include 46,XY/47,XXY mosaicism as well as with karyotypes such as 48,XXXY and 49,XXXXY. A higher incidence of diabetes has been reported in these atypical forms of KS [30], but it is difficult to draw strong conclusions because of small sample sizes. Grouping men with mosaicism together with men with three or more copies of the X chromosome also makes it difficult to assess whether additional copies of the X chromosome raise the risk of diabetes in an additive fashion.

Some attention has also been paid to whether the number of CAG repeats in the androgen receptor, which is located on the X chromosome, affects the metabolic phenotype of KS. Receptors with a higher number of repeats are less sensitive. A few studies have looked at the effect of CAG repeat length on the KS phenotype, and while some anthropometric features such as arm span and leg length are correlated with the number of CAG repeats, there are no consistent correlations involving BMI or insulin sensitivity in KS [31, 32].

Finally, it is likely that at least some of the increased prevalence of diabetes and metabolic disease in men with KS can be attributed to socioeconomic factors as opposed to biochemical underpinnings. A Danish registry study showed that men with KS have lower levels of educational attainment and lower income than men with a 46,XY karyotype, and rates of cohabitation are also significantly lower [33]. This same study showed that while not all excess mortality associated with KS can be attributed to socioeconomic factors, a certain fraction of it disappears when analyses are corrected for these variables, with the hazard ratio for mortality dropping from 1.9 to 1.5. These socioeconomic differences likely influence metabolic outcomes through lifestyle factors including exercise and dietary habits, as well as access to care.

Treatment Options

Despite known connections between testosterone levels and metabolic health, best practices for treating T2DM in KS are not well established. In particular, the effects of testosterone replacement therapy (TRT) on the future risk of T2DM in men with KS as well as glycemic control in those with established diabetes remain poorly understood due to a lack of randomized controlled trials. The effect of TRT on T2DM in men with hypogonadism from other causes (largely obesity and co-morbid illness) has been studied in more detail and may have implications for men with KS. Results from these trials are conflicting with some showing a decline in hemoglobin A1c (HbA1c) [34–37], whereas others show no change [38–41]. The discrepancy between studies likely reflects small sample size, differences in baseline HbA1c levels, degrees of insulin resistance, and the extent to which analyses controlled for the use of oral hypoglycemic agents. A meta-analysis of RCTs of men with T2DM and/or the metabolic syndrome found no evidence of an improvement in HbA1C [41•]. All these results must be interpreted with caution, as the study populations were significantly older than many men with KS, who present with diabetes relatively early in life.

Given the lack of consensus on the role of TRT in managing T2DM in men with other causes of hypogonadism, it is not surprising that testosterone's effects on glycemic control and insulin resistance in KS remain understudied and poorly understood. Given the early onset of diabetes and metabolic syndrome in patients with KS, some investigators have hypothesized that prepubertal initiation of exogenous androgen replacement therapy might reduce their risk of metabolic derangements later in life. Administration of oral oxandrolone, a non-aromatizable androgen, to 93 prepubertal boys for 2 years was shown to modestly improve cardiometabolic outcomes such as triglycerides, fasting blood glucose, and systolic blood pressure, but only triglycerides were found to be significantly different between groups when adjusted for age and baseline cardiometabolic variables [42•]. Potential downsides of this approach include advancement of bone age and accelerating the onset of puberty in a subset of individuals. In the author's clinical experience, the observation that prepubertal boys with hypogonadism from other causes such as Kallmann syndrome do not experience the same metabolic derangements as their KS counterparts suggests that genetic rather than hormonal factors are likely at play. Additional studies using individuals with idiopathic hypogonadotropic hypogonadism (IHH) as a comparison group to those with KS have found a lower incidence of T2DM in the IHH cohort, also suggesting the contribution of genetic factors [30]. Further investigation in a prepubertal subpopulation of KS may provide unique insights into the root causes underpinning the development of diabetes.

In adults with KS, a population in which the underlying cause of insulin resistance becomes even more difficult to identify than in children, data on effects of TRT are even more sparse. Observational studies looking at the prevalence of diabetes in treated and untreated men with KS show that TRT has little to no effect on metabolic outcomes [26, 43]. Thus, at this time, TRT cannot be recommended as a treatment for diabetes in KS. However, testosterone replacement remains the standard of care for men with KS and symptomatic hypogonadism.

While the role of TRT in mediating metabolic health in KS is still unclear, studies conducted in the general population suggest lifestyle interventions are likely to be of benefit to people with KS. Weight loss, whether achieved via surgery or lifestyle change, has been documented to increase endogenous testosterone levels in severely obese men [44–46] and has also been shown to improve insulin resistance [47]. The Diabetes Prevention Program has shown that an intensive lifestyle intervention, with an emphasis on weight loss and nutritional adjustment, can reduce the incidence of T2DM by nearly 60% over the course of 3 years [48]. Given the known efficacy of lifestyle interventions in reducing diabetes risk in the general population, these strategies should be employed for patients with KS. Multidisciplinary care, potentially including neuropsychological evaluation, is often valuable, especially if significant behavioral concerns limit optimal treatment. In the future, with the rise of precision medicine and "omics" approaches to risk identification, there may be innovative testing and surveillance for populations at increased risk for diabetes, with actionable health interventions indicated as a result, and men with KS may comprise one of these populations [49].

Conclusions

Klinefelter syndrome is the most common sex chromosome abnormality in men, affecting between 1:500 and 1:1000 males. It is frequently associated with diabetes, most often type 2 but also, to a lesser extent, type 1. The metabolic phenotypes observed appear to be related to high levels of truncal adiposity, elevated levels of certain inflammatory cytokines, and socioeconomic factors. Despite the prevalence of diabetes in men with KS, comprehensive clinical practice guidelines do not exist. Testosterone replacement is certainly indicated for men with KS who have symptomatic hypogonadism, but it does not seem that hypogonadism alone accounts for the insulin resistance and other metabolic changes that are seen. There are no randomized controlled trials on the impact of testosterone replacement on glycemic control in men with KS. Given the high metabolic risks that men with KS face, attention to physical activity and diet is a critical component of treatment and access to a nutritionist is an important part of the multidisciplinary care of these patients. Additional research is needed to dissect the complex interaction between genotype and metabolic phenotype. In addition, there is a need for international collaboration to conduct randomized clinical trials that are large enough to address the fundamental question of what portion of the phenotype is explained by hormonal versus genetic factors, or both. These investigations will strengthen our understanding of how best to care for these patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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