Anthropometry in Klinefelter Syndrome - Multifactorial Influences Due to CAG Length, Testosterone Treatment and Possibly Intrauterine Hypogonadism

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Context: Klinefelter syndrome, 47, XXY (KS), is underdiagnosed partly due to few clinical signs complicating identification of affected individuals. Certain phenotypic traits are common in KS. However, not all aspects of the KS phenotype are well described.

Objective: To describe anthropometry and body composition in KS and relate findings to biochemistry and X-chromosome related genetic markers.

Design, Setting and Participants: Seventy three KS males referred to our clinic and 73 age-matched controls underwent comprehensive measurements of anthropometry and body composition in a cross-sectional, case-controlled study. Furthermore, genetic analysis for parental origin of the supernumerary X-chromosome, skewed X-chromosome inactivation and androgen receptor (AR) CAG repeat length was done.

Main Outcome Measure: Anthropometry and body composition in KS and the effect of genotype hereon.

Results: KS males were taller (absolute difference: 5.1 cm, $P < .001$) with longer legs (5.7 cm, $P < .001$) compared with controls. Furthermore, 2D:4D was increased in KS males (relative effect size: Cohen's d = 0.40), reflecting reduced fetal testosterone exposure. Also, bi-iliac width (0.41), waist (0.52), and hip circumference (0.47) ($P < .02$ for all), as well as total fat mass (0.74), abdominal fat mass (0.67), and total body fat percentage (0.84) was increased in KS males ($P < .001$ for all), while bitesticular volume was reduced (4.6). AR CAG repeat length was comparable in KS and controls, and among KS CAG correlated to arm length ($P = .04$), arm span ($P = .01$), and leg length ($P = .04$). Effects of parental origin of the supernumerary X-chromosome and skewed X-chromosome inactivation were negligible.

Conclusions: Anthropometry and body composition in KS is specific and dysmorphic and affected by AR CAG repeat length and decreased exposure to testosterone already during fetal life. **(*J Clin Endocrinol Metab* 100: E508–E517, 2015)**

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Abbreviations: AR, androgen receptor; KS, Klinefelter syndrome; SDS, standard deviation scores; U-KS, untreated KS group.

Klinefelter syndrome, 47, XXY (KS) is the most common sex-chromosome disorder in males, affecting 150 per 100 000 males (1). However, KS is underdiagnosed, partly due to few symptoms in early life and a lack of clear pathognomonic features (2). Clinical suspicion of KS is based on physical examination with diagnosis confirmed by chromosomal karyotyping. Small firm testes are a cardinal stigma (3, 4), as is gynecomastia (5). Other common characteristic traits include a body height greater than average, mainly attributed to abnormally long legs, and an arm span exceeding height by 2 cm (6). In spite of this, other aspects of the KS phenotype has not been thoroughly studied in a large cohort.

Abdominal fat accumulation, decreased lean body mass and increased fat mass is common in KS males (7), as is ischemic heart disease (8). The ratio between the length of the second and fourth finger (2D:4D) is related to gender, with men having a lower ratio (9, 10), and may reflect differential estrogen and testosterone exposure during fetal life (10). A recent study showed that KS males have right hand 2D:4D similar to female controls and higher than normal men (11).

The KS phenotype is a consequence of the supernumerary X-chromosome and overexpression of certain X-bound genes is believed to play a pivotal role. Although KS males, like women, are subject to X-chromosome inactivation, some genes escape this mechanism and might define the genetic background for the observed phenotype (12). The origin of the supernumerary X-chromosome in KS is from the mother half of the time and the father half of the time (13). Several studies have failed to show an effect of parental origin of the supernumerary X-chromosome in KS (14, 15), while one study showed that later onset of puberty in KS patient was linked to a paternally derived supernumerary X-chromosomes (16). Normally, random X-chromosome inactivation of the parental X-chromosomes takes place, resulting in an even 50% activation of both chromosomes. However, skewed X-chromosome inactivation may result in almost complete inactivation of genes from either parent. This is a phenomenon seen in aging women (17, 18), but no effect of skewed X-chromosome inactivation has so far been observed in KS males (15, 19, 20) which could be due to low sample size (21). CAG trinucleotide repeats in the androgen receptor (AR) in KS males and 46,XY males vary from just under 10 to about 36 repeats. Sensitivity to testosterone is thought to be highest when the number of CAG repeats are low (22). It has been found that a high number of CAG repeats in KS correlates with development of gynecomastia, small testes and above-average height (21, 23).

Here, we present data on anthropometry, body composition, and sex hormones in 73 KS males and 73 controls, and examine the relation to the abovementioned genetic factors. We hypothesized that the anthropometry and body composition in KS would be specific and dependent on these genetic factors.

Materials and Methods

Participants

We studied 73 males with KS recruited from endocrinology, genetics and fertility clinics in Denmark and 73 men matched for age and educational level. Males aged 18–60 years were included. Sixty-nine KS males had a 47,XXY karyotype and 4 had mosaicism. Of the 73 KS males studied 50 (68%) received testosterone treatment (T-KS) [intramuscular (IM) injections (n = 43), oral (n = 2), transdermal gel (n = 5)] at the time of participation. The remaining 23 KS males constituted the untreated group (U-KS) of whom 15 (65%) had never been treated with testosterone, seven had received testosterone therapy in the past for a period of on average 31.5 months (range: 6 month to 7.3 years) 1–20 years prior to inclusion in the study and one KS patient had received testosterone for an unspecified period. For information on controls, please see the Supplemental Materials. All patients provided signed informed consent. The study was approved by The Danish Data Protection Agency and local ethics committee. Data from this study relating to MRI of cerebrum, neuropsychology and genetics factors has previously been presented (24, 25).

Anthropometric measures

Anthropometric measures were height, sitting height, arm span, length of arm, hand, and foot, biacromial and bi-iliac diameter, hip, waist, and head circumference as well as 2D:4D digit ratio. All measurements were performed by the same observer (AS). Raven magnimeter and Harpenden anthropometer were used for anthropometric measurements, and a tape measure was used for hip and waist measurements. In KS males the presence of gynaecomastia was noted and testicular size was measured using Praders orchidometer and given as bitesticular volume, and compared with a Danish normative material (26). Leg length was found by subtracting sitting height from standing height. The length of 2D and 4D were measured by digital caliper to the nearest mm. Bi-iliacal diameter was measured over the iliac crests at the widest point. All measurements related to the limbs were performed using the participant's right limb. Body weight was measured to the nearest 0.1 kg, and remaining measurements were measured to the nearest millimeter. Lean body mass, total fat mass and abdominal fat mass were measured using DEXA on Hologic 2000/w osteodensitometer (Hologic Inc.).

Genetic analysis

Karyotype, DNA extraction and purification, parental origin of the supernumerary X-chromosome, X-inactivation, and CAG repeats

These analyses were done using standard methodology (for details see Supplemental Material).

Table 1. Anthropometry in Klinefelter Syndrome and Controls (Mean ± SD or Median)

	KS n = 73	Controls n = 73	*P*	Cohen's d[b]
Anthropometry				
Height (cm)	186.1 ± 6.8	181.0 ± 7.0	<.001	−0.74 (−1.07; −0.40)
Weight (kg)	93.6 ± 19.7	85.0 ± 14.4	.003	−0.50 (−0.83; −0.17)
BMI	27.0 ± 5.8	25.9 ± 4.0	.2	−0.23 (−0.55; 0.10)
Sitting Height (cm)	793.6 ± 3.1	93.0 ± 3.6	.3	−0.18 (−0.51; 0.15)
Arm Span (cm)	183.6 ± 12.6	181.7 ± 8.6	.3	−0.17 (−0.50; 0.16)
Biacromical Width (cm)	41.9 ± 2.2	42.5 ± 2.3	.2	0.24 (−0.09; 0.57)
Arm Length (cm)	81.2 ± 4.8	79.9 ± 4.3	.09	−0.29 (−0.61; 0.04)
Hand (cm)	19.0 ± 1.0	19.2 ± 1.0	.2	0.21 (−0.12; 0.53)
Second Digit (cm)	7.4 ± 0.4	7.6 ± 0.5	.06	0.31 (−0.02; 0.64)
Fourth Digit (cm)	7.6 ± 0.4	7.8 ± 0.5	<.01	0.55 (0.22; 0.88)
2D:4D Ratio	0.98 ± 0.03	0.97 ± 0.03	.02	−0.40 (−0.73; −0.07)
Bi-iliac Width (cm)	31.4 ± 3.8	30.2 ± 1.8	.02	−0.41 (−0.74; −0.08)
Leg Length (cm)	94.3 ± 6.9	88.6 ± 5.3	<.001	−0.92 (−1.26; −0.58)
Foot (cm)	26.5 ± 1.4	26.5 ± 1.5	.9	0.02 (−0.31; 0.34)
Hip (cm)	105.6 ± 10.7	101.4 ± 7.3	.006	−0.47 (−0.79; −0.14)
Waist (cm)	96.1 ± 13.3	89.7 ± 11.1	.02	−0.52 (−0.85; −0.19)
Head (cm)	58.0 ± 1.6	58.2 ± 1.9	.5	0.11 (−0.22; 0.43)
Bitesticular Volume (ml)	6.5 ± 4.4	40.8 ± 9.5[a]	<.001	4.6 (3.7; 5.5)
Gynecomastia (%)	33	NA		

Abbreviation: NA, not assessed.

[a] Normative data regarding bitesticular size are from Jørgensen et al (26).

[b] Cohen's d with 95% confidence interval.

Hormone analysis

Testosterone was measured by liquid chromatography tandem mass spectrometry using Perkin Elmer's CHS Steroid MS kit and estradiol was measured using in house liquid chromatography tandem mass spectrometry method as previously reported (27). Free testosterone was calculated based on testosterone and SHBG values (for details regarding measurement of estradiol, SHBG, FSH and LH, see Supplemental Material).

Statistics

Stata version 12.0 and 13.1 (StataCorp LP) was used for statistical data analysis. Normality was assessed by QQ-plots of absolute or log-transformed values and box-plots were scrutinized for outliers. Comparisons of continuous variables were performed using Student's independent *t* test (given as mean ± SD or for transformed values as median with range) or Mann-Whitney U-test (median with range) as appropriate. For anthropometric variables we compared all KS with controls, assuming that testosterone treatment would only have a minor effect, while for the remaining variables, we compared treated KS (T-KS) with controls, assuming that testosterone treatment would normalize body composition, hormone and remaining variables. Multiple linear regression was applied to adjust continuous outcomes for differences in testosterone treatment status in the KS group. Assumptions were checked by QQ plot of the residuals and leverage plot. We calculated Cohen's d as an index of effect size. Spearman correlation was used to investigate correlations between CAG repeat length and measured parameters. $P < .05$ was considered statistically significant. Graphs were made with SigmaPlot version 11 (Systat Software Inc.). Standard deviation scores (SDS) were calculated as $(KS_{value} - Control_{mean})/Control_{SD}$. Due to the explanatory nature of the current study we did not correct for multiple inferences.

Results

Anthropometry

KS males were taller than controls, with no difference in sitting height and thus a significant difference in length of the lower limbs (Table 1). Arm length tended to be longer in KS (Table 1). Both the second ($P = .06$) and fourth ($P = < 0.01$) finger was shorter in KS males compared with controls, but 2D:4D was significantly increased in KS males, and unaffected by treatment with testosterone (Tables 1 and 2 and Figure 1B). Bi-iliac width, hip and waist circumference were all increased in KS (Table 1), while bitesticular volume was reduced and gynaecomastia was seen in 33%. Standard deviation scores for KS illustrate the differential impact of KS on anthropometry (Figure 1A). The effect size for KS males on anthropometry was greatest for height, leg length and bitesticular volume (Table 1). T-KS males were heavier with a greater total and abdominal fat compared with controls (Table 2). For any given BMI among KS, we saw higher abdominal fat mass compared to controls (Figure 2A).

Hormones and additional biochemistry

T-KS males had higher total and free testosterone, androstendione, estradiol, and estrone compared to controls (Table 2), while SHBG and 17-OH-progesterone was lower and FSH and LH was similar in T-KS and controls.

Effect of treatment with testosterone in Klinefelter syndrome

T-KS males had smaller hip circumference, lower total body fat percentage, and a tendency towards higher lean

Table 2. Anthropometry and Biochemistry in Testosterone Treated and Untreated Klinefelter Syndrome (Mean ± SD or Median [CI])

				P Value	
	KS Treated n = 50	**KS Untreated n = 23**	**Controls n = 73**	**T-KS vs Controls**	**U-KS vs T-KS**
Anthropometry					
Height (cm)	186.5 ± 7.5	185.4 ± 5.0	181.0 ± 7.0	<.001	.5
Weight (kg)	92.5 ± 18.0	95.9 ± 23.2	85.0 ± 14.4	.01	.5
BMI	26.6 ± 4.9	28.0 ± 7.4	25.9 ± 4.0	.4	.3
Sitting Height (cm)	93.5 ± 3.2	93.2 ± 3.5	93.0 ± 3.6	.4	.8
Arm Span (cm)	183.6 ± 14.6	183.4 ± 6.4	181.7 ± 8.6	.4	1.0
Biacromical Width (cm)	42.0 ± 2.4	41.8 ± 1.8	42.5 ± 2.3	.3	.8
Arm Length (cm)	81.3 ± 5.5	81.0 ± 2.8	79.9 ± 4.3	.1	.8
Hand (cm)	19.1 ± 1.1	19.0 ± 0.7	19.2 ± 1.0	.4	.7
Second Digit (cm)	7.4 ± 0.4	7.4 ± 0.2	7.6 ± 0.5	.1	.9
Fourth Digit (cm)	7.6 ± 0.4	7.6 ± 0.4	7.8 ± 0.5	.004	.9
2D:4D Ratio	0.98 ± 0.03	0.98 ± 0.04	0.97 ± 0.03	.02	.8
Bi-iliac Width (cm)	31.1 ± 2.4	31.9 ± 5.9	30.2 ± 1.8	.01	.4
Leg Length (cm)	95.1 ± 7.3	92.7 ± 5.7	88.6 ± 5.3	<.001	.2
Foot (cm)	26.6 ± 1.5	26.3 ± 1.0	26.5 ± 1.5	.8	.4
Hip (cm)	103.7 ± 8.8	109.8 ± 13.1	101.4 ± 7.3	.1	.02
Waist (cm)	95.7 ± 11.6	96.9 ± 16.6	89.7 ± 11.1	.005	.7
Head (cm)	58.2 ± 1.6	57.6 ± 1.6	58.2 ± 1.9	1.0	.1
Bitesticular Volume (mL)	6.2 ± 3.1	7.3 ± 6.3	40.8 ± 9.5[a]	<.001	.3
Gynecomastia (%)	28	45	NA		.2
Body Composition					
Total Fat Mass (kg)	24.1 ± 9.9	29.4 ± 14.7	18.4 ± 7.7	<.001	.08
Abdominal Fat Mass (kg)	13.0 ± 5.8	16.1 ± 11.5	9.6 ± 4.7	<.001	.1
Total Lean Body Mass (kg)	63.8 ± 9.0	60.0 ± 6.9	62.3 ± 8.2	.4	.08
Total Body Fat (%)	25.7 ± 6.3	30.2 ± 8.7	21.4 ± 6.3	<.001	.02
Lipid Metabolism					
Apolipoprotein B (g/L)	1.1.±0.0.2	1.0 ± 0.2	1.0 ± 0.3	.002	.01
Total Cholesterol (mmol/L)	5.2 ± 0.9	4.9 ± 0.9	4.9 ± 1.0	.1	.3
HDL Cholesterol (mmol/L)	1.1 ± 0.3	1.4 ± 0.4	1.3 ± 0.4	.001	.002
Triglycerides (mmol/L)	1.5 (0.6–6.1)	1.0 (0.4–3.0)	1.1 (0.4–6.3)	.003	.007
Sex Hormones					
LH (IU/L)	2.9 (0.1–28.9)	24.4 (3.8–33.1)	4.74 (1.6–14.2)	.2	<.001
FSH (IU/L)	6.6 (0.1–61.5)	40.5 (2.2–59.7)	4.1 (1.4–12.2)	.4	<.001
DHEAS (nmol/L)	3524 ± 2329	4409 ± 2546	4126 ± 2238	.2	.2
Testosterone (nmol/L)	20.2 ± 11.4	10.1 ± 5.4	14.3 ± 5.7	<.001	<.001
Androstendione (nmol/L)	3.7 ± 1.7	3.2 ± 1.1	2.7 ± 2.5	<.001	.2
17-OH-progesterone (nmol/L)	1.0 ± 1.1	2.5 ± 1.3	2.8 ± 2.1	<.001	<.001
SHBG (nmol/L)	30.6 ± 12.8	44.6 ± 24.4	36.6 ± 15.5	.02	.002
Free testosterone (nmol/L)	0.6 ± 0.4	0.2 ± 0.1	0.34 ± 0.14	<.001	<.001
Estrone sulphate (pmol/L)	1888 (189–15 291)	1342 (450–7650)	1772 (466–5171)	.6	.07
Estradiol (pmol/L)	80.4 (0.0 − 461.2)	36.0 (0.0–191.5)	25.3 (0.0–217.2)	<.001	.09
Estrone (pmol/L)	135.9 ± 81.0	94.6 ± 40.9	80.1 ± 43.0	<.001	.02
Additional Biochemistry					
Hemoglobin (mmol/L)	9.8 ± 1.6	9.0 ± 0.5	9.6 ± 1.4	.02	.02
Erythrocyte Count (10^9/L)	5.4 ± 0.5	5.0 ± 0.3	5.1 ± 0.3	<.001	<.001
Hematocrit	0.47 ± 0.03	0.43 ± 0.02	0.44 ± 0.03	<.001	<.001
Mean Corpuscular Hemoglobin (fmol)	21.2 ± 0.5	21.0 ± 0.5	21.4 ± 0.4	.05	.2

Abbreviation: NA, not assessed.

[a] Normative data regarding bitesticular size are from Jørgensen et al (26).

body mass and lower total fat mass compared with U-KS (Table 2). Furthermore, there was a tendency towards a lower abdominal fat mass at a higher BMI in T-KS males compared with U-KS (Figure 2B). Lower HDL and higher triglyceride and apolipoprotein B were seen in T-KS compared with U-KS. No difference in 2D:4D ratio was found between T-KS and U-KS. Testosterone treatment resulted in expected changes in hormone variables comparing T-KS and U-KS males (Table 2). We saw an overall effect on hematopoiesis by testosterone with higher hemoglobin in T-KS males compared to U-KS males (Table 2).

We observed a negative correlation between the level of testosterone in KS males (treated or untreated) and weight, BMI, bi-iliac width, hip, waist, total fat mass, abdominal fat

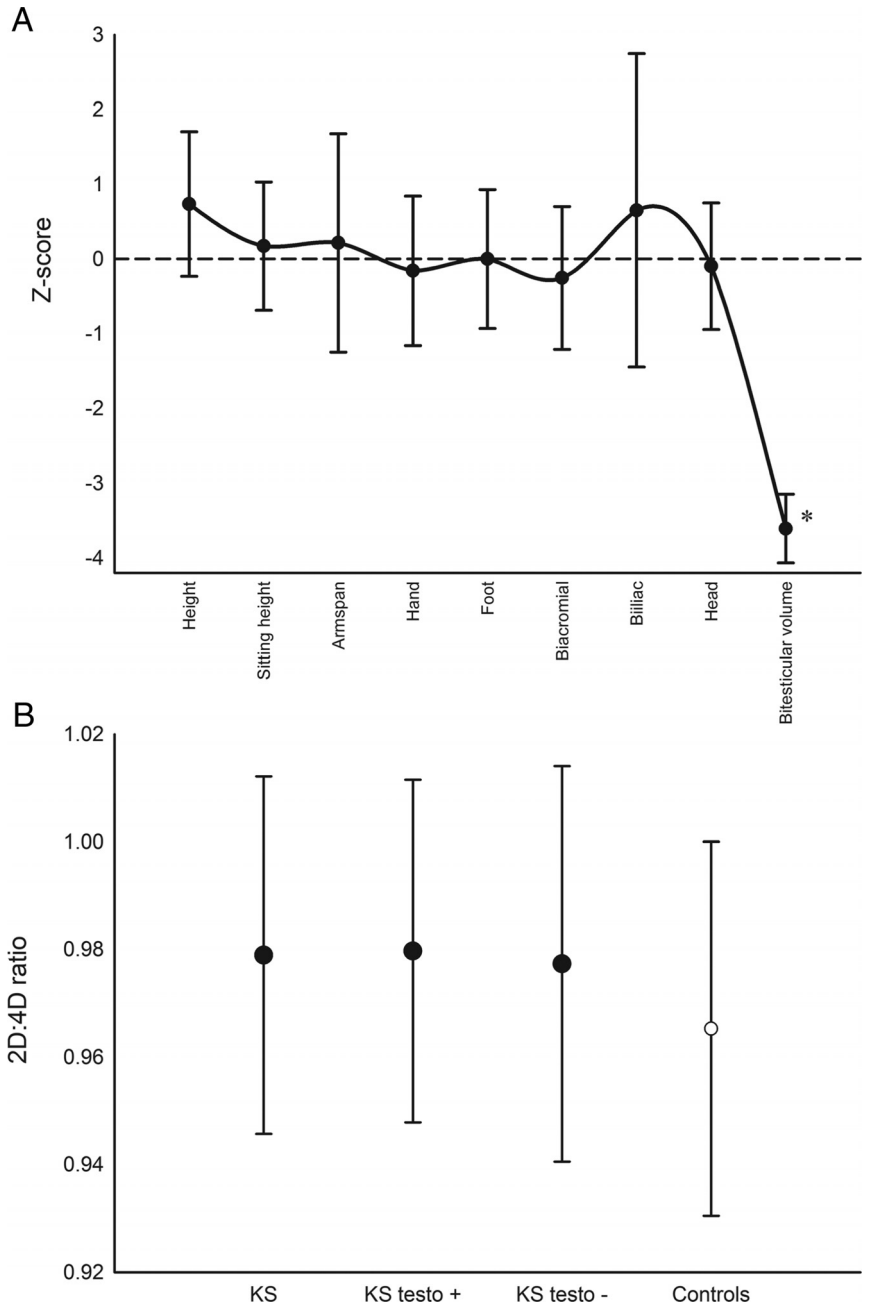

Figure 1. Anthropometric parameters expressed in SDS (mean ± 2 SD). We introduced a simple spline curve between parameters in this way illustrating the differential effects of 47,XXY on anthropometry (A). 2D:4D in Klinefelter syndrome, testosterone naïve and testosterone treated KS and in controls (B). *, Normative data regarding bitesticular size are from Jørgensen et al (26).

mass, fat percentage, LH, FSH, and 17-OH-progesterone (rho [−0.55 to −0.30], $P < .05$). In KS males positive correlations were seen between testosterone and free testosterone, estradiol, estrone, androstendione, hemoglobin, erythrocyte count, and hematocrit (rho [0.33–0.94], all $P < .05$).

AR CAG-repeat length

Length of the AR CAG-repeats did not differ between KS males and controls (21.9 ± 2.0 vs 22.4 ± 3.4; $P = .3$). In KS males a significant positive correlation was seen between CAG-repeat length and arm length (Figure 3A), arm span (Figure 3B), leg length (Figure 3C), HDL cholesterol, and estrone sulfate (Supplemental Table 1). No correlation was seen with 2D:4D. No differences in number of CAG repeats was found between maternal vs paternal origin of the supernumerary X-chromosome, T-KS vs U-KS or KS males with skewed X-chromosome inactivation vs non-skewed genotypes. We then compared KS males with the highest number of CAG repeats (CAGhigh >22 repeats) to those with a lower number of repeats (CAGlow ≤22 repeats) after adjusting for treatment with testosterone. KS males in the CAGhigh group had longer legs compared to the CAGlow group (Table 3). Also, abdominal fat mass and total fat percentage was lower in the CAGhigh group. Furthermore, estrone sulfate was lower in the CAGhigh group compared to CAGlow KS males (Table 3). For controls, no correlation was found between CAG-repeat length and any of the anthropometrical variables, while a positive correlation was seen with hemoglobin (rho = 0.26, $P = .02$).

Parental origin of the supernumerary X-chromosome

After adjustment for testosterone substitution status we found no effect of parental origin of the supernumerary X-chromosome (Table 3). However, for KS males with a paternally derived supernumerary X-chromosome, mean arm span was seen exceeding mean height by >2 cm, while KS with a maternally derived supernumerary X-chromosome had a mean arm span 5 cm shorter than mean height. KS males with a paternally derived supernumerary X-chromosome had lower 17-OH-progesterone (Table 3), while hematocrit was increased.

Skewed X-chromosome inactivation

We found no effect of skewed X chromosome inactivation on any of the measured parameters (Table 3).

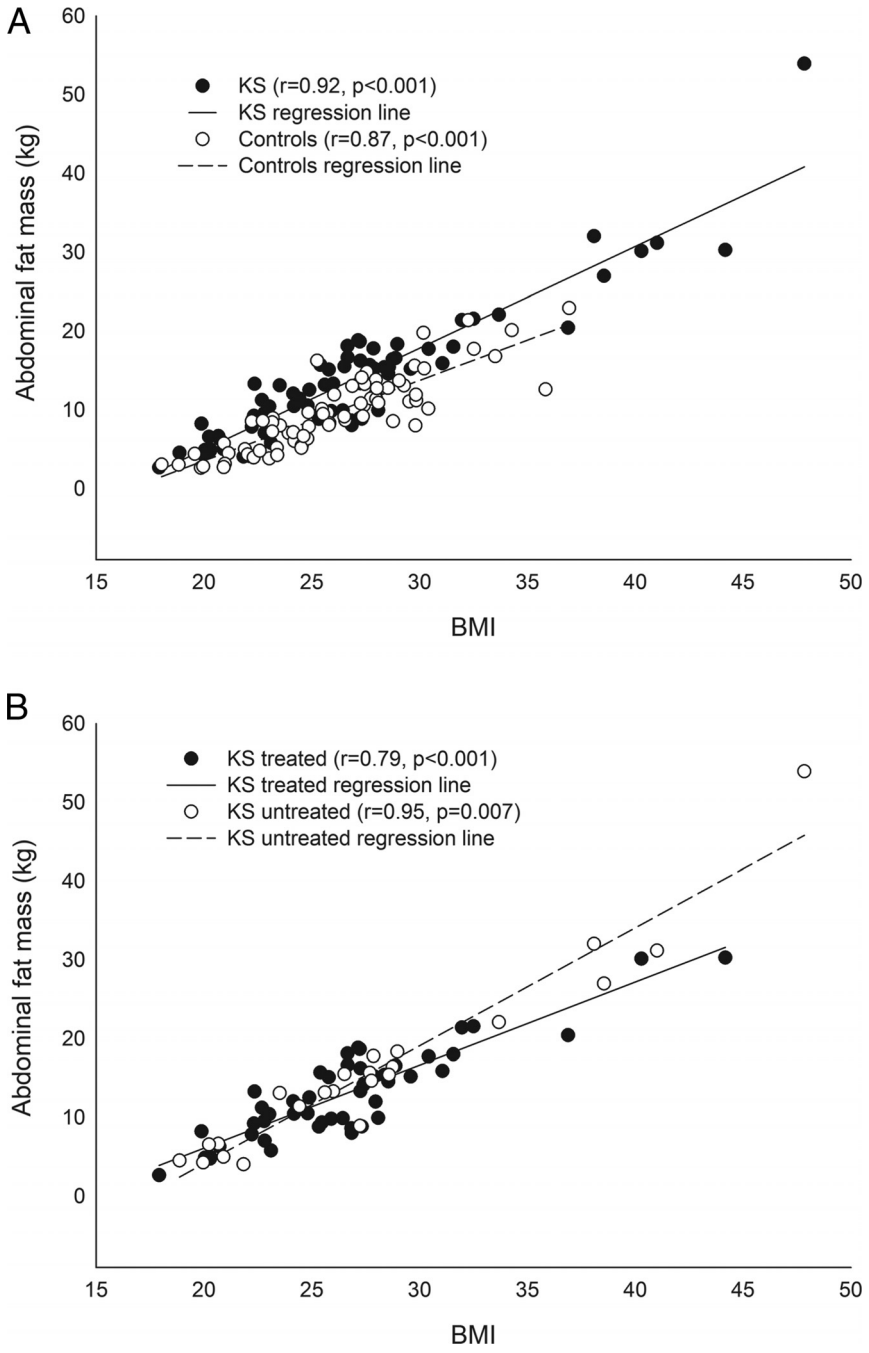

Figure 2. BMI vs abdominal fat mass in Klinefelter and controls (A) and testosterone treated and untreated Klinefelter (B).

Discussion

We present comprehensive anthropometric and body compositional data comparing a Danish cohort of KS males to age-matched controls, linking these data to genetic factors. We show that the anthropometric and body compositional profile of KS is specific and dysmorphic. Furthermore, we demonstrate a differential impact of KS depending on anthropometric measure. For example while height and bi-iliac width is clearly larger among KS, hand length and bitesticular volume is smaller. As expected, about a third of KS had gynecomastia. In addition, we show that CAG repeat length clearly affects the KS phenotype, while other genetic measures, such as parental origin of the supernumerary X-chromosome and skewing does not seem to impact the phenotype. Finally, we provide evidence for intra-uterine hypogonadism, which may well have long-term implications in KS and predict a specific and different trajectory for anthropometric and body compositional measures.

KS males were taller with longer legs and arms when compared with controls. BMI in KS males and controls was comparable, but KS males had significantly higher waist and hip circumference. It is appreciated that for a certain BMI abdominal fat mass is higher in KS compared to controls. This, along with increased fat mass and fat percentage, shows that abdominal obesity is also a common trait among KS males, regardless of whether appropriate hormone replacement therapy is instituted. Previously we described a similar picture in another group of KS males with slightly, but significantly, higher BMI than their controls (7). Important components of the hypothalamus-pituitary-testis axis, permanently missing in KS, such as INSL3, a Leydig cell marker (28), recently suggested to play a role in type 2 diabetes, may play a role in the accumulation of body fat. In addition, it is also plausible that an intra-uterine milieu with relative hypogonadism may combine with these changes and lead to irreversible epigenetic changes in adipocytes and muscle cells. Collectively, our anthropometric data show that the anthropometry of KS males is disproportionate, similar to what is seen in Turner syndrome (29), likely due to a combination of genetic and hormonal events.

Testosterone is a potent anabolic steroid and exerts its functions mainly by binding to the androgen receptor ubiquitously distributed in the body, but also by conversion to estradiol and activation of estrogen receptors. The latter mechanism is particularly important in bone and

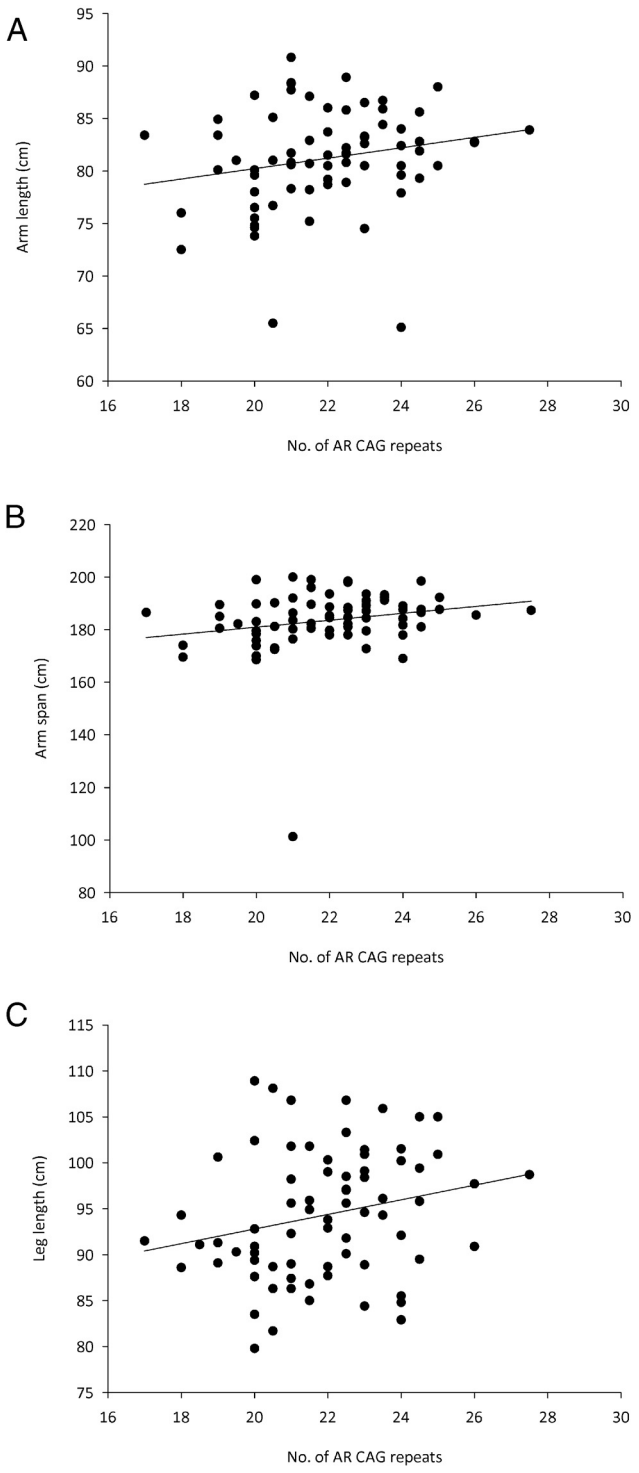

Figure 3. Correlation between number of AR CAG repeats and arm length (A) (rho = 0.24, $P = .04$), arm span (B) (rho = 0.29, $P = .01$), and leg length (C) (rho = 0.26, $P = .03$) in Klinefelter syndrome.

brain tissue. Estradiol plays a pivotal role in the closing of epiphyses and thereby termination of growth. Since testosterone cannot cross the blood-brain barrier, conversion of testosterone to estradiol could be responsible for masculinization of the fetal brain (30) and, although not understood, normal neurocognitive development of the brain. Normal testosterone levels through life and orchestrated hormone bursts in fetal life, infancy and puberty are important for the degree and sustainability of normal physical and mental development in males. 46,XY male fetuses express a peak of testosterone during weeks 12–15 of pregnancy. It is known that KS fetuses during this period express much lower levels of testosterone, resembling that of female fetuses (31). 2D:4D is an established surrogate marker for intrauterine exposure to sex hormones, eg, females have larger 2D:4D ratios than males (9). The effect of fetal testosterone on 2D:4D has been shown to be mainly expressed in the right hand (32). We demonstrated increased right hand 2D:4D in KS males compared to controls indicating decreased masculinization during fetal life. Testosterone replacement therapy later in life had no impact on 2D:4D comparing treated and nontreated KS males, as also shown before (11) and support evidence that KS males already during fetal life are in a hypogonadal milieu, and that this could impact some of the adult phenotypic traits and may provide a basis for some of the neurocognitive deficiencies seen in KS males. It lends credit to thoughts of early testosterone substitution during late childhood in KS (33), and such studies should naturally include anthropometric and body compositional measures.

KS males are known to have low to low-normal testosterone levels and replacement therapy is often indicated based on an individual assessment (34). In aging hypogonadal 46,XY males testosterone replacement therapy is believed to reduce cardiovascular risk via positive effects on body composition and cholesterol as well as glycemic control (35). On the other hand, increased hemoglobin and hematocrit and decreased HDL are known adverse effects (36). These effects of testosterone replacement therapy were also found in the present study. T-KS males had lower HDL and higher hematocrit, which could be seen as adverse effects of substitution, but on the other hand T-KS males had clearly lower total fat percentage, waist circumference and a tendency towards lower abdominal fat when compared to U-KS males, which could be interpreted as clearly beneficial effects of substitution therapy. T-KS had increased 17-OH-progesterone, possibly due to diminished LH effect on the adrenals, and higher androstendione, possibly due to increased conversion by 17α-hydroxy-steroid-dehydrogenase 2, in comparison with controls ("backdoor" production) (37).

The short stature homeobox gene (SHOX) is present on both the X- and Y-chromosome and haploinsufficiency is associated with increased height in Klinefelter syndrome (38). Here, we found higher waist circumference in KS males with a paternally derived supernumerary X-chro-

Table 3. Comparison of Anthropometry and Biochemistry in Klinefelter Syndrome Dependent on Parental Inheritance of the Supernumerary X Chromosome, Skewing of Expression of the X Chromosomes and CAG Repeat Length. All Values are Adjusted for Testosterone Status (Mean ± SE or Mean ×/÷ SE)

	KS PatX n = 20	KS MatX n = 21	*P*	KS Skew n = 11	KS No-skew n = 40	*P*	KS high CAG n = 33	KS low-CAG n = 40	*P*
Anthropometry									
Height (cm)	186.4 ± 2.3	187.0 ± 2.1	.8	183.4 ± 2.5	185.5 ± 1.6	.4	186.2 ± 1.6	184.6 ± 1.6	.3
Weight (kg)	100.8 ± 7.2	93.5 ± 6.7	.3	91.0 ± 7.7	96.8 ± 4.8	.4	92.1 ± 4.7	99.4 ± 4.6	.1
BMI	29.2 ± 2.0	26.7 ± 1.8	.2	27.1 ± 2.3	28.3 ± 1.4	.6	26.7 ± 1.4	29.3 ± 1.3	.05
Sitting Height (cm)	94.4 ± 1.1	95.2 ± 1.0	.5	92.4 ± 1.1	93.8 ± 0.7	.2	93.8 ± 0.8	93.8 ± 0.8	1.0
Arm Span (cm)	189.9 ± 5.3	181.1 ± 4.9	.1	182.9 ± 5.8	183.5 ± 3.4	.9	186.2 ± 3.0	180.7 ± 3.0	.07
Biacromical Width (cm)	42.4 ± 0.7	41.6 ± 0.7	.3	41.8 ± 0.9	41.9 ± 0.5	.9	41.6 ± 0.5	42.0 ± 0.5	.4
Arm Length (cm)	81.1 ± 1.7	81.5 ± 1.6	.8	77.8 ± 2.0	81.2 ± 1.2	.1	81.7 ± 1.2	80.2 ± 1.2	.2
Hand (cm)	19.1 ± 0.3	19.0 ± 0.3	.7	18.5 ± 0.4	19.0 ± 0.2	.2	19.0 ± 0.2	18.9 ± 0.2	.8
Second Digit (cm)	7.4 ± 0.1	7.3 ± 0.1	.3	7.3 ± 0.1	7.5 ± 0 1	.2	7.4 ± 0.1	7.4 ± 0.1	1.0
Fourth Digit (cm)	7.5 ± 0.1	7.5 ± 0.1	.6	7.5 ± 0.2	7.6 ± 0.1	.5	7.6 ± 0.1	7.6 ± 0.1	.9
2D:4D Ratio	0.99 ± 0.01	0.98 ± 0.01	.4	0.97 ± 0.01	0.98 ± 0.01	.4	0.98 ± 0.01	0.98 ± 0.01	.8
Bi-iliac Width (cm)	33.3 ± 1.7	33.3 ± 1.5	1.0	30.4 ± 1.0	31.4 ± 0.7	.3	31.5 ± 0.9	32.4 ± 1.0	.3
Leg Length (cm)	95.0 ± 2.3	92.5 ± 2.1	.3	90.1 ± 2.6	92.9 ± 1.6	.3	94.5 ± 1.6	91.1 ± 1.6	.03
Foot (cm)	26.6 ± 0.5	26.7 ± 0.5	.9	25.8 ± 0.5	26.3 ± 0.3	.3	26.4 ± 0.3	26.2 ± 0.3	.5
Hip (cm)	111.7 ± 4.1	109.4 ± 3.8	.5	107.9 ± 4.0	110.0 ± 2.5	.6	108.1 ± 2.5	111.5 ± 2.4	.2
Waist (cm)	99.6 ± 4.4	91.4 ± 4.1	.05	91.2 ± 5.2	98.8 ± 3.2	.3	93.8 ± 3.2	99.7 ± 3.1	.06
Head (cm)	58.1 ± 0.5	57.4 ± 0.5	.2	58.0 ± 0.6	57.5 ± 0.4	.4	57.6 ± 0.4	57.6 ± 0.4	.9
Bitesticular Volume (mL)	9.6 ± 1.8	8.8 ± 1.6	.6	5.3 ± 1.3	6.4 ± 0.8	.4	8.3 ± 1.1	6.4 ± 1.1	.08
Gynecomastia (+) (%)	25	24	1.0	50	33	.5	24	41	.2
Body Composition									
Total Fat Mass (kg)	33.1 ± 4.5	30.4 ± 4.2	.5	27.6 ±.4.4	29.4 ± 2.8	.7	27.1 ± 2.8	31.8 ± 2.8	.08
Abdominal Fat Mass (kg)	16.7 ± 2.5	14.8 ± 2.3	.4	14.9 ± 3.2	16.4 ± 2.0	.6	13.9 ± 1.9	18.2 ± 1.8	.02
Total Lean Body Mass (kg)	63.0 ± 2.9	58.7 ± 2.7	.1	57.7 ± 3.0	60.4 ± 1.9	.3	59.3 ± 2.1	60.5 ± 2.1	0.5
Total Body Fat (%)	31.2 ± 2.7	30.8 ± 2.5	.9	30.2 ± 2.6	30.2 ± 1.7	1.0	28.5 ± 1.7	31.9 ± 1.7	.04
Lipid Metabolism									
Apolipoprotein B (g/L)	0.95 ± 0.07	0.90 ± 0.07	.5	0.90 ± 0.07	0.98 ± 0.04	.2	0.96 ± 0 05	0.95 ± 0.05	1.0
Total Cholesterol (mmol/L)	4.7 ± 0.3	4.6 ± 0.3	.7	4.7 ± 0.3	5.0 ± 0.2	.2	4.9 ± 0.2	4.9 ± 0.2	.9
HDL Cholesterol (mmol/L)	1.3 ± 0.1	1.3 ± 0.1	.9	1.5 ± 0.1	1.4.± 0.1	.6	1.5 ± 0.1	1.4 ± 0.1	.1
Triglycerides (mmol/L)	1.1 ×/÷ 1.2	1.0 ×/÷ 1.2	.6	1.2 ×/÷ 1.1	0.60 ×/÷ 1.2	.2	1.1 ×/÷ 1.1	1.2 ×/÷ 1.1	.4
Sex Hormones									
LH (IU/L)	10.1 ×/÷ 1.8	31.5 ×/÷ 1.8	.1	24.2 ×/÷ 1.5	25.0 ×/÷ 1.9	1.0	17.2 ×/÷ 1.6	26.0 ×/÷ 1.5	.3
FSH (IU/L)	16.3 ×/÷ 1.8	48.6 ×/÷ 1.7	.1	37.3 ×/÷ 1.4	35.0 ×/÷ 1.8	.9	28.0 ×/÷ 1.5	37.1 ×/÷ 1.5	.5
DHEAS (nmol/L)	4375.1 ± 916.0	5001.3 ± 849.2	.5	4910.6 ± 840.7	4437.0 ± 524.8	.6	4267.1 ± 583.5	4539.4 ± 571.3	.6
Testosterone (nmol/L)	13.1 ± 3.5	8.1 ± 3.3	.1	14.0 ± 3.7	8.8 ± 2.3	.1	11.4 ± 2.4	8.8 ± 2.3	.3
Androstendione (nmol/L)	3.0 ± 0.5	3.6 ± 0.5	.2	3.6 ± 0.5	3.3 ± 0.3	.5	3.0 ± 0.4	3.5 ± 0.4	.2
17-OH-progesterone (nmol/L)	1.9 ± 0.4	2.9 ± 0.4	.009	2.5 ± 0.4	2.4 ± 0.2	.9	2.4 ± 0.3	2.7 ± 0.0 3	.3
SHBG (nmol/L)	45.8 ± 5.8	43.6 ± 5.4	.7	46.1 ± 7.1	45.4 ± 4.4	.9	47.1 ± 4.1	42.4 ± 4.1	.3
Free Testosterone (nmol/L)	0.31 ± 0.11	0.16 ± 0.10	.1	0.34 ± 0.11	0.17 ± 0.07	.1	0.24 ± 0.07	0.18 ± 0.07	.4
Estrone Sulphate (pmol/L)	1367.2 ×/÷ 1.3	1535.6 ×/÷ 1.3	.7	1558.6 ×/÷ 1.2	1539.4 ×/÷ 1.3	1.0	1219.2 ×/÷ 1.2	1827.3 ×/÷ 1.2	.02
Estradiol (pmol/L)	41.2 ×/÷ 1.6	41.1 ×/÷ 1.6	1.0	42.9 ×/÷ 1.3	66.7 ×/÷ 1.5	.2	58.1 ×/÷ 1.3	43.2 ×/÷ 1.3	.3
Estrone (pmol/L)	93.3 ± 22.0	105.5 ± 20.4	.6	101.4 ± 28.9	96.6 ±.18.1	.9	89.3 ± 17.3	99.6 ± 16.9	.5
Additional biochemistry									
Hematocrit	0.44 ± 0.01	0.42 ± 0.01	.04	0.43 ± 0.01	0.43 ± 0.01	.96	0.42 ± 0.01	0.43 ± 0.01	.3

mosome. As this was the only significant finding, it might be due to chance.

We found significant effects of the androgen receptor CAG repeat number. CAG repeat length was positively correlated to arm length, arm span, and leg length. CAG repeat length did not seem to affect bitesticular volume, although such a relation might be difficult to dismiss since long term testosterone treatment might lead to greater reductions in testicular size among the treated KS. Similarly, we could not find a relation between occurrence of gynecomastia and CAG repeat length. No correlations between AR CAG polymorphism and anthropometry were seen for controls. High CAG repeat length is indicative of low androgen receptor activity. In the presence of normal testosterone levels, high CAG repeat length could cause clinical hypogonadism (39). In normal 46,XY males high CAG repeat length leading to lowered androgen receptor activity is balanced out through hypothalamic-pituitary-gonadal feedback loop activation (40). In this study no correlation between CAG repeat length and LH, total or free testosterone was seen for either KS males or controls. The basis for increased length of the extremities observed with high CAG repeat length demonstrated in KS males could then rely on tissue specific variations in androgen activity. In bone testosterone is converted to estradiol by aromatase present in the endoplasmic reticulum. However, this mechanism is dependent on the internalization of extracellular testosterone by the androgen receptor. Hence, subnormal testosterone levels as seen in KS combined with lowered androgen receptor activity due to a long CAG repeat tract could effectively diminish availability of estradiol in bone tissue. This could lead to delayed closing of epiphyses and ultimately the observed elongation of the extremities when comparing KS males with controls.

When comparing the group of KS males with the highest CAG repeats to those with few repeats we saw lower abdominal fat mass, and total body fat percentage. Strikingly these effects are very similar to what was found comparing T-KS and U-KS. The paradox then is that some of the effects seen by raising testosterone levels by means of supplementation are the same as seen in KS males with high CAG repeat length, and thus the least testosterone sensitivity. No difference was seen for CAG repeat length between T-KS and U-KS. Then, with the above in mind, it does not seem that routine testing for CAG repeat length in KS males will be beneficial when assessing who among KS males should be treated with testosterone. No effect of skewed X-chromosome inactivation was observed. The proportion of KS males with skewed X-chromosome inactivation is small. Hence, gaining statistical power for identifying subtle changes in phenotypic traits is demanding. Furthermore, we speculate that such an effect, if present at all, would be miniscule and clinically irrelevant.

The current study represents a heterogeneous group of KS patients with respect to age and treatment with testosterone (68% received substitution therapy), which could be seen as problematic. However, we believe that the study cohort illustrates the clinical situation in the outpatient clinic with a diverse KS population, some being treated with testosterone and others not receiving substitution therapy. The control group is matched on age and educational level, which could pose a problem, but in fact the control group is quite similar on several variables to a control group used in a previous KS cohort study that were not matched on education (7). As such we think the control group has strong external validity. We only assessed testicular volume and gynecomastia among KS and not in controls, and therefore we introduced a normative material regarding testicular volume from elsewhere. It is of course a drawback that we did not also assess these variables among the controls and accordingly the results should be evaluated cautiously. A general problem in all KS research is the fact that only 25% of the expected KS are ever diagnosed, which of course limits the external validity of any KS study. This problem will only be resolved when all KS are diagnosed, a task which so far has not been accomplished anywhere in the world.

In summary, we for the first time clearly demonstrate that anthropometry in KS is distinct and disproportionate when compared to matched controls, although not sufficiently different to aid the clinician in diagnosing KS. Only bitesticular volume and the frequent occurrence of gynecomastia is very different from controls. KS males are taller with longer limbs and increased abdominal fat deposition. The interplay with testosterone, endogenous and exogenous, seems to be of great importance in sculpting the specific phenotype. Specifically, 2D:4D ratio reflecting testosterone exposure during fetal life is changed in KS. Also, CAG repeat length determining testosterone sensitivity is shown to influence adult phenotypic traits in KS males.

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