RESEARCH

Reduced fibrin clot lysis in Klinefelter syndrome associated with hypogonadism

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Abstract

Objective: Klinefelter syndrome (KS) is associated with increased risk of thrombosis. Hypogonadism and accumulating body fat in KS have a potential impact on fibrinolysis. In this study, we assessed the fibrinolytic system and the association with testosterone levels in KS.

Design: This study is a cross-sectional comparison of men with KS and age-matched male controls.

Methods: Fibrin clot lysis was evaluated by turbidity measurements and by measuring levels of individual fibrinolytic proteins in plasma samples. Fibrin clot structure was evaluated by scanning electron microscopy. Total testosterone was measured by liquid chromatography-tandem mass spectrometry. Body fat was evaluated by dual-energy X-ray absorptiometry.

Results: In this study, 45 men with KS and 45 age- and education-matched controls were included. Men with KS had a 24% reduction in fibrin clot lysis compared with controls (46.2 ± 17.1 vs 60.6 ± 18.8 %/h, $P = 0.0003$) and higher levels of fibrinogen, factor XIII ($P \leq 0.01$), and plasminogen activator inhibitor type 1 ($P = 0.04$). Men with KS had lower total testosterone ($P = 0.008$) and higher body fat ($P = 0.001$). In KS, reduced fibrin clot lysability was associated with higher fibrinogen and body fat related to decreasing total testosterone and hypogonadism among men with KS. Fibrin clot structure was not different compared to KS and controls.

Conclusions: Fibrin clot lysis in KS was markedly reduced, potentially contributing to a prothrombotic state and increasing thrombotic risk. Hypogonadism in KS was associated with increased fibrinogen and total body fat, predicting reduced fibrin clot lysis.

Key Words

- fibrinolysis
- obesity
- testosterone
- Klinefelter syndrome
- clinical study

Endocrine Connections (2022) **11**, **e210490**

Introduction

The risk of venous thromboembolism (VTE) among men born with Klinefelter syndrome (KS, 47,XXY) overall is increased more than four-fold (1, 2, 3). In particular, the relative risk of VTE in KS compared with the background population in younger ages is elevated more than ten-fold, and men with KS have a lifetime cumulative risk of

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VTE of around 20% (3, 4). The background for this massive excessive risk of VTE in men with KS is not clear.

The KS phenotype is varied, but hypergonadotropic hypogonadism is virtually omnipresent in adult men with KS (1), resulting in an unfavourable metabolic profile characterized by dyslipidaemia, hypertension and increased visceral fat mass (1, 5, 6). Obesity is considered a causal risk factor for VTE (7) and is capable of skewing the haemostatic balance (8). Thus, hypogonadism could be indirectly driving VTE risk in KS.

We have recently presented data indicating that KS is not associated with a hypercoagulable state (9), while a decreased propensity for fibrinolysis has been previously proposed in KS VTE case series (1, 10, 11).

Decreased fibrinolytic capacity is independently associated with an increased risk of VTE (12, 13). Decreased fibrinolytic capacity has been demonstrated in non-KS obese men with hypogonadism (14) and data from several studies have demonstrated an array of effects of androgenic compounds on fibrinolytic markers, collectively suggesting that normal plasma testosterone actively supports fibrinolysis (15). Thus, hypogonadism could further contribute to the increased risk of VTE among men with KS by introducing a prothrombotic state because of reduced fibrinolytic capacity.

Interestingly, weight loss and correction of obesity also seem to be associated with an improved fibrinolytic capacity (16, 17), and thus, reduction of fat mass as a result of testosterone supplementation in KS (18) has the potential to also improve the fibrinolytic capacity.

This study describes the fibrinolytic system in men with KS compared with male controls expressed as fibrin clot lysis, evaluated by turbidity measurements. Levels of individual proteins within the fibrinolytic system were measured to evaluate underlying changes in the composition of the fibrinolytic system affecting fibrin clot lysis in KS. We further assessed fibrin clot structure by electron microscopy and assessed the association between key aspects of KS, hypogonadism and increased body fat, and fibrin clot lysis.

Materials and methods

Participants

As previously described (9), men who are 18–70 years of age with non-mosaic 47,XXY KS were eligible for inclusion and matched by age and years of education to male controls. Men with KS were either without any history of testosterone treatment or on active treatment with testosterone, while none of the controls had any history of testosterone treatment. Participants were included from endocrinology and fertility clinics across Denmark and by public advertising. Exclusion criteria included prior thrombosis, current anticoagulation therapy or use of platelet inhibitors, current use of narcotics, diabetes mellitus, and prior severe head trauma. Male controls with total testosterone levels below the assay reference were excluded.

Ethics

The study was approved by the Central Denmark Regional Committees on Health Research Ethics (1-10-72-131-15) and the Danish Data Protection Agency (1-16-02-472-15). Informed consent was obtained from all participants and the study was registered with Clinicaltrials.gov (NCT02526628).

Blood sampling and plasma analysis

In order to ensure optimal pre-analytical conditions with respect to assessment of androgen levels and fibrin clot lysis, morning blood samples were collected after overnight fasting, as previously described (9). For fibrinolysis-related assays, tubes with 3.2% final concentration of citrate were used (S-Monovette 9NC, Sarstedt, Nümbrecht, Germany). Citrated plasma was prepared by centrifuging at 2000 ***g*** for 20 min at 20°C and frozen in aliquots at –80°C within 90 min.

Fibrin formation and clot lysability

The polymerization of fibrin and degradation of plasma clots were analysed using turbidity measurements (19). Fibrin polymerization was assessed after mixing 60 µL of the patient's plasma with 120 µL of a reaction mixture consisting of 1 IU/mL of thrombin, 15 mmol/L CaCl2, 50 mmol/L Tris-HCL buffer and 150 mmol/L NaCl in a microtiter plate. Polymerization was subsequently followed by measuring turbidity for 30 min at 340 nm on a microplate reader (Sunrise, Tecan Trading AG, Basle, Switzerland). Vmax was defined as the maximum rate of turbidity increment during polymerization (Fig. 1).

The fibrin clot was kept for 4 h at 25°C to allow complete polymerization. Subsequently, fibrin clot lysis was assessed by preparing a lysis mixture consisting of 50 µg/mL of tPA, 2.5 mmol/L of EDTA stabilized in 0.05% (v/v) Tween 80, 50 mmol/L of Tris-HCl, 150 mmol/L of NaCl,

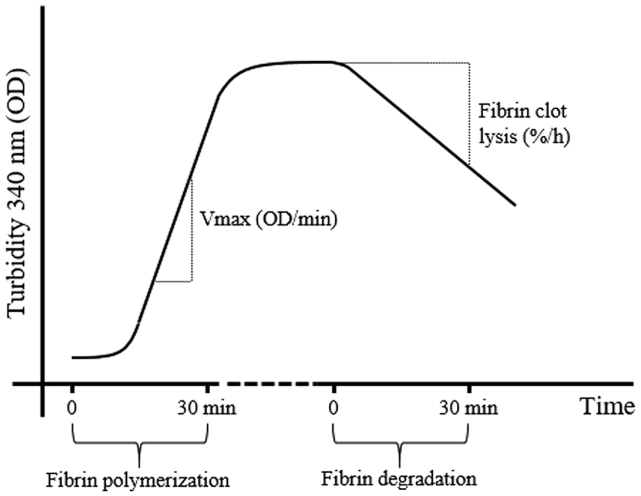

Figure 1
Illustration of changes in turbidity during fibrin polymerization and after addition of the lysis mixture. Initially, polymerization is followed for 30 min and Vmax is defined by the maximum rate of turbidity increment per minute at any point during polymerization. The clots are left to completely polymerize (min. 4 h) and fibrin degradation is then followed for 30 min after addition of lysis mixture containing tissue plasminogen activator. Fibrin clot lysis is defined as the percentage reduction in turbidity per hour.

and pH 7.4. Lysis mixture of 60 µL was applied on top of the completely polymerized fibrin clot and lysis was followed by measuring turbidity for 30 min at 340 nm (Fig. 1). Lysis per hour was calculated based on the recorded changes in turbidity between time = 0 min and time = 30 min after addition of the lysis mixture (Fig. 1).

Fibrinolytic factors

Fibrinogen and D-dimer were quantitatively determined using specific assay kits (STA-Liquid fib, STA Liatest D-Diplus, Stago, Asnieres-sur-Seine, Paris, France) on a STA-R coagulation analyser (Stago). Coagulation factor XIII (FXIII) activity was determined enzymatically using the Berichrom FXIII chromogenic ammonia release assay (Siemens Healthcare Diagnostics) employing a microplate reader (Tecan Trading AG). Plasminogen and plasmin inhibitors were quantitatively determined using automated chromogenic assays (HemosIL, Instrumentation Laboratory, ILS Danmark, Lillerød, Denmark) employing an ACL TOP 350 CTS (Instrumentation Laboratory). The total concentration of plasminogen activator inhibitor type 1 (PAI-1) antigen (16) and t-PA antigen was determined by in-house enzyme-linked immunoassays employing a microplate reader (Tecan Trading AG).

Fibrin clot structure

The fibre diameter and pore area were evaluated by scanning electron microscopy in a subset of participants. We hypothesized that fibrin structure would be associated with fibrin clot lysis, and to avoid having an unrepresentative sample resulting in analytical error due to skewed selection of participants between the groups, we decided that ten participants with fibrin clot lysis closest to the group mean in each patient group along with the respective matched controls should be included for scanning electron microscopy analyses. Coagulation was initiated by adding a final concentration of 1 IU of thrombin and 800 µmol/L of calcium to citrated plasma samples. The samples were left for 2 h and subsequently rinsed in cacodylate buffer and fixed in 2% glutaraldehyde. The samples were then critical point-dried using increasing concentrations of ethanol and hexamethyldisilazane. The samples were suspended on carbon pads prior to sputter coating with 5 nm Pt/Pd, 60:40 ratio, using a Cressington 208HR (Cressington Scientific Instruments UK, Watford, England). Scanning electron microscopy micrographs of ten random areas per sample were obtained at 15,000× magnification employing a Hitachi S-4800 electron microscope (Hitachi High-Technologies Corporation). The images were retrieved from areas of the clot that were visually evaluated to be representative of the overall clot structure. To further prevent bias, the technician operating the electron microscope was blinded to the grouping of the clots. Sputter coating and scanning electron microscopy imaging took place at NanoSYD, The Mads Clausen Institute, Sønderborg, Denmark. The greyscale images were then segmented into binary images, and the fibre diameter and pore area were automatically assessed using DiameterJ 1.018, a validated (20) open-source software package (https://imagej.net/DiameterJ).

Other quantities

Sex hormones were assessed by liquid chromatography-tandem mass spectrometry. For testosterone, the limit of detection was 0.1 nmol/L, and the working range was 0.2–100 nmol/L with a coefficient of variation of <10%. Body fat was assessed by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR2000/w osteodensitometer (Hologic, Inc., Waltham, MA, USA). Metabolic syndrome was assessed according to NCEP ATPIII criteria as the presence of three or more risk factors; large waistline, high triglyceride levels, low HDL, high blood pressure, or high fasting blood sugar (21).

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Statistical analysis

Distributions were evaluated by histograms and quantile–quantile plots. Data are presented as mean ± S.D. or median (25th–75th percentile) and between-group comparisons were performed by Student's *t*-test or Wilcoxon rank-sum test, as appropriate. Associations were evaluated by univariate linear regression and by multiple regression models, after transformation of non-normally distributed variables. Analysis was performed using StataIC 15 (StataCorp LLC).

Results

Participants

The characteristics of the participant have been described in detail previously (9). In this study, 45 men with Klinefelter syndrome and 45 control men were included. Of the included men with KS, 18 had no history of testosterone treatment and 27 were currently treated with testosterone (21 with injectable testosterone, 6 with testosterone gel) and had received treatment for at least 4 years (full range, 4–39 years). Men with KS had decreased total testosterone and increased total body fat compared with controls (Table 1). Criteria for the metabolic syndrome were met in 18 (40%) of men with KS and 12 (27%) of men in the control group.

Fibrin clot lysis and fibrinolytic proteins in KS compared with controls

Fibrin clot lysis was lower in men with KS compared with men in the control group (mean ± S.D., 46.2 ± 17.1 vs 60.6 ± 18.8 %/h, $P = 0.0003$, Table 1). The rate of fibrin formation represented by the Vmax was not different between KS and controls (Table 1). Men with KS had higher levels of fibrinogen, D-dimer, FXIII, plasminogen, and PAI-1 compared with controls ($P \leq 0.04$ for all, Table 1).

Association between fibrin clot lysis and fibrinolytic factors in KS

In univariate regression among men with KS, fibrin clot lysis was inversely associated with levels of FXIII, fibrinogen, and plasminogen (Table 2). Fibrin clot lysis was inversely associated with PAI-1 in controls, but in men with KS, fibrin clot lysis was not associated with PAI-1, t-PA, or the plasmin inhibitor (Table 2). Both FXIII and fibrinogen remained independently and inversely associated with fibrin clot lysis in a multivariate model adjusting for levels of all assayed fibrinolytic proteins (Table 2). In this multivariate model, fibrin clot lysis was further inversely associated with the plasmin inhibitor (Table 2). Collectively, fibrinogen, FXIII, and the plasmin inhibitor explained 55% of the variability of fibrin clot lysis in KS.

Table 1 Fibrin clot lysis, fibrinolytic proteins, fibrin structure, and fat mass and testosterone levels among participants.

	KS (*n* = 45)	**Controls** (*n* = 45)	***P***
Fibrin formation and lysability			
Vmax (OD per min)	0.79 ± 0.14	0.81 ± 0.16	0.6
Fibrin clot lysis (%/h)	46.2 ± 17.1	60.6 ± 18.8	0.0003
Pro-fibrinolytic proteins			
Fibrinogen (µmol/L)	9.6 ± 1.7	8.3 ± 1.6	0.0004
D-dimer (mg/L)	0.30 (0.22–0.45)	0.21 (0.17–0.24)	0.001
FXIII (fraction)	1.40 ± 0.27	1.25 ± 0.26	0.01
Plasminogen (fraction)	1.00 (0.91–1.09)	0.92 (0.88–0.99)	0.002
Fibrinolysis regulation			
PAI-1 (ng/mL)	29.3 (21.2–43.5)	25.5 (16.9–30.6)	0.04
t-PA (antigen) (ng/mL)	6.0 (4.2–8.0)	7.2 (4.8–10.1)	0.1
PI (fraction)	1.09 (1.00–1.14)	1.07 (0.90–1.11)	0.1
Fibrin clot structure[a]			
SEM fibre diameter (µm)	0.12 ± 0.02	0.13 ± 0.02	0.2
SEM pore area (µm^2)	0.09 ± 0.03	0.10 ± 0.04	0.1
Fat mass and testosterone			
BMI (kg/m^2)	27.4 ± 4.3	27.3 ± 4.3	0.9
Total body fat (%)	30.1 ± 7.6	24.2 ± 6.4	0.0001
Total testosterone (nmol/L)	15.1 (7.1–21)	19.4 (15.8–22.5)	0.008

Data are mean ± S.D. or median (25–75 percentiles).
[a]A subgroup of 19 men with KS and 19 control men were included for the scanning electron microscopy analyses.
FXIII, coagulation factor XIII; KS, Klinefelter syndrome; OD, optical density; PAI-1, plasminogen activator inhibitor 1; PI, plasmin inhibitor; t-PA, tissue plasminogen activator; SEM, scanning electron microscopy.

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Table 2 Association between fibrin clot lysis and fibrinolytic proteins in men with Klinefelter syndrome (KS) applying unadjusted univariate regression or a multiple regression model adjusting for levels of all assayed fibrinolytic proteins.

	Fibrin clot lysis (%/h)			
	KS (n = 45)		Controls (n = 45)	
	β (95% CI)	*P*	β (95% CI)	*P*
Univariate linear regression				
FXIII (fraction)	−33.9 (−50.3;−17.4)	<0.0005		0.1
Fibrinogen (µmol/L)	−4.9 (−7.5;−2.3)	<0.0005	−5.1 (−8,4;−1.7)	0.004
Plasminogen (fraction) [b]	−19.0 (−35.4;−2.7)	0.02	−35.5 (−58.4;−12.6)	0.003
PAI-1 (ng/mL)[a]		0.4	−12.0 (−22,6;−1.5)	0.03
t-PA (antigen) (ng/mL)[d]		0.3		0.2
PI (fraction)[b]		0.2		0.052
Multiple regression model				
FXIII (fraction)	−22.7 (−34.7;−10.8)	<0.0005		0.2
Fibrinogen (µmol/L)	−4.0 (−6.0;−1.9)	<0.0005		0.1
Plasminogen (fraction)[b]		0.4		0.4
PAI-1 (ng/mL)[a]		0.1	−13.3 (−23.8;−2.7)	0.01
t-PA (antigen) (ng/mL)[d]		0.9		1.0
PI (fraction)[b]	−33.1 (−63.9;−2.3)	0.04		0.2

Regression β (95% CI) is shown for significant associations only.
Transformations: [a]log, [b]cubic, [c]inverse square root.
FXIII, coagulation factor XIII; PAI-1, plasminogen activator inhibitor 1; PI, plasmin inhibitor; t-PA tissue plasminogen activator.

Association between fibrinolysis and testosterone in KS

Among men with KS applying univariate regression, fibrin clot lysis fell just short of being significantly associated with total testosterone (P = 0.056). In the combined group of KS and the control group, total testosterone was indeed associated with fibrin clot lysis ((β (95% CI), 5.9 (2.5;9.4), P = 0.001). KS remained a significant negative predictor for fibrin clot lysis after adjustment for total testosterone ((β (95% CI), −12.1 (−19.7;−4.5), P = 0.002).

In KS, total testosterone was inversely associated with fibrinogen ((β (95% CI), −0.47 (−0.84;−0.09), P = 0.02), while no association was seen between total testosterone and neither PAI-1 (P = 0.1) nor FXIII (P = 0.9).

In KS, total testosterone was inversely associated with total body fat ((β (95% CI), −0.11 [−0.15; −0.07], P < 0.0005).

Association between fibrinolysis and body composition in KS

Among men with KS, fibrin clot lysis fell short of a statistically significant inverse association with total body fat ((β (95% CI), −0.6 (−1.2;0.1), P = 0.1). However, in an analysis including both KS and controls, fibrin clot lysis was indeed inversely associated with total body fat ((β (95% CI), −1.0 (−1.5;−0.5), P < 0.0005). In addition, fibrin clot lysis remained decreased in KS compared with controls in a multivariate model adjusting for total body fat ((β (95% CI), −10.1 (−18.1;−2.3), P = 0.01).

In KS, total body fat was positively associated with fibrinogen ((β (95% CI), 0.14 (0.08;0.19), P < 0.0005) and PAI-1 ((β (95% CI), 6.5 (2.6;10.4), P = 0.002). Fibrinogen remained increased in KS compared with controls after adjustment for total body fat (P = 0.046), indicating that for any given amount of body fat, fibrinogen is increased in KS. In contrast, PAI-1 was no longer different comparing men with KS and controls in multivariate model adjusting for total body fat (P = 0.8), indicating that for any given amount of total body fat, PAI-1 levels are not different between men with KS and controls.

Fibrin clot structure in KS compared with controls

In Fig. 2, scanning electron microscopy images representative of the mean diameter and pore area for men with KS stratified by testosterone treatment status and controls are presented. There was no difference in fibre diameter or pore area comparing men with KS and controls (Table 1). Fibrin structure evaluated by scanning electron microscopy was not associated with fibrin clot lysis or total body fat (data not shown).

Discussion

Men with KS have a four- to six-fold increased risk of clinical venous thrombosis (1, 3). The pathophysiology causing this massive excess risk is not clear. Impairment of fibrinolytic capacity potentially increases the risk of venous

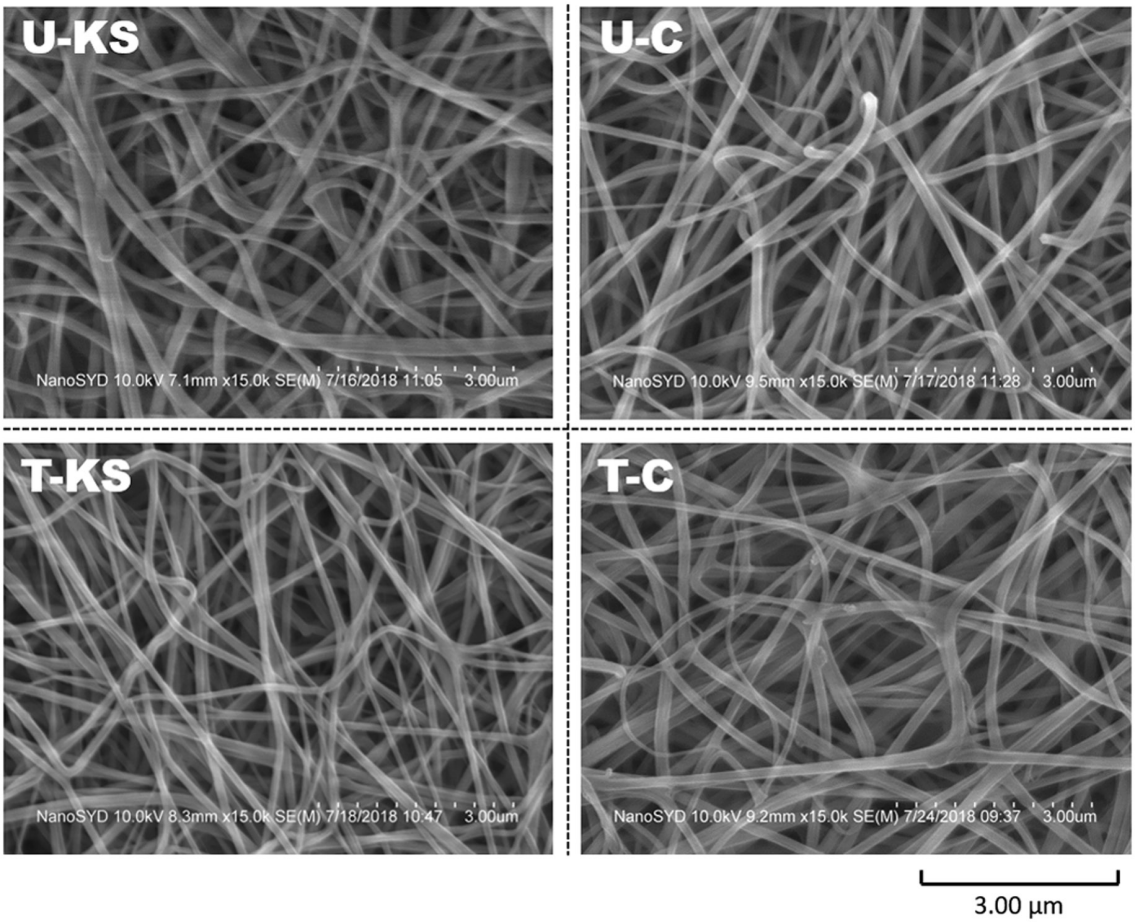

Figure 2
Scanning electron microscopy of fibrin clots. The depicted fibrin networks are representative of the mean fibre diameter and pore area of the respective groups. Magnification ×15,000. U-KS, untreated Klinefelter syndrome; U-C, matched controls for U-KS; T-KS, testosterone-treated Klinefelter syndrome; T-C, matched controls for T-KS.

thromboembolism (12, 13), and men with KS present with hypogonadism and central obesity, conditions associated with poor fibrinolytic capacity.

We applied fibrin clot lysis, as a global *in vitro* assay reflecting *in vivo* fibrin clot lysability, and demonstrated a significant 24% reduction in fibrin clot lysis among men with KS compared with age-matched controls. Among men with KS, we demonstrated underlying pervasive changes in the composition of the fibrinolytic system, with plasma levels of assayed fibrinolytic proteins moving in a direction associated with reduced fibrin clot lysability. In particular, higher levels of fibrinogen and FXIII in men with KS were independently associated with reduced fibrin clot lysability. Increased levels of fibrinogen have been associated with the formation of fibrin clots that are less susceptible to fibrinolysis and with higher risk of clinical thrombosis (22, 23). FXIII plays a pivotal role in stabilizing the fibrin clot through cross-linking of fibres, and increasing FXIII levels are associated with increased resistance to fibrinolysis (24). We were not able to demonstrate alterations in the fibrin clot structure evaluated by SEM, and likely our study was underpowered regarding this separate analysis.

We demonstrated an association between the increased fibrinogen in KS and key traits of the syndrome, namely hypogonadism and increased total body fat. Although the current study design disallows causal conclusions, the findings indicate that low androgen levels lead to increased fibrinogen levels and poor fibrin clot lysability acting either directly on the expression of fibrinogen in the hepatocytes or through secondary mechanisms involving increased deposition of adipose tissue (Fig. 3).

To our knowledge, this was the first study to access global fibrinolysis in KS, and our findings are in line with previous studies demonstrating a supportive effect of androgenic compounds on fibrinolysis in non-KS and non-obese men (15) and poor fibrin clot lysability in obese non-KS

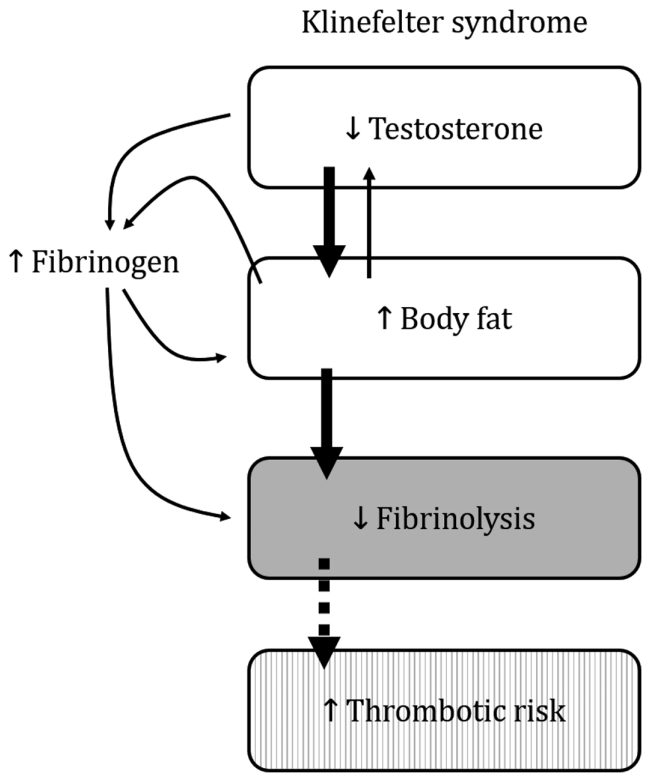

Figure 3
Hypothetic model of how decreasing testosterone and in particular overt hypogonadism in Klinefelter syndrome causes impairment of fibrin clot lysability via increasing fat mass but importantly apparently further by acting on levels of fibrinogen in KS. Ultimately, the link between hypogonadism and fibrinolysis could be partially responsible for the excessive thrombotic risk seen in men with Klinefelter syndrome compared with the background population (3).

men with hypogonadism (14). Androgenic compounds have been shown to support fibrinolysis (15). Ultimately, hypogonadism-induced defective global fibrinolysis could be an essential component behind the marked increased risk of venous thromboembolism seen among men with KS.

We sought to assess if testosterone supplementation directly impacts fibrin clot lysability in KS by increasing the levels of testosterone or whether any such effects could be secondary to androgenic effects on metabolism and body composition. In the compiled analysis including the entire participant cohort, there was a positive association between fibrin clot lysis and testosterone levels. Subgroup analysis in KS or controls alone fell short of being statistically significant, potentially due to power issues. We have previously published epidemiological data supporting that testosterone replacement therapy does not seem to aggravate the already increased risk of VTE in KS but could have an attenuating effect on VTE risk (3). These are important considerations when guiding and discussing prospects of initiating testosterone treatment with individual KS patients.

Among men with KS, total testosterone was inversely associated with fibrinogen and total body fat. Previous studies have similarly found decreasing fibrinogen levels by applying different regimens of testosterone supplementation (15). Total body fat was increased in KS compared with controls, but comparable PAI-1 levels were seen for respective levels of body fat across the two groups. As hypothesised in Fig. 3, it is of interest that the interaction between testosterone, body fat, and fibrin clot lysis in KS seems to associate more prominently with fibrinogen and not PAI-1. This again could point to specific properties of fat tissue in men with KS compared with controls. In a recent study, increased levels of PAI-1 were seen among men with KS compared with controls (25). However, in that study, no data are given concerning the range of BMI in the control population and the men with KS included in the study had a very wide BMI range (16.3–36.3 kg/m^2) and none were currently treated with testosterone and testosterone levels were not assessed.

We found that body composition was an important factor in relation to fibrin clot lysability in men with KS. In men with KS, we found that total body fat was positively associated with levels of fibrinogen and thus poorer fibrin clot lysability. We have previously shown that for any given BMI, men with KS present with increased truncal fat compared with controls (5, 26) and that, as men with KS age, they seem to become more obese (27). Here, we further demonstrate that after adjustment for total body fat, fibrinogen was increased in men with KS compared with controls indicating that fat tissue in KS might have a unique composition and directly influence pathology in KS. However, fibrin clot lysis remained reduced in KS compared with controls even after adjusting for total body fat, indicating that potentially other mechanisms related to the specific genetic composition of KS are affecting the fibrin clot lysability.

It has previously been demonstrated that fibrin clot lysability improves in obese patient following weight loss induced by Roux-en-Y-gastric bypass with lower levels of fibrinogen and increased fibrin clot lysis (17). Collectively, our data indicate that loss of fat mass could be a potential mechanism for reducing fibrinogen and increasing fibrin clot lysis among men with KS.

In addition, recent findings have suggested that fibrinogen could be directly involved in the development of obesity, with accumulation of fibrinogen and fibrin in adipose tissue (28). We have previously demonstrated a fundamentally changed pattern of mRNA expression in

blood among men with KS compared with both male and female controls (29). It would be interesting to investigate whether the expression of the fibrinogen genes (*FGB*, *FGA*, and *FGG*) and other genes influencing the synthesis of fibrinogen (30) could be altered in fat tissue from men with KS compared with controls. The presence of other such unmeasured potential contributors to fibrinolysis in KS can of course not be excluded.

The present study design does not allow for conclusions regarding causality. However, the data suggest that the hormonal imbalance seen with KS is associated with impairment of fibrin clot lysability by increasing total body fat and altering levels of fibrinolytic proteins. In such a circulus vitiosus, increased body fat would then lead to more severe hypogonadism, further aggravating the situation (1). This underlines the need for a concerted effort to ensure optimal care for men with KS, including a regimen of proper testosterone replacement therapy and a focus on weight loss. Whether there might be benefits from choosing a transdermal route of treatment compared with injections remains to be settled (27).

This study applied a matched, cross-sectional design to evaluate several aspects of the fibrinolytic system in men with KS. Despite the potential lack of power, the current study supports that fibrin clot lysability seems impaired in young adult men with KS free of diabetes and without previous thrombotic complications.

Conclusion

In this cross-sectional study, we demonstrated reduced fibrin clot lysis among men with KS compared with controls. Lower testosterone and higher body fat in men with KS were associated with increased fibrinogen and reduced fibrin clot lysability. Prospective studies are needed to evaluate whether testosterone treatment, route of administration, and fat loss in KS could attenuate the excess thrombosis risk in KS through correction of the fibrinolytic deficit.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

S Chang received a PhD scholarship from the University of Southern Denmark and The Region of Southern Denmark. The work was supported by unrestricted grants from Karola Jørgensens Forskningsfond, A.P. Møller Fonden (Lægefonden), the Novo Nordisk Foundation (NNF13OC0003234, NNF15OC0016474, NNF20OC0060610); and the Familien Hede Nielsen foundation.

Acknowledgement

Claus H Gravholt is a member of the European Reference Network on Rare Endocrine Conditions (ENDO-ERN), Project ID number 739543.

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Received in final form 18 February 2022
Accepted 31 March 2022
Accepted Manuscript published online 31 March 2022