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 \( \alpha \), 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 5\( \alpha \)-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:** 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 $\geq 25$ 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>
<thead>
<tr>
<th>Participant characteristics</th>
<th>TF Cohort (n = 624)</th>
<th>TM Cohort (n = 438)</th>
<th>CM Referents (n = 4098)</th>
<th>CF Referents (n = 4797)</th>
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<tbody>
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<td>Membership site</td>
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<td>ALT Difference (%)</td>
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<td>1.67, 2.54</td>
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<td>AST Difference (%) 95% CI</td>
<td>ALT Difference (%) 95% CI</td>
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<td>8 6, 12</td>
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<td>Age group (years) vs. 18-25</td>
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<td>21 15, 28</td>
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<td>Race/ethnicity (vs. NHW)</td>
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<td>Body mass index (kg/m²) ≥25.0 vs. &lt;25.0</td>
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<td>Alcohol use/abuse (yes vs. no)</td>
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<tr>
<td>Time (10-day increments)</td>
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<td>Post-GAHT</td>
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<td>Ratio-of-ratios for 10-day change among TM (post- vs. pre-GAHT)</td>
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<td>Ratio-of-ratios for post-GAHT 10-day change (TM vs. CF)</td>
<td>1.57 1.06, 2.06 1.90 1.50, 2.40</td>
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