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ORIGINAL ARTICLE

Comparison of Estrone/Estradiol Ratio and Levels in Transfeminine Individuals on Different Routes of Estradiol

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Abstract

Purpose: Estradiol for gender-affirming hormone therapy can be taken in different routes: oral, sublingual, transdermal patch or gel, and injectable estradiol. We aimed at comparing the estrone and estradiol ratios and levels achieved in each of these different routes of estradiol.

Methods: We conducted a retrospective chart review of transfeminine individuals attending an endocrinology clinic in Toronto, Canada. Study participants were grouped according to the route of estradiol administration: oral, injectable, transdermal, and sublingual. Our primary outcome was the estrone/estradiol ratio (E1/E2). Our secondary outcomes were the estradiol and estrone levels in each of these four groups.

Results: We included 263 patients. The oral estradiol group had the highest E1/E2 ratio (9.28), followed by the sublingual group (6.88). Both the transdermal and injectable groups had substantially lower E1/E2 ratios (2.22 and 0.84, respectively). We observed a large variability of the E1/E2 ratio in the oral and sublingual groups, whereas the transdermal and the injectable groups' ratios had much smaller standard deviation. The mean estradiol in the injectable group (1557 pmol/L, 424.1 pg/mL) was markedly higher than the estradiol levels observed in all other routes of estradiol.

Conclusion: Our data demonstrate significantly different E1/E2 ratios in the four different routes of estradiol administration, with oral and sublingual routes having the highest E1/E2 ratios followed by transdermal and injectable routes.

Keywords: administration routes; estrone; feminizing therapy; gender affirming therapy; hormone therapy; transgender persons

Introduction

Seventeen-beta estradiol is the recommended type of estrogen used in gender-affirming hormone therapy, and is generally combined with anti-androgen therapies.[1–3] 17-Beta estradiol is favored over other types of estrogen, such as ethinyl estradiol, because it can be measured in the serum, and it appears to have a lower risk of thrombosis.[1,3] It is available in different forms, including oral 17-beta estradiol, transdermal estradiol patch or gel, as well as injectable estradiol (valerate or cypionate).

In addition, the 17-beta estradiol tablet can be taken sublingually, rather than swallowed. There have been insufficient data to determine whether one route of administration is superior to another with respect to inducing feminizing effects. Some transfeminine individuals request to be on injectable estradiol because of the belief of superior effects; however, this has not been demonstrated in clinical data.[4]

It is possible that differing routes of estradiol may have different efficacies in inducing desired changes. When estradiol is administered orally, 17 beta-

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hydroxysteroid dehydrogenase type 2 (17 b-HSD2) catalyzes the conversion of estradiol to estrone in the liver, resulting in higher concentrations of estrone as compared with estradiol in the blood.[5] Estradiol has been thought of as the most potent activator of the estrogen receptor, with estrone having only 4% the activity of estradiol.[5]

It is therefore biologically conceivable that lower levels of estradiol as compared with estrone may result in less effective feminizing changes. When estradiol is administered transdermally or parenterally, there is less conversion of estradiol to estrone due to circumvention of the first pass effect, resulting in higher estradiol levels, and much lower estrone levels.[5,6] We are unaware of any randomized controlled trials comparing the effectiveness of these different routes of estradiol administration.[7]

A prospective cohort study by Tebbens et al. found no association between estrone concentration or route of administration and changes in fat percentage or breast development. However, their cohort did not include injectable estradiol and may have been underpowered.[8]

It is also possible that differing routes of estradiol have differences in long-term safety. Oral estradiol undergoes first-pass metabolism in the liver, which alters production of clotting factors; in several large retrospective studies in postmenopausal women, oral estradiol has been associated with increased risk of venous thromboembolism, whereas transdermal estradiol has not.[9–11] Some have explained this difference through the impact of different routes of estradiol on activated protein C resistance,[12] whereas others have proposed that oral estradiol is more thrombogenic due to estrone production.[13]

While estrone/estradiol concentrations and ratios have been studied in some pharmacokinetic studies in cis-women,[5,6] there is a paucity of clinical data on these levels in transfeminine individuals on feminizing hormone therapy. We aimed at studying the estrone to estradiol concentrations and ratios in a group of transfeminine individuals on hormone therapy receiving different routes of estrogen and anti-androgen therapy.

Methods

We conducted a retrospective chart review of transfeminine individuals attending an endocrinology clinic at Michael Garron Hospital in Toronto, Canada between March 1, 2019 and July 1, 2021. The study received ethics approval through the Michael Garron Hospital ethics board, and consent was waived. We followed study procedures according to the protocol approved by this ethics board. Adult (>18 years) transfeminine patients who received estradiol therapy and had estradiol and estrone values measured within the study timeframe cited earlier were identified through chart review and included in the study.

We included every transfeminine patient who received estradiol therapy and had routine measurements of both estradiol and estrone levels measured as part of their follow-up, which generally occurred every 3 to 6 months. We excluded transfeminine patients on other types of estrogen (such as conjugated equine estrogen) or those not taking any estradiol therapy at the time of the blood test.

Study participants were grouped according to the route of estradiol administration: oral, injectable, transdermal, and sublingual. All patients in the injectable estradiol group were treated with estradiol valerate. Study participants were then stratified into low, medium, and high dosage groups. It was the practice of the clinic to advise patients not to obtain their blood tested either immediately after taking their estradiol or just before their next dose is due, but rather sometime between doses.

This is because we otherwise found levels of estradiol that did not correlate with their dose, that is, very high levels when the patient was on low dose estradiol, or very low levels when the patient was already on a relatively high dose. Therefore, for our data collection, we also determined whether the timing of the blood test was done early, mid, or trough time frames with respect to when estradiol was taken by the patient before the blood test draw.

This was done through careful chart review to see whether any notes about the timing were included in the medical record. If there was no mention of the timing, it was allocated to mid group (See Tables 1 and 2 for definition).

Table 1. Low-, Medium-, and High-dose Estradiol definitions

	Low	Medium	High
Oral (daily)	2 mg or less	>2 to 4 mg	>4 mg
Injectable (per week)[a]	4 mg or less	>4 to 8 mg	>8 mg
Transdermal gel 1% (1.25 g/pump) (daily)	2 pumps or less	3 to 4 pumps	>4 pumps
Transdermal patch (changed 2×weekly)	100 mcg patch or less	100 to 200 mcg	>200 mcg patch
Sublingual (daily)	2 mg or less	>2 to 4 mg	>4 mg

[a]All patients in the injectable group were treated with estradiol valerate.

Table 2. Early, Mid, and Trough Blood Test Timing Definitions

	Early	Mid	Trough
Oral	< 2 h of ingestion	2 to 24 h	24 or more hours
Injectable (given weekly)	Within 2 days of injection	3 to 6 days of injection	7 or more days post-injection
Transdermal gel (applied daily)	< 2 h post-application of gel	2 to 24 h for gel	24 or more hours after gel application
Transdermal patch (changed 2 × per week)	< 4 h post-application of patch	4 to 72 h for application of patch	72 hours or more after application of patch
Sublingual	< 2 h of administration	2 to 24 h	24 or more hours

Our primary outcome was to determine the estrone/estradiol (E1/E2) ratio in each route group. Our secondary outcome was to determine the mean estradiol and estrone levels in each of the four route groups, stratified according to dose group.

Hormone analysis

Blood samples were collected during clinical care. Patients went to one of two community laboratories. For estradiol, laboratory A used the Chemiluminescent Microparticle Immunoassay on Architect instrument by Abbott, with coefficient of variation (CV) of 5.9% at 330 pmol/L (89.9 pg/mL), and 11% at 1050 pmol/L (286 pg/mL). Laboratory B used electrochemiluminescence immunoassay (ECLIA) by Roche, with CV of 10%. For estrone, both laboratories used Beckman Coulter radioimmunoassay kit, with CV of 8–12% at 385 pmol/L (105 pg/mL), and 6–11% at 1350 pmol/L (367.7 pg/mL). Of the 434 laboratory results in our analysis, 354 (82%) were from laboratory A and 77 (18%) were from laboratory B (three entries were manually inputted, with source laboratory unknown).

Statistical analysis

We determined baseline characteristics at the first recorded visit for each participant and grouped according to the routes of administration of estradiol (oral, transdermal, sublingual, and injectable). We reported mean and standard deviation for continuous variables and percentage (%) for categorical variables.

We conducted a one-way Analysis of Variance (ANOVA) test to determine differences in mean E1/E2 ratio, estrone level, and estradiol level at the last visit by route of administration. We then conducted two-way ANOVA analyses to account for dose group (low, medium, or high), timing of lab draw (early, mid, trough), and type of lab, respectively.

Only a small minority of the blood tests were drawn in the early or trough groups and given the extreme values that were observed in these groups (very high estradiol levels even with low doses of estradiol or low levels of estradiol with medium- or high-dose estradiol), we excluded these outliers from our final analysis of estrone and estradiol levels.

We used generalized estimating equations (GEE) to determine the association between the routes of administration (oral, transdermal, sublingual, and injectable) over recurrent visits and the E1/E2 ratio as the primary outcome. Secondary analyses also used GEE to determine the association between routes of estradiol administration over recurrent visits and the estradiol level and estrone level, respectively. We assumed a Gaussian distribution and used the link function for the GEE analyses for continuous outcomes.

We used the first-order autoregressive correlation structure to account for correlations between adjacent visits for all GEE models. We further adjusted the models for age and mean body mass index (BMI). We reported beta coefficients with associated standard errors and p-values for all GEE models.

All statistical analyses were performed using R Studio, version 4.1.2, 2021 (R Foundation for Statistical Computing, Vienna), and p-values < 0.05 were considered statistically significant.

Results

Baseline characteristics

There were 263 unique patient charts from which the data were analyzed. The mean age of our study population was 34 (± 13) years, with a mean BMI of 27 kg/m^2 (Table 3). Patients in the transdermal estradiol group tended to be older than the oral estradiol group. The majority of the study population was on spironolactone (40%), with substantial numbers being on cyproterone (25%) or having had gonadectomy (21%).

Most of our study population was on medium-dose estradiol, and over 90% of the blood tests were done in the mid time range. Table 3 shows the baseline characteristics of participants by routes of administration of estradiol therapy. Given the lower apparent mean LH at baseline in the injectable group as compared with other routes, a one-way ANOVA was run, which found no statistically significant difference in LH values across routes at baseline.

Table 3. Baseline Characteristics at First Visit

Characteristic	Overall, *N*=263[a]	Oral, *N*=153[a]	Patch/gel, *N*=39[a]	Sublingual, *N*=38[a]	Injectable, *N*=33[a]
Age	34 (13)	30 (11)	49 (13)	31 (11)	34 (14)
Body mass index (kg/m^2)	27 (6)	27 (7)	28 (6)	25 (5)	26 (6)
Estradiol (pmol/L)	555 (936)	362 (671)	342 (472)	773 (835)	1450 (1686)
Estrone (pmol/L)	1737 (1546)	2046 (1519)	472 (401)	2678 (1739)	716 (620)
Luteinizing hormone (IU/L)	5 (8)	5 (8)	6 (10)	5 (11)	2 (3)
Follicle stimulating hormone (IU/L)	5 (12)	5 (11)	8 (13)	8 (19)	2 (4)
Type of anti-androgen therapy					
None	23 (8.7%)	12 (7.8%)	1 (2.6%)	3 (7.9%)	7 (21%)
Gonadectomy	54 (21%)	23 (15%)	14 (36%)	9 (24%)	8 (24%)
Cyproterone	66 (25%)	42 (27%)	6 (15%)	12 (32%)	6 (18%)
Spironolactone	106 (40%)	67 (44%)	17 (44%)	13 (34%)	9 (27%)
GnRH agonist	8 (3.0%)	6 (3.9%)	1 (2.6%)	1 (2.6%)	0 (0%)
Bicalutamide	6 (2.3%)	3 (2.0%)	0 (0%)	0 (0%)	3 (9.1%)
Concurrent use of progesterone	27 (10%)	14 (9.2%)	1 (2.6%)	7 (18%)	5 (15%)
Dose group					
Low dose	94 (36%)	60 (39%)	16 (41%)	10 (26%)	8 (24%)
Medium dose	137 (52%)	72 (47%)	21 (54%)	22 (58%)	22 (67%)
High dose	32 (12%)	21 (14%)	2 (5.1%)	6 (16%)	3 (9.1%)
Timing of lab draw					
Early	12 (4.6%)	6 (3.9%)	1 (2.6%)	3 (7.9%)	2 (6.1%)
Middle	240 (91%)	141 (92%)	38 (97%)	35 (92%)	26 (79%)
Trough	11 (4.2%)	6 (3.9%)	0 (0%)	0 (0%)	5 (15%)

[a]Mean (standard deviation), where a % symbol appears: *n* (%).
GnRH, gonadotropin-releasing hormone.

Estrone to estradiol ratio

The oral estradiol group had the highest E1/E2 ratio (9.28) over recurrent visits, followed by the sublingual group (6.88) (Fig. 1). Both the transdermal and injectable groups had substantially lower E1/E2 ratios (2.22 and 0.84, respectively) (Table 4).

We observed a large variability of the E1/E2 ratio in the oral and sublingual groups, whereas the transdermal and especially the injectable groups' ratios were more consistent, and consistently lower. There was no statistically significant difference in the mean E1/E2 ratio due to timing of draw or

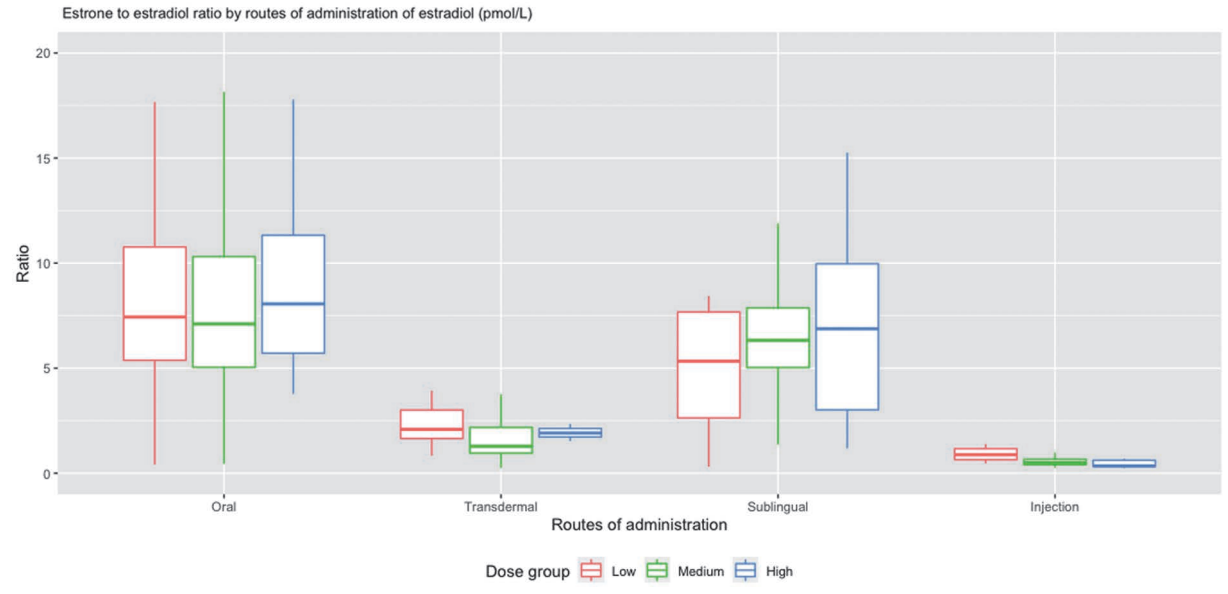

FIG. 1. Mean E1/E2 ratio across routes of administration. Boxplot of estrone/estradiol ratios according to the route of administration, with interquartile ranges shown. E1/E2, estrone to estradiol.

Table 4. Mean Estrone/Estradiol Ratio, Mean Estradiol, and Mean Estrone Across Routes of Administration at the Last Visit, *p*-Values from One-Way Analysis-of-Variance

Route	Oral	Transdermal (patch/gel)	Sublingual	Injection	*p*
Mean E1/E2 Ratio	9.28	2.22	6.88	0.84	<0.001*
Mean estradiol (pmol/L)	390	456	613	1557	<0.001*
Mean estrone (pmol/L)	2152	530	2340	772	<0.001*

*Significant value <0.001.
Estrone/estradiol ratio.

between the two different laboratory assays (Supplementary Table S1).

Mean estradiol and estrone levels

We analyzed the mean estradiol and estrone levels at each patient's last clinic visit during the study period. The mean estradiol in the injectable group (1557 pmol/L, 424.1 pg/mL) was markedly higher than the estradiol levels observed in all other routes of estradiol (Table 4). Oral, transdermal, and sublingual groups achieved similar estradiol levels. The mean estradiol level generally increased with increasing doses of estradiol administered (Fig. 2).

The mean estrone levels were highest in the oral (2152 pmol/L, 586.2 pg/mL), and sublingual (2340 pmol/L, 637.4 pg/mL) groups (Table 4). As predicted by the lower E1/E2 ratio, the estrone levels in the transdermal and injectable groups were much lower (Fig. 3). Similarly, there was no statistically significant difference in the estradiol and estrone levels when accounting for type of laboratory assay, although estradiol levels were affected by the timing of laboratory draw (Supplementary Tables S2 and S3).

GEE models for association between routes of administration and outcomes

The results of the GEE models in Supplementary Tables S4 and S5 show the estimates of the association between routes of administration and the estrone to estradiol ratio (E1/E2 ratio) over repeat visits. For every unit (mg) increase in oral and sublingual estradiol administration, the E1/E2 ratio increased by 7.6 and 5.0 U over multiple visits, respectively, when compared with injectable estradiol (Supplementary Table S4).

These effects persisted even after adjusting for age and BMI. After adjustment, each unit (mg) increase in oral and sublingual estradiol administration led to an increase of the E1/E2 ratio by 7.8 and 5.2 units, respectively, when compared with injectable estradiol (Supplementary Table S5).

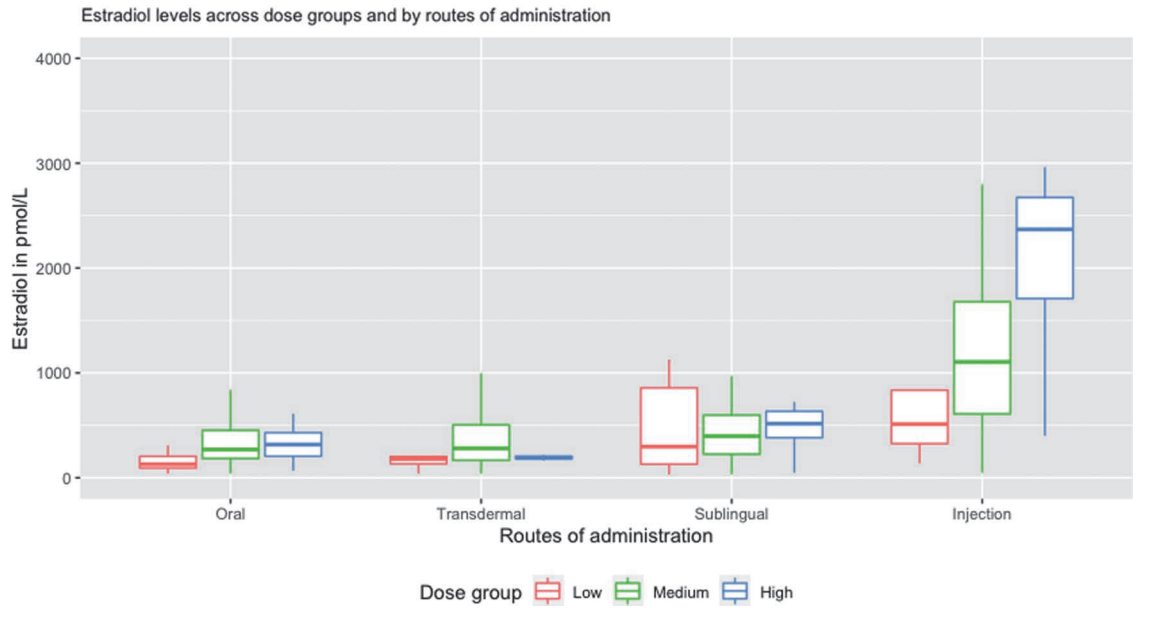

FIG. 2. Mean estradiol level (pmol/L) across dose group and routes of administration. Boxplot of mean estradiol level according to the route of administration, with interquartile ranges shown.

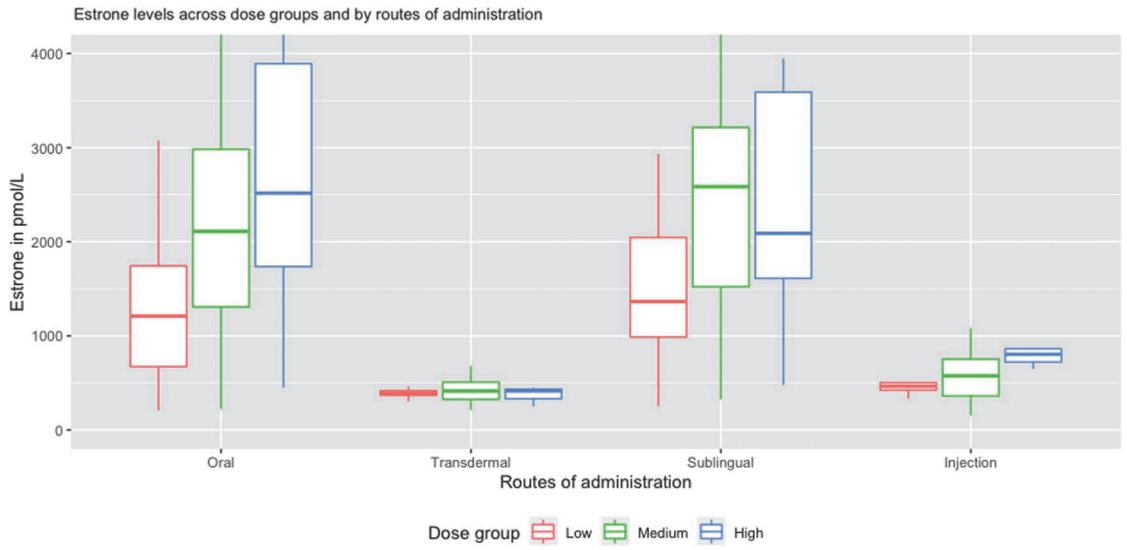

FIG. 3. Mean estrone level (pmol/L) across dose group and routes of administration. Boxplot of mean estrone level according to the route of administration, with interquartile ranges shown.

Similarly, for each unit (mg) increase in oral and sublingual estradiol, the estrone level increased by 1478 pmol/L (402.6 pg/mL) and 1769 pmol/L (481.9 pg/mL), respectively (Supplementary Table S6). Estradiol levels did not increase over multiple visits regardless of the route of administration (Supplementary Table S7).

Discussion

Over recurrent clinical visits, our data demonstrate significantly different E1/E2 ratios in the four different routes of estradiol administration in transfeminine individuals on feminizing hormone therapy, with oral and sublingual routes having the highest E1/E2 ratios followed by transdermal and injectable routes. Even at a cross-sectional snapshot at the last clinic visit, the mean E1/E2 ratio differed significantly between routes of administration and was consistently the highest for oral and sublingual followed by transdermal and the lowest for injectable.

Our secondary outcomes showed that the injectable route resulted in the highest mean estradiol levels by far, compared with the other three routes. One is therefore tempted to speculate whether injectable estradiol would result in superior feminizing changes as compared with the other routes. However, whether higher levels of estradiol are correlated with more effective feminization has never been proven.[14]

In addition to the low conversion of estradiol to estrone leading to higher estradiol levels, another reason for the higher levels of estradiol could be that the patients were treated with too high of a dose. Most patients in this injectable group were in the medium-dose category, receiving between 4 and 8 mg of estradiol weekly whereas doses of 3.75 mg SC (interquartile range [IQR], 3–4 mg)to 4 mg IM (IQR 3–5 mg) per week were recently reported to achieve therapeutic estradiol levels in a cohort of transfeminine individuals.[15]

Other studies have also reported E1/E2 ratios and levels in transfeminine individuals. Cirrincione et al. looked at estrone, estradiol, and E1/E2 ratios in a population of transgender women taking sublingual, transdermal, or injectable estradiol.[16] The E1/E2 ratios found in the sublingual and injectable groups are very similar to our study, whereas the E1/E2 ratio in their transdermal group is slightly lower, closer to 1 versus 2.2 in our study.

They also observed that there was a large variation in the E1/E2 ratio in the sublingual group, as compared with the transdermal and injections groups. They did not have an oral comparator group, whereas in our study, we found a similarly large range in E1/E2 ratios in the oral group. This suggests that different individuals may have different propensities in their conversion of estradiol to estrone when estradiol is taken orally or sublingually.

It would be clinically relevant to uncover whether there is a difference in effectiveness and safety

outcomes between those who have higher E1/E2 ratios (e.g., >10) as compared with those who have relatively lower E1/E2 ratios (e.g., 5) in the oral estradiol group. Another explanation for the large variability is that some in the sublingual group could have swallowed their estradiol on occasion whereas others in the oral group could have taken their estradiol sublingually some of the time; we were unable to capture these subtleties in our data.

Tebbens et al. examined estradiol and estrone concentrations in a group of trans women on oral estradiol compared with transdermal estradiol.[8] Similar to our study, they observed much higher estrone levels, as well as a higher E1/E2 ratio in the oral estradiol group. In a subset of 23 trans women, they were able to compare the breast growth between the oral and transdermal groups, and did not find a significant difference.

They also compared fat percentage change in a subset of 53 patients and found that it was not correlated to estrone levels. They concluded that measuring estrone levels was, therefore, not useful, but the study was limited by low sample sizes, and did not include injectable estradiol. Our study found a large difference in the E1/E2 ratio between oral and injectable estradiol groups and a much higher estradiol level achieved in the injectable group, and future study on clinical implications of these patterns is necessary.

Moreover, the results of this study are novel and important because they provide insight into the association between routes of estrogen administration and the estrone to estradiol ratio (E1/E2 ratio) in transfeminine individuals over multiple visits and recurrent laboratory values. Our study found that oral and sublingual administration of estradiol led to a significantly higher E1/E2 ratio compared with injectable estradiol, and this effect persisted even after adjusting for age and BMI.

Our modeling showed that each unit increase in oral and sublingual estradiol administration led to a significant increase in the estrone levels. These findings have significant implications for the clinical management of transfeminine individuals, as they suggest that the route of estrogen administration impacts the E1/E2 ratio and estrone levels over time.

This may be particularly relevant for the risk of adverse health outcomes associated with high estrone levels, such as venous thromboembolism and breast cancer.[13,17] Clinicians may need to consider the potential risks and benefits of different routes of estrogen administration when prescribing hormone therapy to transfeminine patients.

Conclusion

In summary, this study yields valuable insights into the variations in estrone to estradiol concentrations and ratios among transfeminine individuals undergoing feminizing hormone therapy. Our study found that the route of administration of estradiol affects these concentrations and ratios, with injectable estradiol resulting in the lowest E1/E2 ratio, highest levels of estradiol, and lower levels of estrone compared with all other routes. Our study, therefore, highlights the importance of future research into whether injectable estradiol exhibits any differences in efficacy for clinical feminization as compared with other routes of estradiol.

Finally, our study contributes to an emerging pool of data for this population with future studies directed toward understanding the effectiveness of feminization, and determination of the optimal route and dosage of estrogen administration that minimizes the risk of adverse health outcomes, while maximizing the benefits of hormone therapy in transfeminine individuals.

Strengths and limitations

Our study has several important strengths and unique contributions to advancing our understanding of estradiol therapy in transfeminine individuals. First, we included individuals on all four different routes of estradiol, whereas previous studies were limited to two or three routes. Second, we used a range of doses in the different route groups, within guideline recommended parameters, providing a realistic estimation of what clinicians can expect when they measure estradiol ± estrone levels in their own patients.

This retrospective study used real-world data with currently used anti-androgen agents, and biochemical measurements were done at two different laboratories, therefore extending its generalizability. Third, we have tried to eliminate spurious results from our data by categorizing the timing of the blood test with respect to when the estradiol hormone was taken.

However, our study has its limitations, including the absence of data on the direct effects of E1/E2 ratios and estradiol levels on feminizing changes. Data on testosterone levels were not available due to limited data collection, but would have been valuable in further elucidating any differences in route of administration. Further, the use of immunoassays, while common in clinical settings, may introduce variability and are more prone to error compared with more precise liquid chromatography mass spectrometry methods.

Our study was retrospective and dependent on chart review, and there may have been misclassification in how the patient was taking their estradiol (swallowing, orally vs. putting underneath their tongue, sublingually), as well as timing of the blood test with respect to estradiol ingestion/administration based on the clinical note reviewed. We did assume a timing of "mid" when no timing was otherwise specified. In addition, the study's focus on one clinic in a specific urban center (Toronto, Canada) may limit its generalizability to the broader population of transfeminine individuals undergoing hormone therapy.

Lastly, this study did not investigate the long-term safety of the different routes of estradiol therapy. Therefore, it is imperative to conduct further investigations to confirm these findings and thoroughly examine potential differences in long-term safety among the various routes of estradiol administration.

Authors' Contributions

N.M.K.: Investigation, data curation, writing—original draft, review, and editing. T.A.: Conceptualization, methodology, writing—original draft, review, and editing, and project administration. S.S.: Methodology, writing, editing, software, and statistical analysis. R.F.: Conceptualization, investigation, methodology, writing—original draft, review, and editing, resources, and supervision.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4
Supplementary Table S5
Supplementary Table S6
Supplementary Table S7

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Abbreviations Used

ANOVA = Analysis of Variance
BMI = body mass index
CV = coefficient of variation
E1/E2 = estrone/estradiol ratio
ECLIA = electrochemiluminescence immunoassay
GEE = generalized estimating equations