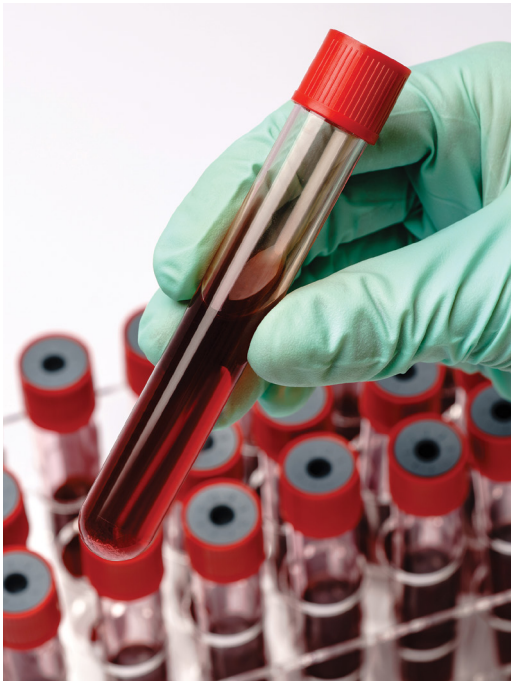
Interpretation of blood test results in transgender and gender diverse people undergoing gender-affirming hormone therapy



Brendan J Nolan, Portia Predny

Background
Increasing numbers of transgender and gender diverse (TGD) people are seeking initiation of gender-affirming hormone therapy (GAHT) in general practice. GAHT influences interpretation of common blood test results.

Objective
This article outlines the impact of GAHT on common blood test results.

Discussion
For individuals undergoing GAHT, haemoglobin/haematocrit and serum creatinine should be interpreted according to the reference range of an individual's affirmed gender.

GENDER-AFFIRMING HORMONE THERAPY (GAHT) is an integral component of care for many transgender and gender diverse (TGD) people. Estradiol- and testosterone-based GAHT regimens induce changes to blood tests which have sex-specific reference ranges, and ensuring the appropriate reference range is used could minimise unnecessary investigations and associated patient stress.

Objective

This article provides an overview of the impact of estradiol- and testosterone-based GAHT on common blood test results with a focus on sex steroid concentrations, haemoglobin/haematocrit and renal function.

Discussion

General practitioners (GPs) are well placed to initiate and monitor GAHT. Table 1 demonstrates standard GAHT regimens and typical doses available in Australia. A detailed description of GAHT regimens is beyond the scope of this article and has been described elsewhere.[1] In brief, estradiol-based GAHT typically encompasses oral or transdermal estradiol with or without an anti-androgen, and testosterone-based GAHT typically encompasses intramuscular or transdermal testosterone.

Sex steroid concentrations

Estradiol-based gender-affirming hormone therapy

Consensus guidelines provide recommendations for serum sex steroid concentrations in adults undergoing estradiol-based GAHT which are based on expert opinion, and notably, differences exist between different guidelines. In Australia, typical target ranges for serum estradiol and total testosterone concentrations are 250 to 600–1000 pmol/L and <2 nmol/L, respectively.[2,3] It is important to note that the serum estradiol concentration must be interpreted with consideration given to the timing of the blood test in relation to the last administered dose. Additionally, serum total testosterone concentrations might not be suppressed with spironolactone given its mechanism of action as an androgen receptor antagonist.[4] Some transgender people prefer to avoid testosterone suppression, in which case the estradiol and resultant serum total testosterone concentration are titrated to clinical response. Importantly, reference ranges provide a guide for dose titration, but this should also occur in conjunction with clinical response and client wishes.

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Testosterone-based gender-affirming hormone therapy

In general, serum testosterone targets are the same as those for hypogonadal cisgender men treated with testosterone. For individuals treated with intramuscular testosterone undecanoate, the general aim is trough testosterone concentration 10–15 nmol/L, whereas for people treated with transdermal testosterone, serum testosterone concentrations should fall within the cisgender male reference range (approximately 10–30 nmol/L).[1] Notably, some people might request lower testosterone doses for slower, or a lesser degree of, physical changes in line with their embodiment goals, and dose should be titrated according to clinical response and client wishes. Serum estradiol concentrations are not routinely monitored for people undergoing testosterone-based GAHT.[2]

Table 1. Gender-affirming hormone therapy regimens available in Australia

Formulation	Standard dosing regimen
Estradiol-based gender-affirming hormone therapy	
Oral	
Estradiol valerate (Progynova)	2–8 mg daily
Estradiol hemihydrate (Zumenon)	2–8 mg daily
Transdermal	
Patch (Estradot, Estraderm, Estramon)	50–200 mcg/24 hours twice weekly
Estradiol gel 0.06% (EstroGel)	2–4 pump actuations (0.75 mg/actuation) daily
Estradiol gel 0.1% (Sandrena)	1–2 sachets (1 mg estradiol) daily
Anti-androgen	
Spironolactone	50–200 mg daily
Cyproterone acetate	12.5 mg once weekly – 25 mg daily
Testosterone-based gender-affirming hormone therapy	
Intramuscular	
Testosterone undecanoate (Reandron)	1000 mg every 10–14 weeks (loading dose at 6 weeks)
Testosterone enanthate (Primoteston)	250 mg every 2–4 weeks
Transdermal	
1% testosterone gel (Testogel)	4 pump actuations (12.5 mg/actuation) daily or 1 sachet (50 mg/5 g) daily
2% testosterone gel (Testavan)	1–2 pump actuations (23–46 mg) daily
5% testosterone cream (AndroForte)	2 mL (50 mg/mL) daily

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Haemoglobin, haematocrit and red cell count

Testosterone is known to stimulate erythropoiesis, and resultant changes to haemoglobin, haematocrit and red cell count are seen in TGD people following initiation of GAHT. In TGD people treated with estradiol-based GAHT for ≥6 months, longitudinal studies demonstrate that haemoglobin, haematocrit and red cell count decrease to the cisgender female reference range, whereas in TGD people treated with testosterone-based GAHT for ≥6 months, haemoglobin, haematocrit and red cell count increase to the cisgender male reference range.[5–7] Mean cell volume remains within the reference interval.[8]

These changes have implications for interpretation of polycythaemia with testosterone-based GAHT. There is a well-documented risk of polycythaemia in those treated with testosterone-based GAHT,[5,9,10] and the risk appears higher with intramuscular, as opposed to transdermal, testosterone formulations.[9,10] We recommend that the cisgender male reference range is used to define polycythaemia, with readings above the upper limit of the laboratory reference range or haematocrit >0.50 both used in the literature.[11] A detailed approach to polycythaemia is beyond the scope of this article but can be found elsewhere.[1]

Renal function

Changes in body composition, including lean mass, are seen after initiation of GAHT,[12] which is associated with changes in serum creatinine and estimated glomerular filtration rate (eGFR) from as early as 3 months in some studies.[13] Longitudinal studies have documented decreases in serum creatinine in TGD people treated with estradiol-based GAHT,[6,14] and increases in serum creatinine for those treated with testosterone-based GAHT.[6,14] However, there is variability between studies with many limited by small sample sizes and variability in GAHT regimens.[15]

Based on the current evidence, it is recommended that for those receiving estradiol-based GAHT, which typically induces a decrease in muscle mass, the female eGFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula is most appropriate.[6,14] Conversely, for those receiving testosterone-based GAHT, which typically induces an increase in muscle mass, the male eGFR CKD-EPI formula is most appropriate after ≥3 months GAHT.[6,14]

In clinical situations where accurate assessment of renal function is necessary, it might be appropriate to use measures of renal function that are less affected by sex and not affected by muscle mass, including 24-hour urinary creatinine clearance, urinary inulin clearance, or serum cystatin c concentration. Of note, only serum cystatin c concentration has been evaluated in TGD people treated with GAHT.[16]

Other laboratory results

Liver enzymes

Several studies have documented changes to liver enzymes in TGD people treated with GAHT.[6,8,17,18] The largest longitudinal study demonstrated decreases in alanine

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aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) but no change in gamma-glutamyl transferase (GGT) following initiation of estradiol-based GAHT, whereas increases in all liver enzymes were seen in people treated with testosterone-based GAHT.[6] Overall, several studies suggest there are modest changes in liver enzymes toward the range of the affirmed gender, though in most cases these changes are not clinically significant.

Cardiac troponin and brain natriuretic peptide

One longitudinal and two cross-sectional studies have evaluated cardiac biomarkers in TGD people treated with GAHT. A 12-month longitudinal study demonstrated that cardiac troponin I shifts towards the range of the affirmed gender,[19] whereas the cross-sectional studies had discrepant findings; one study found that cardiac troponin I and troponin T were lower in TGD people treated with estradiol-based GAHT compared to testosterone-based GAHT,[20] whereas the other found no difference in cardiac troponin I and troponin T between the two groups.[21]

Two cross-sectional studies have evaluated B-type natriuretic peptide (BNP) concentrations in TGD populations. Consistent with the cisgender population, TGD people treated with estradiol-based GAHT had higher BNP concentrations than cisgender men[22] and TGD people treated with testosterone-based GAHT,[20] whereas those treated with testosterone-based GAHT had lower BNP than cisgender women[22] and TGD people treated with estradiol-based GAHT.[20]

There is currently insufficient data regarding the appropriate reference ranges for cardiac biomarkers in TGD people treated with GAHT, though it appears cardiac biomarkers shift toward the ranges of the affirmed gender. Emphasis must be placed on clinical history and examination, electrocardiogram changes and serial trajectory of cardiac biomarkers if levels fall between sex-specific reference ranges.

Prostate-specific antigen

There are limited data examining the effect of estradiol-based GAHT on prostate-specific antigen (PSA). However, a retrospective cohort study of 210 TGD people treated with estradiol-based GAHT reported a median PSA of the cohort was 0.02 ng/mL (0–0.2) and the 95th percentile value was 0.6 ng/mL.[23] Notably, this is lower than that in cisgender men without prostate cancer[24] and more closely aligns with hypogonadal cisgender men undergoing androgen deprivation therapy for prostate cancer or following prostatectomy.

Overall, there are insufficient data evaluating reference ranges to recommend a specific PSA cutoff in TGD people treated with estradiol-based GAHT. As such, clinicians should make individualised decisions based on clinical history to inform the need for PSA monitoring and/or follow-up imaging.

Recommendations

From a practical perspective, we recommend that the clinician specify the desired sex-specific reference range on the laboratory request, particularly in those with a discordant gender marker (Table 2).

Given that serum sex steroid concentrations and resultant changes to body composition begin to occur within 3 months of initiation of GAHT, we recommend that the reference range of the individual's affirmed gender should be used for tests with sex-specific reference ranges after 3 months GAHT.

Individualised interpretation will still need to occur, particularly for individuals with recent GAHT commencement or for those treated with low-dose GAHT in whom sex-specific parameters could be between the male and female reference ranges. Notably, some TGD individuals do not desire GAHT, and the reference range of their sex recorded at birth should be used. It is important to explain the rationale underlying the requested reference range to the patient.

Conclusion

With an increasing number of TGD people treated with GAHT, it is important that GPs can interpret common blood test results using the correct, sex-specific ranges. For individuals undergoing standard doses of GAHT, the reference range of the affirmed gender should be used for blood tests with sex-specific reference ranges. Clinicians can request the desired reference range or provide appropriate history to ensure the appropriate range is provided.

Table 2. Recommended reference ranges for transgender individuals undergoing ≥3 months gender-affirming hormone therapy

Blood test	Recommended reference range	
	Affirmed gender	Sex recorded at birth
Estradiol	✓	
Total testosterone	✓	
Haemoglobin/haematocrit/red cell count	✓	
Creatinine	✓	
Liver enzymes	✓	
Cardiac troponin	Insufficient data but move toward affirmed gender	
B-type natriuretic peptide	Insufficient data but move toward affirmed gender	
Prostate specific antigen[A]		✓ (appear closer to men undergoing ADT)

[A] Only relevant for people with a prostate.

ADT, androgen deprivation therapy.

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Key points

- GAHT influences interpretation of common blood test results with sex-specific reference ranges.
- Consensus guidelines provide target ranges for sex steroid concentrations for people established on GAHT.
- The reference range of the affirmed gender should be used for haemoglobin/haematocrit and creatinine for people established on GAHT.
- Individualised interpretation is needed for people on low-dose hormone therapy.
- Clinicians should specify whether the male or female reference range should be reported on the blood test request.

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