Effects of Gender-Affirming Hormone Therapy on Insulin Sensitivity and Incretin Responses in Transgender People

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OBJECTIVE

The long-term influences of sex hormone administration on insulin sensitivity and incretin hormones are controversial. We investigated these effects in 35 transgender men (TM) and 55 transgender women (TW) from the European Network for the Investigation of Gender Incongruence (ENIGI) study.

RESEARCH DESIGN AND METHODS

Before and after 1 year of gender-affirming hormone therapy, body composition and oral glucose tolerance tests (OGTTs) were evaluated.

RESULTS

In TM, body weight (2.8 ± 1.0 kg; $P < 0.01$), fat-free mass (FFM) (3.1 ± 0.9 kg; $P < 0.01$), and waist-to-hip ratio (−0.03 ± 0.01; $P < 0.01$) increased. Fasting insulin (−1.4 ± 0.8 mU/L; $P = 0.08$) and HOMA of insulin resistance (HOMA-IR) (2.2 ± 0.3 vs. 1.8 ± 0.2; $P = 0.06$) tended to decrease, whereas fasting glucose (−1.6 ± 1.6 mg/dL), glucose-dependent insulinotropic polypeptide (GIP) (−1.8 ± 1.0 pmol/L), and glucagon-like peptide 1 (GLP-1) (−0.2 ± 1.1 pmol/L) were statistically unchanged. Post-OGTT areas under the curve (AUCs) for GIP (2,068 ± 1,134 vs. 2,645 ± 1,248 [pmol/L] × min; $P < 0.01$) and GLP-1 (2,352 ± 796 vs. 2,712 ± 1,015 [pmol/L] × min; $P < 0.01$) increased. In TW, body weight tended to increase (1.4 ± 0.8 kg; $P = 0.07$) with decreasing FFM (−2.3 ± 0.4 kg; $P < 0.01$) and waist-to-hip ratio (−0.03 ± 0.01; $P < 0.01$). Insulin (3.4 ± 0.8 mU/L; $P < 0.01$) and HOMA-IR (1.7 ± 0.1 vs. 2.4 ± 0.2; $P < 0.01$) rose, fasting GIP (−1.4 ± 0.8 pmol/L; $P < 0.01$) and AUC GIP dropped (2,524 ± 178 vs. 1,911 ± 162 [pmol/L] × min; $P < 0.01$), but fasting glucose (−0.3 ± 1.4 mg/dL), GLP-1 (1.3 ± 0.8 pmol/L), and AUC GLP-1 (2,956 ± 180 vs. 2,864 ± 93 [pmol/L] × min) remained unchanged.

CONCLUSIONS

In this cohort of transgender persons, insulin sensitivity but also post-OGTT incretin responses tend to increase with masculinization and to decrease with feminization.

Despite the well-established influence of sex hormones on body composition (1–3), and the evident association between body composition and insulin sensitivity (4), the direct effects of sex hormones on insulin sensitivity are inconclusive. Results of in vivo administration of sex hormones on (markers of) whole-body insulin sensitivity vary greatly, among others, according to the physiological circumstances of their administration and research setting. For instance, estrogens increase hepatic insulin

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sensitivity as well as pancreatic insulin release in mice (5–7); however, when administered to women, both before menopause as oral contraceptives and after menopause as hormone replacement therapy, estrogens have been demonstrated to both increase (8) and decrease (9–11) whole-body insulin sensitivity.

Analogously, although hypogonadism is associated with an unfavorable metabolic profile and higher risk of insulin resistance and type 2 diabetes (12), exogenous testosterone administration in hypogonadal men with or without the metabolic syndrome and/or type 2 diabetes has only shown minimal and inconsistent improvements in insulin sensitivity (13–18). Moreover, total testosterone levels are generally increased in viscerally obese and insulin-resistant women, but decreased in obese, insulin-resistant men (19).

Apparently, effects of sex hormones on whole-body insulin sensitivity are complex and might differ between sexes and in physiological versus pathophysiological circumstances. In addition, they may be confounded and perhaps overwhelmed by other variables such as genetic determinants, age, physical activity, or smoking.

Particularly interesting components in this complex relationship are the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), because they are linked to both insulin resistance and sex hormones. In physiological circumstances, incretins amplify the insulin response to oral glucose ingestion two- to threefold and increase net insulin sensitivity (20); conversely, postprandial incretin response is thought to be impaired in obesity, insulin resistance, and type 2 diabetes in most (20–23), but not all (24,25), reports. However, because GLP-1 receptors are also abundantly represented throughout the reproductive system (26), it is has been suggested that incretins and fertility/sex hormones are also interconnected. Indeed, GLP-1 and its receptor agonists are suggested to exert positive influences on different aspects concerning fertility, such as gonadotropin-releasing hormone and leutinizing hormone release (26), polycystic ovary syndrome (26), and male testosterone production; however, results of the latter two might be confounded by the direct or indirect insulin-sensitizing effects of GLP-1 agonists (27), and it therefore remains unclear if, and to what extent, sex hormones and incretins actually affect each other directly, within or without the context of insulin sensitivity.

A study design involving long-term cross-gender sex hormone administration could shed light on the matter and help distinguish the effects of sex hormones on *1*) in vivo human insulin sensitivity and *2*) incretin hormone dynamics from other influences. Short-term administration of one single sex hormone might not represent the full physiological reality, and, in addition, sex hormones are mutually interactive and may influence similar compensatory mechanisms in parallel or opposite directions.

The purest manner to examine whether any differences in insulin sensitivity between sexes are truly sex dependent is to study people undergoing hormonal sex change.

The European Network for the Investigation of Gender Incongruence (ENIGI) is an ongoing multicenter prospective cohort study in transgender people (see Research Design and Methods) (28), which allows for longitudinal assessment of gender differences and changes. At the Ghent, Belgium site, we studied the effects of gender-affirming hormone therapy on markers of insulin sensitivity and glucose metabolism during an oral glucose tolerance test (OGTT). Given the above-mentioned complicated relationship among insulin resistance, incretins, and sex hormones, we made use of this unique opportunity to include incretin dynamics in this evaluation in order to increase insight into this potential physiological correlation.

RESEARCH DESIGN AND METHODS

Subjects

Between February 2010 and September 2014, 313 hormone-naive transgender persons were treated at the Department of Endocrinology of Ghent University Hospital and included in the ENIGI study. This multicenter prospective cohort study, conducted by four major European gender centers (Amsterdam, Ghent, Florence, and Oslo), systematically records data from exogenous sex hormone-naive transgender people upon first clinical contact. Protocolled endocrine and psychological analysis were performed before initiation of gender-affirming hormones and at regular prospective intervals. Approval by our local institutional review board was obtained for this study, as well as written informed consent from the patients.

Between February 2010 and July 2013, an OGTT was performed at baseline and after a year of gender-affirming hormone treatment until this was removed from the ENIGI protocol for logistic reasons. At the Ghent site, we obtained complete pre- and posttreatment OGTTs from 35 Caucasian transgender men (TM; birth-assigned women with masculinizing hormone treatment) and 55 Caucasian transgender women (TW; birth-assigned men with feminizing hormone treatment) between the ages of 18 and 64 years.

Gender-Affirming Hormone Treatment

Following World Professional Association for Transgender Health Standards of Care, version 7 guidelines (28), TW were given the antiandrogen cyproterone acetate (Androcur; Bayer, Brussels, Belgium) 50 mg once daily, usually in combination with oral estradiol valerate (Progynova; Bayer) 2 mg twice daily. In patients older than 45 years, however, estradiol was administered in patches (Dermestril; Besins Healthcare, Brussels, Belgium) (100 μg/72 h) or transdermal gels (Estrogel; Besins Healthcare) (1.5 mg twice daily) to decrease the risk of deep venous thrombosis. In TM, testosterone was administered via intramuscular long-acting testosterone (Nebido; Bayer) 1,000 mg, once every 12 weeks.

Study Protocol and OGTTs

At baseline and after 1 year of hormone treatment, we assessed body height and weight as well as minimal and maximal circumferences of waist and hip, respectively. Body composition and bone mineral content were measured using DXA.

After an overnight fast, baseline blood samples were drawn for sex steroid and pituitary hormone assessment. Plasma glucose, insulin, GLP-1, and GIP were measured at baseline as well as 30, 60, and 120 min following ingestion of 75 g glucose in 200 mL water (OGTT). In addition, areas under the curve (AUCs) of all hormones were assessed. All studies were repeated after 1 year of hormone therapy. Of note, the timing of the last

hormone dosing before an OGTT was not taken into account.

Daily physical activity (both exercise and habitual "nonexercise" movement) was assessed using the questionnaire by Baecke et al. (29) and expressed as a total activity score, a higher score indicating higher overall physical activity.

Laboratory Analysis

Serum levels of estradiol, total and free testosterone, sex hormone–binding globulin, and albumin were assessed as described previously (30). Plasma glucose (Cobas 8000 c701 module; limit of quantitation [LOQ]: 2 [−750] mg/dL; coefficient of variation [CV]: 0.92%) (Roche), total cholesterol (Cobas 8000 c502 module; LOQ: 3.86 [−800] mg/dL; CV: 1.33%) (Roche), free fatty acids (FFAs) (Cobas 8000 c701 module; LOQ: 0.01 [−4.00] mEq/L; CV: 1.5%) (Roche), and HDL cholesterol (Cobas 8000 c701 module; LOQ: 3 [−120] mg/dL; CV: 1.82%) (Roche) were assessed using competitive chemoluminescent assays. Serum LDL levels were calculated using Friedewald's formula: (LDL-cholesterol [mg/dL] = total cholesterol [mg/dL] − triglycerides [mg/dL]/5) − HDL cholesterol (mg/dL). A HOMA index was calculated using: HOMA of insulin resistance (HOMA-IR) = (glucose [mg/dL] × insulin [mg/dL])/405 (31).

GIP and GLP-1 were measured at the Novo Nordisk Foundation Center for Basic Metabolic Research using methods described previously in several articles (23). Total GIP and GLP-1 concentrations in plasma were measured after extraction of plasma with 70% ethanol (v/v, final concentration). For the GIP radioimmunoassay, we used the C-terminally directed antiserum code 867, which was raised against a synthetic peptide corresponding to the C-terminus of human GIP. It does not cross-react with the so-called GIP 8000, for which chemical nature and relationship to GIP secretion is uncertain. It reacts fully with the primary metabolite GIP 3-42. Human GIP and ^{125}I human GIP (70 MBq/nmol) were used for standards and tracer. The plasma concentrations of GLP-1 were measured against standards of synthetic GLP-1 7-36 amide using antiserum code number 89390, which is specific for the amidated C-terminus of GLP-1 and therefore does not react with GLP-1–containing peptides from the pancreas. The results of the assay accurately reflect the rate of secretion of GLP-1 because the assay measures the sum of intact GLP-1 and the primary metabolite, GLP-1 9-36 amide, into which GLP-1 is rapidly converted. For both assays, sensitivity was <1 pmol/L, intrassay CV <6% at 20 pmol/L, and recovery of standard, added to plasma before extraction, ~100% when corrected for losses inherent in the plasma extraction procedure.

Statistical Analysis

Data were analyzed using IBM SPSS 24.0 software. Intervention effects were analyzed using paired *t* tests for normally distributed data and nonparametric Wilcoxon matched-pairs signed-ranks test for nonnormally distributed data. Between-group differences were assessed with independent *t* tests and ANOVA. The significance level was set at $\alpha = 0.05$. Bonferroni-Holm correction was performed to adjust for multiple comparisons.

RESULTS

Baseline

Baseline characteristics are shown in Table 1. TW comprised a larger cohort and were older than TM ($P < 0.001$). Both populations were lean and differed in body composition as expected, TW having a more centripetal fat distribution and TM a lower waist-to-hip ratio (WHR) at baseline compared with the other group.

Two TM and three TW had impaired fasting glucose/prediabetes based on the 2019 American Diabetes Association guideline classifications; for all other subjects, fasting plasma glucose and insulin levels could be classified as normal. Four additional TM and four TW had 120-min plasma glucose levels >140 mg/dL, but none reached American Diabetes Association criteria for type 2 diabetes. Insulin ($P < 0.001$) and HOMA-IR ($P < 0.01$), but not fasting plasma glucose and AUC of plasma glucose and insulin during OGTTs, were somewhat higher in TM than TW. Fasting triglycerides and FFA concentrations were similar. TM were therefore somewhat more insulin resistant at baseline.

Posttreatment

Transgender Men (Masculinization)

After gender-affirming hormone therapy, plasma levels of sex hormones changed as expected (Table 1). Both groups gained body weight, TM by increasing fat-free mass at the expense of fat mass. Their waist circumference increased, as did WHR ($P < 0.05$ for both). Hip circumference was unchanged. The total activity score increased ($P < 0.001$), indicating increased reported physical activity.

Fasting plasma glucose was unchanged postintervention; the lower fasting insulin levels ($P = 0.08$) and lower HOMA index ($P = 0.06$), however, did not reach statistical significance. Lipids did not change into the same expected direction: FFAs were unchanged, LDL increased ($P < 0.05$), and HDL increased ($P < 0.05$). Neither the decreases in fasting GIP ($P = 0.10$) nor in GLP-1 were statistically significant.

Results from OGTTs showed unchanged AUCs of glucose and insulin, whereas there was an increase in both AUC GIP and AUC GLP-1 (both $P < 0.01$) (Figs. 1 and 2).

Transgender Women (Feminization)

The expected increase in estrogen and decrease in testosterone after the gender-affirming hormone therapy in TW (Table 1) was associated with a tendency to an increase in body weight ($P = 0.07$). Hip circumference and absolute and relative fat mass increased (all $P < 0.001$) (Table 1), and WHR dropped, as well as fat-free mass (both $P < 0.001$) despite increased reported physical activity ($P < 0.05$).

Fasting plasma glucose remained unchanged in the context of higher fasting insulin levels and HOMA-IR indices (both $P < 0.001$). Nonetheless, total and LDL cholesterol ($P < 0.001$) as well as triglycerides ($P < 0.05$) decreased somewhat, as did HDL cholesterol ($P < 0.001$). FFAs remained unchanged. Fasting GIP ($P = 0.002$), but not GLP-1, decreased.

In the dynamic postintervention values (AUCs during an OGTT), we observed a decrease in glucose, and GIP ($P < 0.001$), while insulin and GLP-1 remained unchanged (Figs. 1 and 2).

CONCLUSIONS

We describe the effects of gender-affirming sex hormone therapy on parameters reflecting insulin sensitivity and incretins in 90 transgender people, both in male-to-female and female-to-male gender transition, among others using OGTTs in a longitudinal study design. The data allowed for evaluation of net

Table 1—Antropometric and laboratory values at baseline and after 1 year of sex hormone administration

	TM (female to male)		TW (male to female)	
	Baseline	1 year	Baseline	1 year
N	35		55	
Age (years)†††	26.1 ± 1.3		34.4 ± 1.5	
Height (cm)†††	164.4 ± 0.9		178.8 ± 8.6	
Weight (kg)†††	63.1 ± 2.2	65.9 ± 2.1**	75.7 ± 1.9	77.0 ± 1.9
BMI (kg/m^2)	23.2 ± 0.7	24.1 ± 0.6*	23.7 ± 0.6	24.2 ± 0.6*
Waist (cm)†††	74.2 ± 1.7	76.3 ± 1.7*	83.4 ± 1.5	82.9 ± 1.7
Hip (cm)	97.6 ± 1.4	96.5 ± 1.5	95.7 ± 1.2	99.0 ± 1.1***
WHR†††	0.76 ± 0.01	0.79 ± 0.01*	0.87 ± 0.0	0.84 ± 0.01**
Fat percentage (%)†††	28.5 ± 1.0	24.3 ± 1.2***	18.6 ± 0.7	24.5 ± 1.4***
Truncal fat (kg)	7.2 ± 0.7	6.7 ± 0.7	6.8 ± 0.5	7.9 ± 0.5***
Leg fat mass (right, kg)†††	3.9 ± 0.3	3.3 ± 0.3***	2.6 ± 0.2	3.6 ± 0.2***
FFM including bone (kg)†††	45.2 ± 1.1	49.8 ± 1.9***	60.5 ± 1.2	58.2 ± 1.2***
Truncal lean mass (kg)†††	22.8 ± 0.6	24.4 ± 0.5***	29.6 ± 0.7	28.6 ± 0.7***
Leg lean mass (right, kg)†††	7.4 ± 0.2	8.3 ± 0.3***	10.0 ± 0.2	9.6 ± 0.2***
Total activity score	7.30 ± 2.56	9.05 ± 2.46***	7.07 ± 2.46	7.70 ± 2.07*
Estradiol (ng/L)†††	91.6 ± 13.1	45.2 ± 6.3**	30.1 ± 1.5	120.5 ± 22.6***
Testosterone (ng/dL)†††	41 ± 6	642 ± 39***	523 ± 26	42 ± 12***
SHBG (nmol/L)††	71.10 ± 8.4	20.0 ± 2.5***	42.6 ± 3.8	46.6 ± 2.9
Free testosterone (ng/dL)†††	0.60 ± 0.12	34.7 ± 2.3***	10.0 ± 0.49	0.89 ± 0.28***
Fasting glucose (mg/dL)††	81.0 ± 1.4	79.3 ± 1.6	86.1 ± 1.1	85.9 ± 1.3
Fasting insulin (mU/L)††	10.9 ± 1.6	9.5 ± 0.8	7.8 ± 0.5	11.2 ± 0.8***
HOMA-IR index†	2.2 ± 0.3	1.9 ± 0.2	1.7 ± 0.1	2.4 ± 0.2**
Fasting GIP (pmol/L)	3.8 ± 1.0	2.6 ± 0.4	3.6 ± 0.5	2.2 ± 0.3**
Fasting GLP-1 (pmol/L)	18.0 ± 1.0	17.8 ± 1.1*	18.9 ± 0.8	20.2 ± 0.8
AUC glucose ([mg/dL] × min)†††	14,154 ± 392	15,049 ± 482	16,286 ± 386	15,135 ± 430*
AUC insulin ([mU/L] × min)	8,097 ± 640	9,016 ± 656	8,213 ± 683	8,599 ± 627
AUC GIP ([pmol/L] × min)	2,165 ± 216	2,671 ± 241***	2,374 ± 205	1,834 ± 207**
AUC GLP-1 ([pmol/L] × min)†	2,400 ± 154	2,693 ± 190	2,906 ± 164	2,883 ± 105**
Fasting FFAs (mEq/L)	469 ± 34	426 ± 27	496 ± 39	534 ± 30
LDL (mg/dL)	99 ± 5	109 ± 5*	111 ± 5	96 ± 4***
HDL (mg/dL)	57 ± 2	53 ± 2*	56 ± 2	49 ± 2***
Cholesterol (mg/dL)	172 ± 33	178 ± 32	187 ± 4	162 ± 32***
Triglycerides (mg/dL)†	74.5 ± 6.6	86.5 ± 7.3	111.6 ± 15.8	89.8 ± 8.9*

Data are means ± SEM. FFM, fat-free mass; SHBG, sex hormone–binding globulin. †$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$ baseline difference TM vs. TW; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ pre– vs. post–hormone treatment.

effects of complex physiological interactions rather than those of single hormone interventions in (sub)physiological conditions.

We found that several, but not all, parameters of insulin sensitivity changed after gender-affirming hormone treatment, most, but certainly not all, suggesting a tendency toward increasing insulin sensitivity in TM (masculinization) and decreasing insulin sensitivity in TW (feminization). These changes in insulin sensitivity were mostly congruent with body composition changes, particularly with those that would be expected of respective testosterone introduction and subtraction: lean (muscle) mass increased and fat mass decreased in TM, whereas lean mass decreased and fat mass increased in TW. In addition, the direction of the changes in insulin resistance seemed to coincide with those in body composition shifts rather than weight change per se and, in turn, with changes in lean and fat mass/percentage more than with changes in waist circumference and WHR.

Even though not all parameters and markers changed significantly, nor into the same direction, the fact that the changes in insulin sensitivity largely tended toward opposite directions in both groups suggests that, at least in our study cohort, people were more insulin sensitive under male than under female hormone exposition. Possible confounders, however, include a lower baseline insulin sensitivity in TM and changing physical activity levels in both groups as assessed by questionnaires. The latter was nonetheless less likely to have been responsible for this divergence, because physical activity increased in both groups.

Previous reports of interventions in several concomitant sex hormones only partly support our findings. Most report either unchanged (32–36) or decreasing (33,35,37), but never improving, insulin sensitivity after both feminization and masculinization, usually after short-term

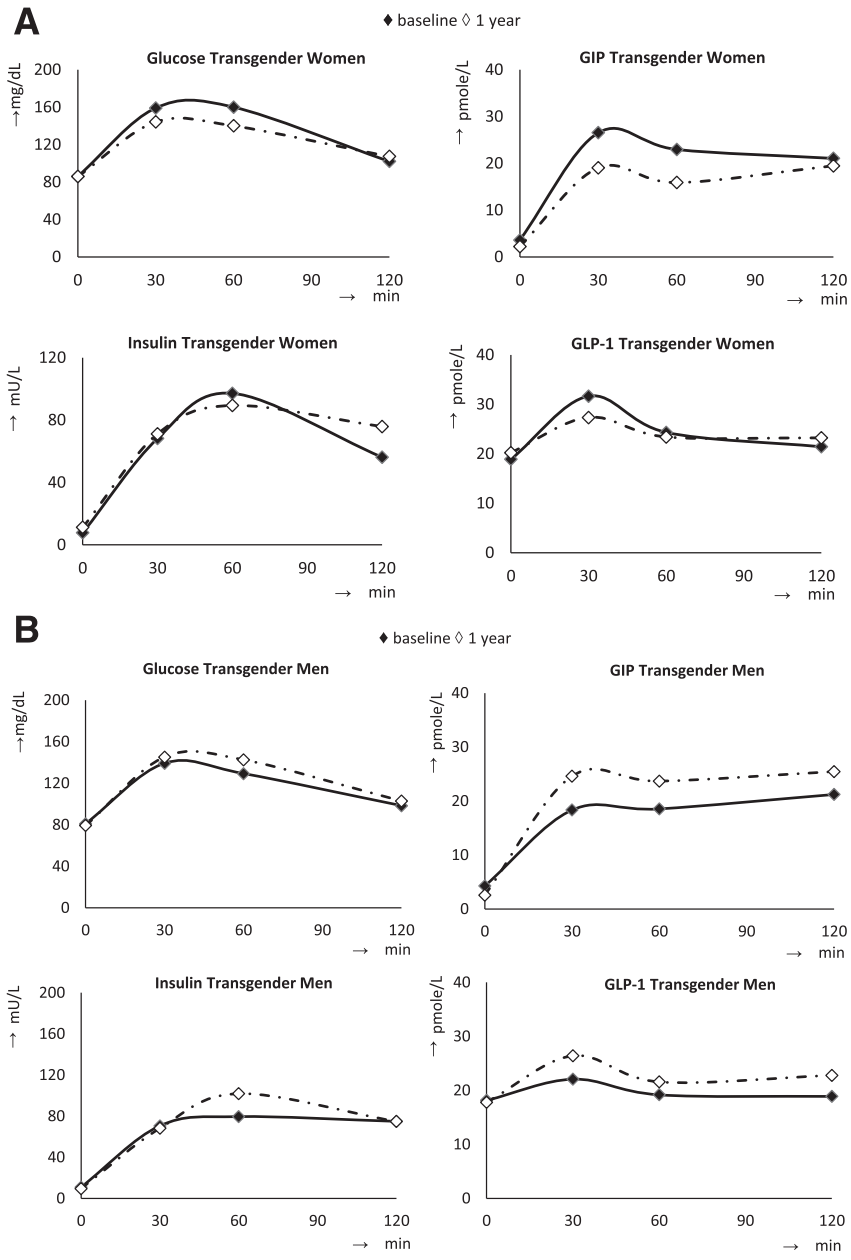

Figure 1—*A*: Values of glucose, insulin, GLP-1, and GIP in TW after a 75-g OGTT before and after gender-affirming therapy. *B*: Values of glucose, insulin, GLP-1, and GIP in TM after a 75-g OGTT before and after gender-affirming therapy.

(1–4-week) interventions in small numbers of healthy men, but also after longer-term treatment (up to 1 year) in TW; most assessed static insulin sensitivity markers only. The one study similar to ours used state-of-the art dynamic testing (euglycemic-hyperinsulinemic clamp) but described worsening insulin sensitivity in both TM and TW ($n = 31$) after 4 months of cross-sex hormone therapy (38). Thus, in general, this report corroborates our effects of feminization, but not those of masculinization.

To the extent that insulin resistance is, indeed, associated with diminished incretin responses, the increased GIP and GLP-1 responses to OGTTs in TM would be consistent with increased insulin sensitivity; in contrast, in TW, the decreasing GIP (but not GLP-1) response could perhaps parallel decreasing insulin sensitivity in this context. However, this very association is somewhat controversial and not that straightforward. More importantly, it is unclear whether our altered incretin responses resulted from direct sex hormone effects or whether they are reflections of changed insulin sensitivity.

The relationship between incretins and fertility/sex hormones is complex and still largely unknown. A large study in >1,400 subjects with a large range of BMI and insulin sensitivity suggested that post-OGTT GLP-1 response was higher in women than in men, but this difference was lost with increasing insulin resistance (39).

Most other available reports describe the effect of sex hormone interventions on incretins in study designs and/or target groups that cannot be compared with ours, such as women with polycystic ovary syndrome (see above) or postmenopausal women. In the latter, combined estrogen/progesterone therapy had insulin-sensitizing effects (40), but in addition reduced postprandial GIP and GLP-1 levels after 1 year. These results are discongruent with ours; however, as mentioned, these physiological contexts are incomparable to the one presented in this study by us; it therefore remains unclear to what extent any modulations in incretin secretion and/or response directly result from sex hormone changes and vice versa.

However, to our knowledge, there are no other reports of post-OGTT incretin responses after longer-term cross-gender sex hormone interventions as described. One short-term (1-week) intervention by our own group showed that, in healthy young men, lowering estrogen and increasing testosterone using an aromatase inhibitor increased both insulin sensitivity and postprandial GIP response, whereas lowering testosterone and raising estrogen did neither. Although not inconsistent with our data, a 1-week intervention cannot necessarily be extrapolated to an 18-month steady state.

In summary, various variables complicate comparison of our results to previous studies and put them into perspective, such as variations in sample size, definition, and method of measurement of insulin sensitization, the achieved plasma sex hormone levels, and the use of fasting incretin levels versus responses to oral glucose challenges. Most important, however, is the variation in study groups and designs: metabolic effects of single hormone administrations given as substitutions (e.g., estrogen in postmenopausal women) are likely different from intensifications of a given hormonal status

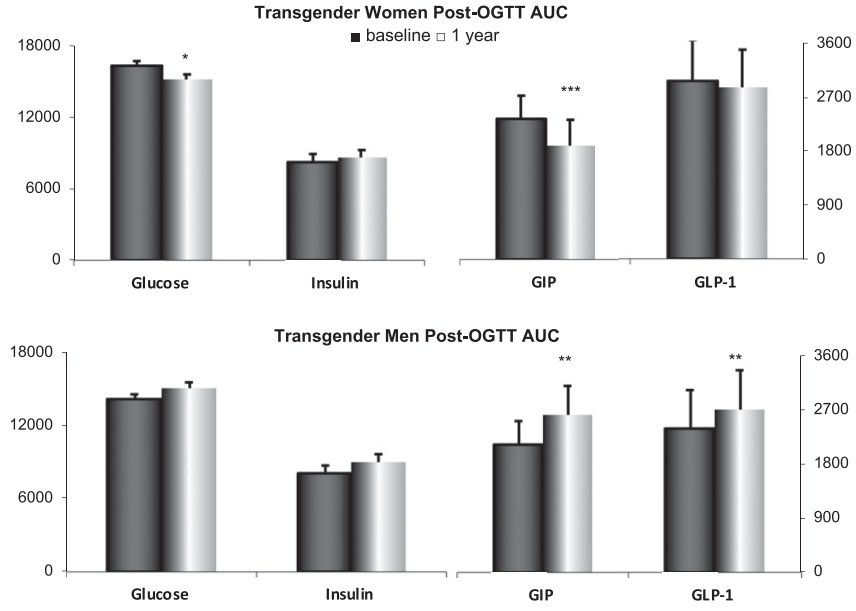

Figure 2—Post-OGTT AUC of glucose ([mg/dL] × min), insulin ([mU/L] × min), GLP-1 ([pmol/L] × min), and GIP ([pmol/L] × min) at baseline and after 1 year of sex hormone therapy. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

(testosterone in men or oral contraception in women) or from administration of either in healthy men or women with or without concomitant blocking of "opposite" sex hormones. In this respect, the metabolic effects of estrogen administration to healthy men might be overwhelmed by their endogenous testosterone, and adding estrogen to women could be underwhelmed by endogenous hormone production. In contrast, transgender studies approach simulation of intrinsic hormonal physiology as closely as possible.

Our study does so in a large, longitudinal cohort using a relatively robust measurement for insulin sensitivity. Our report, however, does not provide mechanistic insights, nor does it clarify whether men and women intrinsically differ in insulin sensitivity or whether this can be consistently shifted by masculinization or feminization. In addition, our data may have been confounded by relatively low insulin sensitivity at baseline in TM and by altered physical activity levels that cannot be quantified reliably.

Despite these limitations, we believe that, in this cohort, we observed increasing insulin sensitivity in TM and decreasing in TW following cross-sex hormonal therapy, which mostly paralleled changes in lean body mass as well as altered incretin responses to OGTT. To what extent these observations are reproducible has yet to be determined; until then, it might be advisable to monitor insulin sensitivity parameters regularly in transgender people after gender-affirming hormone therapy.

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