

Host: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

A number of studies have highlighted the importance of tight glycemic control in management of patients.

However, measurement of blood glucose maybe performed by laboratory instrumentation or by hand-held glucose meters. Glucose meters have been shown to be less precise than laboratory-based instrumentation, and results can differ significantly from laboratory methods.

A perspective in the January issue of the journal *Clinical Chemistry* asks if these glucose meters were up to the task. One of the authors of that article is Dr. David Sacks, an Associate Professor of Pathology at Harvard Medical School and Medical Director of Clinical Chemistry at Brigham & Women's Hospital in Boston, and he is our guest today in this podcast.

Tell us, Dr. Sacks, does published research and evidence support the use of tight glycemic control in non-diabetic hospitalized patients.

Dr. David Sacks: Well, I think, perhaps the best way to answer that question, I'll begin by explaining the rationale behind tight glycemic control. It's become clear that in critically ill patients, for example, those with severe injury or infection, they exhibit alteration in carbohydrate metabolism, and this results in insulin resistance producing hyperglycemia or increased blood glucose concentrations. And the hyperglycemia is common even in patients who don't have diabetes. This is often referred to as "stress hyperglycemia."

Based on this, studies were conducted to determine whether this hyperglycemia was producing deleterious effects in the patients. And the first study, which was a landmark study, was in 2001 where Greet Van Den Berghe and her colleagues in Leuven, Belgium, performed a perspective controlled study on adults who were receiving mechanical ventilation in the Surgical Intensive Care Unit. And the way they designed the study, the patients were randomized to receive intensive insulin therapy to maintain their blood glucose concentrations between 80 and 110 mg/deciliter, which is based on fasting glucose concentrations in normal healthy populations.

The second group were those who received conventional therapy, which was designed to achieve glucose concentrations of about 180-200 mg/deciliter. And the studies included 1548 patients, and the findings were very

dramatic in that they showed that intensive insulin therapy maintaining blood glucose at less than 110 mg/deciliter reduced mortality in the Surgical Intensive Care Unit by 42%.

So these dramatic findings prompted numerous hospitals all over the world to institute tight glucose-control protocols, and these have essentially become a standard of care in most hospitals. In typical tight glycemic-control protocols, patients are put on continuous infusion of insulin intravenously. The patients have blood glucose values checked usually about once an hour and the insulin infusion rate is changed based on the results of the glucose measurement.

In addition to these protocols in Intensive Care Units, they've actually become widely outside Intensive Care Units and this approach is based in part on predominantly observational studies, which have showed poor clinical outcomes in-patients with hyperglycemia outside the Intensive Care Unit. And a consensus statement supporting improved glucose control for in patients has been published by the American College of Endocrinology and the American Diabetes Association with the participation and agreement of prominent cardiology, critical care, and anesthesiology organizations.

Now, notwithstanding the implementation of these regimens, some clinical trials have failed to observe benefits with tight glucose controlling. Numerous studies have been done subsequent to the initial Van den Berghe study. So for example, a paper was published in the *Journal of American Medical Association* in August of last year, 2008, where they did a meta-analysis and evaluated 29 randomized controlled trials, which totaled 8432 patients. Analysis showed no significant difference in mortality in patients in Intensive Care Units between those who received intensive insulin therapy versus those who did not.

The publication in the *New England Journal* in March this year of the NICE-Sugar study has intensified the debate.

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The multinational NICE-Sugar trial was designed to test the hypothesis that intensive glucose control reduces mortality at 90 days, and this is the largest study of tight glucose control ever conducted. It was done in 42 hospitals all over the world and included 6104 adults. The way the study was designed was that any patient, who was expected to require three or more consecutive days in the Intensive Care Unit, either the medical or the surgical ICU, was randomly

assigned to either intensive or conventional glucose control. This randomization was done within 24 hours of admission to the ICU.

The target glucose range for the intensive control group was 80-100 mg/deciliter and the conventional group was to keep it under 180 mg/deciliter, and they found that, that was significantly lower mean blood glucose values in the intensive control group than the conventional control group. A very unexpected finding which has generated lot of concern was that the mortality in the intensive control group was 27.5% significantly higher than that in the conventional control group of 24.9%.

Severe hyperglycemia, which was defined in the study as the blood glucose of less than 40 mg/deciliter was present in 206 patients in the intensive control group, that's 6.8% of that group, compared to only 15 patients was 0.5% in the conventional group. And this has been hypothesized the increased prevalence of hyperglycemia in the intensive group is believed to be the cause for the increased mortality in that group. So I think that based on the studies, there's some concern as to whether tight glucose control should be used in non-diabetic hospitalized patients.

Host: So in tight glycemetic-control protocols, are portable meters suitable?

Dr. David Sacks: It's quite clear that glucose meters are less precise than central laboratory or blood gas analyzer methods. For example, the College of American Pathologist Proficiency testing data in 2008 showed that the CVs for all 29 central laboratory methods, which includes 5664 laboratories, the CVs range from about 2.5 to 4.3 % and the bias between any two methods is no more than 11%.

This contrasts dramatically with glucose meter methods. There are 17 different glucose meter methods in CAP surveys at over 19,000 sites, and the CVs were found to be between 12 and 14% and the bias between any two methods was as high as 41%. It should be noted that obviously some of the bias between methods could be due to matrix effect but large CVs are found even for single meters from a single manufacturer.

Also a study from the CDC, Centers for Disease Control, a five common glucose meters showed mean differences from a central laboratory method to be as high as 32% and CVs in the hands of a single trained medical technologist could range from 6 to up to 11%. Patient factors, especially in critically ill subjects, also contribute to inaccurate results with meters and this is particularly important in Intensive

Care Units. So, for example, it's known that some glucose meters are affected by PO₂ and hematocrit. Many patients who have low blood pressure in Intensive Care Units have reduced tissue perfusion which results in large differences in glucose concentrations in capillary blood samples with minimal alterations in arterial blood samples.

Another variable is that the glucose concentrations in arterio-venous and capillary blood differ. Now, these differences are minimal in fasting subjects, but after eating, capillary glucose values can be 25 mg/deciliter higher than those in venous blood and in many of these protocols, the meters are using capillary blood to measure glucose.

Host: Well, how accurate the glucose meters need to be for patients with diabetes who monitor blood glucose by themselves.

Dr. David Sacks: That's a very difficult question to answer. Multiple performance goals for portable glucose meters have been proposed and these targets vary widely and are highly controversial. This lack of consensus reflects the absence of agreed objective criteria.

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I want to make it clear that several technological advances that decrease operator error have been made by manufacturers of glucose meters. These include smaller blood volumes, no timing is required by the user, the reagent stability has been improved, giving longer shelf life to the reagents, and the meter displays are enhanced, which allow people with diabetes, many of whom have impaired vision from complications of diabetes to clearly read the values.

Also, current meters as one would predict exhibit performance characteristics that are superior to those of prior generation meters but there remains room for improvement. The big fear in patients with diabetes is hypoglycemia, for example, patients with type 1 diabetes on insulin usually experience one to two episodes of symptomatic hypoglycemia a week.

Intensive control of glucose, which has been shown in several studies to reduce the rate of development of complications of diabetes generates a significant increase in hypoglycemic episode, and studies have shown that severe hypoglycemia, which is defined as hypoglycemia which requires the assistance of a third party, in other words, the patient themselves, is unable to relieve the hypoglycemia by

ingesting food or glucose drink has increased three-fold by intensive control.

There's also an addition to these well-known acute effects of hypoglycemia, there's now in the last few years evidences accumulated about the delayed risk of hypoglycemia. Severe hypoglycemia has been shown in some studies to be associated with increased mortality, this is cardiovascular mortality thought to be predominantly arrhythmia, although it's not quite clear. And also, recent evidence indicates that hypoglycemia is associated with subsequent dementia.

So the ISO or the International Organization for Standardization in 2003 published criteria for blood glucose monitoring systems for self-testing, so this is for glucose meters for patients with diabetes to use. And the guidelines state that if the glucose value is less than or equal to 75 mg/deciliter, the meter results must fall within 15 mg/deciliter of the true result.

So, for example, one could take a concentration of 45 mg/deciliter of true glucose concentration, which is clearly hypoglycemia, the meter could read anywhere from 30 mg/deciliter to 60 mg/deciliter and 60 mg/deciliter would not be considered hypoglycemia. And these values would be considered acceptable within the current ISO standards.

Clearly these errors are not acceptable for reliable detection of hypoglycemia.

Host: But with that in mind, what degree of accuracy is needed for tight glycemic control and can this accuracy actually be achieved with current glucose meters?

Dr. David Sacks: Well again, there are no objective criteria by which one could accurately answer that question. In the original study by Van den Berghe and colleagues, glucose concentrations in the tight glycemic-control protocols were measured using a blood gas analyzer. This is much more accurate than the glucose meter.

Subsequent studies have used different method to measure glucose and in fact, it's often difficult when one looks at these studies to determine exactly what method was used. For example, in the meta-analysis that I discussed earlier, looking at the original articles, the glucose method was described in any 10 of the 27 studies that is certainly possible that some of the discrepancies in the tight glucose-control protocols, some of which have, as I mentioned earlier, have shown significant reduction in mortality while others have failed to show this, maybe due to inaccurate glucose measurements.

I think it would be reasonable to suggest that the accuracy for tight glycemic-control protocols should be similar to those obtained in the central laboratory where glucose is measured.

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As mentioned earlier, the CVs for central laboratory methods are between 2.5% and 4.3% and values less than 10% are acceptable for passing in CAP survey. So I think it's reasonable to propose that these accuracy criteria should be achieved for glucose measurements in tight glucose-control protocols.

Host: Okay. Well, in your opinion, should new glucose meters be developed specifically for using tight glycemic-control protocols?

Dr. David Sacks: I think that would depend on the manufacturers of glucose meters. Certainly, the manufacturers have focused a lot of efforts as I mentioned earlier on improving the meters for use by patients with diabetes, and these meters are small, they are portable, patients have to be able to carry them in a purse or jacket pocket. Sometimes they drop the meter; the meter needs to be resistant to those sorts of things. The volume has to be very small, the timing should be short.

These criteria are obviously not necessary for a meter that would be used in an Intensive Care Unit, and I think that if the manufacturers could develop meters that fulfill the characteristics of accuracy at the expense of some of these other features which would be valuable for patients but would not apply to a meter in an Intensive Care Unit, then I think these meters should be developed if they could be.

Host: Will continuous glucose monitoring have a future role in protocols for tight glycemic control?

Dr. David Sacks: Well, for some people, this would be the Holy Grail of glucose measurements in tight glycemic-control protocols. Clearly, if one is getting continuous or every few seconds, a glucose value, then you could tolerate less accuracy than if the glucose is being measured once an hour, because the accumulation of all these results would give you the true glucose value.

Having said that, the current generation of continuous glucose monitoring devices suffer from a number of deficiencies that make it very difficult to use them in these settings. The first is that the CGMS instruments are calibrated using glucose meters, so you already have the

inherent inaccuracy in the glucose meters, and this is added to the inaccuracy of the Continuous Glucose Monitoring Systems, or CGMS, as they call it.

Another problem which is perhaps less of a major problem is that the current generation of CGMS devices are inserted subcutaneously and are measuring glucose in the subcutaneous fluid not in the blood. When the glucose concentration in the blood changes, there's a delay of several minutes before the glucose concentration in the subcutaneous tissue changes. So that lags behind the changes in the blood glucose, and as I mentioned earlier, it's absolutely critical in these protocols to avoid severe hypoglycemia, which appears now based on a number of studies to result in mortality.

Host: Dr. David Sacks is an Associate Professor of Pathology at Harvard Medical School and the Medical Director of Clinical Chemistry at Brigham & Women's Hospital in Boston, and he's been our guest today on this podcast from the journal *Clinical Chemistry*. I am Bob Barrett. Thank you for listening.

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