# The importance of addressing the research gap in transmasculine individuals: pharmacokinetic and research considerations.

Jordan Goodridge[1]

[1]University of Toronto Temerty Faculty of Medicine

March 23, 2024

J D GOODRIDGE

jordan.goodridge@utoronto.ca

University of Toronto, Temerty Faculty of Medicine

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Transgender and gender diverse (TGD) individuals have been both understudied and underrepresented in research,[1] and many of our epidemiological estimates have been based on those TGD individuals who sought care specific to medical transition with hormones or surgery. Overall, the number of TGD individuals seeking care is growing. Historically, transfeminine individuals sought care more frequently than transmasculine individuals; however, recent trends in North America suggest that these populations are now approximately equal in size overall, with a notable shift towards a predominantly transmasculine demographic in children and adolescents.[1] In this commentary, the term "transmasculine" is used rather than "transgender men" or "trans men" to more inclusively refer to all individuals who were assigned female at birth but identify with masculinity in some way, aiming to encompass a broader range of gender identities and experiences within the transmasculine community. While language evolves to align with patient identifications, there may be continued discrepancy in terms of the language used in this article and community preferences—it is always best to ask each patient what language they use to describe their gender and reflect this language in your conversations with them.

Despite an increasing proportion and total number of transmasculine individuals seeking transition-related care, including testosterone provision, research into the testosterone doses or serum concentrations required to reliably achieve specific effects is limited. Much of the existing literature on gender-affirming hormone therapy is focused on outcomes like safety, morbidity, and mortality. There is comparatively little research on the outcomes that patients are most interested in, such as 'masculinizing' changes and subjective satisfaction. In general, testosterone prescribing should be guided by each individual's embodiment goals, while also taking into consideration concerns around individualized risks and side effects. Being able to counsel clients on what formulation, dose and frequency might be needed to realistically achieve each of their goals—and recognizing that this may vary based on genetic and other factors—would allow for more fulsome shared decision-making. While this has been better studied for certain clinical effects, such as deepening of the voice and facial and body hair growth,[2,3] many would benefit from further evaluation.

Recent research has attempted to predict testosterone dosage necessary to achieve outcomes such as cessation of menses and body fat redistribution. However, methodological limitations hinder applicability of these findings. In these clinical datasets, there is either no protocol to standardize testosterone dosing,[4] or no standardization of timing between testosterone dosing and serum level measurement,[5,6,7] making it difficult to draw clinically-relevant conclusions. In certain circumstances, there is no reporting of serum testosterone

levels at all.[4] With respect to cessation of menses, results conflict as to the extent to which testosterone dose or serum testosterone levels correlate with the time required to reliably achieve amenorrhea. Some studies evaluating cessation of menses and body fat redistribution suggest that testosterone gel may be less efficacious as opposed to injectable testosterone.[5,6] However, these studies used only 50mg per day of testosterone gel, which is in the lower end of the typical dosage range cited by various guidelines.[8] Indeed, lower achieved serum testosterone levels with this dose of testosterone gel was observed.[6] Thus, future studies should evaluate the impact of different doses of transdermal testosterone and other formulations for these purposes using comparable serum levels and standardized testosterone measurement strategies, which could even include multiple measurements such as peak and trough concentrations or area-under-the-curve, to clarify contributions of dosage and formulation to clinical outcomes.

Certain questions with respect to desired testosterone effects remain largely unanswered. For instance, there are still no studies to date that compare different testosterone regimens and dosages and the extent to which they induce clitoral enlargement. This outcome can be gender-affirming in its own right, and can also enhance satisfaction with metoidioplasty, a genital surgery in which the hormonally-enlarged clitoris is reconstructed to become a penis. As well, there is substantial interest by patients and providers in determining whether topical testosterone or topical DHT applied directly to the clitoris, in addition to receiving parenteral testosterone, can lead to additional clitorophallus growth.[9] Local effects and systemic absorption of clitorally-applied testosterone are largely unknown, highlighting the need for pharmacokinetic research into this area.

Another critical area deserving attention is the differential risk profiles associated with various testosterone formulations. While some studies provide reassurance regarding the risks of conditions like ischemic heart disease and cerebrovascular disease, these data are not consistent. Some studies have found an elevated risk of ischemic heart disease among transmasculine individuals on testosterone,[10,11] but without reporting the specific hormone regimen(s) in the cohorts, making it challenging to identify whether dosing or frequency could exacerbate or mitigate this risk. A systematic review and meta-analysis evaluating various cardiovascular outcomes concluded that a longer duration of gender-affirming testosterone therapy is associated with undesirable effects on the lipid profile, but recognizes the potential for confounding variables that were not consistently reported in the studies it drew from, such as smoking history, testosterone dosage, and formulations used.[11] Similarly, the effects of testosterone therapy on diabetes mellitus risk and blood pressure are areas with conflicting evidence.[10] This inconsistency in data highlights the need for more robust and longitudinal studies to better understand the long-term implications of testosterone therapy. With regards to these potentially-increased metabolic risks, it would be also relevant to understand whether exogenous testosterone has similar metabolic effect to endogenous testosterone, making it possible to compare risk profiles between cis men and transmasculine people.

In conclusion, while the state of research in testosterone therapy for transmasculine individuals has progressed substantially, some significant gaps persist in our understanding of how effects and risks of testosterone may differ based on its formulation, dosage, frequency, and pharmacokinetic profiles. Future studies should evaluate these principles, and in many cases, incorporating consistent serum testosterone measurements relative to dose administrations—for instance, measuring trough levels or area-under-the-curve—may help to enable more definitive conclusions. This information would ultimately allow us to better tailor hormone prescribing to patients based on their unique goals and avoid concerning adverse effects, important tenants in shared decision-making between patients and clinicians.

**Conflict of interest** : None.

**Funding information** : None.

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