THE RECEPTOR

Message from the Past-Chair
Hubert Vesper, PhD,
Centers for Disease Control and Prevention

Dear Endocrinology Division Members,

I hope you are in good health and high spirits. Through your participation in two surveys conducted this year in collaboration with the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) Committee for Standardization of Thyroid Function Tests (C-STFT) and the American Thyroid Association (ATA) Laboratory Services Committee, you helped to enhance AACC’s role in endocrinology and ensured the laboratory’s position and points of view are heard by other organizations. The results from these surveys will be shared with you, with initial findings from the IFCC survey being summarized in this newsletter by Dr. Linda Thienpont. The findings from the ATA survey are currently being finalized and will be available soon as well. I would like to thank all of you for your help and support with these surveys!

As scheduled, I handed over the division lead to Dr. Ross Molinaro on June 15, who is now chairing the Endocrinology Division. Ross is one of the founding fathers of the division and a great colleague. Please welcome him to his new position! It was an honor and pleasure to work with you creating this new division and to serve as its chair. I would like to thank all of you for your help and support. Very special thanks to my steering committee members, who worked hard to get this division of the ground and flying high!

Speaking of change, I would like to welcome our new elected members: I am very pleased to welcome Dr. Daniel T. Holmes from St. Paul's Hospital, Department of Pathology and Laboratory Medicine in Vancouver as chair-elect, Dr. Qing He Meng from the University of Texas MD Anderson Cancer Center in Houston, as the new treasurer, and Dr. Damodara Rao Mendu from Montefiore Medical Center, Bronx, NY as a new member of the Nominating Committee. I am very excited to have such great team members and am looking forward to working with them in the future.

At the annual AACC meeting in Philadelphia, there will be an educational event at our annual Division mixer. The event will be held on August 1, 2016 from noon to 2 pm in
the Marriott Philadelphia Downtown, Room Franklin 3. Mark your calendars! We will have three very distinguished speakers: Dr. Patrick Sluss will provide an overview on AMH and its clinical applications, Dr. Daniel Holmes will talk about primary aldosteronism and factors affecting aldosterone and renin testing, and Dr. Jim Faix will give an update on standardization of thyroid function tests. ACCENT credit will be available for this event.

This year, we had many excellent abstract submissions on endocrinology. The awards committee identified two most outstanding posters. The authors will receive our Endocrinology Division award at our Division mixer. So, come and join us to celebrate the awardees. The posters will also be highlighted at the Poster Walks which will be held on Tuesday August 2nd and Wednesday August 3rd. The Endocrinology Division Poster Walks are a great opportunity to get in depth information about the latest research. I encourage you to attend and bring your colleagues along.

I am looking forward to seeing you all at the AACC meeting.

With best regards,

Hubert Vesper

AACC Student Poster Contest – the Final Four!

Of the four student posters being considered in for oral presentation, one has an endocrinology topic. “Clinical utility of aldosterone, renin mass and the aldosterone/renin mass ratio for the workup of suspected primary aldosteronism.” Please consider attending this event to show support for our trainees and future division members.

**Date:** Monday, August 1, 2016  
**Events:** Student Poster Contest  
**Location:** Pennsylvania Convention Center,  
**Oral Presentations:** 1:00 pm-2:00 pm, Room 201A  
**Poster Presentations:** 2:15 pm-3:15 pm, Room 201B

**Summary of the survey “Standardized Reference Intervals for Thyroid Testing”**

Linda M. Thienpont
In the spring edition of the Endocrine Division Newsletter the IFCC Committee for Standardization of Thyroid Function Tests (C-STFT) called upon experts in laboratory endocrinology for help with preparing the future implementation of standardized FT4 and harmonized TSH testing. After consultation with the FDA, C-STFT understood that in preparation of an adequate implementation plan, reaching out to different stakeholders and eliciting their opinion on how to best move forward was needed. Therefore, the committee was pleased to receive the opportunity to launch a survey entitled “Standardized Reference Intervals for Thyroid Testing” among the members of the Endocrine Division. The emphasis of the survey was to obtain information on the estimated risks to patient safety as a consequence of changing the reference interval for patients with thyroid disorders, and what measures your laboratory would take to minimize these risks.

In total, the survey was completed by 27 experts in laboratory endocrinology, predominantly (>95%) having an academic degree (MD, PhD, MD/PhD). About 78% of the survey participants are working in a hospital, academic, core lab or private practice setting, 11% are from industry, while the other 11% are professionally active in a government/military-, managed care-, and research surrounding. They mention to be director/administrator (70%) or consultants (11%), while 19% describe their working role either as supervisor/team leader, or coordinator, clinical lab scientist/medical technologist, educator/trainer, and clinical fellow.

In answer to the questions related to risks to patient safety after a considerable change in reference intervals, the opinions were divided: 50% of the responders say that they estimate the risk for misinterpretation not likely, while the other 50% do because – as some indicate in the free comments – physicians sometimes misunderstand reference intervals, or are so used to certain numbers that they are reluctant to changes. With regard to the measures taken by the laboratory to avoid misinterpretation by clinicians, the majority of the responders believe they are adequate: 85% confirm the establishment of a communication policy to inform the physician in advance about upcoming changes, although – again from the free comments – some seem to doubt about the effectiveness of the used communication lines. In general, it is difficult to convey information to busy physicians, who lack time to read electronic messages from the laboratory. Messages are read when results don’t make sense and usually are presented as complaints. It was also mentioned that the larger the medical center, the higher the likelihood of misinterpretations after changes, because it is difficult to communicate with every clinician on time.

With regard to highlighting the changed reference intervals on the reports, 67% of the survey participants think that their laboratory has a good policy (e.g., communication of the changes in the electronic health record system), although 30% are not satisfied with the duration thereof; 67% are not in favor of parallel reporting of the old and the new reference intervals, nor want to see the mathematical relationship between the old and the new values on the reports.
Regarding the policy to report longitudinal results after the changes, the opinions are divided: 50% of the survey participants think that the report adequately mentions against which reference intervals the past and current results should be compared, while the other half think that this is a difficult-to-manage issue; also 56% of the responders think there is room for improvement when it comes down to implementing the changes in the recommended treatment protocols. In the free comments, the following suggestions are made to avoid misinterpretation of results by physicians: keep the comments attached to the laboratory results as simple and straightforward as possible; to assure that the changes draw the attention of physicians, particularly in monitoring of patients, use decision support tools associated with the LIS, evaluate and discuss the impact of the changes on treatment with the physicians and convey the need to update their treatment protocols accordingly; also Subject Matter Expert committees have proven their usefulness according to one of the participants.

The second set of questions concerned the patients with thyroid disease and asked whether they receive their laboratory reports and know their values. Half of the participants confirm that they share the laboratory reports with the patients, and all of the “yes” responders believe patients know their values, however, only 63% communicate the impact of a change of reference intervals on the current versus old laboratory values to the patients. From the free comments, it is obvious that the survey participants are aware that communication on the results with patients is needed to avoid that these use Google for interpretation of their reports; however, they believe that the process to do so is not yet established and/or needs improvement. One participant claims that in their practice setting the laboratory communication with the patients by means of a published memo is effective, while in another, the patients are offered the option for online access of their test results. Here again it is suggested to keep the comments on the laboratory results as ‘patient friendly’ as possible. On the other hand, one responder remarks that if a change in reference intervals is not communicated (well) to the physician, how would the patient then find out?

Altogether, the replies let us conclude that laboratory endocrinologists in general are open to standardization/harmonization of thyroid hormone testing, simply because they consider comparability of measurement results an asset to patient care; aware as laboratories are that standardization/harmonization implies changes in numerical results and reference intervals, most already have processes in place to adequately communicate these changes both to physicians and patients.

Nevertheless, several experts recognize that there is room for improvement in communication with physicians and patients, but, from the suggestions in the free comments, it is obvious that the surveyed experts are already working on it. Notwithstanding these efforts by the laboratory community, some remark that the success of a solid communication system also depends on the receptiveness of physicians for changes in reference intervals according to current IFCC/AACC recommendations on lab test standardization. The message is that to solve this issue an active laboratory-physician interface is needed, one in which both parties try to find out what they should expect from each other to optimize their collaboration and
services. Laboratories and physicians should also make work of better communication with the patients, who more than ever want to know and follow-up their values.

Note that this survey only provides the opinion of those experts in laboratory endocrinology participating in the survey, and thus that findings may not be representative for all clinical laboratories.

Last but not least, the chair of the C-STFT, Linda Thienpont, thanks all participants to the survey for their time and constructive comments.

How is diabetes mellitus diagnosed?

William E. Winter, MD

This is a fairly routine question that should not be considered esoteric in nature. While the cut-points used to define hyperglycemia have changed over the years, analytically the only new “actor” in this “story” is the 2010 acceptance by the American Diabetes Association (ADA) of hemoglobin A1c (HbA1c) measurements as markers of hyperglycemia when the HbA1c is 6.5% or greater.

. . . So here is where this column begins with a query from a clinician on the pediatric endocrinology listserve [note: the communications have been edited for clarity and brevity and to preserve the anonymity of the patient and physician (Dr. Y):]

“I got a curbside consult from a colleague and wanted to get the group’s input. Dad has type 1 diabetes and his daughter, now 16 years old, was part of a clinical trial which showed she was at high risk for developing type 1 diabetes. A recent OGTT revealed: 0 time - 103 mg/dL (5.7 mmol/L); 1 hour - 234 mg/dL (12.9 mmol/L); and 2 hours - 217 mg/dL (11.9 mmol/L). HbA1c was 5.4% (reference interval given as: 4.0-6.0%). She is athletic and asymptomatic. Her BMI is 18 kg/m².

I recommended a well-balanced diet with avoidance of simple sugars. I don’t think there is a role for insulin at this stage. Does anyone think otherwise and if so what type/dose would you recommend? I suggested monitoring occasional fasting and post-prandial numbers, but I wonder if this may be overkill and may just add to the family’s stress.”

My first thought was, while hyperglycemia is present [the 2-hour plasma glucose (PG) was elevated (e.g., 200 mg/dL or greater], the diagnosis of diabetes has not been
established. Had the physician already diagnosed this asymptomatic teenage with diabetes? I also wondered why a 1-h PG was drawn unless this is part of a research study. The ADA recommends that if an oral glucose tolerance test (OGTT) is to be performed for diagnostic purposes, the OGTT test is 2 hours and 2 time points: the fasting plasma glucose (FPG) and the 2-h PG level. This girl’s FPG was in the impaired fasting glucose (IFG) range; however, this value is “trumped” by the 2-h hyperglycemic value.

I then wrote back on the listserve:

“Hyperglycemia is present. According to ADA guidelines, in an asymptomatic subject you need to repeat the OGTT. If hyperglycemia is confirmed, diabetes is diagnosed. The ADA advises that the test that was first found to be abnormal should be repeated.

I think you need to establish whether or not the patient meets diagnostic criteria for diabetes. If the patient is indeed diabetic, one can argue that an HbA1c of 5.4% requires little if any therapy other than diet and exercise.”

A series of short communications followed:

Another pediatric endocrinologist (Dr. X) wrote:

“Fructosamine?”

I responded:

“Fructosamine may be used to monitor short term glycemia but it has no ADA-approved use as a diagnostic marker.”

Response from Dr. X.:

“If the fructosamine is elevated, then a hereditary hemoglobin variation might be present that might make the hemoglobin A1c unreliable. It does not sound like the child has a condition that can shorten hemoglobin half-life such as cystic fibrosis, another possibility.”

Me:

Good point… In many A1c immunoassays and CE (capillary electrophoresis) and HPLC measurements of HbA1c, Hb A1c can be measured reliably in Hb AS and Hb AC patients. Immunoassays provide a HbA1c result even in persons lacking HbA1c (e.g., HbSS, HbCC, HbSC, etc.). However, HPLC and CE measurements of HbA1c would report no HbA1c present because no HbA is
Persons with HbAS and HbAC are not anemic (unless some other cause of anemia is present such as iron deficiency).

Shortened RBC life span will reduce HbA1c by all HbA1c methods.

If there is no hematologic history of anemia, the HbA1c may be reliable. Benign hemoglobinopathies such as Hb Raleigh falsely raise A1c (up to 50%).

Even if the HbA1c were elevated, in an asymptomatic patient, a confirmatory test is required to rule in or rule out diabetes.

In the setting of type 2 diabetes, HbA1c is less sensitive than FPG or a 2-h PG on an OGTT for the detection of hyperglycemia. Furthermore, in children, HbA1c has not been found to be of great value in screening for type 2 diabetes.

Note: I made no comment about cystic fibrosis (CF) and HbA1c. However, it is worth knowing that HbA1c measurements are not sensitive for the diagnosis of diabetes in CF. The reason for this is unknown.

Dr X.: “Good points too. Thanks”.

Dr. Q. wrote: “He doesn't need symptoms of hyperglycemia to meet ADA and ISPAD criteria for diabetes if based on formal OGTT.”

Please note that the above statement is NOT consistent with present ADA guidelines. Regarding: “He doesn't need symptoms of hyperglycemia to meet ADA and ISPAD criteria for diabetes if based on formal OGTT,” excluding an elevated random PG in a symptomatic patient, the type of hyperglycemia (elevated FPG, 2-h PG on an OGTT or an elevated HbA1c) does not determine whether diabetes is present or absent.

I then wrote: “According to ADA criteria, in an individual who is not in a hyperglycemic crisis and lacks classic symptoms of hyperglycemia, to diagnose diabetes, hyperglycemia (FPG =>126 mg/dL; or 2-h PG during an OGTT =>200 mg/dL or Hb A1c =>6.5%) needs to be identified on 2 separate occasions (at least 2 separate days). The ADA recommends that the initial abnormal test be repeated; however, if a second test is run that is different from the first and this test is not
consistent with hyperglycemia, you need to order a "tie-breaker" test. See below:

[1.]

In a symptomatic individual (e.g., a hyperglycemic crisis is present or symptoms of classic diabetes are present), only 1 episode of hyperglycemia is needed to diagnose diabetes: FPG =>126 mg/dL; or 2-h PG during an OGTT =>200 mg/dL or Hb A1c =>6.5%, or a random PG value =>200 mg/dL (e.g., DKA or HHS).

[1] From: Classification and Diagnosis of Diabetes. Diabetes Care 2016;39(Suppl. 1):S13–S22: It is recommended that the same test be repeated without delay using a new blood sample for confirmation because there will be a greater likelihood of concurrence. For example, if the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), the diagnosis of diabetes is confirmed. If two different tests (such as HbA1c and FPG) are both above the diagnostic threshold, this also confirms the diagnosis. On the other hand, if a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated. The diagnosis is made on the basis of the confirmed test. For example, if a patient meets the diabetes criterion of the HbA1c (two results =>6.5%[48mmol/mol]) but not FPG (=>126 mg/dL [7.0 mmol/L]), that person should nevertheless be considered to have diabetes. Since all the tests have preanalytic and analytic variability, it is possible that an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This scenario is least likely for HbA1c, more likely for FPG, and most likely for the 2-h PG, especially if the glucose samples remain at room temperature and are not centrifuged promptly. Barring laboratory error, such patients will likely have test results near the margins of the diagnostic threshold. The health care professional should follow the patient closely and repeat the test in 3–6 months.”

Dr. Y then wrote:

“Thanks for the comments regarding this case and the reminder on the diagnostic criteria for type 1 diabetes. This patient had a prior OGTT with a 2-hour glucose >200 mg/dL (11.0 mmol/L) per mom. It was part of a study protocol so mom wanted an "official" result and had the testing done as reported in my post.

I will try to get further details on his antibody testing and confirm the prior OGTT. Mom is worried about when the other shoe will drop and if we need to start treatment now.”
... So we don’t need to worry about the diagnosis of diabetes (which was established with the second abnormal OGTT); in an asymptomatic subject, evidence of hyperglycemia on 2 separate occasions does establish the diagnosis of diabetes. Hyperglycemia in asymptomatic individuals is defined as a FPG of 126 mg/dL or greater, a 2-h PG on an OGTT of 200 mg/dL or greater or a HbA1c level of 6.5% or greater. If a person has frank symptoms of diabetes [including a hyperglycemic crisis such as diabetic ketoacidosis (DKA) or hyperglycemic, hyperosmolar state (HHS)] any of the above criteria also define hyperglycemia, as well as, a random PG level of 200 mg/dL or greater. This is the only situation where a random PG is used diagnostically. In symptomatic patients, a single episode of hyperglycemia is sufficient to establish the diagnosis of diabetes.

The further discussion about the case is interesting: Dr. Z. wrote:

“If his antibodies were negative, it might be worth exploring his mom’s diagnosis a little more and considering possible monogenic diabetes. Otherwise I agree that it’s probably just type 1 diabetes, and the question is really just when and how to introduce insulin.

I can’t find any good data on when to intervene when diabetes is picked up so early and you’re just waiting for deteriorating glycemia. DKA and higher HbA1c at presentation is associated with a shortened honeymoon period, so I guess it is best to use insulin sooner rather than later!”

Dr. A. wrote:

“One of our patients with Type 1 diabetes who presented with DKA and was positive for GADA and IA-2A has also MODY 2 [a heterozygous loss-of-function mutation in glucokinase (GCK)]. Testing was done as other family members might also have MODY 2. Does having MODY 2 change the management of the type 1 diabetes in this patient?”

Still another doctor wrote:

“The co-occurrence of GCK-MODY (MODY 2) and type 1 diabetes is rare but we do have a case within our files. The expected range of fasting PG’s and HbA1c’s for GCK-MODY (MODY 2) typically falls well within range for type 1 diabetes goals so I don’t think you need specific adjustment.”
I hope you enjoyed this discussion of how to diagnose diabetes. Things we did not discuss (but are interesting questions) include: “Can I use jelly beans for an OGTT?,” “Should urine glucose be measured during an OGTT?,” “Should a 1-h sample be drawn during an OGTT for a person with cystic fibrosis?,” “Can HbA1c be used to screen for diabetes in children?” . . . but those questions can be for another column.

THE END