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ABSTRACT N. CO15

LABORATORIO E FATTORI PREDITTIVI

LONGITUDINAL COAGULATION PROFILING OF INDIVIDUALS UNDERGOING GENDER-AFFIRMING HORMONE THERAPY: THE HYPER-GENDER STUDY.

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Background and aims: Transgender individuals appear to have an increased risk of thrombosis due to hypercoagulability associated with gender-affirming hormone therapy (GAHT). The aim of the study was to investigate the effects of GAHT on coagulation, metabolism, and erythropoiesis, and to explore the mechanisms underlying hypercoagulability in the transgender population. A better understanding of these mechanisms may help guide risk stratification and inform clinical monitoring strategies during hormone treatment.

Methods: We enrolled 112 adult transgender individuals initiating GAHT. Plasma samples were collected at baseline (prior to GAHT initiation) and at 3, 6, and 12 months thereafter. Parameters assessed included hereditary thrombophilia, procoagulant factors (factor VIII, fibrinogen), natural anticoagulants (protein C, protein S, antithrombin), thromboelastometry, whole blood aggregometry, thrombin generation with and without thrombomodulin, iron metabolism, and erythropoietin levels. Written informed consent was obtained from all participants.

Results: The cohort included 41 Assigned Male at Birth (AMAB) and 71 Assigned Female at Birth (AFAB) individuals; 7.1% had hereditary thrombophilia (7 mild, 2 severe). At baseline, AFAB participants exhibited higher levels of factor VIII and fibrinogen, lower protein C and protein S levels, shorter EXTEM clotting time, and greater maximum clot firmness (MCF) on thromboelastometry, as well as increased ASPI-induced platelet aggregation compared to AMAB individuals.
AMAB participants received transdermal estrogen therapy with or without anti-androgens, while AFAB individuals were treated with testosterone. Over the 12-month follow-up, AMAB individuals showed increased platelet count, enhanced thrombin-driven aggregability, decreased hemoglobin, and elevated peak thrombin generation and endogenous thrombin potential ratio. In contrast, AFAB individuals exhibited significant increases in hemoglobin, hematocrit, and iron parameters. A significant reduction in MCF on thromboelastometry was observed, alongside a non-significant increase in thrombin-generation peak (Table). No thrombotic events occurred during the study period.
Conclusions: We found that 7% of transgender individuals initiating GAHT carry hereditary thrombophilia, including 2% with severe forms. Baseline sex-assigned differences in coagulation profiles were evident, with AFAB individuals displaying a more procoagulant phenotype. GAHT induced distinct biological effects: in AMAB individuals, it enhanced platelet reactivity and thrombin generation, while in AFAB individuals, the predominant changes were related to erythropoiesis and iron metabolism. These findings provide insight into sex-specific haemostatic responses to GAHT and underscore the importance of individualized thrombosis risk assessment in this population.

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Longitudinal trend of blood count, sex hormones, coagulation and iron metabolism parameters in transgender subjects undergoing gender-affirming hormone therapy.

Assigned Male At Birth - AMAB				
Parameter	Baseline	6 months	12 months	p for trend
Blood count				
Hb - g/dL	15.3 [15-16]	14.5 [12.8-15.9]	14.4 [14.2-15.0]	<0.01
HCT - %	45.9 [44.2-48.5]	40.4 [37.4-42.2]	42.6 [40.9-44.6]	<0.001
Erythrocytosis (HCT>48%)	14 (14%)	0	0	<0.001
Anemia (Hb<12 g/L)	1 (2.4%)	1 (2.4%)	2 (4.9%)	ns
Platelets - x 10^9/L	244 [203-276]	291 [210-349]	277 [206-369]	0.0035
Sex steroids				
Testosterone - ng/mL	5.5 [4.2-6.5]	0.2 [0.1-0.3]	0.3 [0.2-1.2]	0.006
Estradiol (E2) - ng/L	32.5 [26-55]	40.7 [34-83]	167 [51-249]	0.007
LH - U/L	5.1 [3.5-7.5]	0.2 [0.1-0.3]	0.2 [0.1-2.5]	0.0002
FSH - U/L	2.4 [1.9-3.9]	0.4 [0.35-0.5]	0.5 [0.4-1.5]	<0.001
Procoagulant factors				
Factor VIII activity - %	112 [97-133]	115 [96-131]	108 [92-127]	ns
Fibrinogen activity - mg/dL	323 [290-390]	318 [252-353]	307 [282-340]	ns
Anticoagulant factors				
Protein C activity - %	100 [85-106]	95 [87-101]	101 [94-108]	ns
Protein S activity - %	109 [102-123]	123 [114-125]	128 [122-134]	0.007
Protein S free antigen - %	102 [96-115]	107 [99-115]	110 [101-121]	ns
Antithrombin - %	98 [89-102]	101 [88-119]	97 [94-109]	ns
Thromboelastometry				
CFT-INTEM - sec	89 [71-99]	177 [147-204]	59 [57-76]	0.003
MCF-INTEM - mm	61 [57-66]	62 [61-64]	63 [62-65]	ns
MCF-EXTEM - mm	65 [61-67]	63 [62-67]	65 [65-69]	ns
MCF-FIBTEM - mm	16 [12-18.5]	15 [13.5-23]	16 [15.7-20.5]	ns
Whole blood aggregometry				
TRAP - AUC	99 [94-117]	108 [87-154]	142 [135-145]	0.05
Thrombin generation				
Peak - nM	218.6 ± 64.8	275.2 ± 51.2	281.6 ± 57.8	< 0.0001
ETP+TM - nM*min	842 ± 333	1075 ± 314	1171 ± 294	<0.0005
ETP ratio (with/without TM)	0.6 ± 0.2	0.7 ± 0.2	0.8 ± 0.1	<0.013
Iron metabolism				
Iron - umol/L	9.5 [5.9-15.4]	19.5 [11.5-20]	15.4 [11.6-19]	0.018
Transferrin saturation - %	28 [21-39]	36 [28-49]	51 [22-41]	0.011
Assigned Female At Birth - AFAB				
Parameter	Baseline	3 months	6 months	p for trend
Blood count				
Hb - g/dL	13.5 [12.8-15.5]	14 [13.5-14.5]	14.6 [14.4-14.9]	0.0006
HCT - %	40.5 [39.9-40.9]	43 [42-44.2]	44.8 [43-46.4]	<0.0001
Erythrocytosis (HCT>48%)	0	3 (4.2%)	9 (12.7%)	0.0019
Anemia (Hb<12 g/L)	10 (14%)	4 (5.6)	0	0.012
Sex steroids				
Testosterone - ng/mL	0.3 [0.24-0.39]	3 [2.5-5.2]	4.8 [2.3-14.9]	<0.0001
Estradiol (E2) - ng/L	89 [43-111]	40 [32-75]	42 [29-67]	ns
SHBG - nmol/L	80.7 [53-99]	47.9 [33.4-54.3]	37.2 [27-43]	0.02

Procoagulant factors				
Factor VIII activity - %	133 [97-149]	134 [125-159]	130 [94-159]	ns
Fibrinogen activity - mg/dL	357 [314-424]	332 [289-371]	339 [290-359]	ns
Anticoagulant factors				
Protein C activity - %	109 [89-118]	102 [89-129]	110 [91-128]	ns
Protein S activity - %	107 [91-114]	131 [104-146]	128 [116-134]	0.002
Protein S free antigen - %	95 [91-108]	113 [106-115]	109 [103-119]	ns
Antithrombin - %	98 [95-109]	99 [93-108]	98 [94-102]	ns
Thromboelastometry				
CFT-EXTEM - sec	70 [61-86]	77 [71-85]	93 [71-95]	0.01
MCF-INTEM - mm	65 [61-69]	62 [58-67]	60 [56-66]	0.02
MCF-EXTEM - mm	69 [64-72]	65 [63-69]	64 [61-68]	0.04
MCF-FIBTEM - mm	20 [14-24]	15 [14-17]	15 [11-17]	0.0007
Whole blood aggregometry				
ASPI - AUC	73 [49-92]	60 [52-69]	74 [59-90]	ns
Iron metabolism				
Iron - umol/L	7.9 [7.4-12]	5.2 [4.5-6.7]	20.3 [10.5-36]	0.01
Ferritin - ng/mL	28 [15-86]	12 [6-15.5]	19 [15-25.2]	0.02
Transferrin saturation - %	9 [8.9-12.1]	6 [5.2-7.6]	1.9 [1.4-3.1]	0.04
Thrombin generation				
Peak - nM	225 ± 37.9	245.7 ± 42.6	252.3 ± 50.1	0.054
ETP ratio (with/without TM)	0.7 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	ns

Hb: hemoglobin; HCT: hematocrit; LH: luteinizing hormone; FSH: follicle-stimulating hormone; CFT: clotting formation time; MCF: maximum clot firmness; AUC: area under the curve; TRAP: thrombin receptor-activating Protein; ETP: endogenous thrombin potential; TM: thrombomodulin; SHBG: sex hormone-binding globulin.

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