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TRANSGENDER HEALTH

Biochemical Changes During the First Year of Feminizing Hormone Therapy in Transfeminine Individuals

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ABSTRACT

Background: Persons with assigned male sex at birth (AMAB) might wish to obtain feminization and/or demasculinization according to the person's gender identity and are therefore treated with estradiol and/or antiandrogens.

Aim: The aim was to evaluate biochemical changes and side effects in AMAB individuals treated with guideline-based feminizing hormone treatment (FHT).

Methods: Medical charts of 99 AMAB individuals ≥ 18 years referred to the Center for Gender Identity; Aalborg University hospital, Denmark, between January 2017 and July 2019 were reviewed to identify adverse side effects. Furthermore, data from the laboratory information system (Labka II) were retrieved to obtain biochemical parameters. Biochemical plasma concentrations after initiation of FHT were compared to concentrations prior to FHT and to existing guidelines.

Outcomes: After 11−19 months, 29% of the trans feminine individuals had plasma estradiol concentrations within the treatment target.

Results: The plasma concentration of estradiol varies greatly during FHT. Plasma levels of estrogen were within the treatment target after 11−19 months of treatment, whereas 100% had concentrations within the reference range for premenopausal cis-women. Furthermore, plasma concentrations of lipids and hematological parameters approached female reference ranges after 11 months of FHT.

Clinical Implications: The target levels of plasma estradiol concentrations during FHT could be expanded, making the wanted physiological changes easier to obtain.

Strengths & Limitation: This cohort study included 99 AMAB individuals and biochemical evaluation was possible in 67 individuals. Only one individual was lost during follow-up. However, the follow-up period was limited making evaluation of long-term side effects impossible.

Conclusion: Plasma concentration of estradiol varies greatly during guideline based FHT, making plasma estradiol levels within the target level difficult to attain. **JA Hojbjerg, AD Højgaard, A-M Hvas. Biochemical Changes During the First Year of Feminizing Hormone Therapy in Transfeminine Individuals. Sex Med 2021;10:100472**.

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INTRODUCTION

A marked increase in the demand for gender affirming hormone therapy (GAHT) has been observed worldwide.[1−3] GAHT is distributed in specialized clinics to support the gender affirmation in transgender persons.[4] Current clinical guidelines are formulated by the Endocrine Society[5] and recommends that "administered sex steroids are maintained in the normal physiologic range for the affirmed gender."[5] On that basis, biochemical analyses are a key element in the monitoring of efficacy but also in the detection of potential side effects. A recent study demonstrated that in the Nordic countries these guidelines are primarily followed however, pronounced differences in biochemical treatment target ranges still exist.[6]

Persons with assigned male sex at birth (AMAB) are treated with estradiol and/or antiandrogens in order to obtain feminization and/or demasculinization according to the person's gender identity.[5] Both estradiol and antiandrogenic drugs are known to induce unfavorable physiological[7] and biochemical changes[8,9] leading to dose restriction. Yet, the aim of feminizing hormone treatment (FHT) is to obtain plasma concentrations of estradiol within the normal physiologic range of estradiol in cis-women.[5] However, the reference range for estradiol in premenopausal cis-women varies greatly with both age and menstrual cycle.[10] The wide reference range makes treatment targets for AMAB persons harder to establish which is also reflected in the differences in treatment targets.[6] Hence, it is crucial to evaluate efficacy and safety according to plasma levels of sex hormones in order to approach specific reference ranges for biochemical analyses in transgender persons.[11] Therefore, the objective of this study was to determine if trans feminine individuals attain the recommended target level of plasma estradiol and secondly to evaluate if other biochemical markers approach the reference intervals for cis-women when initiating guideline-based FHT.

MATERIAL AND METHODS

The study was conducted as a cohort study. Medical charts of all individuals ≥ 18 years referred to the Center for Gender Identity; Aalborg University Hospital, Denmark, between January 2017 and July 2019 were reviewed to identify AMAB individuals. In these 2.5 years, 242 individuals were referred to the specialized outpatient clinic. Ninety-seven individuals were excluded because treatment was started prior to referral and another 25 were excluded because treatment was not initiated at the time of chart review. Ten individuals refrained from FHT and 11 individuals were excluded due to insufficient information. Of the 242 referrals, 99 hormone-naïve individuals initiated FHT and were enrolled in the study.

All individuals were treated at this single center by the same multidisciplinary team consisting of specialists in the fields of gynecological endocrinology, psychiatry, psychology, plastic surgery, and nursing. FHT was initiated according to international guidelines.[5] At the Center for Gender Identity; Aalborg University Hospital, Denmark, treatment was registered by the contact code DZ768e1. At this center, FHT consisted of estradiol in combination with cyproterone acetate in order to reach the target levels of plasma estradiol concentrations between 367 and 734 pmol/L (equivalent to 100−200 pg/mL). The target levels for testosterone plasma concentrations in transfeminine individuals at the Center for Gender Identity were as follows: Testosterone: < 1.9 nmol/L and free testosterone: 0.003−0.032 nmol/L.[6]

The efficacy and side effects were evaluated every 2−3 months and blood samples were collected in connection with these check-ups. During the check-up the individuals were asked about side effects including headache, dyspnea and pain. Treatment was subsequently adjusted based on side effects, clinical examination and biochemical results in order to obtain the plasma target level (367−734 pmol/L (100−200 pg/mL)). The risk profile of each individual was assessed prior to treatment start and treatment was adjusted accordingly.

Biochemical parameters of the 99 enrolled individuals were subsequently acquired by retrieving data from the laboratory information system (LABKA II).

Statistics

Biochemical results are presented as median and 25;75 percentiles. Blood samples collected before treatment initiation, were compared to the blood samples collected nearest to 12-month treatment time to calculate significant differences between plasma levels before and after treatment initiation. The paired *t*-test was used for normally distributed data, otherwise Wilcoxon matched pairs signed rank test was used. All statistics were performed using GraphPad Prism version 8.0.1 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com.

Ethics

The study was approved by the hospital administration, Aalborg University Hospital, Denmark. According to Danish law, the present study did not require approval from the Central Denmark Region Committees of Health Research Ethics since the study was a retrospective study on accrued data conducted as part of a quality assurance project.

RESULTS

Study Population

In total, 99 AMAB individuals were included in the study. The majority of individuals receiving FHT were young adults with a mean age of 29 years (range 18−70). Almost half of the study group (47%) had normal body weight but both obese and underweight individuals were included in the study (body mass index range 16−36 kg/m^2). Seven individuals had physical morbidities with diabetes mellitus occurring most frequently (n = 4).

Two individuals had dyslipidemia and one received antihypertensive treatment. The predominant morbidity was mental disorders with 43% of the individuals being affected by mental illness. Autism (n = 22) and depression (n = 11) represented the majority of diagnoses. Sixteen individuals had 2 or more mental disorders.

Medication

Dose and administration of estradiol was selected based on the risk profile and individual preference with transdermal formulations being the preferred way of administration. The daily dosage ranges of transdermal administration were: Spray (3.06−7.65 mg), patches (100−200 μg/24 h), and gel (2−8 mg) whereas the dosage range for oral administration was (2−6 mg). Spray was chosen in 66 (67%) of the individuals. Patches and gel were equally used and accounted for 16 (16%) and 12 (12%) individuals, respectively, whereas 5 (5%) individuals received oral treatment. Sublingual administration and injections were on no occasion prescribed. All individuals were treated with genuine estradiol and no individuals received progesterone. During follow-up, only one individual discontinued treatment; she failed to show up at the clinic and as a result FHT was discontinued after 14 months.

Cyproterone acetate was the drug of choice to block androgen production in all individuals (n = 97) receiving androgen blockage. Treatment was initiated by 25 mg/day cyproterone acetate with subsequent reduction to 12.5 mg/day after a 3 months' treatment period. Two individuals did not initiate androgen blockage; one individual rejected antiandrogenic treatment due to the possible side effects while the underlying cause for the other is unknown. No individuals were treated with spironolactone. During the observation period 8 individuals discontinued cyproterone acetate due to depressive symptoms (n = 5) and dyspnea (n = 3). In the case of dyspnea, the individuals were initially screened for thromboembolism by testing for increased plasma levels of fibrin D-dimer and subsequently by performing an ultrasound examination of the lower extremities and a thoracic computed tomography (CT)-scan. In one case of dyspnea gonadectomy was performed to enable discontinuation of antiandrogen medication.

A total of 6 individuals received cyproterone acetate for less than 12 months and were therefore excluded from the statistical analyses.

Efficacy

Baseline biochemical characteristics are presented in Table 1 alongside the corresponding plasma concentrations. The blood sample taken prior to treatment start was compared to the sample taken after approximately 1 year of treatment resulting in a median treatment period of 11 months (range 5−14). Only individuals with a blood sample preceding treatment start were included in the statistical analysis of biochemical changes during treatment. The continuous individual plasma concentrations of estradiol during the first months of FHT are illustrated in Figure 1. Among 61 individuals, 54 (89%) had plasma estradiol concentrations within the reference range for premenopausal cis-women after 1−5 months FHT and 38 individuals out of 38 (100%) after 11−19 months. By contrast, after a treatment period of 1−5 months, only 5 out of 61 (8%)

Table 1. Median plasma levels [25%;75% percentiles] before treatment start and median 11 (range 5−14) months after

	Pretreatment n = 78			Follow-up n = 67				Reference interval*
Cholesterol mmol/l	4.2	[3.6;4.7]	77	3.7	[3.4;4.1]	24	<0.05	<5.0
HDL mmol/l	1.2	[1.0;1.4]	68	1.1	[0.9;1.3]	22	<0.05	>1.2
LDL mmol/l	2.5	[1.8;3.0]	28	2.1	[1.9;2.4]	19	0.43	<3.0
Triglyceride mmol/l	1.2	[0.8;1.8]	63	0.8	[0.6;1.1]	19	0.46	<2.0
Bilirubin μmol/l	9	[6.7;15.0]	71	9	[6.3;14.0]	24	0.29	5−25
Alanine transaminase U/l	22	[17;35]	74	21	[14;30]	27	0.05	10−45
Alkaline phosphatase U/l	70	[62;80]	46	65	[57;77]	20	0.06	35−105
Prolactin IU/l	138	[104;186]	73	594	[403;788]	53	<0.05	90−580 $\times$ 10^{-3}
Testosterone nmol/l	17	[13;22]	73	0.4	[0.4;0.6]	50	<0.05	<2.4
Testosterone free nmol/l	0.32	[0.27;0.39]	70	0.0079	[0.0054;0.012]	38	<0.05	0.006−0.034
Estradiol pmol/l	80	[50;113]	22	386	[193;579]	56	<0.05	40−2,400
Erytrocyte volumen fraction	0.45	[0.43;0.47]	73	0.41	[0.39;0.43]	26	<0.05	0.35−0.46
Hemoglobin mmol/l	9.4	[9.1;9.9]	74	8.7	[8.2;9.2]	30	<0.05	7.3−9.5
GGTU/l	18	[13;29]	6	N/A	N/A	0	N/A	10−45
SHBG nmol/l	39	[29;59]	71	35	[26;46]	44	0.94	20−150
HbA1c mmol/mol	32	[30;34]	76	32	[30;35]	24	0.14	31−44
TSH int.enh./l	1.9	[1.3;2.4]	71	1.6	[1.2;2.1]	23	0.25	0.3−4.5

*Reference interval for premenopausale cis-women.GGT = Gamma-glutamyl transferase; HbA1c mmol/mol = HbA1c hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SHBG = sexual hormone binding globulin; TSH = thyroid-stimulating hormone.

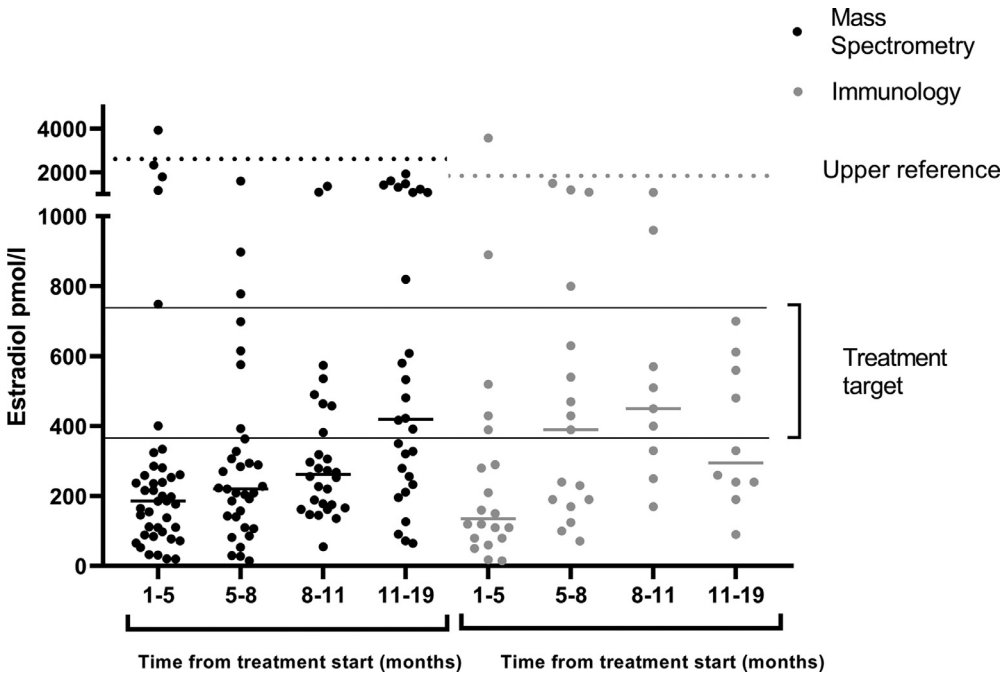

Figure 1. Plasma concentrations of estradiol during the first months of FHT. The fully drawn lines define the treatment target. Estradiol was analyzed at 2 laboratories with different methods of measurement (mass spectrometry and immunological). The dotted lines indicate the upper reference range for premenopausal cis-women for the respective method.

individuals had plasma estradiol concentrations within the treatment target (367−734 pmol/L (100−200 pg/mL)). Likewise, after 11−19 months of FHT only 11 out of 38 individuals (29%) obtained plasma estradiol concentrations within the treatment target.

A total of 19 samples had plasma estradiol concentrations exceeding 1,000 pmol/L during the observational period. Two individuals had plasma estradiol concentrations above 1,000 pmol/L at 2 occasions. All 17 individuals with plasma levels above 1,000 pmol/L received transdermal estradiol treatment.

On the contrary, 50 individuals out of 61 (82%) had plasma estradiol concentrations below the lower limit of the treatment target after 1−5 months of FHT, and throughout the observational period more than 40% of the transfeminine individuals had sub therapeutic estradiol plasma levels.

Plasma concentrations of testosterone and free testosterone were all within the established target range (identical to the reference range for cis-women) for FHT after 1−5 months of therapy and remained within the target range throughout the observational period (data not shown).

Safety

No adverse side effects were observed during the observational period. Particularly, there were no cases of thromboembolic disease. The predominant unintended biochemical side effect was hyperprolactinemia. All individuals had normal plasma prolactin levels prior to FHT however, after 1−5 months of FHT, 24 individuals (33%) had plasma prolactin levels above the upper reference level and 20 individuals (54%) after 11 months of FHT (Figure 2). Despite relevant treatment adjustment including reduction of cyproterone acetate and/or estradiol dose, plasma prolactin levels remained elevated throughout our observation. No correlation between increased plasma estradiol concentrations and hyperprolactinemia was found (data not shown). During the observational period no individuals were diagnosed with

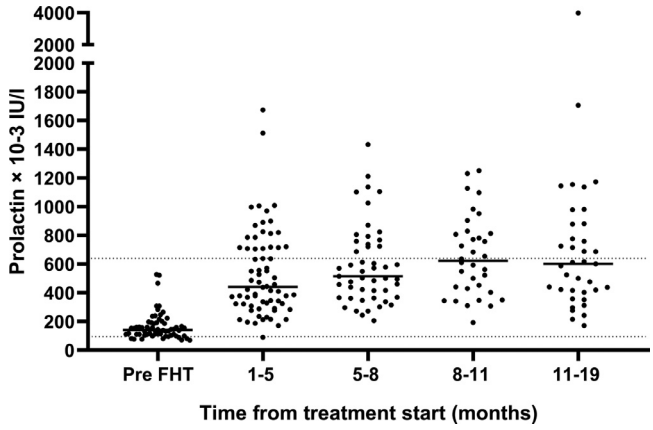

Figure 2. Plasma concentrations of prolactin during the first months of FHT. The dotted lines define the reference range for premenopausal cis-women. Prolactin was analyzed by electrochemiluminescence.

prolactinomas. Magnetic resonance imaging (MRI) is not routinely performed at the Center for Gender Identity; Aalborg University Hospital. MRI of the pituitary gland is performed if seprolactin exceeds 2,000 IU/l at 2 consecutive measurements, which did not occur in any of the transfeminine individuals.

A significant decrease in total cholesterol was observed after the initiation of FHT. Likewise, high-density lipoprotein decreased significantly whereas low-density lipoprotein remained unchanged during the first year of FHT. Hemoglobin and erythrocyte volume fraction also decreased significantly approximating female reference ranges. Markers of liver damage remained unchanged along with hemoglobin A1c (HbA1c) which was also unaffected (Table 1).

DISCUSSION

Evaluation of guideline-based treatment is of great importance in order to ensure and improve efficacy and safety of GAHT. In this study, we evaluated plasma hormone concentrations in transfeminine individuals during the start-up of their gender transition. The focus of the study was primarily on the biochemical changes because these analyses are a compelling measure used in the guidance of FHT.[5] Plasma estrogen levels are used to evaluate estradiol treatment efficacy. Likewise, biochemical changes are monitored in the assessment of potential side effects including prolactinomas.[6] On that ground, we brought special focus on the plasma concentrations of estrogen and prolactin.

In this cohort study, we found a considerable variation of estrogen plasma concentrations. Pronounced increases in both estrogen and prolactin levels were observed after the initiation of FHT. Despite the widespread plasma concentrations of both estrogen and prolactin, FHT seems to be well tolerated. No adverse side effects were observed despite plasma concentrations sporadically exceeding the upper reference range. The guidelines for FHT recommended by the Endocrine Society have given rise to different interpretations at clinics in the Nordic countries. Both levels and breadth of the hormone target ranges vary considerably across the clinics. This study demonstrates that regardless of the intention of implying a narrow target range the actual plasma estradiol concentration varies greatly. However, despite plasma estradiol concentrations being scattered over the comprehensive reference range for cis-women, we do not observe any adverse metabolic changes or thromboembolic events. This result indicates that despite the difficulties in obtaining plasma levels within the locally determined treatment target FHT is safe.

Individuals with plasma estrogen concentrations exceeding 1,000 pmol/L were all treated with transdermal estradiol. Whether these increased levels are true, or some samples are elevated due to contamination or self-medication is unknown. However, it is well-known that transdermal administration of estradiol provides more consistent plasma concentrations.[12]

Prolactin plasma concentrations are monitored in all clinics in the Nordic countries. Many clinicians reduce the dose of estradiol if hyperprolactinemia occurs.[6] Our data show a significant increase in prolactin concentrations after 11 months of FHT in accordance with previous observations[13] but no correlation between estradiol levels and prolactin levels was observed. Bisson et al did not find increasing prolactin levels in transfeminine individuals. However, the individuals in that study received spironolactone and not cyproterone acetate.[14] Unfortunately, due to the limited size of our study population regarding statistical analyses, no definite conclusion can be drawn on this matter. However, our observations support that cyproterone acetate triggers hyperprolactinemia and the specific effect of reducing estradiol based on plasma prolactin concentrations should be investigated further in a larger cohort. Furthermore, it might be too soon to conclude that there were no prolactinomas in individuals with elevated prolactin, since MRI was not performed during the study period.

In accordance with previous observations,[15] no unfavorable biochemical changes were observed during the first year of FHT. Liver enzymes and HbA1c were stable in the lower end of the reference range. Total cholesterol decreased to a more desirable level and hemoglobin concentration together with erythrocyte volume fraction decreased approximating the normal level for cis-women. This decrease in hematological values manifests the need for specific reference range for transgender persons. In order to provide a sufficient standard of medical care for transgender persons, it is essential to clarify how GAHT affects all biochemical analyses with gender specific reference range.[16]

Being transgender is no longer a diagnosis in Denmark and the treatment has been depathologized accordingly.[17] Hence the treatment aim is alleviating relevant somatic and psychiatric morbidities. This study shows a pronounced psychiatric comorbidity burden in these transgender individuals, in accordance with previous studies.[18,19] Awareness of this issue is crucial since evaluation of treatment efficacy must also focus on the improvement of the psychological discomfort of these individuals. Hence, the improvement of the psychological discomfort in transgender individuals after initiating FHT should be investigated further in future studies.

The present study is partly limited by the short follow-up. To fully understand the biological and biochemical changes induced by FHT long time follow-up is essential. Furthermore, although this cohort shows no adverse effect, it should be noted that many of the transfeminine individuals had subtherapeutic plasma estradiol concentrations. However, this study elucidates the short-term biochemical changes that occur when FHT is initiated. These observations provide indispensable knowledge to the sparse evidence in the area of transgender medicine.

CONCLUSION

The recommended target levels are difficult to attain in transfeminine individuals in the first year of FHT. However, all individuals had plasma estradiol levels within the reference range of cis-

women including the reference range covering the ovulation phase after 11−19 months. An extension of the existing narrow target range would enable a tailored treatment for transfeminine individuals thus accommodating their needs. This would relieve the psychological discomfort and prevent the urge to self-medicate. Furthermore, it seems that individuals in FHT approach female reference ranges concerning hematological parameters. This observation calls for further investigations with the intention of determining specific transgender reference ranges.

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STATEMENT OF AUTHORSHIP

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