The Utility of Monitoring Potassium in Transgender, Gender Diverse, and Nonbinary Individuals on Spironolactone

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Abstract

Context: Current Endocrine Society guidelines recommend that transgender women taking spironolactone have their potassium levels checked every 3 months for the first year after initiating therapy and annually thereafter to monitor for hyperkalemia.

Objective: The goal of this study was to assess the need for such frequent potassium monitoring and to investigate whether age plays a role in potassium abnormalities in transgender, gender diverse, and nonbinary (TGDNB) individuals taking spironolactone.

Methods: Using EPIC-Clarity, a retrospective study of healthy, adult individuals with gender-identity disorder listed in their problem list and taking spironolactone was performed. We analyzed the incidence of hyperkalemia in this population. Data from June 2006 through November 2021 were obtained. Exclusion criteria included hypertension, renal failure, diabetes mellitus, heart failure, and medications that affect the renin–angiotensin–aldosterone system.

Results: 318 healthy TGDNB individuals met our inclusion criteria. We identified 8/318 (2.5%) individuals with hyperkalemia on spironolactone. There was a significant difference in incidence of hyperkalemia events in those >45 years old and those ≤45 years old (8.9% vs 1.5%, \( P < .016 \)).

Conclusion: Our data suggest the incidence of hyperkalemia in our TGDNB population is low, particularly in those ≤45 years old; however, this risk increases with age. These findings suggest practice guidelines may need to be adjusted to minimize unnecessary testing in the population ≤45 years old who are not plagued by comorbidities that affect potassium handling.

Key Words: spironolactone, transwomen, potassium, nonbinary, hyperkalemia, transgender

Abbreviations: MCW, Medical College of Wisconsin; TGDNB, transgender, gender diverse, and nonbinary.

The cost of healthcare in the United States has been steadily rising for the past 50 years. In 2020, the country spent approximately 4.1 trillion dollars in healthcare expenses [1]. To address the increasing costs, there have been numerous efforts to evaluate and address sources of superfluous healthcare spending, such as unnecessary laboratory testing [2-4]. When determining the need for laboratory testing, many physicians rely on evidence-based clinical practice guidelines. Such is the case regarding potassium monitoring in patients taking the mineralocorticoid receptor antagonist spironolactone.

Spironolactone was initially approved in the 1960s for treatment of heart failure, hypertension, edema, and primary hyperaldosteronism [5]. However, it was found to have anti-androgenic effects leading to its off-label use for acne, female pattern hair loss, and hirsutism [6]. For transgender, gender diverse, and nonbinary (TGDNB) individuals and especially transgender women in the United States, it has become a part of standard hormone therapy.

The Endocrine Society recommends that transgender women taking spironolactone have their potassium levels checked every 3 months for the first year after initiating therapy and annually thereafter [7]. These guidelines were informed by studies monitoring the effects of spironolactone on heart failure patients, which indicated that spironolactone usage is associated with an increased risk of hyperkalemia within an aging population [8-10]. Conversely, guidelines released by the American Academy of Dermatology indicate that it is not necessary to screen potassium levels in healthy women who are between 18 and 45 years old and taking spironolactone, as studies have shown that the risk of hyperkalemia in this population is low [11, 12]. There have been few studies directly investigating the utility of potassium monitoring in young, healthy, TGDNB individuals. Millington et al investigated the use of spironolactone specifically among adolescent transgender females (16-18 years of age) and found that there was no correlation between spironolactone dose and incidence of hyperkalemia [13]. Similarly, SoRelle et al also examined the effect of spironolactone usage on potassium levels in transgender patients through retrospective chart review and found no significant change [14].
The goal of our study was to evaluate the incidence of hyperkalemia in TGDNB individuals taking spironolactone and to assess whether age is associated with an increased risk of hyperkalemia. We hypothesized that the risk of hyperkalemia in healthy TGDNB individuals aged ≤45 years is low; therefore, the recommended laboratory monitoring guidelines for this group may be unnecessary.

Materials and Methods
We conducted a retrospective chart review of TGDNB individuals attending Froedtert and Medical College of Wisconsin (MCW) between June 2006 and November 2021. The database used was EPIC-Clarity. ICD-10 codes relating to gender identity disorder were used to identify our cohort. Data were then filtered to patients medicated with spironolactone as outlined in Fig. 1. Exclusion criteria based on ICD-10 codes (listed in Fig. 1) included hypertension, renal failure, diabetes mellitus, heart failure, and medications that affect the renin–angiotensin–aldosterone system [15]. The reference range for potassium is 3.4 to 5.1 mmol/L based on Froedtert and MCW institutional laboratory cut-offs. Therefore, hyperkalemia was defined as a serum potassium of greater than 5.1 mmol/L. Baseline laboratory tests were identified as either the level prior to the initiation of spironolactone or the level prior to the abnormality.

Data about a patient’s date of birth, race, age, and dose at the time spironolactone was first recorded at our institution was extracted. Of those that became hyperkalemic, charts were further reviewed looking for confirmation of hyperkalemia, dose of spironolactone at time of hyperkalemia, and context surrounding a hyperkalemic episode. Gender identity and use of estradiol were also noted in the hyperkalemia cohort.

This study was reviewed and approved by the MCW Institutional Review Board.

Results
We identified 2218 patients in EPIC-Clarity with ICD-10 codes relating to gender identity disorder included in their problem list (Fig. 1). A total of 318 patients met the inclusion criteria and were subsequently included in our analysis (Table 1). The overall age range for our cohort was 16-68 years with a mean age of 30 years and a median age of 26 years. For analysis purposes, the cohort was separated into age groups ≤45 and 45 years. Most of this cohort were taking oral estradiol and 1 subject was using estradiol patches. The mean baseline potassium level was 4.5 mmol/L. At the time of hyperkalemia, the maximum potassium level was 5.8 mmol/L, the median was 5.2 mmol/L, and the mean was 5.3 mmol/L. Only 1 of these subjects had more than 1 episode of hyperkalemia, with a potassium level variable for patients with hyperkalemia and patients without hyperkalemia. For univariate statistical comparisons between the 2 groups, we performed chi-squared tests to compare categorical variables and 2-sample t tests for numeric variables. If fewer than 5 observations existed in a cell, Fisher’s exact test was used instead of the chi-squared test. Statistical significance was assessed at $P \leq .05$. Complete statistical analysis was performed using R-4.1.2 software.

Hyperkalemia
We identified 8/318 (2.5%) individuals with 1 or more episodes of hyperkalemia. Of these 8 subjects, 4 (50%) were age ≥45 and 4 (50%) subjects were age ≤45. Within the age ≥45 cohort, 4/45 (8.9%) developed hyperkalemia. Within the age ≤45 group, 4/273 (1.5%) developed hyperkalemia. There was a significant difference in hyperkalemia events between age groups on spironolactone (8.9% vs 1.5%, $P = .016$). Ages ranged from 21 to 68 years with a median age of 50 years. Most of this cohort were taking oral estradiol alongside spironolactone (7/8). One of these oral users was administering sublingual estradiol and 1 subject was using estradiol patches. The mean baseline potassium level was 4.5 mmol/L. At the time of hyperkalemia, the maximum potassium level was 5.8 mmol/L, the median was 5.2 mmol/L, and the mean was 5.3 mmol/L. Only 1 of these subjects had more than 1 episode of hyperkalemia, with a potassium level...
of 5.2 mmol/L at episode 1 and 5.4 mmol/L at episode 2 6 months later.

The dose of spironolactone for the hyperkalemia group (n = 8) ranged from 100 to 300 mg daily at the time of the hyperkalemic episode. One subject was on 300 mg daily, 4 subjects were on 200 mg daily, 2 subjects were on 150 mg daily, and 1 subject was on 100 mg daily. For the nonhyperkalemia group (n = 310), the mean spironolactone dose was 91 mg daily (SD 60.7), the median dose was 100 mg daily, and the range was 25 to 400 mg daily. Of note, doses were obtained from the date medication was first recorded at our institution.

None of our subjects reached the threshold of severe hyperkalemia of 6.5 mmol/L as defined by the American Academy of Family Physicians [16]. No clinical intervention (including reduced spironolactone dosing) was initiated for 4 (50%) subjects. Furthermore, chart review done 1 to 6 years from the date of hyperkalemia demonstrated normalization of their potassium levels. The remaining 4 (50%) subjects with an episode of hyperkalemia were recommended to decrease their spironolactone dose (1 from 300 to 200 mg, 2 from 200 to 150 mg, and 1 from 150 to 50 mg) following the episode. Following dose reductions of spironolactone, there were no recurrent episodes of hyperkalemia, and no patients had related hospitalizations. Time between initiation of spironolactone to a hyperkalemic episode ranged from 4 months to 4 years, with 6 (75%) subjects being on spironolactone for less than 1 year at the time of the hyperkalemic episode.

### Discussion

To our knowledge, this is the largest cohort of TGDNB individuals looking at the incidence of hyperkalemia associated with spironolactone therapy. We demonstrated that there is a small increased risk of hyperkalemia in our overall population (2.5%), and that it is more pronounced in those >45 years old (8.9%), albeit this was a smaller proportion of our cohort (14%). TGDNB individuals >45 years of age may warrant monitoring of serum potassium as they are at greater risk of developing hyperkalemia. These findings are similar to the rates of hyperkalemia found in previous projects investigating rates of hyperkalemia in female cisgender and adolescent transgender patients [11-14].

We found a significant difference between the mean dose of spironolactone in the hyperkalemia vs nonhyperkalemia groups. There was a significant difference in the age and dose of daily spironolactone between the hyperkalemia and the nonhyperkalemia group.

Of note, doses were obtained from the date medication was first recorded at our institution for the nonhyperkalemia group and from the date of hyperkalemia for the hyperkalemia group.

Baseline and maximum potassium were not included at time of initial data extraction. These values were obtained for the hyperkalemia group by manual chart review.

### Table 1. Results of the patients included in the analysis

|                                    | Overall (n = 318) | Hyperkalemia (n = 8) | Nonhyperkalemia (n = 310) | P value |
|------------------------------------|------------------|----------------------|---------------------------|---------|
| **Age (years)**                    |                  |                      |                           |         |
| Mean (SD)                          | 30 (10.9)        | 47 (18.1)            | 29 (10.3)                 | <.001** |
| Range                              | 16-68            | 21-68                | 16-66                     |         |
| Median                             | 26               | 50                   | 26                        |         |
| **Age groups (years), n (%)**      |                  |                      |                           | .016**  |
| ≤45                                | 273 (85.8)       | 4 (50)               | 269 (86.8)                |         |
| >45                                | 45 (14.2)        | 4 (50)               | 41 (13.2)                 |         |
| **Race, n (%)**                    |                  |                      |                           | .725    |
| Caucasian                          | 251 (78.9)       | 8 (100)              | 243 (78.4)                |         |
| Non-Hispanic Black                 | 27 (8.5)         | 0                    | 27 (8.7)                  |         |
| Asian                              | 6 (1.9)          | 0                    | 6 (1.9)                   |         |
| Hispanic/Latino American           | 23 (7.2)         | 0                    | 23 (7.4)                  |         |
| Other                              | 7 (2.2)          | 0                    | 7 (2.3)                   |         |
| Unknown                            | 4 (1.3)          | 0                    | 4 (1.3)                   |         |
| **Dose of daily spironolactone (mg)** |        |                      |                           | <.001** |
| Mean (SD)                          | 90 (60.2)        | 178 (58.3)           | 91 (60.7)                 |         |
| Median                             | 100              | 200                  | 100                       |         |
| Range                              | 25-400           | 100-300              | 25-400                    |         |
| **Baseline potassium (reference range 3.4-5.1 mmol/L)** | | | | |
| Mean (SD)                          | c                | 4.5 (0.345)          | c                         |         |
| Median                             | 4.5              |                      | c                         |         |
| Range                              | 4.1-5.0          |                      | c                         |         |
| **Max potassium (reference range 3.4-5.1 mmol/L)** | | | | |
| Mean (SD)                          | c                | 5.3 (0.207)          | c                         |         |
| Median                             | 5.2              |                      | c                         |         |
| Range                              | 5.2-5.8          |                      | c                         |         |

Demographics, dose of spironolactone and potassium levels overall and in the hyperkalemia and nonhyperkalemia groups. There was a significant difference in the age and dose of daily spironolactone between the hyperkalemia and the nonhyperkalemia group.

P values are based on a Fisher's exact or chi-squared test based on group size.

Dose of daily spironolactone was retrieved from date the medication was first recorded at our institution for the nonhyperkalemia group and from the date of hyperkalemia for the hyperkalemia group.

Baseline and maximum potassium were not included at time of initial data extraction. These values were obtained for the hyperkalemia group by manual chart review.
group (P ≤ .001). However, there were only 8 individuals who developed hyperkalemia vs 310 who did not. Furthermore, the dose of spironolactone for the nonhyperkalemia group was retrieved from the date spironolactone was first recorded at our institution. Unless patients were started on spironolactone at an outside institution, this was likely a starting dose, which is often later increased to optimize gender-affirming goals. Therefore, we assume many individuals in our nonhyperkalemia group were later on higher doses of spironolactone similar to our hyperkalemia group but did not develop hyperkalemia. Our data would have captured any episode of hyperkalemia between June 2006 and November 2021.

The American Academy of Dermatology determined that it is not necessary to monitor potassium levels in healthy women, aged ≤ 45 years, on spironolactone for acne treatment. They continue to recommend that women >45 years have baseline potassium levels monitored prior to spironolactone initiation, as well as during therapy, and again after dose increases [6]. Of note, the study that inspired these guidelines also only had 12 patients on spironolactone who were aged >45 years [12]. Like the American Academy of Dermatology, our study suggests that potassium monitoring may not be necessary in healthy TGDNB individuals aged ≤ 45 years. Potassium levels should likely be monitored in patients >45 years or in those with comorbidities, such as heart failure, renal disease, diabetes, or those taking antihypertensive agents that affect the renin–angiotensin system, as patients with these conditions had been excluded both from this study and from prior studies.

At the institution in which this study was performed, the usual and customary cost of obtaining a basic metabolic panel is approximately $87 and for a comprehensive metabolic panel is $141. The usual and customary cost for a potassium level alone is $28; however, many providers may opt to order a panel rather than a singular laboratory test. With the current Endocrine Society screening recommendations, in the first year following initiation of spironolactone patients at our institution would require between $112 and $564 worth of laboratory testing. Again, this is specific to our institution and does not necessarily reflect the cost to each patient. Costs vary depending on institution and insurance coverage. While cost is relative depending on one’s financial stability, I study found that “financial issues” were the number 1 reported barrier to gender-affirming care in transgender and gender nonconforming individuals [17]. Thus, by decreasing the frequency of unnecessary laboratory monitoring, we could help mitigate these cost barriers and potentially increase access to care.

The limitations of this study include the use of a single institution, which may affect the generalizability of these results. A large majority of our patients were Caucasian, which does not represent the entirety of the TGDNB population. Our study was not designed to assess whether risk of hyperkalemia is associated with dose of spironolactone. This could be an area of future research to better guide clinicians and to provide cost-effective care.

**Conclusion**

Our data suggest the risk of hyperkalemia is low (1.5%) in a healthy TGDNB population aged ≤45 years. We propose that frequent potassium monitoring may be unnecessary and should be reserved for those aged >45 years and those with medical comorbidities such as hypertension, diabetes, renal disease, heart failure, and/or on medications that affect the renin–angiotensin system.

**Disclosure Statement**

The authors have nothing to disclose.

**Data Availability**

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

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