LONGITUDINAL CHANGES IN LIVER ENZYME LEVELS AMONG TRANSGENDER PEOPLE RECEIVING GENDER AFFIRMING HORMONE THERAPY

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BACKGROUND & METHODOLOGY

- **Hypothesis:** Data from animal models and also epidemiological studies have shown that estrogen plays a protective effect against NAFLD while testosterone has the opposite effect, also animal models have shown that the extra dose of X chromosome in absence of estrogen accelerates fat deposit in the liver, we hypothesize that estradiol in transfemale decreases the level of liver enzyme and therefore the risk of NAFLD whereas testosterone increases the level of hepatic enzymes and therefore steatohepatitis and NAFLD in transmale.
- **Terminology:** Transfemale (TF), Transmale (TM), cisgender, sex, gender, transsexual, Gender Affirming Hormone Treatment (GAHT)
- Estradiol may affect liver function through its action on estrogen receptor α, which acts as a coordinator of energy metabolism in the liver. Estrogen fluctuation affects synthesis of fatty acids and cholesterol, which in turn may be linked to liver enzyme production and regulation
- The effect of testosterone on liver function is less understood although it is known that liver contains androgen receptors and testosterone is converted to estradiol by sequential actions of 5α-reductase and aromatase.
- Both lack of testosterone in men with hypogonadism and excess of testosterone in women diagnosed with polycystic ovary syndrome increase the risk of non-alcoholic fatty liver disease, and therefore may result in abnormal levels of liver enzymes.
- The data for this longitudinal study included 624 transfeminine (TF) and 438 transmasculine (TM) people and 4,090 cisgender males and 4,797 cisgender females enrolled in three integrated health systems. Time under observation in both groups was divided into two intervals: from the first blood test to the first filled GAHT prescription and from GAHT initiation to the most recent blood test result.

RESULTS AND CONCLUSION

- **Results:** Among TM study participants, the post GAHT ratios-of-ratios for AST were 1.61 (95% CI: 1.13, 2.31) and 1.57 (95% CI: 1.06, 2.31) relative to cisgender males and females respectively. For ALT, the corresponding comparisons yielded the ratios-of-ratios (95% CIs) of 2.06 (1.67, 2.54) and 1.90 (1.50, 2.40).
- No discernable changes were observed among TF participants. Other factors associated with higher enzyme levels included alcohol use/abuse and BMI ≥25 kg/m^2.

- **Conclusion:** Feminizing GAHT is unlikely to influence ALT and AST levels. Clinical significance of the observed association between masculinizing GAHT and liver enzymes levels is not clear and requires further investigation

- **Limitation: Lack of access to ICD codes for non-Alcoholic Fatty Liver disease (NAFLD), therefore unable to explore the association of these changes to clinical outcomes like NAFLD,**

Acronyms: ALT= alanine aminotransferase; AST= aspartate transaminase; CI= confidence interval; CM= cisgender males; GAHT= gender affirming hormone therapy; KPNC= Kaiser Permanente Northern California; TM= transmasculine

TABLE 1. CHARACTERISTICS OF THE TRANSGENDER AND MATCHED REFERENCE COHORTS*

Participant characteristics	TF Cohort (n = 624)	TM Cohort (n = 438)	CM Referents (n = 4090)	CF Referents (n = 4797)
Membership site				
KPNC	359 (57.5)	300 (68.5)	2494 (61.0)	3026 (63.1)
KPSC	252 (40.4)	135 (30.8)	1536 (37.6)	1725 (36.0)
KPGA	13 (2.1)	3 (0.7)	60 (1.5)	46 (1.0)
Race/ethnicity				
Non-Hispanic white	348 (55.8)	271 (61.9)	2533 (61.9)	2914 (60.7)
Non-Hispanic black	47 (7.5)	45 (10.3)	338 (8.3)	469 (9.8)
Hispanic	119 (19.1)	69 (15.8)	653 (16.0)	812 (16.9)
Asian/Pacific Islander	70 (11.2)	31 (7.1)	412 (10.1)	425 (8.9)
Other/Unknown	40 (6.4)	22 (5.0)	154 (3.8)	177 (3.7)
Age at index date, years				
18-25	195 (31.3)	185 (42.2)	682 (16.7)	987 (20.6)
26-35	155 (24.8)	148 (33.8)	915 (22.4)	1235 (25.7)
36-45	122 (19.6)	58 (13.2)	903 (22.1)	988 (20.6)
46-55	81 (13.0)	37 (8.4)	870 (21.3)	859 (17.9)
>55	71 (11.4)	10 (2.3)	720 (17.6)	728 (15.2)
BMI at index date				
Normal weight/Underweight	275 (44.1)	161 (36.8)	918 (22.4)	1626 (33.9)
Obese	165 (26.4)	118 (26.9)	1431 (35.0)	1228 (25.6)
Overweight	144 (23.1)	142 (32.4)	1414 (34.6)	1603 (33.4)
Unknown	40 (6.4)	17 (3.9)	327 (8.0)	340 (7.1)
Alcohol use/abuse				
Yes	70 (11.2)	56 (12.8)	595(14.5)	566 (11.8)
No	554 (88.8)	382 (87.2)	3495(85.5)	4231 (88.2)
Lab test data available				
ALT	618 (99.0)	432 (98.6)	4002 (97.8)	4619 (96.3)
AST	240 (38.5)	150 (34.2)	1469 (35.9)	1952 (40.7)
ALT average level				
pre-GAHT	24.0 (19.0)	20.0 (15.0)	28.0 (22.0)	19.0 (15.0)
on-GAHT	19.0 (14.0)	22.0 (18.0)	27.0 (20.0)	19.0 (15.0)
AST average level				
pre-GAHT	23.0 (12.0)	22.0 (12.0)	26.0 (18.0)	21.0 (12.0)
on-GAHT	21.0 (12.0)	23.0 (11.5)	25.0 (17.0)	22.0 (13.0)

Acronyms: ALT= alanine aminotransferase; AST= aspartate transaminase; CI= confidence interval; CM= cisgender males; GAHT= gender affirming hormone therapy; KPNC= Kaiser Permanente Northern California; TM= transmasculine

TABLE 2. MULTIVARIABLE MODELS EVALUATING FACTORS ASSOCIATED WITH LEVELS OF AST AND ALT AMONG TM AND CM STUDY PARTICIPANTS

Parameter of interest	AST		ALT	
	Difference (%)	95% CI	Difference (%)	95% CI
Gender identity (TM vs. CM)	-13	-20, -5	-27	-31, -23
Site (KPNC vs. other)	1	-4, 6	8	5, 12
Age group (years) vs. 18-25				
26-35	3	-3, 9	9	5, 15
36-45	11	3, 17	13	8, 19
46-55	1	-5, 8	1	-3, 6
56+	-1	-7, 6	-8	-12, -3
Race/ethnicity (vs. NHW)				
Non-Hispanic Black	3	-5, 11	-7	-11, -2
Hispanic	3	-3, 9	9	6, 14
Asian/Pacific Islander	-4	-10, 4	3	-1, 8
Other/Unknown	-9	-19, 2	4	-3, 12
Body mass index (kg/m^2) ≥25.0 vs. <25.0	7	3, 13	30	26, 34
Alcohol use/abuse (yes vs. no)	19	13, 25	11	6, 14
Time (10-day increments)				
Pre-GAHT	-2	-7, 2	-10	-12, -7
Post-GAHT	-7	-17, 5	1	-6, 8
Pre-GAHT*gender identity	21	1, 45	26	12, 42
Post-GAHT*gender identity	34	-15, 110	63	26, 114
Calculated adjusted average 10-day change (%)				
TM pre-GAHT	18	-1, 40	14	2, 28
TM post-GAHT	47	4, 108	89	54, 131
CM pre-GAHT	-2	-7, 3	-10	-13, -6
CM post-GAHT	-9	-17, 0	-8	-13, -4
Ratio-of-ratios for 10-day change among TM (post- vs. pre-GAHT)	1.25	0.81, 1.92	1.65	1.28, 2.14
Ratio-of-ratios for post-GAHT 10-day change (TM vs. CM)	1.61	1.13, 2.31	2.06	1.67, 2.54

TABLE 3. MULTIVARIABLE MODELS EVALUATING FACTORS ASSOCIATED WITH LEVELS OF AST AND ALT AMONG TM AND CF STUDY PARTICIPANTS

Parameter of interest	AST		ALT	
	Difference (%)	95% CI	Difference (%)	95% CI
Gender identity (TM vs. CF)	6	-2, 15	7	2, 13
Site (KPNC vs. other)	4	0, 8	8	6, 12
Age group (years) vs. 18-25				
26-35	1	-4, 5	1	-3, 5
36-45	3	-2, 8	3	0, 7
46-55	8	3, 15	12	7, 17
56+	21	15, 28	17	13, 22
Race/ethnicity (vs. NHW)				
Non-Hispanic Black	-2	-7, 4	-12	-16, -8
Hispanic	8	3, 13	7	3, 11
Asian/Pacific Islander	1	-5, 8	-1	-5, 4
Other/Unknown	-3	-11, 6	1	-5, 8
Body mass index (kg/m^2) ≥25.0 vs. <25.0	3	-1, 6	21	19, 25
Alcohol use/abuse (yes vs. no)	11	6, 15	12	7, 15
Time (10-day increments)				
Pre-GAHT	2	-2, 5	-2	-5, 1
Post-GAHT	-5	-15, 6	1	-6, 8
Pre-GAHT*gender identity	13	-4, 31	17	4, 31
Post-GAHT*gender identity	39	-12, 120	62	21, 116
Calculated adjusted average 10-day change (%)				
TM pre-GAHT	15	-1, 33	15	2, 28
TM post-GAHT	52	4, 122	88	49, 136
CF pre-GAHT	2	-2, 6	-2	-5, 1
CF post-GAHT	-3	-11, 6	-1	-6, 4
Ratio-of-ratios for 10-day change among TM (post- vs. pre-GAHT)	1.32	0.85, 2.06	1.64	1.24, 2.17
Ratio-of-ratios for post-GAHT 10-day change (TM vs. CF)	1.57	1.06, 2.31	1.90	1.50, 2.40