An Examination of the Use of Reference Ranges of Common Chemistry Analytes for Transgender Individuals

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Abstract

As transgender individuals undergo hormone therapy, their bodily physiology undergoes significant changes due to the introduction of hormones. As their bodily physiology changes, the reference ranges used to measure their bodily chemistry values needs to change as well. The lack of proper reference ranges could lead to misdiagnosis and delay in treatment. This literature review examines the critical issue of reference range selection for monitoring chemistry values in transgender healthcare. Since transgender medical care is recent, the information was gathered from online sources such as Google Scholar and the University of Minnesota online library. The sources used for this literature review specifically addressed transgender reference values or transgender chemistry analytes. The selected studies included transgender men and women, common chemistry analytes, and utilized standard clinical chemistry laboratory instruments. Multiple studies came to a similar conclusion that transgender individuals' sex-specific bodily chemistry values should be compared to their affirming gender's reference ranges. However, few studies indicated some chemistry values such as sex-specific hormones should be compared to the reference ranges of the patient's gender assigned at birth. Also, there are suggestions of developing intermediate reference ranges for transgender patients that have bodily chemistry values that do not fall under cisgender male or cisgender female reference ranges. To advance the quality of transgender healthcare within the laboratory, there must be studies conducted to establish proper reference ranges and a mechanism of including a patient's affirming gender within the laboratory information system.

Background

Reference ranges are used daily within the clinical laboratory to assess bodily chemistry values. These reference ranges are necessary to diagnosis a disease state, determine need for treatment, and monitor treatment. Reference ranges are determined by patient population factors such as sex, age, race, etc. However, these reference ranges neglect a patient population that does not abide by the cisgender binary. Transgender individuals do not identify with their assigned birth listed on their patient chart. Also, these individuals may be undergoing gender affirming treatment that impacts their bodily physiology.

Transgender affirming care can range from body modification surgeries, gender affirming voice therapy, and hormone replacement therapy. Within the laboratory, the hormone replacement therapy has the largest impact on how the specimen should be analyzed due to the impact of bodily chemistry analytes. For transwomen, hormone replacement therapy includes a form of estrogen and can be used with a testosterone blocker. Estrogen therapy can lead to breast development, subcutaneous fat redistribution, and softening of the skin (Goldstein, 2017). For transmen, hormone replacement therapy includes the administration of testosterone. Testosterone therapy can lead to body hair growth, cessation of a mensural cycle, subcutaneous fat redistribution, and voice change (Goldstein, 2017).

Due to social stigma and lack of accommodation, transgender individuals are hesitant to seek healthcare treatment. For a transgender individual, their preferred name, gender identity, and gender affirming therapy are often not considered within their laboratory testing. This issue is exacerbated by the lack of proper reference range values for transgender individuals. Thus, a disease state may be missed or misidentified due the lack of knowledge on how to analyze sex-related and non-sex-related chemistry analytes. This lack of basic healthcare accommodation for specific patient population should be addressed. My capstone aims to gather current research on adapting chemistry reference ranges for transgender individuals and summarize it for other laboratory personnel.

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Methods

A literature review was conducted using Google Scholar and the University of Minnesota online library. Since transgender medical care is an emerging field, there are not many physical written sources due to the lack of research before the late 2010s. During my use of these search engines, I used keywords such as 'transgender reference values' or 'transgender chemistry analytes'. For this literature review, I wanted to specifically address chemistry analytes and their reference values. Many studies only measured hormone reference values and did not address my research. I chose to only include patient studies and literature reviews. I ensured that each patient study assessed transwomen and transmen, measured chemistry analytes, and used common chemistry analyzers. For the literature reviews, I collected sources that discussed the impact of hormones on bodily physiology and past laboratory procedures for addressing transgender patient values.

Results

Figure 1: Comparison of Sex-Dependent and Sex-Independent Chemistry Analytes

Sex-Dependant Chemistry Analytes	Sex-Independent Chemistry Analytes
Hormone Levels: • Testosterone • Estrogen • Progesterone Complete Blood Count: • Hemoglobin • Hematocrit • Red cell indices Cholesterol Panels: • Total cholesterol • Triglycerides • HDL • LDL Iron and Ferritin Creatinine Prolactin	Glucose Electrolytes: • Sodium • Potassium • Choloride • Bicarbonate Liver Function Tests: • ALT • AST • ALP • Bilirubin Kidney Function Tests: • BUN • GFR Calcium Phosphorus

Figure 1: Within the chemistry laboratory, reference ranges are highly dependent on the patient's sex. However, there are analytes that do not show a significant difference between the two sexes. This distinction provides the framework of determining which analytes to measure based on the patient's assigned gender at birth or their affirming gender's reference ranges. (*Pharmacotherapy self-assessment program*, 2017)

Figure 2: Comparison of Chemistry Analyte Reference Intervals of Cisgender Women to Transgender Women

Analyte	Cisgender Female Reference Interval	Transgender Female Reference Interval	Cisgender Female Reference Interval Mean	Transgender Female Reference Interval Mean
Sodium (mmol/L)	136-145	134-144	141	139
Potassium (mmol/L)	3.5-5.1	3.5-5.5	4.3	4.4
Urea (mmol/L)	2.1-7.1	2.5-7.6	4.6	4.0
Creatinine (µmol/L)	49-90	51-117	70	75
Albumin (g/L)	35-52	41-52	44	46
Total Bilirubin (µmol/L)	5-21	3-20	13	6
ALT (U/L)	7-35	9-50	21	16
AST (U/L)	13-35	12-50	24	19
ALP (U/L)	42-98	34-118	70	71
GGT (U/L)	0-39	11-74	20	29
Oestradiol (pmol/L)	183-213	19-934	198	167
Testosterone (nmol/L)	0.2-2.9	0.1-31.2	1.6	0.7
TSH (mlU/L)	0.27-4.2	0.75-3.84	2.24	1.41
Prolactin (µg/L)	4.8-23.3	4.8-70.8	14.1	15.8

Figure 2: A comparison of the chemistry analyte reference intervals of cisgender women to transgender women from the study conducted by Morné C Bezuidenhout. The following chemistry analytes were statistically analyzed using Statistica V13.5 to determine significant variation (Bezuidenhout, 2022).

Discussion

Based on the results provided in the highlighted studies, the sex-specific chemistry analytes should be compared to their affirming gender's reference ranges. However, non-sex-specific chemistry analytes did not reflect their affirming gender's reference ranges, but rather their gender assigned at birth. These analytes included common electrolytes, hemoglobin A1c, hsCRP, and albumin (Humble, 2022). For transgender males, the chemistry analytes that were frequently measured within the cisgender males reference ranges were serum creatinine and red blood cell indices (SoRelle, 2019). During the administration of testosterone for transgender men, the muscle mass of the individual increases. The increased muscle mass leads to an increase in muscle breakdown products, therefore matching the serum creatinine values of a cisgender male (Bezuidenhout, 2022). Also, the administration of an androgen such as testosterone will stimulate erythropoiesis. The simulation of erythropoiesis will increase the hemoglobin and hematocrit concentration to ranges congruent with cisgender males (SoRelle, 2019). The other sex-specific analytes demonstrated only slight changes that were not significant. For the liver panel analytes, alanine aminotransferase and aspartate aminotransferase slightly increased due to the increased presence of testosterone. However, alkaline phosphatase and total bilirubin remained unchanged (SoRelle, 2019). For the lipid panel analytes, triglyceride values increased, and HDL values decreased (SoRelle, 2019).

For transgender women, the changes of bodily chemistry values were more complex. However, there was still a slight trend of sex-specific chemistry analytes matching cisgender women values. The sex-specific analyte that commonly matched cisgender women reference ranges was prolactin. The increase of prolactin is attributed to the estrogen therapy causing lactotroph hyperplasia (Bezuidenhout, 2022). For the other sex-specific chemistry analytes, there is notable trend of the patient values falling between cisgender male and female reference ranges. The notable analyte that displayed this trend was serum creatinine (SoRelle, 2019). Similar to other sex-specific analytes within transgender men, there were only slight changes. For the liver panel analytes, there was either slight decrease or no significant change to the liver enzymes (Humble, 2022). For the lipid panel analytes, a slight decrease in total cholesterol and triglycerides was noted. However, there was a slight increase in HDL values (Bezuidenhout, 2022).

Throughout the various studies, there were common limitations such as small sample size, differences in hormone therapy, and varying stages of transition. Many of the studies attributed the small sample sizes to a mistrust of healthcare systems due to the stigma of transgender individuals and overall lack of knowledge. However, these limitations can be addressed by conducting further studies with a large sample size that have similar concentrations of hormone therapy and stage of transition. In the meantime, the laboratory information systems should take the patient's transgender history into account when providing reference ranges.

Conclusion

Healthcare for transgender individuals is highly stigmatized due to the current political climate. However, this should not prevent the development of mechanisms to properly diagnosis and treat these individuals. The clinical laboratory should enhance the healthcare of transgender individuals by establishing proper reference ranges and updating the Laboratory Information System (LIS) to account for these individuals. For transmen, the established reference ranges for cisgender men should be referenced for some sex-specific chemistry analytes. For transwomen, intermediate reference ranges should be further developed. To further the development of these ranges, we must conduct studies with a large transgender patient population and develop mechanisms to incorporate an individual's identifying gender within LIS.

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