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Implementing a Reference Measurement System for C-Peptide: Successes and Lessons Learned

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Guest: Dr. Little is a Professor in the Departments of Pathology & Anatomical Sciences and Child Health at the University of Missouri.

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

C-Peptide is a proinsulin cleavage product released from the pancreas in amounts equal to insulin, but with a half-life about 10 times longer than that of insulin. As a result, measurement of C-Peptide can be used as a substitute marker for monitoring endogenous insulin production, which is particularly important in diabetes research. The Diabetes Control and Complications Trials showed that in subjects with Type 1 Diabetes, higher C-Peptide concentrations were associated with improved Hemoglobin A1c, less hypoglycemia, and less retinopathy and necropathy. Thus, C-Peptide measurements and stabilization are often used as end points in clinical trials and other research studies. A major limitation to comparing and interpreting results across various studies has been the lack of harmonization in C-Peptide measurements. A Review article in the September 2017 issue of *Clinical Chemistry* provides an overview of the general process of harmonization and standardization and the challenges encountered with implementing a Reference Measurement System for C-Peptide.

The lead author, Dr. Randie Little, joins us in this podcast. Dr. Little is a Professor in the Departments of Pathology & Anatomical Sciences and Child Health at the University of Missouri and is Director of the Diabetes Diagnostic Laboratory. Dr. Little is the Coordinator of the NGSP Network, a member of the NGSP Steering Committee, and also coordinates the NIDDK C-Peptide Standardization Activity.

So Dr. Little, what was the main purpose of writing this Review article?

Dr. Randie Little: Well, that purpose was really twofold. First, we wanted to lay out the problems that we encountered with standardizing C-Peptide, so that some of these problems can be avoided in the future with other tests. And the other purpose was, that we wanted to make people, especially

people measuring C-peptide, aware that C-peptide is being standardized and that, soon, hopefully, manufacturers will begin recalibrating their methods, now that there's a referenced measurement system developed and in place.

Bob Barrett: And, why is it important to harmonize C-Peptide results? What are the clinical implications and benefits?

Dr. Randie Little: Well, assessment of insulin that's secreted by a person's body, by measuring C-peptide is widely accepted. When insulin is secreted, you get actually get two things in the blood stream, proinsulin divides into insulin and C-Peptide, and C-Peptide stays in the bloodstream longer, so it's a better measure of insulin secretion. And, recent studies have shown that preserving even small amounts of a patient's own C-peptide production with Type 1 Diabetes reduces the risk for some diabetic complications and also lowers the risk of hypoglycemia. And because of this, C-Peptide is being used as a measureable endpoint in clinical trials that are aimed at preserving beta cell function or insulin secretion in people with Type 1 Diabetes. So, harmonization of C-Peptide results will facilitate the comparison of data from these different research studies and clinical trials.

Bob Barrett: What were the biggest challenges associated with establishing a reference measurement system for C-Peptide?

Dr. Randie Little: Well, it became clear as we stumbled through the process that different organizations and laboratories and individuals at universities are involved in harmonization or standardization efforts. And, all these different groups and individuals are often separated by distance and funding mechanisms. So you might have someone in Japan, and someone is Europe, someone in the U.S. all working on different parts of the same process. And so there was -- and still is -- a lack of coordination among all of these groups that really hinders the process of achieving global harmonization of measurements. And, effective communication and coordination of all these activities is important for progressing through the harmonization or standardization process. So, the current C-Peptide situation is a good example where better communication would've led to earlier implementation of a reference system, so that manufacturers can begin recalibrating their assays and we can have measurement of C-Peptide be the same in different laboratories globally.

Bob Barrett: Doctor, talk about your plans to continue with the standardization process, what's the next step?

Dr. Randie Little: Well, we have some next steps almost in place. One thing that's important is to have C-peptide used in proficiency testing where labs measure the same C-Peptide in the same sample. And the important thing is to have it set up with a large proficiency testing survey, and set up so that, proficiency testing results could be compared to a reference value. So, the CAP, or College American Pathologists, has agreed to run a C-Peptide survey where appropriate samples would be used and we could assign reference values to that. And once that's starts, laboratories, --and we can explain in that survey report that C-peptide standardization is under way, and then we can show how results look now and then follow it along so that, we can see the effect of standardization, once manufacturers recalibrate.

And then, the other thing is -- well the first, more important thing is to convince manufacturers that now is the time to recalibrate their methods. We don't want to wait any longer because this process has taken so long.

Bob Barrett: Well, finally doctor, can you give any advice to others who may be trying to standardize important clinical measurements?

Dr. Randie Little: Well, one thing that's been put in place is a group called ICHCLR, and that stands for International Consortium for Harmonization of Clinical Laboratory Results. And this is a group that was set up by the AACC, American Association for Clinical Chemistry, and this wasn't set up when we started the process for C-Peptide, but now they have a list of analytes, or tests, and what standardization efforts are occurring now, and what organizations and groups are doing it.

So, if I was to start wanting to standardize some other analyte, I could look on this website and see who's already involved and what they're doing and contact them. So, that's something that will help a great deal in the future.

Bob Barrett: Dr. Randie Little, is a Professor in the Departments of Pathology & Anatomical Sciences and Child Health at the University of Missouri. She is also Director of the Diabetes Diagnostic Laboratory. She has been our guest in this podcast from *Clinical Chemistry*.

I'm Bob Barrett. Thanks for listening!