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Association between gender affirming hormone therapy and measures of glucose metabolism: A longitudinal study

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Association between gender affirming hormone therapy and measures of glucose metabolism: A longitudinal study

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ABSTRACT

Association between gender affirming hormone therapy and measures of glucose metabolism: A longitudinal study

By Olivia Anike

Background: The effect of gender affirming hormone therapy (GAHT) on glucose metabolism and insulin resistance is an area of priority in transgender health research.

Aim: To analyze longitudinal changes in fasting glucose (FG) and hemoglobin A1c (HbA1c) levels in transfeminine (TF) and transmasculine (TM) persons following GAHT initiation in comparison to corresponding changes in cisgender reference groups.

Methods: The data for this study were collected from electronic health records of individuals enrolled in the Study of Transition and Gender (STRONG) cohort nested within 3 large integrated healthcare systems. The analysis dataset i included 2,735 TF persons compared to 21,447 cis-male (CM) and 23,632 cis-female (CF) referents as well as 2,276 TM participants compared to 14,741 CM and 16,935 CF referents. The follow up time was divided into two intervals: between first blood test (FG or HbA1c) and the day before GAHT initiation, and between GAHT initiation date and the date of the most recent blood test. Linear mixed models were used examine changes in log-transformed FG and HbA1c levels among TF and TM cohorts following GAHT initiation in comparison to cisgender referents. These changes were expressed as relative differences (%) and ratios-of-ratios along with 95% confidence intervals (CI).

Results: Among TF participants, post-GAHT ratios-of-ratios for FG were 7.9 (95% CI: 1.3, 14.6) and 8.1 (95% CI: 2.4, 13.9) depending on the model. The results were in the same direction but not significant for HbA1c. Among TM participants, the model-specific post-GAHT ratios-of-ratios for HbA1c were 8.7 (95% CI: -2.5, 19.9) and 10.0 (95% CI: 0.4, 19.7), while the corresponding results for FG were weaker and not statistically significant. None of the ratio-of-ratios comparing post-GAHT changes among transgender and cisgender study participants were significant. Other factors consistently associated with significantly higher measures of glucose metabolism were advanced age and being obese/overweight.

Conclusion: Though the within-transgender cohort data suggest a slight increase in the levels of FG and HbA1c following GAHT initiation, these changes were not significant when compared to the corresponding changes in cisgender referents. Based on these results it appears unlikely that GAHT has a clinically important effect on glucose metabolism.

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INTRODUCTION

Transgender and gender diverse (TGD) people are characterized by having a gender identity that differs from the sex to which they were assigned at birth (UCSF Gender Affirming Health Program, 2016). TGD individuals are a sizable and growing community that represents approximately 0.5% - 4.5% of the general adult population (Zhang et al., 2020).

TGD people face a number of health risks, some attributable to the unique circumstances associated with their gender identity and some caused by the intersectional social stressors that may result in marginalization of this vulnerable population (Puckett et al., 2018). It has been shown that general health status is the least researched aspect of the global burden of disease for TGD populations, with particularly notable knowledge gaps pertaining to overall and cause-specific mortality as well as various measures of morbidity including incidence of cancer, endocrine and metabolic conditions, and cardiovascular disease (Reisner et al., 2016).

Many TGD people seek gender-affirming hormone therapy (GAHT), a multimodality treatment that involves suppression of endogenous sex hormone secretion from an individual's gonadal sex and continuous maintenance and monitoring of sex hormone levels within a suitable range for an individual's affirmed gender (Hembree et al., 2017). For transfeminine (TF) individuals who choose to receive GAHT, the therapy usually includes one or more medications that reduce androgen production by suppressing pituitary gonadotropin secretions (e.g., leuproreline), competitively block androgen receptors (e.g. spironolactone), or inhibit conversion of testosterone to the more potent dihydrotestosterone (e.g. finasteride). The main feminizing therapy is delivered in the form of oral, parental, or transdermal estradiol sometimes in combination with progesterone (Unger, 2016). Similarly, GAHT for transmasculine (TM) individuals most commonly includes testosterone therapy that reduces gonadotropins and

prolactin hormone concentration levels released by the pituitary gland. There is no standard starting or maintenance dose of testosterone, but it is most commonly taken in intramuscular or topical forms (Irwig, 2017).

The possible metabolic effects of GAHT constitute an important research priority (Feldman et al., 2016; T'Sjoen et al., 2019). Previous studies observed that TGD individuals on feminizing hormones tend to experience a decrease in lean mass and increase in adiposity, while masculinizing GAHT may produce an opposite effect (Spanos et al., 2020). There is also some evidence that feminizing GAHT may worsen insulin resistance and masculinizing GAHT increases early insulin response (Auer et al., 2018; Spanos et al., 2020). These considerations motivated two recent studies evaluating the association between GAHT and risk of type 2 diabetes mellitus (T2DM) in TGD individuals (Islam et al., 2022; Velzen et al., 2022); however, the results of these studies indicated no evidence that incidence of T2DM in persons receiving GAHT differs from that observed in the general population.

The discrepancy between possible GAHT-induced changes in insulin resistance and the lack of clear association between GAHT and overt TD2M requires further exploration. It is important to keep in mind that most studies assessing changes in markers of insulin resistance and glycemic control were relatively small and used either cross sectional or relatively simple before-and-after analytic design without an outside comparison group. For this reason, larger follow up studies of both TGD and cisgender people are needed to better understand the relation of between GAHT and longitudinal changes in measures of glucose metabolism.

With these methodological needs in mind, the goal of the present project was to use data from a large cohort of TGD people to evaluate the relation between GAHT and changes in glucose metabolism over time. Specifically, we sought to estimate the distributions of fasting

blood glucose (FG) and glycosylated hemoglobin (HbA1c) among TM and TF persons receiving GAHT, relative to the corresponding measures in cisgender reference groups, and to evaluate longitudinal changes in these laboratory measures following GAHT initiation.

METHODS

Cohort Ascertainment and Data Collection

All components of this study were reviewed and approved by the Institutional Review Boards from all participating Kaiser Permanente (KP) sites. The details of the study that provided the data for this analysis have been provided in previous publications. (Gerth et al., 2018; Getahun et al., 2018; Quinn et al., 2017). To summarize, the purpose of the Study of Transition, Outcomes, and Gender (STRONG) was to examine the health status of TGD individuals in comparison to cisgender reference cohorts. Members of the STRONG cohort were selected from electronic medical records of individuals enrolled in KP health plans at sites located in Georgia, Northern California, and Southern California from 2006 to 2014.

This study focused on the hormone initiation subcohort, which includes TGD individuals who started GAHT at a KP site after the index date. The index date is defined based on the first recorded evidence of TGD status at KP. The GAHT initiation date was ascertained based on first filled prescription documented in the pharmacy records. The eligible TGD cohort members were categorized as TM or TF based on the organ inventory evidence available in their health records. Each TGD participant was matched to 20 cisgender referents, 10 cis-males (CM) and 10 cis-females (CF), based on index date, age, site and race; however, for the purposes of the current analysis it was not possible to maintain matching strata due to inconsistently available data for the measures of interest. The TGD cohort members and cisgender referents were considered eligible for inclusion in the present analysis if they were at least 18 years old at index date, and had at least one relevant blood test (FG or HbA1c) before and after the GAHT initiation date.

The follow up time was divided into two intervals: between first blood test (FG or HbA1c) and the day before GAHT initiation, and between GAHT initiation date and the date of the most recent blood test. The date of GAHT initiation for TGD individuals was set to a value of 0 so that pre-GAHT time consisted of negative values and post-GAHT time consisted of positive values, all in years. CF and CM referents had time 0 assigned based on GAHT initiation date of their matched TGD counterpart regardless of the available FG or HbA1c levels for the matched TGD participant.

Statistical Analysis

All data analyses were conducted using SAS, version 9.4 (SAS Institute). The main independent variable of interest in all analyses was gender identity (TM, TF, CF, and CM) and the main dependent variables were FG and HbA1c levels. Several longitudinal analyses were performed using linear mixed models to examine how FG and HbA1c levels change over time in relation to GAHT use among TM and TF cohort participants compared to their CF and CM reference groups. Due to inconsistently of the available data for FG and HbA1c across matched sets, we used unmatched data and all models included matching variables: race/ethnicity, age and study site. As obesity may influence FG and HbA1c levels and GAHT may influence adiposity (Spanos et al., 2020), all models also controlled for body mass index (BMI) recorded at or close to the index date. The BMI variable was dichotomized as <25 vs. ≥ 25 kg/m^2.

The linear mixed models method takes into account variation in repeated measures within participants and allows modeling of heterogeneity in FG and HbA1c changes over time by adding a randomized time slope. To assess the change of FG and HbA1c slopes before and after GAHT initiation time separately, the follow up time was centered on this date and coded as

linear splines with a knot at GAHT initiation. These are the scalar forms of the linear mixed models for FG and HbA1c:

$$FG_{ij} = \beta_0 + b_{0i} + \beta_1 trans_{ij} + \beta_2 time\_ht_{ij} + b_{1i} time\_ht_{ij} + \beta_3 posttime_{ij} + b_{2i} posttime_{ij} + \beta_4 trans_{ij} * time\_ht_{ij} + \beta_5 trans_{ij} * posttime_{ij} + \beta_{6*age} + \beta_{7*site} + \beta_{8*race} + \beta_{9*BMI} + e_{ij}$$

$$HbA1c_{ij} = \beta_0 + b_{0i} + \beta_1 trans_{ij} + \beta_2 time\_ht_{ij} + b_{1i} time\_ht_{ij} + \beta_3 posttime_{ij} + b_{2i} posttime_{ij} + \beta_4 trans_{ij} * time\_ht_{ij} + \beta_5 trans_{ij} * posttime_{ij} + \beta_{6*age} + \beta_{7*site} + \beta_{8*race} + \beta_{9*BMI} + e_{ij}$$

In these models, "trans" indicates an individual's TGD status vs. cisgender, "time_ht" is the centered time variable with negative values before GAHT and positive values after, and "posttime" is the time interval from GAHT to the blood test measurement level of FG or HbA1c. "$trans_{ij}$*$time\_ht_{ij}$" and "$trans_{ij}$*$posttime_{ij}$" are interaction terms that show the difference in FG and HbA1c level changes between TGD and cisgender participants. "b_{0i}" is the random intercept for subject i; "b_{1i}" is the random slope over time before GAHT initiation date for subject i; and the sum "b_{1i}+ b_{2i}" is the random slope after GAHT for subject i.

The FG and HbA1c values were log-transformed in all models due to skewed distributions. Linear regression coefficients from the models were exponentiated to find a ratio of mean blood glucose values across different categories of covariates with the final result expressed as a percentage of relative difference. Pre- and post- GAHT changes over time were expressed as the difference by percentage per 10 days. Each model was used to derive these pre- and post-GAHT changes over time as well as 2 relative difference ratios, otherwise known as ratios-of-ratios. The first ratio-of-ratios compared the pre- and post-GAHT changes within each

group separately, while the second ratio-of-ratios compared post-GAHT change in each TGD group to their respective cisgender referents. The measures of association were reported with their corresponding 95% confidence intervals (CIs).

RESULTS

Characteristics of Study Participants

Table 1 summarizes participant characteristics. The dataset included 2,735 TF persons compared to 21,447 CM and 23,632 CF referents as well as 2,276 TM participants compared to 14,741 CM and 16,935 CF referents. Slightly more than half of all TGD and cisgender participants identified as Non-Hispanic white. While age at index date was about evenly distributed across the TF cohort, the TM cohort tended to be younger with 56% of participants under the age of 35 years. The TF cohort included a greater proportion of "normal weight" or "underweight" individuals (39%) compared to their CM (22%) and CF (35%) referents. The corresponding proportions for the TM cohort members and for their CM and CF referents were 35%, 26%, and 38%, respectively. After GAHT initiation, the average FG level among TF cohort members decreased slightly from 98.7 to 96.5 mg/dL, but increased from 91.6 to 94.0 mg/dL among TM participants. The post- and pre-GAHT average HbA1c levels were 6.2% and 6.0%, respectively among TF individuals, and 5.9% and 6.0%, respectively among TM persons (Table 1).

Changes in HbA1c and FG in TF Study Participants Compared to CM and CF Referents

Tables 2 and 3 summarize the results of longitudinal changes in FG and HbA1c levels among TF participants. The measures of glucose metabolism were generally lower among TF participants compared to CM referents (Table 2), with a statistically significant percentage difference for both HbA1c (-3.9, 95% CI: -5.8, -2.1) and FG (-3.6, 95% CI: -5.2, -2.0). When TF participants were compared to CF referents (Table 3) the relative difference was also statistically

significant for HbA1c (-2.1, 95% CI: -3.7, -0.6), but no longer evident for FG (0.9, 95% CI: -0.5, 2.3).

Both FG and HbA1c levels among the TF cohort increased following initiation of feminizing GAHT. The post- vs. pre-GAHT ratio-of-ratios for HbA1c was 5.6 (95% CI: -2.7, 13.8) in Table 2 and 5.4 (95% CI: -1.9, 12.7) in Table 3. For FG, the same ratio-of-ratios was more pronounced and ranged from 7.9 (95% CI: 1.3, 14.6) to 8.1 (95% CI: 2.4, 13.9), depending on the model. When the post-GAHT change was compared in the TF and the two cisgender reference groups, the ratios-of-ratios were small and not statistically significant.

Other factors consistently associated with significant higher measures of glucose metabolism were advanced age and elevated BMI (Tables 2-3). In addition, the minority racial/ethnic groups had consistently higher levels of HbA1c relative to non-Hispanic Whites, while FG levels were significantly elevated only in Hispanics.

Changes in HbA1c and FG in TM Study Participants Compared to CM and CF Referents

Both HbA1c and FG levels were significantly lower among TM participants than in CM reference group (Table 4), but not when compared to CF referents (Table 5). The post- vs. pre-GAHT increases in HbA1c among TM participants were also evident with ratio-of-ratios ranging from 8.7 (95% CI: -2.5, 19.9) to 10.0 (95% CI: 0.4, 19.7), depending on the model. By contrast, the pre- vs. post-GAHT changes in FG were small with all 95% CIs including zero. When post-GAHT laboratory values were compared in TM and CM participants the ratio-of-ratios (95% CI) estimates were 5.6 (-3.0, 14.2) for HbA1c and 0.1 (-9.8, 9.9) for FG (Table 4). The corresponding post-GAHT ratios-of ratios for TM vs. CF cohort members were 6.8 (-0.4, 14.1) for HbA1c and 1.1 (-7.1, 9.4) for FG (Table 5).

As in the analyses of TF and reference cohorts, factors consistently associated with higher HbA1c among TM participants and their respective referents included older age, BMI >25 kg/m^2, and racial/ethnic minority status. For FG, similar associations were observed with older age and BMI >25 kg/m^2, whereas racial/ethnic disparities were primarily evident among Hispanics.

DISCUSSION

These analyses, based on a large longitudinal dataset, yielded several notable findings pertaining to the potential effect of GAHT on basic clinical measures of glucose metabolism. The data showed that at baseline, both TF and TM people had lower levels of HbA1c and, to a lesser extent, FG when compared to CM and CF referents. From the models, we observed that both TGD cohort groups experienced a slight increase in HbA1c and FG following GAHT initiation, but this increase was not always statistically significant. When compared to CM and CF referents, this increase did not result in significant differences in the time period post-GAHT initiation.

It is also important to note that several factors including older age, overweight/obesity, and racial/ethnic minority status were consistently associated with higher FG and HbA1c across all models. As these associations are concordant with expectation, they should increase the level of confidence in the underlying data and modeling approaches.

Several European research groups have analyzed the changes in glucose metabolism in TGD populations following GAHT initiation. A study from Italy investigated metabolic changes in a population of 50 TM individuals following 5 years after GAHT initiation. The researchers found that markers of glucose metabolism, including FG, serum insulin, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) did not change significantly over time (Gava et al., 2018). A different study that looked at metabolic changes in 79 TF participants following feminizing GAHT for 2 years found that there was a significant increase in FG levels (Colizzi et al., 2015). A European study looked at the changes in insulin sensitivity before vs after 1 year of GAHT in 35 TM and 55 TF individuals and found no significant change in FG levels for both

TM and TF groups (Shadid et al., 2020). In another European study with 24 TF and 45 TM individuals that assessed metabolic changes following GAHT initiation, researchers found that there were no significant changes in FG levels for either TM or TF groups (Auer et al., 2018). As noted in a recent review of the literature, a common finding reported across several studies is the GAHT-induced increase in lean muscle mass among TM individuals, and a similar increase in adipose tissue among TF individuals (Spanos et al., 2020). This observation along with results from studies that focused on FG, serum insulin and HOMA-IR (Gava et al., 2018; Colizzi et al., 2015; Shadid et al., 2020) suggest that glucose metabolism is not significantly influenced by testosterone, but it may be plausibly affected by feminizing hormones. These concerns notwithstanding, there is little evidence that GAHT is associated with increased risk of clinically apparent diabetes mellitus in TGD individuals (Islam et al., 2022).

The results discovered in this research are mostly consistent with those found in previous studies. The increase in HbA1c and stagnancy in FG levels reported in the Italian study was also expressed in the results for TM participants compared to CM and CF referents in this research (Gava et al., 2018). The decrease in HbA1c for TF participants was expected and consistent in the results; however, an increase in FG levels for the TF group was expected, and while FG levels slightly increased among TF participants, this change was not significant when compared to CM and CF reference groups (Colizzi et al., 2015). The lack of significant change was reflected in the previous European studies (Auer et al., 2018; Shadid et al., 2020).

This analysis has some notable differences in comparison to previous studies on this topic. A major strength of this analysis was the ability to compare both TF and TM cohorts to cisgender references, while previous studies compared FG and HbA1c levels among TGD from baseline. Another notable difference is the cohort size and duration of follow up. The majority of the

previously mentioned studies also only followed GAHT for up to 5 years, while this research analyzed an average of 2.8 years, with a maximum of up to 10 years, following GAHT initiation. However, the scope of analysis in other studies seems to be greater with outcomes of interest including a broader range of metabolic measures such as HOMA-IR, hematocrit, and serum insulin. A couple analyses also address possible areas of weakness such as including a hormone-naïve population (Shadid et al., 2020) and specifying type of GAHT administered (Gava et al., 2018).

There are several limitations apparent with this research mainly due to the nature of passive data collection through electronic health records. Due to the setup of the STRONG cohort and passive data collection, glucose metabolism lab measures were collected at irregular intervals with different participants having different frequencies of data collection. This inconsistency in frequency in blood test collection can occur due some plausible reasons including missed or forgotten appointments. By collecting these measures passively, they were not initially drawn or scheduled with this research in mind, so more consistent blood tests per participant could have produced more definite results.

Another limitation of this research is that there is no information on GAHT specifics. Although information on GAHT received through KP is accurately recorded, some participants may have received GAHT elsewhere. It is possible that the time of actual GAHT initiation is not aligned with the time recorded in data collection, meaning not every TGD participant would be hormone-naïve, having received GAHT before time 0. The information collected on GAHT does not include specifics on information such as therapy administration, type, or number of doses, which could have contributed to a more specific analysis.

Another limitation is that data collected for BMI per participant was only collected at index date. It is possible for BMI level to change over time, so if that information had been collected and treated as a time-dependent variable, that may have appeared differently throughout this analysis. Although these analyses were performed with these limitations in mind, it may be helpful regarding data collection for future research.

In future research endeavors, measures that are more sensitive than FG or HbA1c may be useful to analyze changes in glucose metabolism over time, such as HOMA-IR to estimate insulin resistance (Gayoso-Diz et al., 2011). HOMA-IR would offer a more direct measure of insulin resistance for analyses concerned with T2DM outcomes. Several studies do consider HOMA-IR levels when researching insulin resistance and metabolic changes in a TGD population following GAHT initiation (Auer et al., 2018; Shadid et al., 2020). Additional analyses would be necessary to determine if TGD people experience glucose metabolism changes and insulin resistance, with a measure such as HOMA-IR, due to GAHT initiation that are clinically significant in association with T2DM.

CONCLUSION

In summary, although the within-TGD cohort data suggest a GAHT-induced inflection point in the levels of FG and HbA1c, there is little evidence that these changes are clinically significant especially when compared to the corresponding changes in cisgender referents. Taken together, these results offer reassurance that the effect of GAHT on glucose metabolism, if any, should be viewed as relatively minimal. Further investigation of association between GAHT use and more sensitive markers of glucose metabolism, including various measures of insulin resistance, may offer additional insight into this issue.

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TABLES

Table 1. Characteristics of the Transgender and Matched Reference Cohorts[a]

Participant Characteristics[b] (N =81766)	TF Cohort (n = 2735)	CM Referents (n = 21447) [c]	CF Referents (n =23632)	TM Cohort (n =2276)	CM Referents (n = 14741)	CF Referents (n =16935)
Membership site						
KPNC	1112 (40.7%)	8954 (41.8%)	10171 (43.0%)	737 (32.4%)	5002 (33.9%)	6079 (35.9%)
KPSC	1579 (57.7%)	12141 (56.6%)	13079 (55.3%)	1498 (65.8%)	9470 (64.2%)	10527 (62.2%)
KPGA	44 (1.6%)	352 (1.6%)	382 (1.6%)	41 (1.8%)	269 (1.8%)	329 (1.9%)
Race/ethnicity						
Non-Hispanic white	1495 (54.7%)	12130 (56.6%)	13053 (55.2%)	1346 (59.1%)	8903 (60.4%)	10032 (59.2%)
Non-Hispanic black	183 (6.7%)	1412 (6.6%)	1676 (7.1%)	204 (9.0%)	1279 (8.7%)	1654 (9.8%)
Asian/Pacific Islander	250 (9.1%)	2122 (9.9%)	2237 (9.5%)	160 (7.0%)	1101 (7.5%)	1193 (7.0%)
Hispanic	563 (20.6 %)	4303 (20.1%)	4932 (20.9%)	395 (17.4%)	2667 (18.1%)	3094 (18.3%)
Other/unknown	244 (8.9%)	1480 (6.9%)	1734 (7.3%)	171 (7.5%)	791 (5.4%)	962 (5.7%)
Age at index date, years						
18-25	428 (19.4%)	2262 (12.4%)	2888 (14.5%)	520 (32.1%)	2633 (23.2%)	3373 (26.3%)
26-35	417 (18.9%)	3115 (17.0%)	3661 (18.4%)	527 (23.5%)	3570 (31.4%)	4179 (32.4%)
36-45	444 (20.1%)	4042 (22.1%)	4288 (21.6%)	281 (17.4%)	2331 (20.5%)	2468 (19.1%)
46-55	453 (20.5%)	4256 (23.2%)	4349 (21.9%)	177 (10.9%)	1698 (15.0%)	1745 (13.5%)
>55	468 (21.2%)	4645 (25.4%)	4706 (23.7%)	115 (7.1%)	1122 (9.9%)	1129 (8.8%)
BMI at index date, kg/m^2						
Normal/Underweight (<25)	1064 (38.9%)	4642 (21.6%)	8168 (34.6%)	784 (34.5%)	3782 (25.7%)	6331 (37.4%)
Overweight (25-30)	760 (27.8%)	7434 (34.7%)	6001 (25.4%)	575 (25.3%)	4904 (33.3%)	4072 (24.0%)
Obese (>30)	682 (24.9%)	7186 (33.5%)	7300 (30.9%)	771 (33.9%)	4922 (33.4%)	5358 (31.6%)
Unknown	229 (8.4%)	2185 (10.2%)	2163 (9.2%)	146 (6.4%)	1133 (7.7%)	1174 (6.9%)
# FG tests pre-HT						
1-2	1834 (55.7%)	8761 (35.2%)	10198 (40.1%)	1118 (46.1%)	4290 (41.2%)	5438 (44.6%)
3-6	967 (29.4%)	8598 (34.6%)	9505 (37.4%)	998 (41.2%)	3631 (34.8%)	4732 (38.8%)
>6	490 (14.9%)	7526 (30.2%)	5709 (22.5%)	308 (12.7%)	2505 (24.0%)	2015 (16.5%)
# FG tests on-HT						
1-2	1564 (48.5%)	8857 (44.1%)	10256 (50.3%)	1269 (68.6%)	4041 (66.8%)	4866 (74.0%)
3-6	1072 (33.3%)	7383 (36.8%)	6841 (33.5%)	434 (23.5%)	1561 (25.8%)	1442 (21.9%)

>6	588 (18.2%)	3837 (19.1%)	3303 (16.2%)	147 (8.0%)	452 (7.5%)	269 (4.1%)
# HbA1c tests pre-HT						
1-2	1087 (57.0%)	6313 (38.0%)	7147 (44.3%)	1096 (65.4%)	3172 (46.8%)	4039 (51.9%)
3-6	429 (22.5%)	3675 (22.1%)	3295 (20.4%)	344 (20.5%)	1308 (19.3%)	1637 (21.0%)
>6	392 (20.6%)	6623 (39.9%)	5706 (35.3%)	236 (14.1%)	2293 (33.9%)	2111 (27.1%)
# HbA1c tests on-HT						
1-2	1268 (43.2%)	8159 (38.5%)	9445 (44.8%)	1120 (62.5%)	3665 (55.0%)	4816 (61.0%)
3-6	945 (32.2%)	6270 (29.6%)	6344 (30.1%)	490 (27.4%)	1785 (26.8%)	2273 (28.8%)
>6	725 (24.7%)	6739 (31.8%)	5303 (25.1%)	181 (10.1%)	1209 (18.2%)	807 (10.2%)
FG level pre-HT, mean (SD), mg/dL	98.7 (25.0)	108.5 (39.6)	100.4 (33.1)	91.6 (19.2)	102.6 (35.0)	96.1 (30.1)
FG level on-HT, mean (SD), mg/dL	96.5 (19.8)	107.0 (35.0)	101.0 (31.2)	94.0 (27.7)	103.2 (34.7)	95.8 (26.1)
HbA1c level pre-HT, %	6.2 (1.5)	7.0 (1.8)	6.8 (1.8)	5.9 (1.23)	6.8 (1.9)	6.7 (1.9)
HbA1c level on-HT, %	6.0 (1.2)	6.8 (1.7)	6.5 (1.6)	6.0 (1.3)	6.5 (1.6)	6.3 (1.6)

KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPGA = Kaiser Permanente Georgia; FG = fasting glucose' HbA1c= glycosylated hemoglobin; HT= hormone therapy; TF= transfeminine; TM= transmasculine; CF= cis-females, CM= cis-males

[a] Average number of matched referents to each transgender cohort member is <10 because data are limited to subjects with at least one blood test available before and after HT date

[b] Calculated as n (%) for membership site, race/ethnicity, age, and # lab tests, and as mean (standard deviation) for average FG (mg/dL) and HbA1c (%) levels.

Table 2. Multivariable models evaluating factors associated with levels of HbA1c and FG among TF and CM study participants

Parameter of interest		HbA1c		FG	
		Difference (%)	**95% CI**	**Difference (%)**	**95% CI**
Gender identity (TF vs. CM)		-3.9	-5.8, -2.1	-3.6	-5.2, -2.0
Site (KPNC vs. other)		-0.1	-1.0, 0.8	-2.5	-3.3, -1.6
Age group (years) vs. 18-25					
	26-35	3.1	1.7, 4.5	2.9	1.7, 4.2
	36-45	7.4	5.9, 8.8	7.4	6.1, 8.6
	46-55	10.2	8.7, 11.6	11.5	10.2, 12.8
	56+	11.9	10.4, 13.5	14.6	13.1, 16.0
Race/ethnicity (vs. NHW)					
	Non-Hispanic Black	6.1	4.5, 7.7	1.1	-0.5, 2.6
	Hispanic	4.8	3.5, 6.0	2.8	1.6, 3.9
	Asian/Pacific Islander	3.6	2.1, 5.1	1.0	-0.3, 2.3
	Other/Unknown	5.7	3.4, 8.0	1.5	-0.5, 3.5
Body mass index (kg/m^2) ≥25.0 vs. <25.0		4.8	3.7, 5.9	5.1	4.2, 6.1
Time (10-day increments)					
	Pre-GAHT	0.3	0.1, 0.4	0.3	0.2, 0.4
	Post-GAHT	0.1	-0.1, 0.4	0.1	-0.1, 0.3
	Pre-GAHT*gender identity	-0.6	-1.1, 0.01	-0.5	-0.9, -0.1
	Post-GAHT*gender identity	0.4	-0.4, 1.3	0.7	0.01, 1.4
Calculated adjusted average 10-day change (%)					
	TF pre-GAHT	-3.1	-8.7, 2.5	-2.4	-6.3, 1.5
	TF post-GAHT	2.5	-2.3, 7.3	5.6	1.0, 10.1
	CM pre-GAHT	2.6	1.3, 3.9	2.9	1.9, 3.8
	CM post-GAHT	3.9	2.3, 5.5	3.8	2.1, 5.4
Ratio-of-ratios for 10-day change among TF (post- vs. pre-GAHT)		5.6	-2.7, 13.8	7.9	1.3, 14.6
Ratio-of-ratios for post-GAHT 10-day change (TF vs. CM)		-1.4	-6.5, 3.7	1.8	-3.1, 6.7

Acronyms: HbA1c = glycosylated hemoglobin, FG=fasting glucose; CI= confidence interval; CM= cisgender males; GAHT= gender affirming hormone therapy; KPNC= Kaiser Permanente Northern California; TF= transfeminine, NHW: non-Hispanic White

Table 3. Multivariable models evaluating factors associated with levels of HbA1c and FG among TF and CF study participants

Parameter of interest	HbA1c		FG	
	Difference (%)	**95% CI**	**Difference (%)**	**95% CI**
Gender identity (TF vs. CF)	-2.1	-3.7, -0.6	0.9	-0.5, 2.3
Site (KPNC vs. other)	0.0	-0.8, 0.7	-1.2	-1.9, -0.5
Age group (years) vs. 18-25				
26-35	-0.1	-1.1, 0.9	0.8	-0.2, 1.8
36-45	3.1	2.0, 4.2	3.9	2.9, 4.9
46-55	8.5	7.3, 9.6	9.2	8.1, 10.3
56+	10.4	9.1, 11.7	13.0	11.8, 14.2
Race/ethnicity (vs. NHW)				
Non-Hispanic Black	4.0	2.7, 5.2	-0.7	-2.0, 0.5
Hispanic	3.1	2.3, 4.9	1.4	0.4, 2.3
Asian/Pacific Islander	3.6	2.1, 4.0	1.1	-0.01, 2.3
Other/Unknown	5.3	3.5, 7.2	1.8	0.1, 3.4
Body mass index (kg/m^2) ≥25.0 vs. <25.0	4.6	3.8, 5.4	6.0	5.3, 6.7
Time (10-day increments)				
Pre-GAHT	0.2	0.1, 0.3	0.3	0.2, 0.4
Post-GAHT	0.2	-0.02, 0.4	0.0	-0.2, 0.2
Pre-GAHT*gender identity	-0.5	-1.0, 0.03	-0.6	-0.9, -0.2
Post-GAHT*gender identity	0.4	-0.4, 1.1	0.8	0.2, 1.4
Calculated adjusted average 10-day change (%)				
TF pre-GAHT	-2.9	-8.2, 2.3	-2.4	-5.8, 1.0
TF post-GAHT	2.5	-1.6, 6.5	5.7	1.8, 9.6
CF pre-GAHT	2.1	0.9, 3.2	3.2	2.4, 4.0
CF post-GAHT	3.8	2.5, 5.1	3.2	1.8, 4.6
Ratio-of-ratios for 10-day change among TF (post- vs. pre-GAHT)	5.4	-1.9, 12.7	8.1	2.4, 13.9
Ratio-of-ratios for post-GAHT 10-day change (TF vs. CF)	-1.3	-5.5, 2.9	2.5	-1.6, 6.7

Acronyms: HbA1c = glycosylated hemoglobin, FG=fasting glucose; CF= cisgender females; CI= confidence interval; GAHT= gender affirming hormone therapy; KPNC= Kaiser Permanente Northern California; TF= transfeminine, NHW: non-Hispanic White

Table 4. Multivariable models evaluating factors associated with levels of HbA1c and FG among TM and CM study participants

Parameter of interest	HbA1c		FG	
	Difference (%)	95% CI	Difference (%)	95% CI
Gender identity (TM vs. CM)	-3.2	-5.3, -1.2	-5.3	-7.2, -3.3
Site (KPNC vs. other)	-0.1	-1.0, 0.9	-2.4	-3.3, -1.5
Age group (years) vs. 18-25				
26-35	3.3	1.9, 4.7	3.1	1.8, 4.3
36-45	7.6	6.2, 9.1	7.5	6.2, 8.7
46-55	10.3	8.8, 11.8	11.8	10.4, 13.2
56+	11.9	10.3, 13.6	14.6	13.2, 16.1
Race/ethnicity (vs. NHW)				
Non-Hispanic Black	5.9	4.3, 7.5	0.8	-0.7, 2.4
Hispanic	4.8	3.5, 6.0	2.7	1.5, 3.9
Asian/Pacific Islander	3.5	1.9, 5.0	1.1	-0.3, 2.5
Other/Unknown	6.5	4.1, 8.9	1.6	-0.4, 3.7
Body mass index (kg/m^2) ≥25.0 vs. <25.0	4.8	3.7, 5.9	5.1	4.1, 6.1
Time (10-day increments)				
Pre-GAHT	0.3	0.1, 0.4	0.3	0.2, 0.4
Post-GAHT	0.1	-0.1, 0.3	0.1	-0.1, 0.3
Pre-GAHT*gender identity	-0.2	-0.8, 0.4	-0.1	-0.6, 0.3
Post-GAHT*gender identity	0.8	-0.4, 1.9	0.2	-1.0, 1.3
Calculated adjusted average 10-day change (%)				
TM pre-GAHT	0.7	-4.8, 6.1	1.4	-2.8, 5.6
TM post-GAHT	9.3	0.9, 17.8	3.8	-5.9, 13.5
CM pre-GAHT	2.7	1.4, 3.9	2.8	1.9, 3.8
CM post-GAHT	3.8	2.2, 5.3	3.7	2.1, 5.4
Ratio-of-ratios for 10-day change among TM (post- vs. pre-GAHT)	8.7	-2.5, 19.9	2.5	-9.0, 13.9
Ratio-of-ratios for post-GAHT 10-day change (TM vs. CM)	5.6	-3.0, 14.2	0.1	-9.8, 9.9

Acronyms: HbA1c = glycosylated hemoglobin, FG=fasting glucose; CI= confidence interval; CM= cisgender males; GAHT= gender affirming hormone therapy; KPNC= Kaiser Permanente Northern California; TM= transmasculine, NHW: non-Hispanic White

Table 5. Multivariable models evaluating factors associated with levels of HbA1c and FG among TM and CF study participants

Parameter of interest	HbA1c		FG	
	Difference (%)	95% CI	Difference (%)	95% CI
Gender identity (TM vs. CF)	-1.8	-3.6, -0.1	-1.1	-2.3, 0.6
Site (KPNC vs. other)	0.0	-0.8, 0.7	-1.2	-1.9, -0.5
Age group (years) vs. 18-25				
26-35	0.1	-1.0, 1.1	0.9	-0.09, 1.9
36-45	3.3	2.2, 4.4	3.9	2.9, 4.9
46-55	8.7	7.4, 9.8	9.4	8.3, 10.5
56+	10.5	9.2, 11.8	13.0	11.8, 14.3
Race/ethnicity (vs. NHW)				
Non-Hispanic Black	3.8	2.6, 5.0	-0.9	-2.2, 0.3
Hispanic	3.0	2.0, 4.0	1.2	0.2, 2.2
Asian/Pacific Islander	3.5	2.2, 4.8	1.2	0.02, 2.4
Other/Unknown	6.0	4.1, 7.9	1.8	0.2, 3.5
Body mass index (kg/m^2) ≥25.0 vs. <25.0	4.7	3.9, 5.4	6.0	5.3, 6.8
Time (10-day increments)				
Pre-GAHT	0.2	0.1, 0.3	0.3	0.2, 0.4
Post-GAHT	0.1	-0.05, 0.3	0.0	-0.2, 0.2
Pre-GAHT*gender identity	-0.2	-0.7, 0.3	-0.2	-0.6, 0.2
Post-GAHT*gender identity	0.9	-0.1, 1.8	0.3	-0.7, 1.3
Calculated adjusted average 10-day change (%)				
TM pre-GAHT	0.4	-4.6, 5.5	1.1	-2.6, 4.8
TM post-GAHT	10.5	3.4, 17.6	4.3	-3.8, 12.4
CF pre-GAHT	2.2	1.0, 3.3	3.2	2.4, 4.0
CF post-GAHT	3.6	2.3, 4.9	3.2	1.8, 4.6
Ratio-of-ratios for 10-day change among TM (post- vs. pre-GAHT)	10.0	0.4, 19.7	3.2	-6.5, 12.9
Ratio-of-ratios for post-GAHT 10-day change (TM vs. CF)	6.8	-0.4, 14.1	1.1	-7.1, 9.4

Acronyms: HbA1c = glycosylated hemoglobin, FG=fasting glucose; CI= confidence interval; CF= cisgender females; GAHT= gender affirming hormone therapy; KPNC= Kaiser Permanente Northern California; TM= transmasculine, NHW: non-Hispanic White