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Potassium Reference Intervals: A Need for Separate Reference Intervals for Serum and Plasma.

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Guest: Dr. Glen Hortin is a senior member of the Departments of Pathology and Translational Pathology at Moffitt Cancer Center and Medical Director of Chemistry. He also is Professor of Oncologic Science in the Morsani College of Medicine at University of South Florida.

Randye Kaye:

Hello and welcome to this edition of *JALM Talk*, from *The Journal of Applied Laboratory Medicine*, a publication of the Association for Diagnostics & Laboratory Medicine. I'm your host, Randye Kaye.

Accurate measurement of potassium is important because extracellular potassium levels affect neural and muscular membrane potentials and risk of cardiac arrhythmias. Even mild abnormalities in potassium are associated with adverse patient outcomes.

Laboratories routinely test both plasma and serum samples for potassium levels, but plasma and serum potassium levels can differ due to platelets releasing potassium during the clotting process. Due to the clotting process, serum potassium levels can be higher than plasma potassium levels by 0.2-0.4 millimoles per liter. Even though this difference is well-known, most laboratories use the same reference interval for serum and plasma potassium.

The July 2026 issue of *JALM* features a focused report where the authors surveyed 60 laboratory reference intervals for serum and plasma potassium and examined the effects of varying reference intervals on the interpretation of patient results.

Today we are joined by the article's first and corresponding author, Dr. Glen Hortin. Dr. Hortin is a senior member of the Departments of Pathology and Translational Pathology at Moffitt Cancer Center and Medical Director of Chemistry. He also is Professor of Oncologic Science in the Morsani College of Medicine at University of South Florida. He has practiced clinical pathology for nearly 40 years after residency training at Washington University/Barnes Hospital.

Welcome, Dr. Hortin. Why is accurate measurement of extracellular potassium levels important?

Glen Hortin:

Potassium level is important for determining the neural and muscular function. It's a primary determinant of the resting

membrane potential. So usually, the intracellular potassium is an order of about 100 millimolar and extracellular potassium is about 4 millimolar. So, there is a large gradient and potassium is trying to get out of the cells and that's creating a fairly substantial negative membrane potential. That's important of course for the function of any muscle cells and nerve cells, and if your potassium level either becomes too high or too low then you are prone to muscle weakness and cardiac arrhythmias and all sorts of problems. So it's important to kind of really have a relatively narrow balance in terms of your potassium.

Randy Kaye: Alright. Thank you. Can you tell me what are some common physiological causes of high or low potassium levels?

Glen Hortin: Well, low potassium levels, our common western diets really tends to be somewhat deficient in potassium. We kind of got into more processed foods and kind of compared to the caveman diet where they would eat largely fruits and vegetables, they would eat perhaps two or three times as much potassium, whereas now, eating processed foods we tend to eat about as half as much of the recommended daily allowance and to have much higher intakes of sodium, so the balance between sodium and potassium is unfavorable. That's important because it tends to promote high blood pressure and other problems.

General studies of dietary intake have found that a high dietary intake of potassium is favorable in terms of blood pressure and kidney function in a variety of measures, so that's important.

And then of course many medications that we take, medications such as thiazides, many other antihypertensives. Some of them tend to cause high potassium, while the thiazides and loop diuretics like Lasix tend to cause low potassium. The common disorders like diarrhea, laxative abuse, vomiting, in the summertime heavy sweating, all can cause depletion of potassium levels. So, it's relatively common that you can run into either high or low potassium level.

For the high potassium level, the most common concern is usually for people who have renal failure, where you are unable to do your normal excretion of potassium. In those situations then you become more concerned about the high potassium levels.

Randy Kaye: Alright. Thank you. So now why is measurement of potassium one of the most problematic laboratory tests?

Glen Hortin: Well, because there's such a large gradient between the intracellular and extracellular potassium. When you draw a

blood sample, the red cells containing 100 millimolar potassium can exchange potassium with the extracellular compartment where you are trying to measure potassium. So if you either get a smaller amount of hemolysis, it takes a fairly small amount of hemolysis to substantially affect the serum or plasma potassium level, and even if the red cells are left in contact with the serum or plasma for extended periods of time, you can have exchange.

Then you have other factors in terms of phlebotomy technique and other things going on. Phlebotomists have patients do hand flexion and fist clenching, that can drive your potassium up fairly acutely or if you leave the tourniquet on a long time, that might have a slight effect.

So, there are multiple factors in terms of getting samples drawn quickly, avoiding hemolysis, getting them to the laboratory in a timely way, that can cause problems with potassium measurements. And when you're talking about even fairly small shifts in the potassium can have a significant factor.

Randy Kaye: What is the difference between serum and plasma potassium?

Glen Hortin: Serum and plasma potassium differ on the average by approximately 0.3 millimolar. Plasma represents really the extracellular concentration while serum represents the extracellular concentration plus potassium that's released by platelets during clotting. So serum is usually about 0.3 higher but it varies depending on your platelet count and how much is released out of the platelet counts.

Randy Kaye: So knowing all that, do you think there should be separate reference intervals for serum and plasma potassium?

Glen Hortin: Yes, probably. I thought this really had resolved and worked out about 50 years ago. We started looking at this a little bit. I was wondering whether our plasma potassium reference rate interval was somewhat narrow, because I noticed that some other laboratories had a much broader reference interval.

So, I have had one of our residents, Joe Leonard, kind of do a survey and he checked laboratory directors from around the world and accumulated information about reference intervals and found that there was significant elevation, and most laboratories actually, I'm somewhat surprised, used the same reference interval for serum and plasma potassium. Again, I thought this had been worked out and resolved like 50 years ago, but by using a single reference range you're going to tend to underestimate the hypokalemia, the low potassium occurrence when you use a serum sample and you're going

to tend to underestimate the hyperkalemia when you're doing a plasma measurement.

My initial thought was that, well, maybe 0.3 difference was not really such a big deal that maybe just a little bit of variation and minor hypokalemia is not so important because usually in the hospital we don't detect any EKG abnormalities or clear symptoms at very slight high or low potassium.

But then I started looking, there have been like more than 30 different outcome studies examining patient outcomes, a variety of outcomes, sometimes mortality, stroke, frequency of arrhythmias and things, and outcome studies generally have found that there is a relatively narrow optimal potassium range, really even probably a little bit narrower than the common reference intervals that we have for potassium. So that was emphasizing that actually even fairly small potassium abnormalities might be clinically significant and we should probably not provide overly broad reference intervals that might underestimate a mild hypo and hyperkalemia.

Randy Kaye: Dr. Hortin, is there anything I haven't asked you or anything you wanted to add, I didn't give you a chance to say?

Glen Hortin: I just wanted to make a few other comments. One issue is, many laboratory measurements we have problems with laboratory standardization, but that really hasn't been the case so much for potassium measurements. Our laboratory measurements in general have been pretty well-standardized.

And over the years there has been some global harmonization efforts that actually conducted quite a few reference interval studies for serum potassium and they generally found that the reference intervals in multiple studies were really about 3.7 or 3.8 millimolar on the low side, to approximately 5 millimolar on the upper side.

So, reference interval studies generally had found significantly narrower ranges than most laboratories have used. And some of the wide ranges were set by expert opinion that some groups such as the United Kingdom, Australia, set wider ranges based on expert opinion and they consider that the pre-analytical variables pose such a problem that they needed to widen the ranges a little bit.

So, I think that these ranges that have been in common practice have been artificially expanded and have been really not serving well to detect the mild hypo and hyperkalemia. But again, they have represented real world compromises for laboratorians that felt that they could not kind of fully address the pre-analytical issues.

Randy Kaye: Alright. Thank you so much. Very interesting information and you make the case in *JALM*, and thank you for joining us.

Glen Hortin: Okay.

Randy Kaye: That was Dr. Glen Hortin, discussing the *JALM* focused report, "Potassium Reference Intervals: A Need for Separate Reference Intervals for Serum and Plasma."

Thanks for tuning into this episode of *JALM* Talk. See you next time, and don't forget to submit something for us to talk about.