Bob Barrett: This is the podcast from '*Clinical Chemistry*'. I am Bob Barrett. In February, '*Clinical Chemistry*' produced a special themed issue on the subject of diabetes mellitus.

Dr. David Sacks: Diabetes has been recognized for more than 3,500 years since the early description in 1552 B.C.E. in Papyrus of Ebers from Egypt. And there has been a recent very dramatic increase in the prevalence of diabetes all over the world.

For example, in the United States, between 1999 and 2002, the prevalence was 9.3%, but data from 2005-2006 indicate that there are probably 42 million adults in the United States with diabetes.

Bob Barrett: That was Dr. David Sacks of the National Institutes of Health speaking about diabetes. Dr. Sacks is co-editor of that special issue of the journal *'Clinical Chemistry'* that appeared in February.

Dr. Sacks, why devote an entire issue of the journal to the single topic of diabetes?

Dr. David Sacks: We have made our progress in understanding diabetes over the years, but despite this a lot remains to be done. And the intent of the special issue was to both promote our knowledge of diabetes and get people who are not quite active in reading about the disease to understand this and hopefully to get some of these people involved in understanding diabetes.

But the other aspect that we thought was important was to emphasize what is unknown and what needs to be done, again, to try to stimulate people to fill some of these gaps in our knowledge.

Bob Barrett: Well, let's get to the meat of the issue. What are some of the recent advances in diabetes research?

Dr. David Sacks: Well, I will break these down into several different categories. The first is, which is very important is, diabetes is associated with many complications. These specific complications to the disease or microvascular complications which affect the small vessels, and these include retinopathy that produces blindness; nephropathy, kidney damage that results in dialysis, so diabetes is the most common reason for people being on dialysis in Western world, and neuropathy.

So those are the microvascular complications, but there are also macrovascular complications, which affect the large vessels, and these cause stroke and heart attacks.

And it has been shown that the complications of diabetes can be reduced by up to 50% with intensive control of glucose, especially if this is done early in the disease.

Also, there are two types of diabetes; I should have mentioned this earlier, there is Type 1, which affects only about 5% of people and this is the sort of classic diabetes that many laypeople think of as diabetes where you get explosive onset of the disease, usually it occurs in younger people. And that's due to autoimmune damage usually to the pancreas.

And then there is Type 2 diabetes, which is more common in older people, and that makes up about 95% of the diabetes in the world. And many of these people are overweight, and it has been shown now that weight loss in people with Type 2 diabetes results in improved control of their glucose, blood pressure, and cholesterol, and less medication.

Another type of diabetes is called gestational diabetes, which occurs in pregnancy, and it has also been shown that intensive control of blood glucose during the pregnancy can reduce birth defects in babies, birth injuries, and the need for caesarean sections in the mothers.

Another important area in which we have made some advances recently is in preventing or delaying Type 2 diabetes, and this has been shown that people at high risk for Type 2 diabetes through diet and exercise to promote modest weight loss can dramatically reduce their risk of developing diabetes and the benefits persist for about ten years or more.

Another important area is restoring insulin production in individuals with severe Type 1 diabetes where you can transplant islet cells of the pancreas and produce independence of insulin at the moment, just for a short time, but these are encouraging studies.

And finally, another recent area that's generated a lot of interest is gastric bypass surgery and other bariatric surgeries to treat extreme obesity, appeared to resolve Type 2 diabetes independently of the effects of weight loss. And so this has stimulated potentially new therapeutic options for some individuals and generated lot of research to try to understand the mechanisms operating here.

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Bob Barrett: And now we turn to another editor of that special diabetes edition, Dr. Vivian Fonseca, Professor of Medicine and Chief of the Section of Endocrinology at Tulane University.

Dr. Fonseca, who should read this issue of '*Clinical Chemistry*'?

Dr. Vivian Fonseca: I think the way the issue has turned out is that it certainly covers a wide range of topics, both clinical, but also people who want to understand the pathophysiology of the disease better, understand some controversial issues such as some of the changes that have come in testing such as the hemoglobin A1c for diagnosis, its strengths and limitations, and so on.

Bob Barrett: Well, that is one recent advance in diabetes research and testing. What are some important areas for future research?

Dr. Vivian Fonseca: I think understanding of the limitations of the disease, where we are, and what the unmet needs are, and then try to identify new therapeutic targets, not only for treatment of the disease but also prevention. Because we do have an article in this issue on prediabetes, in fact, it's entitled *'Prediabetes as a Therapeutic Target'*, because with so many people with diabetes out there, it's a challenge to treat, and prevention is, in my opinion, the better part of cure.

Bob Barrett: Besides prediabetes, what other aspects of the disease are covered in this special issue?

Dr. Vivian Fonseca: Well, we cover a wide range of topics. First of all, as I commented on earlier, we look at hemoglobin A1c as a tool to diagnose diabetes, we look at its status for measurement of diabetes, and try to see what can be done in terms of A1c utilization for improving diabetes care, including some of the recent advances in the Glycohemoglobin Standardization Program and that steering committee's report.

And then we have a clinical case study on unexpected A1c results, which happen fairly frequently in practice.

And then we look at a number of things related to the pathophysiology of diabetes and review them. So for example, in Type 1 diabetes, we look at autoimmune markers, which is a very important and evolving field. We look at the genetics of Type 1 diabetes, which is also an important topic, because we want to identify people at risk for Type 1 diabetes early and look for ways to prevent it. And then we also look at drug-induced changes and risk markers and biomarkers that have a relationship, not only with diabetes, but also diabetes complications.

As part of this whole thing about autoimmune markers and genetics, we have an article, a mini review on *'Diabetes as a Continuous Spectrum'*. We look at it as just one disease or two diseases, Type 1 and Type 2, but there is a lot of overlap between the two. And it may be that as we get

 

better in characterizing the disease and its biomarkers and genetic markers, we will recognize that there are multiple types of diabetes.

Going on from there, we look at the complications of diabetes, the relationship between diabetes control and its complications. We look at progression of nephropathy, and particularly, an article on Glycation Gap and Diabetic Nephropathy.

We look at other methods to assess controls such as glycated albumin. We also, in relation to Type 2 diabetes, look at insulin resistance; what are the methods for determining insulin resistance clinically, including things like the Homeostatic Model Assessment or HOMA Model.

We look at lipids, which are very important in relation to Type 2 diabetes. There is an article on fasting and postprandial lipids on the relationship between insulin resistance and lipids and other cardiovascular risk markers, including markers of inflammation such as variations in the genes encoding C-reactive protein, TNF alpha, IL-6, etcetera.

And with that, we look at inflammation as a therapeutic target with an article by Allison Goldfine, Steve Shoelson, and myself. We also look at other biomarkers of insulin sensitivity, insulin secretion, etcetera. And we have identified a citation classic in relation to diabetes, which is the Framingham Study Insights into diabetes and cardiovascular disease.

Bob Barrett: And are there any parts of the issue that just stand out as highlights for you?

Dr. Vivian Fonseca: I think an interview with Dr. Ronald Kahn, who has been a leader in the field, who has been running the Joslin Diabetes Center for many years, an outstanding investigator. That interview gives us a lot of insights into where diabetes was, how it is evolving, where it's going. From a researcher's perspective, it gives you a very nice overview of diabetes.

Bob Barrett: Thank you, Dr. Fonseca. Now let's return to Dr. Sacks and get his perspective on future research in the area of diabetes.

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Dr. David Sacks: Well, there are obviously a very large number of them. I won't be comprehensive, but I will try to highlight some of the areas that I think are important for future research. I will break these down into different categories.

 

One of them would be the genetic basis. So Type 1 diabetes, Type 2 diabetes, obesity and the complications have a very strong genetic basis that interact with environmental and behavioral factors, and to identify these factors that influence the disease susceptibility is very important to develop strategies to prevent and treat diabetes.

Also, understanding how these susceptibility genes contribute to a person's risk and to elucidate into action among these genes at a cellular level will help researchers discover common pathways of risk.

Another important area is to understand how genes associated with risk interact with potential environmental factors such as viral infections, nutrition, and another area that's just beginning to be studied is gut microbes.

It would be important also in terms of pharmacogenetics or pharmacogenomics as it's being called to identify genes invariance that influence both positive and negative responses to diabetes therapies, because this could open up prospects of personalized medicine in which the use of specific pharmacologic agents can be tailored to individuals based on their genetic profile. And this could reduce the risk of adverse effect in some people and also allow lower doses of drugs and have more specifically targeted therapy.

Another important area is, in Type 1 diabetes, where autoimmunity is important, is to understand these mechanisms, what destroys the pancreatic beta cells and try to ultimately delay or even prevent the onset of the disease.

In terms of Type 2 diabetes, also in addition to the beta cell failure, there are also metabolic abnormalities in different organ systems; fat, muscle, liver, and research efforts are needed to understand these metabolic abnormalities, also try to link recent evidence of inflammation, which is quite common in people with Type 2 diabetes and may have some role in both insulin signaling and the development of complications.

Another area that would be important, which has links to less commonly thought of areas of diabetes, at least from a clinical perspective, would be bioengineering, where one would develop an artificial pancreas to deliver insulin. This would also require better glucose sensors. You need small, implantable glucose sensors that could accurately measure glucose inside the body for a long time to warn of impending hypoglycemia or low glucose and also to try to stimulate release of insulin from an artificial pancreas.

So I think those aspects are very important for future research.

Bob Barrett: Well, finally, getting back to the issue, what aspects of diabetes itself are covered in the special issue?

Dr. David Sacks: Well, the special issue has three editors in addition to myself, there's Vivian Fonseca from Tulane University. He is Editor of *'Diabetes Care'*. And Allison Goldfine from the Joslin Diabetes Center and Harvard Medical School. Both of these are very well-recognized clinicians who are active in translational research, and we together intentionally decided to cover broad range of topics. And these include, I am going to go through just the general topics briefly.

The pathophysiology of Type 1 and Type 2 diabetes, what causes the disease. So for Type 1 diabetes, some understanding of the genetics of the disease as well as the autoimmune aspect and autoimmune markers; Type 2, the influence of genetics and how the environment interacts with this.

The second broad area involves lab tests. These include both tests that are well-recognized, for example, hemoglobin A1c and LDL cholesterol have been used for many years, but we are updating readers on advances and progress in these assays.

And also recently developed tests, for example, biomarkers, things like soluble CD163, and urinary catalytic ion, which are sort of more at the forefront of new developers.

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In terms of treatment, there is a focus on prediabetes before people actually develop the disease. Then there is treatment of inflammation in Type 2 diabetes, which I mentioned briefly is important in the constellation or complications. And then there is a section on the current status of personalized medicine, which obviously is just in its infancy.

Another broad area that's covered are the implications of some of the clinical studies. These range from the well-known Framingham Study, which is an old study that's been ongoing for many, many years, and there are some insights in the special issue into both diabetes and cardiovascular disease from the Framingham Study.

More recent studies include the ACCORD Study, ACCORD stands for Action to Control Cardiovascular Risk in Diabetes. This was a study in which there was very tight control of glucose, and very surprisingly, this resulted in increase mortality in the patient's with intensive treatment, resulted in the study being stopped early. The causes of the

increased mortality are not actually known, but there is some discussion about this in one of the papers in the issue.

And finally, we thought it important to include controversial areas where people who disagree about different things, these include hemoglobin A1c for diagnosis, which was recommended last year by the American Diabetes Association and endorsed a few months ago by the World Health Organization.

And then a topic called the Glycation Gap, which some people believe is important and other people remain less convinced.

So there are a broad diversity of topics. The hope is to stimulate people who are not necessarily in the area of diabetes to get them to get involved, participate in advancing the understanding and knowledge of diabetes, and the hope ultimately of this special issue is that people with this disease will have improved diagnosis and therapy in the future to reduce the terrible burden of the disease.

Bob Barrett: Dr. David Sacks and Dr. Vivian Fonseca have been our guests in this podcast from '*Clinical Chemistry'*. They and Dr. Allison Goldfine were co-editors of a special issue of the journal '*Clinical Chemistry'* that appeared in February, devoted to the single topic of diabetes.

I am Bob Barrett. Thanks for listening.

Total Duration: 17 Minutes