June 26, 2017

Use of Cystatin C in Transsexual Patients

Introduction

Sex-Specific Testing and Transgender Patients

Further confounding to providing transgender healthcare is that the interpretation of many laboratory tests and functional testing utilizes reference ranges or interpretations which are sex-specific. Examples of sex-specific tests or interpretations include: hemoglobin and hematocrit, lipids, metabolic functioning, hormone assays, eGFR, PFTs, echocardiograms even QTc interval.

There has been little investigation into laboratory reference or normal ranges for transsexual* patients. This is similar to the situation years ago in pediatrics. But the ethics of studying children was figured out, the funding was obtained, and now we have explicit age and sex pediatric reference ranges. A similar effort is necessary for the transsexual patient population

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Consider this example of interpretation of blood count in the transsexual patient at the onset of transition:

The m<F transsexual, who as a male had a typical "male" hematocrit of 45; at the onset of her transition a hematocrit of 45 will be interpreted as high, now using female reference ranges.

Conversely for the f<M transsexual, who as a female had a typical "female" hematocrit of 32; at the onset of his transition a hematocrit of 32 will be interpreted as low, now using male reference ranges.

Estimating renal function using eGFRcr

Perhaps the "most famous" sex-specific test is eGFR, an estimation of renal function. GFR is defined by creatinine, a marker of muscle mass, in the eGFR equation.[1]

Affecting creatinine are meat diet, exercise and general good health; and none of these are easily measurable. And because of this, creatinine generation has approximated clinically by using the demographic markers of sex, age, race and/or body mass, in equations which estimate GFR.

Why are there different estimated levels of GFR for males and females?

The MDRD study equation includes a term for female sex to account for the fact that men, (as defined in this discussion by people who have testosterone), have a higher (better) GFR than women, (as defined for this discussion as people who have estrogen), at the same level of serum creatinine.

Conversely, women have a lower (worse) GFR than men at the same serum creatinine. This term is in the equation because men on average have higher muscle mass and therefore higher creatinine generation than women.

Consider this example of calculating eGFR using the MDRD calculator:[2]

A non-black **male** age 60 with creatinine of 1.0 will have a GFR of **81.0.**

(Normal GFR is: > 60 mL/min of creatinine cleared /1.73 m^2 of body surface)

Using the MDRD calculator, and changing (only) the selection of male to female:

A non-black **female** age 60 with creatinine of 1.0 will have a GFR of **60.1**.

(Normal GFR is: > 60 mL/min of creatinine cleared /1.73 m^2 of body surface)

This is a notable difference in eGFR of 21.1, between male and female, at the same age of 60 and with same creatinine of 1.0.

Staying with this example, what creatinine must the female have to equal the male GFR of 81?

Keeping age 60 in the MDRD calculator; if the woman's creatinine is changed to 0.78, her GFR improves to 80.1, which is close to male eGFR of 81 at age 60.

In other words, for a woman aged 60 to have an equivalent eGFR to a man's GFR of 81, her creatinine must be 0.78, while his is 1.0

You might think this male vs. female eGFR gap of 21.1 would improve with younger age. It does not. The gap is even more increased, at 23.3

Using the MDRD calculator, decreasing the age from 60 to 40 for both, while keeping the same creatinine of 1.0:

A non-black male age 40; creatinine 1.0: **GFR: 88.0**

A non-black female age 40; creatinine 1.0: **GFR: 65.3**

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Consider the possible clinical and practical ramifications of this difference, in the transsexual population, especially those with CKD:

Recall that to get on transplant list GFR must be < 20 (or currently on dialysis):

Follow this thought experiment with me:

In the genetic male transitioning to female:

The eGFR calculation is now lower (worse) using female sex in the MDRD calculator. This may result in inaccurate categorization of CKD, with the possible clinical ramification that patient may fall within the recommended range of initiating RRT (renal replacement therapy) which is eGFR <15, when in actuality this is not the patient's true physiologic eGFR. On the other hand, this m<F transsexual patient may have improved her position on a transplant list, as her eGFR is now inaccurately categorized as lower (worse). The m<F transsexual

using androgen blockers and estrogen, will eventually loss muscle mass, causing female sex in the MDRD calculator to be more physiologically correct; but that will not happen overnight. A cystatin C may "save" this m<F patient from an inaccurate diagnosis of CKD or even ESRD.

In the genetic female transitioning to male:

The eGFR calculation is now higher (better) using male sex in the MDRD calculator. However, consider that the eGFR may appear better than it truly physiologically is. As a genetic female, with the lower (worse) eGFR, the patient had better positioning on a transplant list. However, now with the male sex selection in the MDRD calculator, and the higher (better) eGFR, the f<M patient moves down on the transplant list. The f<M who is now on testosterone and typically has had, or will have TAH-BSO, will eventually gain muscle mass, and a higher lean to fat ratio, but this does not happen overnight. Using a cystatin C may assure that renal function of the f<M is not understated, and renal replacement therapy therefore delayed.

Rhetorical question to be studied:

When should we change from female to male, in the MDRD calculator? Age of initiation of GnRH or cross-sex hormones would certainly be a consideration. Transitioning at a younger age such as the adolescent on GnRH puberty suppression therapy would make "the muscle mass factor" less of a problem.

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I propose for your consideration an alternative to eGFRcr: serum Cystatin C

To eliminate the muscle mass factor from eGFR, order a serum cystatin C. As a marker for renal function, it is not driven by creatinine, hence eliminates the indeterminate muscle mass problem of transsexual persons, especially at the onset of their transition.

What is cystatin C?

Cystatin C is a low molecular weight (13 kD), non-glycosylated, cysteine proteinase inhibitor, basic protein that is generated into the bloodstream constitutively, which means at a constant rate by all nucleated cells, independent of internal or external stimuli. "The serum concentration of cystatin C is unchanged with infections, inflammatory or neoplastic states, and is not affected by body mass, diet or drugs,"[3] and is more homogenous across populations. "Thus cystatin C may be a more reliable marker of renal function (GFR) than creatinine, in patients both with and without renal disease.[3]

Is cystatin C a more accurate filtration marker than creatinine?

Several studies show that serum levels of cystatin C estimate GFR better than serum creatinine alone. And another study "provides evidence that the use of cystatin C improves the role of eGFR in risk categorization, "[4]

For the **past decade**, cystatin C has been used extensively as a research tool for understanding how kidney function affects health **outcomes**, particularly within the presumed normal range of kidney function: eGFR > 60 mL/min/1.73 m^2.[5]

These outcomes studies have compared associations of creatinine and cystatin C with longitudinal complications of kidney disease, such as cardiovascular disease, heart failure, ESRD and death.[5]

In these settings, cystatin C level has demonstrated much stronger associations than eGFR, with cardiovascular disease, HTN, infection risk, heart failure, frailty and all-cause mortality.[5]

However, in the past 2 years several studies have spurred broader interest in cystatin C as a clinical test of kidney function. These studies have had immediate impact upon the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline relating to the evaluation and management of chronic kidney disease (CKD).[5,6]

Potential settings for cystatin C screening already include the following patients with indeterminate muscle mass: patients of extremes in body size or age,

malnutrition or obesity, skeletal muscle disease, rhabdomyolysis, multiple sclerosis especially in crisis, malignancy, HIV infection, paraplegia, quadriplegia, amputees, vegan, pregnant, type 1 diabetics, especially in DKA with ARI, rapidly changing kidney function, patients with borderline eGFRcr, or who otherwise at high risk for CKD, or in the acutely-ill, hospitalized patient when renal function is rapidly changing and we're not supposed to be using the MDRD eGFRcr equation anyway.

Cystatin C should also be considered in patients who are undergoing cardiac cath or angiograms, chemotherapy, surgery—especially those whose kidney function is in flux, or on the borderline and an **accurate assessment of kidney function is needed for the best risk/benefit analysis.**

Conclusion

To these aforementioned patients for whom a cystatin C has been shown to be a more reliable indicator of renal function due to indeterminate muscle mass; I recommend additionally the transsexual patient, especially at the onset of their transition, as they are also persons whose creatinine generation is in flux due to changing muscle mass, in association with initiation of cross-sex hormonal treatment, anti-androgens or GnRH; and therefore GFR is unreliable.

Inaccurate assessment of kidney function can result in unnecessary diagnostic testing and/or therapeutic interventions in the m<F transsexual patient, or possible inadvertent delay of treatment in the f<M transsexual patient. There could also be insurance implications.

Generally speaking, we clinicians will necessarily become more discerning in our interpretation of lab results and/or functional testing results, as pertaining to the care of our transsexual patients.

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*The term transsexual is used, as by definition these are persons who seek at least some medical or hormonal treatments, such as cross-sex hormones, anti-androgens, GnRH, and/or surgical treatments; and this discussion is pertinent to such patients.

Acknowledgements:

Drs. Kathresal, Verma, Wachter at Duke Regional Hospital for their feedback and support; and to Michael G. Shlipak, UCSF for his generously informative and supportive email correspondence.

Resources:

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2. National Kidney Foundation. GFR Calculator https://www.kidney.org/professionals/kdoqi/gfr_calculator

3. Mayo Clinic. Test ID: CYSTC. http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/35038

4. Schlipak, MG, et al: Cystatin C verses creatinine in determining risk based on kidney function. N Engl J Med. 2013 Sept 5;369(10):932-43

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