Ther Adv Endocrinol Metab

2021, Vol. 12: 1–12

DOI: 10.1177/2042018820985681

Insulin resistance in transgender individuals correlates with android fat mass

Ingrid Bretherton, Cassandra Spanos, Shalem Y. Leemaqz, Gehan Premaratne, Mathis Grossmann, Jeffrey D. Zajac and Ada S. Cheung

Abstract

Background: Transgender individuals receiving gender-affirming hormone therapy (GAHT) are at increased risk of adverse cardiovascular outcomes. This may be related to effects on body composition and insulin resistance.

Aims: To examine relationships between body fat distribution and insulin resistance in transgender individuals on established GAHT.

Methods: Comparisons of body composition (dual energy X-ray absorptiometry) and insulin resistance [Homeostasis Model of Insulin Resistance (HOMA2-IR)] were made between transgender individuals (43 trans men and 41 trans women) on established GAHT (>12 months) and age-matched cisgender controls (30 males and 48 females). Multiple linear regressions were used to examine the relationship between HOMA2-IR and fat mass with gender, adjusting for age and total duration of GAHT and Pearson correlation coefficients are reported.

Results: Compared with control cisgender women, trans men had mean difference of +7.8 kg (4.0, 11.5), $p < 0.001$ in lean mass and higher android:gynoid fat ratio [0.2 (0.1, 0.3), $p < 0.001$], but no difference in overall fat mass or insulin resistance. Compared with control cisgender men, trans women had median difference in lean mass of −6.9 kg (−10.6, −3.1), $p < 0.001$, fat mass of +9.8 kg (3.9, 14.5), $p = 0.001$, lower android:gynoid fat ratio −0.1 (−0.2,−0.0), $p < 0.05$), and higher insulin resistance 1.6 (1.3–1.9), $p < 0.001$). Higher HOMA2-IR correlated with higher android ($r^2 = 0.712$, $p < 0.001$) and gynoid ($r^2 = 0.572$, $p < 0.001$) fat mass in both trans men and trans women.

Conclusion: Android fat more strongly correlates with insulin resistance than gynoid fat in transgender individuals. Higher fat mass and insulin resistance in trans women may predispose to increased cardiovascular risk. Despite adverse fat distribution, insulin resistance was not higher in trans men.

Keywords: body composition, gender dysphoria, gender identity, insulin resistance, transgender persons, transsexualism

Received: 22 June 2020; revised manuscript accepted: 13 December 2020.

Correspondence to:
Ada S. Cheung
Department of Endocrinology, Austin Health, 145 Studley Road, Heidelberg, Victoria, 3084, Australia

Department of Medicine (Austin Health), The University of Melbourne, Victoria, Australia
adac@unimelb.edu.au

Ingrid Bretherton
Mathis Grossmann
Jeffrey D. Zajac
Department of Medicine (Austin Health), The University of Melbourne, Victoria, Australia

Department of Endocrinology, Austin Health, Heidelberg, Victoria, Australia

Cassandra Spanos
Gehan Premaratne
Department of Medicine (Austin Health), The University of Melbourne, Victoria, Australia

Shalem Y. Leemaqz
College of Medicine and Public Health, Flinders University, Adelaide, South Australia

Introduction

Background

It is estimated that 0.6–1.2% of the population identify as transgender (or trans)[1,2] and the number of individuals presenting to medical services for assistance with gender transition is rapidly rising.[3,4] Transgender individuals experience incongruence between the sex assigned to them at birth and their deeply held sense of gender identity. Gender-affirming hormone therapy (GAHT) is used by many transgender individuals to align physical characteristics with their gender identity. Masculinising hormone therapy with testosterone for trans men and feminising hormone therapy with oestradiol and anti-androgen agents for trans women are both associated with improvements in psychological outcomes and quality of life.[5]

GAHT is usually continued lifelong; however, little is known about the long-term effects. Two large cohort studies suggest higher rates of cardiovascular events in transgender individuals on hormone therapy compared with cisgender individuals. Trans men on testosterone had higher rates of myocardial infarction compared with cisgender women, and trans women on oestrogen had an increased risk of ischaemic stroke and venous thromboembolism when compared with both cisgender men and cisgender women.[6,7]

Regional fat distribution, in particular central adiposity, is an important contributor to cardiovascular risk and is heavily influenced by sex steroids.[8] A recent systematic review confirmed that feminising hormone therapy is consistently associated with increases in fat mass and decreases in lean mass, while trans men experience decreases in fat mass and increases in lean mass with masculinising hormone therapy.[9] In cisgender populations central abdominal fat, also referred to as android fat, is associated with high cardiovascular risk and one of its measures, the waist:hip ratio, is more strongly correlated with cardiovascular outcomes than is body mass index (BMI).[10] Trans men, but not trans women, have an increase in waist:hip ratio 12 months after commencing hormone therapy,[9] suggesting higher cardiovascular risk. Additionally, the route of administration of hormone therapy may influence fat mass. In postmenopausal women, oral conjugated equine oestrogen is associated with higher body fat and loss of lean tissue when compared with transdermal oestradiol, thought to be mediated *via* insulin-like growth factor 1 (IGF-1) production.[11–13]

Insulin resistance is also an important contributor to cardiovascular risk. Both oestrogen and testosterone are capable of altering insulin sensitivity *via* a direct effect on liver, muscle and endothelial tissues, as well indirect effects *via* changes in body fat distribution.[14–18] Although central to the pathogenesis of type 2 diabetes mellitus, insulin resistance also independently predicts a variety of poor outcomes in otherwise well non-diabetic individuals including hypertension, obesity and dyslipidaemia, as well as cardiovascular and all-cause mortality.[19–22]

Regional fat distribution and insulin resistance in cisgender individuals are well correlated. Adipose tissue, particularly central adiposity, has been shown to induce insulin resistance through release of multiple mediators including free fatty acids, steroid hormones and proinflammatory cytokines.[18] Given the significant body composition changes known to occur in transgender individuals with gain in fat mass and loss of lean mass with feminising hormone therapy and the reverse seen with masculinising hormone therapy,[9] determining whether a correlation exists between regional fat mass and insulin sensitivity is important, yet not previously described. Understanding this link will provide insights into whether GAHT affects insulin resistance predominantly through direct *versus* indirect (*via* changes in body composition) mechanisms, and guide clinicians in providing more accurate preventative strategies.

We aimed to further investigate the effect of GAHT on insulin resistance and body composition as surrogate markers of cardiovascular risk. We hypothesised that, first, trans men on testosterone therapy would have higher lean mass, lower fat mass and greater android:gynoid body fat distribution compared with control cisgender women and that opposite effects would be seen in trans women on oestradiol therapy compared with control cisgender men. Second, we hypothesised that insulin resistance would correlate with higher android fat and, therefore, would be higher in trans men compared with control cisgender women, with opposite effects seen in trans women.

Materials and methods

Study design and participants

We conducted a cross-sectional study between 1 April 2017 and 30 April 2018 in transgender individuals aged 18 years and over who had been on continuous GAHT for 12 months or more. Trans men on standard dose testosterone therapy were compared with individuals of the same sex assigned at birth; cisgender female controls. Trans women receiving standard doses of oestradiol-based therapy for feminisation were compared with cisgender male controls. Transgender participants were recruited from endocrinology outpatient clinics and from primary care general practice clinics specialising in transgender health in Melbourne, Australia. These participants were compared with age-matched cisgender control groups. Healthy control individuals were additionally recruited as control participants for a longitudinal study in bone health in transgender individuals and exclusion criteria included

diabetes, established osteoporosis, metabolic bone disease, glucocorticoid therapy, bisphosphonate therapy, antiepileptic medication, HIV pre-exposure prophylaxis, pregnancy, thromboembolic disease, liver disease, or any disease likely to lead to impairment in bone health. All participants provided written informed consent and the protocol was approved by the Austin Health Human Research Ethics Committee (approval no. HREC/17/Austin/74).

Data collection

All participants underwent fasting blood testing to measure oestradiol, testosterone, sex hormone binding globulin (SHBG), blood glucose, insulin, C-peptide and IGF-1 levels. Where possible blood testing was undertaken as a trough level for those on depot medications (such as testosterone undecanoate). In cisgender female participants blood testing was not able to be timed to a particular point in the menstrual cycle. Oestradiol was measured using immunoassay (Cobas E801, Roche Diagnostics, inter-assay variation 25% at level of 100 pnmol/L or less and 25% at a level of greater than 100 pmol/L). Those on unmeasurable forms of oestradiol (such as ethinyloestradiol) were not included in the calculation of median oestradiol levels. Testosterone was measured using immunoassay (Cobas E801, Roche Diagnostics, inter-assay variation 14.8% at level of 2.7 nmol/L or less and 15% at a level of greater than 2.7 nmol/L). SHBG was measured on immunoassay (Cobas E801, Roche Diagnostics, interassay variation 6% at a level of 21 nmol/L and 6% at a level of 40 nmol/L). Fasting plasma glucose was measured using hexokinase photometric assay (Cobas C8000, Roche Diagnostics, inter-assay variation 1.5 at levels of 4.8 and 15.5 mmol/L). Electrochemiluminescence immunoassay (Cobas C8000, Roche Diagnostics) was used to measure insulin (interassay variation 4% at 16.3 mIU/L and 5% at 154 mIU/L) and C-peptide (interassay variation 4.5% at a level of 2.5 nmol/L and 6.8% at 0.55 nmol/L). Fasting blood glucose and C-peptide were used to calculate insulin resistance using updated Homeostasis Model of Insulin Resistance (HOMA2-IR),[23] which is available for download from The Oxford Centre for Diabetes, Endocrinology and Metabolism.[24] This is a non-linear model, which accounts for variations in hepatic and peripheral glucose resistance. C-peptide can be used to model both beta-cell function and insulin resistance and compared with insulin is less likely to degrade if any haemolysis of the sample occurs.[25] IGF-1 was measured using chemiluminescence immunoassay (Liaison XL, DiaSorin); interassay at a level of 11.4 nmol/L is 10% and at 42.2 nmol/L is 8.5%. Body composition was measured using dual energy X-ray absorptiometry (DXA) (Prodigy Version 7.51 GE Lunar, Madison, WI, USA). Coefficient of variation was $<2\%$.[26]

Statistical analysis

Characteristics and body composition parameters of participants were summarised as median and interquartile ranges for each group. Multiple linear regressions were used to examine the relationship between HOMA2-IR and fat mass with sex, adjusting for age and total duration of GAHT. HOMA2-IR, android fat mass, gynoid fat mass and total fat mass were log-transformed to approximate normality, and results were back-transformed to estimate the ratio of geometric means with corresponding 95% confidence intervals (CIs). The mean difference with corresponding 95% CI (denoted in round brackets) were reported for fat mass measures that were not log-transformed. Separate analyses were done comparing females *versus* transgender men, and males *versus* transgender women. Further analysis of correlation between HOMA2-IR with fat mass was also performed using linear regression, and the Pearson correlation coefficients and *t*-tests for regression coefficient slope were reported. All statistical analyses were performed using R (version 3.6.0, R Foundation for Statistical Computing). A *p*-value of less than 0.05 was considered statistically significant. No adjustment for multiple comparisons was performed as the analysis is of an exploratory nature.

Results

Participant characteristics

This study recruited a total of 162 participants: 84 transgender individuals (41 trans women and 43 trans men) and 78 controls (30 cisgender females and 48 cisgender males). Participant characteristics are summarised in Table 1. Mean age in the cisgender male controls was younger than in trans women and as such analyses were adjusted for age.

All 43 trans men were receiving testosterone [intramuscular (IM) testosterone undecanoate

Table 1. Results (participant characteristics and effect sizes).

	Trans men ***n*** **= 43**	**Control cisgender women** ***n*** **= 48**	**Effect (95% CI)**
Age, years	28.8 (25.0–33.0)	28.1 (24.0–38.7)	–
BMI	25.2 (23.1–28.6)	22.7 (20.9–26.1)	–
Total duration of GAHT, months	44.0 (22.6–67.0)	–	–
Oestradiol, pmol/L	115.0 (93.0–164.0)	177.0 (32.5–359.2)	1.12 (0.57, 2.22)
Testosterone, nmol/L	15.6 (13.2–19.7)	0.9 (0.4–1.2)	**22.62 (15.73, 32.53)****
SHBG	31.5 (21.0–41.0)	98.5 (73.8–132.0)	**0.30 (0.21, 0.44)****
IGF-1	29.0 (22.0–33.5)	36.2 (28.1–40.2)	↓4.40 (–10.52, 1.73)
HOMA2-IR	1.2 (1.0–1.6)	1.1 (0.9–1.4)	0.99 (0.75, 1.30)
Total fat mass, kg	18.4 (14.3–28.0)	20.1 (14.6–25.4)	↑5.0 kg (–1.7, 11.8)
Android fat mass	2.0 (1.3–2.7)	1.4 (1.0–2.0)	1.4 (1.0, 2.1)
Gynoid fat mass	3.8 (2.9–5.4)	4.7 (3.5–5.5)	1.0 (0.8, 1.3)
Android:gynoid fat ratio	1.0 (0.9–1.1)	0.8 (0.7–0.9)	↑**0.2 (0.1, 0.3)****
Total lean mass, kg	48.1 (44.9–51.7)	40.7 (37.0–43.7)	↑**7.8 kg (4.0, 11.5)****
	Trans women ***n*** **= 41**	**Control cisgender men** ***n*** **= 30**	**Effect (95% CI)**
Age, years	41.1 (26.4–52.7)	32.0 (26.3–40.9)	–
BMI	23.6 (21.7–29.2)	23.8 (23.1–25.8)	–
Total duration of GAHT, months	39.0 (19.9–60.0)	–	–
Oestradiol, pmol/L	327.0 (147.2–460.5)+	72.5 (49.5–93.8)	**5.12 (3.44, 7.61)****
Testosterone, nmol/L	0.6 (0.4–0.9)	20.5 (16.0–24.1)	**0.04 (0.03, 0.06)****
SHBG	86.0 (59.5–116.8)	51.5 (39.0–75.2)	**1.37 (1.06, 1.76)***
IGF-1	22.5 (16.5–27.5)	28.3 (23.0–35.2)	↓1.86 (–6.57, 2.86)
HOMA2-IR	1.5 (1.3–2.2)	1.1 (0.8–1.3)	**1.6 (1.3, 1.9)****
Total fat mass, kg	22.5 (17.3–34.2)	15.7 (11.6–20.5)	↑**9.8 kg (3.9, 14.5)****
Android fat mass	2.1 (1.3–3.6)	1.5 (1.1–2.0)	**1.40 (1.05, 1.87)****
Gynoid fat mass	4.5 (3.9–6.4)	3.1 (2.5–4.1)	**1.53 (1.26, 1.85)****
Android:gynoid fat ratio	1.0 (0.8–1.0)	1.0 (0.9–1.2)	↓**0.1 (–0.2, 0.0)***
Total lean mass, kg	51.5 (47.0–55.7)	58.3 (54.2–64.0)	↓**6.9 kg (–10.6, –3.1)****

Results are presented as median (interquartile range).
Effect adjusted for age and total duration of GAHT is presented as a ratio of geometric means, or mean difference (where arrows are shown).
*$p < 0.05$.
**$p < 0.001$.
+Those on unmeasurable forms of oestradiol (such as ethinyloestradiol) were not included in the calculation of median oestradiol levels.
BMI, body mass index; CI, confidence interval; GAHT, gender-affirming hormone therapy; HOMA2-IR, Homeostasis Model of Insulin Resistance; IGF-1, insulin-like growth factor 1; SHBG, sex hormone binding globulin

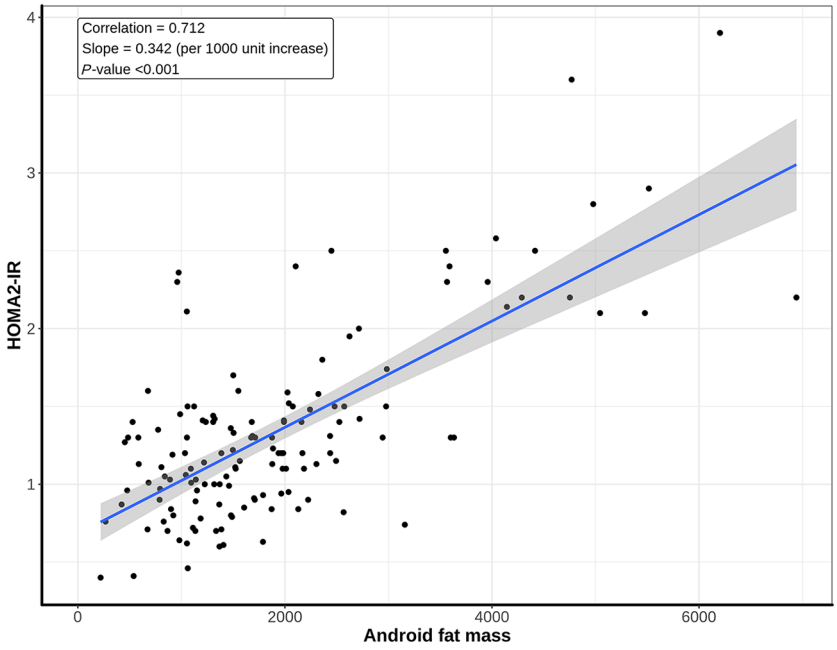

Figure 1. Correlation between android fat mass and Homeostasis Model of Insulin Resistance (HOMA2-IR).

$n=30$, IM testosterone enanthate $n=8$, topical testosterone gel 1% $n=5$] and all 41 trans women were receiving oestradiol (oral oestradiol valerate $n=34$, oral ethinyloestradiol $n=3$, transdermal oestradiol $n=4$). Seventy-eight per cent ($n=32$) of the trans women were taking anti-androgen therapy in addition to oestradiol therapy (cyproterone acetate $n=21$, spironolactone $n=5$, progestogens=5) (levonorgestrel $n=3$, medroxyprogesterone $n=1$, micronised progesterone $n=1$), gonadotropin releasing hormone analogue $n=1$. Twenty-seven per cent ($n=11$) of the trans women had undergone orchidectomy and 5% ($n=2$) of the trans men had undergone oophorectomy. In both trans men and trans women, the median oestradiol and testosterone levels were within the target reference range for their affirmed gender. In trans men, median oestradiol was 115.0 (93.0, 164.0) pmol/L (laboratory male reference range for oestradiol was <160 pmol/L) and median testosterone was 15.6 nmol/L (13.2, 19.7) (laboratory male reference range for testosterone was 9.9–27.8 nmol/L). In trans women, median oestradiol concentration was 327.0 (147.2, 460.5) pmol/L (laboratory female reference range for oestradiol during follicular phase was 46–607 pmol/L) and mean testosterone concentration was 0.6 (0.4, 0.9) nmol/L (laboratory female reference range for testosterone was <1.8 nmol/L).

Masculinising hormone therapy

Trans men had significantly higher lean mass than cisgender women with mean difference +7.8 kg 95% CI (4.0, 11.5), $p<0.001$) (Table 1). Other absolute body composition parameters (total fat mass, android and gynoid fat mass) were not significantly different from cisgender female controls; however, android:gynoid fat mass ratio was higher [mean difference +0.2 (0.1, 0.3), $p<0.001$]. Total fat mass was lower and android: gynoid fat mass was higher in trans men compared with cisgender female controls.

There was no difference in HOMA2-IR in trans men compared with cisgender female controls. Insulin resistance as estimated by HOMA2-IR was significantly correlated with android fat mass ($r^2=0.712$, $p<0.001$) and gynoid fat mass ($r^2=0.572$, $p<0.001$); see Figures 1 and 2. HOMA2-IR was also weakly correlated with android lean mass ($r^2=0.449$, $p<0.001$) and gynoid lean mass ($r^2=0.220$, $p=0.01$) (data not shown).

Whilst not the primary aim of our analyses, when comparing trans men with cisgender male controls, there was also no difference in HOMA2-IR (Supplemental Material Appendix 1 online). Although trans men were younger [trans men median 28.8 years (25.0–33.0)] compared with cisgender

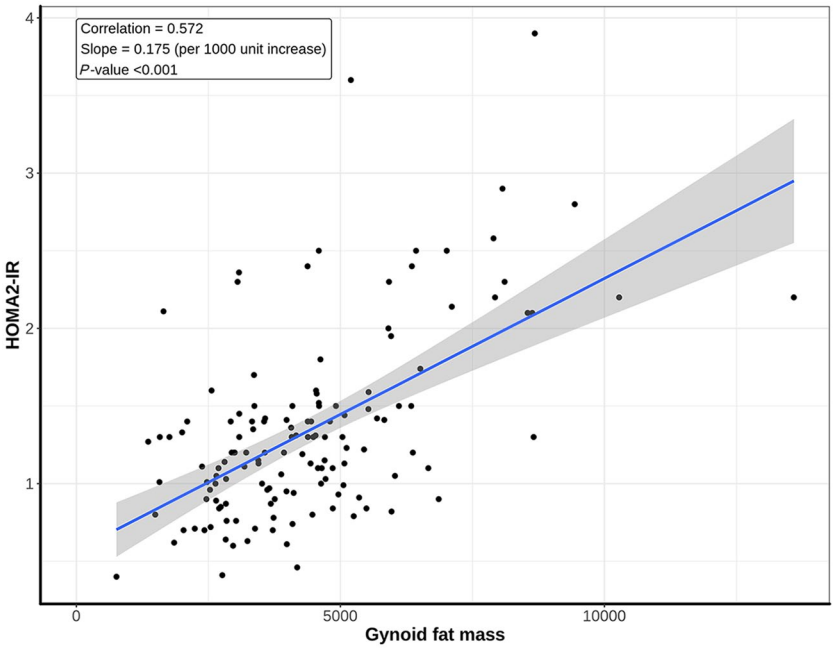

Figure 2. Correlation between gynoid fat mass and Homeostasis Model of Insulin Resistance (HOMA2-IR).

male controls [32.0 years (26.3–40.9)], they had a higher BMI and lower lean mass. Testosterone levels between groups were similar, but trans men had higher median oestradiol than cisgender male controls [115.0 pmol/L (93.0–164.0) *versus* 72.5 (49.5–93.8), $p < 0.01$] (Supplemental Appendix 1).

Feminising hormone therapy

Trans women had significantly lower lean mass [mean difference –6.8 kg (–10.6, –3.1), $p < 0.001$] and all fat mass parameters were significantly higher than cisgender male controls (Table 1). Android fat mass and gynoid fat mass were 40% and 53% higher respectively in trans women compared with cisgender male controls. There was a significantly lower android:gynoid fat ratio [mean difference –0.1 (–0.2, –0.0), $p < 0.05$].

Despite a lower android:gynoid fat mass, the total android fat mass was still high amongst trans women [median 2.1 kg (1.3–3.6)]. HOMA2-IR in trans women was 1.5; significantly higher than cisgender male controls ($p < 0.001$).

As with trans males, insulin resistance as estimated by HOMA2-IR was significantly correlated with android fat mass and, to a lesser degree, gynoid fat mass. See Figures 1 and 2.

As an exploratory analysis, when trans women were compared with cisgender female controls, HOMA2-IR was significantly higher in trans women [mean difference 1.47 (1.22, 1.77), $p < 0.01$] as was android fat mass [mean difference 1.39 kg (1.06, 1.83), $p < 0.001$]. Trans women were, however, significantly older [trans women median 41.1 years (26.4, 52.7)] compared with cisgender female controls [28.1 years (24.0, 38.)], had a significantly higher median oestradiol [327.0 pmol/L (147.2–460.5) *versus* 177.0 pmol/L (32.5–359.2), $p < 0.01$], but median testosterone concentrations and BMI were not different (Supplemental Appendix 1).

Trans women who had undergone orchidectomy ($n = 11$) had a significantly lower HOMA2-IR than trans women who had not ($n = 30$) [1.3 (1.1–1.5) *versus* 1.8 (1.4–2.3) $p < 0.03$]. This is despite trans women who had undergone orchidectomy being older in age [57.0 years (40.5, 68.4) compared with 33.5 (25.5, 48.9)] ($p < 0.03$), having longer duration of GAHT [115.1 months (41.7, 180.9) *versus* 27.0 months (15.3, 47.1)] ($p < 0.002$), yet similar body composition (no significant difference between BMI, fat mass, or lean mass). See Supplemental Appendix 2.

Discussion

This cross-sectional study showed a correlation between insulin resistance and fat mass in transgender individuals on established GAHT. Trans men had significantly higher lean mass as well as a higher android:gynoid fat ratio with no significant differences in insulin resistance or overall fat mass compared with control cisgender women. Trans women were more insulin resistant than control cisgender men and had lower lean mass, higher fat mass and a lower android:gynoid fat ratio. Insulin resistance correlated with android fat mass but, contrary to our original hypothesis, trans men did not have higher insulin resistance, most likely because higher lean mass may be protective in trans men.

Masculinising hormone therapy

Our findings of higher lean mass (median 7.8 kg) and a higher android:gynoid fat ratio are consistent with previous studies investigating masculinising hormone therapy in trans men.[27–39] Testosterone is known to increase the synthesis of muscle tissue by promoting differentiation of cells of the myogenic lineage and to inhibit the differentiation of adipocyte precursor cells.[40] Moreover, testosterone also inhibits lipoprotein lipase activity in adipocytes, an enzyme that increases fat deposition by decreasing adipose tissue lipolysis.[14]

We found no significant difference in insulin resistance between trans men and cisgender female controls, in keeping with all but one prior study in transgender men that showed either no change[27–29,31–37,41] or a decrease[30,39] in insulin resistance. All these studies were prospective longitudinal in design but only one had a control group.[33] The lack of change in insulin resistance is consistent with data that found no change in incretin (glucagon-like peptide-1 and gastric inhibitory polypeptide) responses in trans men before and after 12 months of GAHT.[41] The importance of body composition – which takes many months to change with masculinising hormone therapy – is highlighted by a small study demonstrating an increase in insulin resistance measured by hyperinsulinaemic euglycaemic clamps in 13 transgender men over the first 4 months,[38] but with follow-up over 12 months, no significant differences in insulin resistance over time emerged.[34]

It is important to note that the roles of sex steroids in insulin sensitivity in cisgender populations are not fully understood. Men with hypogonadism have increased insulin resistance;[15,42] however, exogenous testosterone replacement is associated only with a small, likely clinically insignificant, improvement in insulin sensitivity.[43] Elevated testosterone levels in women, such as in polycystic ovary syndrome, are associated with increased, rather than decreased, insulin resistance,[14] suggesting that the primary driver of insulin sensitivity may be due to the indirect, rather than direct, effects of testosterone.

The association observed between android fat mass and insulin resistance in trans men also supports the importance of body composition. Whilst there is also a significant correlation with gynoid fat mass and insulin resistance, it is stronger for android. This is in keeping with the predisposition to insulin resistance associated with abdominal adiposity in cisgender populations.[10]

Feminising hormone therapy

Trans women in our study had a significantly higher fat mass (median 9.8 kg) and lower lean mass (median 6.9 kg) compared with cisgender male controls. These results are in line with previous studies that have evaluated body composition using DXA in trans women.[29,30,41,44–50] Only four studies have also previously looked specifically at android and gynoid fat mass regions, either using DXA or magnetic resonance imaging, and, like this study, found an increase in fat mass in both regions.[41,34,45,51] These findings support the theory that activation of oestrogen receptors can lead to stimulation of adipocyte proliferation as well as lipoprotein lipase activity.[52,53] Oestrogen may also act indirectly *via* oestrogen receptors in the hypothalamus to regulate energy expenditure.[53,54]

We found that trans women have significantly higher levels of insulin resistance estimated by HOMA2-IR compared with cisgender male controls. Nine studies have previously looked at insulin resistance in trans women on feminising hormone therapy and, of these, six similarly showed worsening insulin resistance.[29,30,32,34,38,41] Three did not detect a significant change – one showed a trend towards increase insulin resistance but failed to reach statistical significance,[55] another had a sample size of only six participants[27] and the remaining study did not measure body composition changes so it is unclear whether changes to this occurred.[39] All but one study[55] was prospective longitudinal in design but none had a control group.

Only four studies have specifically looked at android and gynoid fat mass regions, and of these only one sought to correlate insulin resistance and regional fat mass. This 2003 case–control study found a small increase in visceral fat area in both trans males and trans females; however, it failed to find a correlation with insulin sensitivity or fasting insulin levels in either group, likely due to small sample size and lack of control group.[34]

It is important to note that our findings, and others', contradict existing theories and animal models suggesting that oestradiol has direct beneficial effects on insulin sensitivity.[14,16,56]

In studies of cisgender women, oestrogen has generally been associated with a favourable effect on insulin sensitivity.[57] Low oestrogen states such as menopause are associated with a decrease in insulin sensitivity, increased central adiposity and a higher risk of metabolic disease, and subsequent administration of oestrogen therapy in menopausal women is associated with an improvement in insulin sensitivity.[58]

One proposed explanation for the differences seen in trans women is the high amount of overall fat as well as retention of central fat, which may indirectly lead to increased insulin resistance. This may mitigate any potentially beneficial direct effect of oestrogen on the insulin receptor.[16]

The route of oestrogen administration may also be important, with the majority of trans women in this study taking oral oestradiol valerate. Oral, but not transdermal, oestrogen has been shown to impair the metabolic effect of growth hormone in the liver, resulting in lower IGF-1 production and fat oxidation with a subsequent gain of body fat and loss of lean tissue seen in postmenopausal women.[11–13] Our study showed that trans women had a lower IGF-1 than both cisgender male and cisgender female controls. This is in contrast to the only other study investigating IGF-1 and body composition in trans women, which found serum IGF-1 levels at 24 months were similar to baseline, and that any changes were independent of the route of administration of oestrogen.[59] All participants aged under 45 years ($n = 34$) were taking oral oestradiol and those aged 45 years and over ($n = 15$) were taking transdermal oestradiol, so participant age may have been a factor. Interestingly, another study showed that there was no difference in total regional fat mass between trans women on oral or transdermal oestrogen.[45] Oestrogen doses in GAHT are generally higher than for menopausal hormone therapy, so further prospective studies in the transgender population are warranted.

Our findings of lower HOMA2-IR in the subset of trans women who had undergone orchidectomy are in keeping with a small prospective study from 2016,[60] which hypothesised that orchidectomy in this context may be protective due to the ratio of circulating sex hormone levels; however, further research is needed to confirm this.

Limitations

Limitations of the study include its cross-sectional design. Characteristics were not assessed prior to GAHT and baseline differences may have existed. In fact, two previous studies suggest that trans women have lower muscle mass and higher fat mass than cisgender male controls at baseline and reported doing significantly less physical activity.[47,50] The trans women were slightly older than the cisgender male controls. For simplicity the data were presented uniformly using the median and interquartile range; however, the mean age between the two groups was more closely matched – trans women were aged 40.8 $\pm$15.7 years *versus* cisgender male controls aged 36.0 $\pm$ 14.2 years. Data were adjusted for age. Trans men had a higher median BMI than cisgender female controls; however, if anything, this should lead to an overestimation of insulin resistance in the trans male group. Whilst our participants had undertaken GAHT for several years (median 44 months in trans men and 39 months in trans women) it is possible that changes to body composition are still ongoing. Participants were not on standardised GAHT regimens and we cannot discount that different hormone formulations, particularly oral *versus* transdermal oestradiol, may have differential effects on body composition and insulin resistance. Many participants were on a progestogen and this may affect the outcomes measured in this study. Testosterone and oestradiol assays used measured *via* immunoassay rather than liquid chromatography mass spectrometry. Although this study focuses on body composition and insulin resistance there are other contributors to cardiovascular risk. Additional research is needed and a prospective longitudinal study with a cisgender control group is needed to further investigate the impact of GAHT on body composition and insulin resistance.

Conclusion

We highlight the importance of lean and fat mass and the correlation with insulin resistance among transgender individuals and the relatively stronger correlation of insulin resistance with android over gynoid fat. Significantly higher levels of fat mass and lower lean mass in trans women is associated with insulin resistance, and whilst there is some degree of higher fat mass in trans men on established GAHT, the significantly higher lean mass relative to fat mass appears to be protective. These findings provide insights into sex hormone action and suggest a predominantly indirect mechanism of action (*via* changes in body composition) in mediating insulin resistance. Longitudinal studies are needed to further investigate this correlation and to better guide clinical practice. Until then, a proactive clinical approach to mitigate gain in fat as well maintain or increase lean mass, particularly in trans women, should be strongly encouraged.

Acknowledgement

The authors would like to acknowledge contribution of the participants who volunteered their time for this study.

Author contributions

IB was involved in the conception, design, analysis, interpretation of data and writing the manuscript. CS and SYL were involved in data analysis and revising the manuscript. GP, MG, JDZ were involved in revising the manuscript. ASC was involved in the conception, design, funding acquisition, analysis, interpretation of data, as well as revising the manuscript.

Conflict of interest statement

AC has received speaker's honoraria from Astra Zeneca and Merck Sharp & Dohme. MG has received research funding from Bayer, Weight Watchers, Lilly Otzuka, and speaker's honoraria from Besins Health Care and Novartis. All other authors have no conflicts of interest to declare.

Data availability

The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: IB is supported by an Australian Government Research Training Program Scholarship and a Rowden White Scholarship (# 184409), The University of Melbourne. AC is supported by an Australian Government National Health and Medical Research Council Early Career Fellowship (#1143333) and receives research support by the Viertel Charitable Foundation Clinical Investigator Award, Endocrine Society of Australia Postdoctoral Award, Austin Medical Research Foundation and the Royal Australasian College of Physicians Vincent Fairfax Family Foundation.

Orcid iD

Ada S. Cheung https://orcid.org/0000-0002-7158-8804

Supplemental material

Supplemental material for this article is available online.

References

1. Dhejne C, Lichtenstein P, Boman M, *et al.* Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011; 6: e16885.
2. Flores AR, Herman JL, Gates GJ, *et al. How many adults identify as transgender in the United States?* Los Angeles: The Williams Institute, 2016.
3. Telfer M, Tollit M and Feldman D. Transformation of health-care and legal systems for the transgender population: the need for change in Australia. *J Paediatr Child Health* 2015; 51: 1051–1053.
4. Cheung AS, Ooi O, Leemaqz S, *et al.* Sociodemographic and clinical characteristics of transgender adults in Australia. *Transgend Health* 2018; 3: 229–238.
5. White Hughto JM and Reisner SL. A systematic review of the effects of hormone therapy on psychological functioning and quality of life in transgender individuals. *Transgend Health* 2016; 1: 21–31.
6. Getahun D, Nash R, Flanders WD, *et al.* Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. *Ann Intern Med* 2018; 169: 205–213.
7. Nota NM, Wiepjes CM, de Blok CJM, *et al.* Occurrence of acute cardiovascular events in transgender individuals receiving hormone therapy. *Circulation* 2019; 139: 1461–1462.

8. Palmer BF and Clegg DJ. The sexual dimorphism of obesity. *Mol Cell Endocrinol* 2015; 402: 113–119.
9. Spanos C, Bretherton I, Zajac JD, *et al.* Effects of gender-affirming hormone therapy on insulin resistance and body composition in transgender individuals: a systematic review. *World J Diabetes* 2020; 11: 66–77.
10. Despres JP. Body fat distribution and risk of cardiovascular disease: an update. *Circulation* 2012; 126: 1301–1313.
11. Moller N, Jorgensen JO, Abildgard N, *et al.* Effects of growth hormone on glucose metabolism. *Horm Res* 1991; 36(Suppl. 1): 32–35.
12. Leung KC, Johannsson G, Leong GM, *et al.* Estrogen regulation of growth hormone action. *Endocr Rev* 2004; 25: 693–721.
13. O'Sullivan AJ, Crampton LJ, Freund J, *et al.* The route of estrogen replacement therapy confers divergent effects on substrate oxidation and body composition in postmenopausal women. *J Clin Invest* 1998; 102: 1035–1040.
14. Geer EB and Shen W. Gender differences in insulin resistance, body composition, and energy balance. *Gend Med* 2009; 6(Suppl. 1): 60–75.
15. Dhindsa S, Ghanim H, Batra M, *et al.* Insulin resistance and inflammation in hypogonadotropic hypogonadism and their reduction after testosterone replacement in men with type 2 diabetes. *Diabetes Care* 2016; 39: 82–91.
16. Mauvais-Jarvis F, Clegg DJ and Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. *Endocr Rev* 2013; 34: 309–338.
17. Salpeter SR, Walsh JM, Ormiston TM, *et al.* Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. *Diabetes Obes Metab* 2006; 8: 538–554.
18. Simon D, Charles MA, Lahlou N, *et al.* Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone: a 3-month randomized placebo-controlled trial. *Diabetes Care* 2001; 24: 2149–2151.
19. Esteghamati A, Khalilzadeh O, Abbasi M, *et al.* HOMA-estimated insulin resistance is associated with hypertension in Iranian diabetic and non-diabetic subjects. *Clin Exp Hypertens* 2008; 30: 297–307.
20. Geloneze B, Vasques AC, Stabe CF, *et al.* HOMA1-IR and HOMA2-IR indexes in identifying insulin resistance and metabolic syndrome: Brazilian Metabolic Syndrome Study (BRAMS). *Arq Bras Endocrinol Metabol* 2009; 53: 281–287.
21. Zhang X, Li J, Zheng S, *et al.* Fasting insulin, insulin resistance, and risk of cardiovascular or all-cause mortality in non-diabetic adults: a meta-analysis. *Biosci Rep* 2017; 37: BSR20170947.
22. Porte D Jr and Kahn SE. Beta-cell dysfunction and failure in type 2 diabetes: potential mechanisms. *Diabetes* 2001; 50(Suppl. 1): S160–S163.
23. Levy JC, Matthews DR and Hermans MP. Correct Homeostasis Model Assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 1998; 21: 2191–2192.
24. Diabetes Trials Unit. HOMA2 calculator, https://www.dtu.ox.ac.uk/homacalculator/. (2004, accessed 28 December 2020).
25. Wallace TM, Levy JC and Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; 27: 1487–1495.
26. Hamilton EJ, Gianatti E, Strauss BJ, *et al.* Increase in visceral and subcutaneous abdominal fat in men with prostate cancer treated with androgen deprivation therapy. *Clin Endocrinol (Oxf)* 2011; 74: 377–383.
27. Aranda G, Fernandez-Rebollo E, Pradas-Juni M, *et al.* Effects of sex steroids on the pattern of methylation and expression of the promoter region of estrogen and androgen receptors in people with gender dysphoria under cross-sex hormone treatment. *J Steroid Biochem Mol Biol* 2017; 172: 20–28.
28. Aranda G, Mora M, Hanzu FA, *et al.* Effects of sex steroids on cardiovascular risk profile in transgender men under gender affirming hormone therapy. *Endocrinol Diabetes Nutr* 2019; 66: 385–392.
29. Auer MK, Cecil A, Roepke Y, *et al.* 12-months metabolic changes among gender dysphoric individuals under cross-sex hormone treatment: a targeted metabolomics study. *Sci Rep* 2016; 6: 37005.
30. Auer MK, Ebert T, Pietzner M, *et al.* Effects of sex hormone treatment on the metabolic syndrome in transgender individuals: focus on metabolic cytokines. *J Clin Endocrinol Metab* 2018; 103: 790–802.
31. Berra M, Armillotta F, D'Emidio L, *et al.* Testosterone decreases adiponectin levels in female to male transsexuals. *Asian J Androl* 2006; 8: 725–729.

32. Colizzi M, Costa R, Scaramuzzi F, *et al.* Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *J Psychosom Res* 2015; 78: 399–406.
33. Cupisti S, Giltay EJ, Gooren LJ, *et al.* The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril* 2010; 94: 2647–2653.
34. Elbers JMH, Giltay EJ, Teerlink T, *et al.* Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. *Clin Endocrinol (Oxf)* 2003; 58: 562–571.
35. Gava G, Mancini I, Cerpolini S, *et al.* Testosterone undecanoate and testosterone enanthate injections are both effective and safe in transmen over 5 years of administration. *Clin Endocrinol (Oxf)* 2018; 89: 878–886.
36. Meriggiola MC, Armillotta F, Costantino A, *et al.* Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. *J Sex Med* 2008; 5: 2442–2453.
37. Pelusi C, Costantino A, Martelli V, *et al.* Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med* 2014; 11: 3002–3011.
38. Polderman KH, Gooren LJG, Asscheman H, *et al.* Induction of insulin resistance by androgens and estrogens. *J Clin Endocrinol Metab* 1994; 79: 265–271.
39. Yahyaoui R, Esteva I, Haro-Mora JJ, *et al.* Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab* 2008; 93: 2230–2233.
40. Miller KK. Androgen deficiency: effects on body composition. *Pituitary* 2009; 12: 116–124.
41. Shadid S, Abosi-Appeadu K, De Maertelaere AS, *et al.* Effects of gender-affirming hormone therapy on insulin sensitivity and incretin responses in transgender people. *Diabetes Care* 2020; 43: 411–417.
42. Cheung AS, Hoermann R, Dupuis P, *et al.* Relationships between insulin resistance and frailty with body composition and testosterone in men undergoing androgen deprivation therapy for prostate cancer. *Eur J Endocrinol* 2016; 175: 229–237.
43. Mohler ER III, Ellenberg SS, Lewis CE, *et al.* The effect of testosterone on cardiovascular biomarkers in the testosterone trials. *J Clin Endocrinol Metab* 2018; 103: 681–688.
44. Haraldsen IR, Haug E, Falch J, *et al.* Cross-sex pattern of bone mineral density in early onset gender identity disorder. *Horm Behav* 2007; 52: 334–343.
45. Klaver M, de Blok CJM, Wiepjes CM, *et al.* Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. *Eur J Endocrinol* 2018; 178: 163–171.
46. Fighera TM, da Silva E, Lindenau JD, *et al.* Impact of cross-sex hormone therapy on bone mineral density and body composition in transwomen. *Clin Endocrinol (Oxf)* 2018; 88: 856–862.
47. Van Caenegem E, Wierckx K, Taes Y, *et al.* Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol* 2015; 172: 163–171.
48. Wierckx K, Van Caenegem E, Schreiner T, *et al.* Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *J Sex Med* 2014; 11: 1999–2011.
49. Mueller A, Zollver H, Kronawitter D, *et al.* Body composition and bone mineral density in male-to-female transsexuals during cross-sex hormone therapy using gonadotrophin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes* 2011; 119: 95–100.
50. Lapauw B, Taes Y, Simoens S, *et al.* Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. *Bone* 2008; 43: 1016–1021.
51. Elbers JM, Asscheman H, Seidell JC, *et al.* Reversal of the sex difference in serum leptin levels upon cross-sex hormone administration in transsexuals. *J Clin Endocrinol Metab* 1997; 82: 3267–3270.
52. Karastergiou K, Smith SR, Greenberg AS, *et al.* Sex differences in human adipose tissues – the biology of pear shape. *Biol Sex Differ* 2012; 3: 13.
53. Lovejoy JC and Sainsbury A. Sex differences in obesity and the regulation of energy homeostasis. *Obes Rev* 2009; 10: 154–167.
54. Brown LM, Gent L, Davis K, *et al.* Metabolic impact of sex hormones on obesity. *Brain Res* 2010; 1350: 77–85.

55. Gava G, Cerpolini S, Martelli V, *et al.* Cyproterone acetate vs leuprolide acetate in combination with transdermal estradiol in transwomen: a comparison of safety and effectiveness. *Clin Endocrinol (Oxf)* 2016; 85: 239–246.

56. Nokoff NJ, Scarbro SL, Moreau KL, *et al.* Body composition and markers of cardiometabolic health in transgender youth compared with cisgender youth. *J Clin Endocrinol Metab* 2019; 105: e704–e714.

57. Meyer MR, Clegg DJ, Prossnitz ER, *et al.* Obesity, insulin resistance and diabetes: sex differences and role of oestrogen receptors. *Acta Physiol (Oxf)* 2011; 203: 259–269.

58. D'Eon TM, Souza SC, Aronovitz M, *et al.* Estrogen regulation of adiposity and fuel partitioning. Evidence of genomic and non-genomic regulation of lipogenic and oxidative pathways. *J Biol Chem* 2005; 280: 35983–35991.

59. Van Caenegem E, Wierckx K, Taes Y, *et al.* Preservation of volumetric bone density and geometry in trans women during cross-sex hormonal therapy: a prospective observational study. *Osteoporos Int* 2015; 26: 35–47.

60. Nelson MD, Szczepaniak LS, Wei J, *et al.* Transwomen and the metabolic syndrome: is orchiectomy protective? *Transgend Health* 2016; 1: 165–171.