The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 11, e4791–e4792
https://doi.org/10.1210/clinem/dgab515
Letter to the Editor Response

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Response to Letter to the Editor From Laidlaw: "Erythrocytosis in a Large Cohort of Trans Men Using Testosterone: A Long-Term Follow-Up Study on Prevalence, Determinants, and Exposure Years"

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Received: 1 July 2021; Editorial Decision: 9 July 2021; First Published Online: 20 July 2021; Corrected and Typeset: 3 August 2021.

We want to thank Michael Laidlaw and colleagues for their interest in our article. The point that they make is that cutoff values for natal females should be used in defining erythrocytosis in transgender men instead of the cutoff value of the identified gender. In the slipstream of this argument, the authors raise the point that adolescents and young adults should be afforded clear facts about potential complications of testosterone treatment, such as erythrocytosis and related risks. They wonder whether adolescents could really provide informed consent (1).

We feel that the societal debate pro and contra hormonal treatment in transgender adolescents has its own rights, but this was not the subject of our article; neither do we think that it could be settled by the definition of cutoff levels for erythrocytosis. In our study we looked at the time relation between testosterone therapy and hematocrit. We also looked at determinants for an increase in hematocrit levels. To express these relationships, we had to choose certain cutoff levels (0.50, 0.52, 0.54). The prevalence for hematocrit levels of 0.48 measured twice was 26%; we did indeed not present this number in our article.

The debate on reference values in transgender people is obscured by an unclear and uncritical use of the terms *reference values* or *cutoff points*. In a recent review by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) committee, a clear distinction was proposed between reference intervals (RI) and clinical decision limits (CDL) (2). Reference intervals are usually based on 95% intervals of a population, while clinical decision limits are based on clinical outcome studies. In clinical practice, we often use reference intervals as a method to compare results with those of a comparable population. We use reference intervals for men and women, but also for certain age groups and in special conditions like pregnancy. For many laboratory measures, it is shown that reference intervals for transgender men using testosterone are more similar to those

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

of cis men (vice versa for transwomen). What really is at stake is whether the associated risks for certain values (ie, the clinical decision limits) are also similar. The answer to that question, for many laboratory tests, is that we simply do not know the relation between certain values and the associated risk in transgender population.

Literature indeed has shown an increased cardiovascular risk in transgender men compared with cisgender women (3, 4). However, it is not known whether the increased cardiovascular risk in transgender men can be attributed to the increase in hematocrit levels. Previous studies highlighted other possible factors for the increased cardiovascular risk in transgender men, such as an unfavorable change in lipid profile (5). Furthermore, lifestyle factors might also play a role. Extrapolating risk estimates for certain hematocrit levels from cis women to transgender men overlooks that the spectrum of underlying causes for secondary erythrocytosis, such as smoking, obstructive sleep apnea syndrome, and other lung diseases are different and might have their own relation with cardiovascular events.

In conclusion, in the absence of reliable data on the relation between hematocrit and cardiovascular events in transmen, it seems reasonable to at least avoid levels above the cutoff point of cis men (ie, 0.54). Clinicians can choose lower decision levels if there are patient-specific reasons for that (eg, other factors that increase blood viscosity). Future studies should focus both on the general increase in cardiovascular risk associated with trans masculine treatment as well as on the hematocrit-mediated risk.

Additional Information

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