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Moving beyond mean glycemia: 1,5-anhydroglucitol and microvascular complications of diabetes

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Guest:
Dr. Patrick Lawler is from the Cardiovascular Division and the Division of Preventive Medicine at Brighman and Women's Hospital, Harvard Medical School in Boston.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

Hemoglobin A1C is the standard clinical measure used to monitor glycemic control and is recommended for use in the diagnosis of diabetes.

Although hemoglobin A1C has high reliability, there are certain settings in which hemoglobin A1C testing is thought to be problematic. 1,5-anhydroglucitol or 1,5-deoxyglucose is a monosaccharide originating mainly from foods and closely resembles glucose in structure, but is usually excreted by the kidneys.

During hyperglycemia high amounts of glucose block tubular reabsorption of 1,5-anhydroglucitol causing serum concentrations to fall and decreases in its concentrations are thought to be an indicator of shot-term hyperglycemia.

In the November 2014 issue of *Clinical Chemistry*, a multi-center study found that blood concentrations of 1,5-anhydroglucitol are associated with long-term risk of important microvascular outcomes. That paper was accompanied by an editorial in the same issue by Drs. Patrick Lawler and Samia Mora.

In this podcast we are joined by Dr. Lawler. He is from the Cardiovascular Division and the Division of Preventive Medicine at Brigham and Women's Hospital, Harvard Medical School in Boston.

Dr. Lawler, this article highlights interesting findings published recently in *Clinical Chemistry* about microvascular risk prediction. Can you tell us a little bit about the scope of the problem that this study hoped to address?

Dr. Patrick Lawler: Yeah, absolutely Bob, and I think that's a great question. The release of defining the risk of microvascular

complications in diabetes is critically important and central to our approach to how we treat these individuals, but also to how we evaluate efficacy of various treatment strategies.

Of course the hemoglobin A1C, the glycated hemoglobin as our standard measure of effectively mean glycemia, but we know from studies that that biomarker probably doesn't explain all the risks in terms of microvascular complications.

So for example, in the landmark diabetes control and complications trial, that looked at conventional diabetes therapy versus intensive insulin therapy, when you match the hemoglobin A1Cs across different patients, across the two different treatment arms, there wasn't a similar reduction in the incidence of microvascular complications, in fact, they were lower in the group that had more intensive insulin treatment.

And one thought is that perhaps that group is on a more regular, and more regulated insulin regimen; it's possible that the glycemic excursions that occurred with less frequent insulin in the conventional therapy arm may have contributed.

And so this concept of glycemic excursion adding something beyond mean glycemia has been of interest in the diabetic community and we've sort of been looking for a marker as to whether or not this could be something that might improve our clinical care-based patients.

Bob Barrett: What is 1,5-anhydroglucitol and what does it tell us about long-term glycemia beyond glycated hemoglobin?

Dr. Patrick Lawler: Effectively 1,5-AG, as it's called, is a candidate biomarker for such glycemic excursions. And essentially it's a dietary monosaccharide similar to glucose that's freely filtered in the renal glomerulus and then subsequently competes with glucose for reabsorption in the renal tubules.

In the presence of high serum glucose, most frequently post-prandial state obviously, absorption of 1,5-AG from the renal tubules is reduced, and so the concentration overall in the serum will drop. And it's felt that the concentration of 1,5-AG reflects glycemic excursions over usually about a one to two-week time period.

Now 1,5-AG is currently marketed in the US under the trade name GlycoMark, but it of course-- I think as this article highlights—there is sort of only an evolving understanding of what it might mean clinically.

Bob Barrett: Doctor, what are the key study findings in terms of predicting microvascular complications about diabetic patients?

Dr. Patrick Lawler: Key findings essentially were that the risk of prevalent retinopathy detected with mydriatic retinography -- retinography scans, rather, was significantly increased in the group who had lower levels of 1,5-AG, which in other words reflects more frequent or more severe glycemic excursions.

That risk was 11-fold in an unadjusted model, and then substantially attenuated after adjusting for hemoglobin A1C in fasting glucose, but it did remain nonetheless significant with about a 5-fold increased risk among diabetic patients.

And furthermore nephropathy or the risk at least of incident chronic kidney disease in diabetic patients, as the ARIC (Atherosclerosis Risk in Communities) investigators here looked at it, was associated also with low levels of 1,5-AG. Here it was above greater than a 2-fold risk or so.

Again, a little bit of attenuation once you adjust for hemoglobin A1C and fasting glucose but still the suggestion of something there.

Bob Barrett: Well how about that in terms of predicting incident diabetes itself?

Dr. Patrick Lawler: So the risk of diabetes also seemed to be predicted by low levels of 1,5-AG, and there the risks were lower compared to the risk of microvascular complications among diabetics, but it did nonetheless seem that as an independent predictor 1,5-AG could stand on its own in predicting incident diabetes in this population.

Bob Barrett: Doctor, beyond its potential role as a biomarker, what can the finding of an association between glycemic excursions beyond hemoglobin A1C, tell us about the mechanism of pathogenesis of diabetic microvascular complications?

Dr. Patrick Lawler: That's a great question and I think to put it in context, it's helpful to know what this biomarker, how this biomarker rather relates to existing biomarkers. So it was well-correlated with what fasting glucose and hemoglobin A1C with Spearman correlations in about the -0.7 to -0.8 range, of course they are inverse because low levels of 1,5-AG reflect a worsened degree of glycemic excursions.

But that was in the diabetic population. When you look at the non-diabetic patients, the Spearman correlation is really quite low, and all less than 0.1 with absolute value that is less than 0.1, and so in the non-diabetic participants it seem like 1,5-AG might be adding a new dimension to predicting

risk, and so there might be something incremental here, something that's unrelated to just mean glycemia, not that this biomarker is capturing.

When you look then to say, well, what about using this biomarker in addition to hemoglobin A1C, will adding it on to standard risk prediction models add much? The investigators here did that with the use of a statistic and also an integrated discrimination of improvement index which sort of reflects the classification index.

Although there was a very modest improvement that was statistically significant, it was really clinically modest, suggesting that although the biomarker did seem to be reflecting a new dimension of glycemia in the non-diabetic patients, it looked like there was nonetheless only a limited incremental value to adding it to standard measures of glycemia currently.

So I think it helps to inform our awareness that perhaps these glycemic excursions do contribute to microvascular risk, perhaps do even reflect to some extent the risk of incident diabetes, but adding incremental clinical value beyond what we already have I think that remains to be shown. I think finding sub-groups of patients where that biomarker might be particularly relevant I think would be the next step, most logical next step.

Bob Barrett: Well, finally Dr. Lawler, what do you think? Is 1,5-anhydroglucitol ready for prime time?

Dr. Patrick Lawler: Yeah, I think not quite yet with the evidence base that we have. I think a couple of limitations need to be addressed before we consider this. I think first, as we mentioned, it doesn't necessary add a lot of incremental predictive value. So perhaps finding subsets of patients where this biomarker is more meaningful clinically and is divergent from hemoglobin A1C and other markers of glycemia that we have would be most -- I think would be the first step.

Furthermore, I think there are populations that aren't represented here that we need to learn a little bit more about first. I think particularly the investigators, to remove the potential effects of effect modification, screened out patients that had low GFR baseline for much of their analysis, and I think clearly tubular absorption is an important mechanism for regulating the kinetics of this biomarker, and so low levels, in a sense, might sort of be inferred to be a reverse causation where this one has diminished tubular absorption from renal dysfunction possible then they may have a low level of 1-AG.

So, perhaps by excluding these patients we failed to learn a little bit about what the findings in that group would have been. And I think we know from previous studies that at least stage 4 and stage 5 CKD do have a strong influence on the levels of 1,5-AG and it remains uncertain I think whether this early stage chronic kidney disease also has the similar impact on 1,5-AG, but that would be a population that I think we need to see studied a little better.

Bob Barrett: Dr. Patrick Lawler is from the Cardiovascular Division and the Division of Preventive Medicine at Brighman and Women's Hospital, Harvard Medical School in Boston. He has been our guest in this podcast from *Clinical Chemistry* on 1,5-anhydroglucitol as a biomarker in diabetes.

I am Bob Barrett. Thanks for listening!