A Review of the Role of Incretin-Based Therapies in the Management of Type 2 Diabetes

Interview with A. Enrique Caballero, MD

A. Enrique Caballero, MD, graduated from the National University of Mexico Medical School, where he received the Gabino Barreda Medal for being the top student in his program. He completed his residency in internal medicine and fellowship in endocrinology at the National Institute of Nutrition in Mexico. Dr Caballero later received a master's degree in clinical epidemiology in Mexico. He also completed a fellowship program in endocrinology and metabolism at the Lahey Clinic, Deaconess Hospital, and Joslin Diabetes Center, in addition to a program on clinical effectiveness at the Harvard School of Public Health. Dr Caballero currently serves as Director of the Joslin Latino Diabetes Initiative, and is a clinical investigator, staff endocrinologist, and the Associate Director of Professional Education at Joslin Diabetes Center. Dr Caballero is also an Assistant Professor of Medicine at Harvard Medical School and has written various publications on prediabetes and endothelial dysfunction in addition to diabetes in various ethnic groups, particularly the Latino population. Dr Caballero frequently lectures about diabetes, cardiovascular disease, and diabetes in culturally diverse populations.

A senior clinical editor for Johns Hopkins Advanced Studies in Medicine (JHAS&M) interviewed Dr Caballero to discuss incretin therapy for type 2 diabetes.

JHAS&M: In June 2005, Mexico's Health Ministry published a report stating that deaths from diabetes are increasing by 3% each year, making diabetes the leading cause of deaths in Mexico.1 How can health systems in Mexico address the low diagnosis rates for type 2 diabetes and improve early detection and management?

Dr Caballero: This is a complex situation resulting from a combination of factors, including the fact that the Mexican population is at risk for the development of type 2 diabetes and lifestyle has worsened in Mexico as it has in other countries around the world. People have become more sedentary and the rates of obesity have increased. There are studies showing abdominal obesity is also becoming more prevalent in the Mexican population, and although we might not see the same rates of obesity as seen in other countries—including the United States—increasing levels of intra-abdominal fat in combination with the genetic predisposition for diabetes are the factors leading to the high rates of this condition.2

Another problem is the late diagnosis of diabetes; physicians and specialists most often see patients when they have already developed symptoms. At that point, a precious opportunity has been lost in terms of identifying people early enough to prevent the complications of diabetes. It is crucial that massive campaigns to raise awareness about this serious condition be established for the Mexican population. Media and formal educational activities for the general public can inform people about the fact that diabetes is a silent disease that can kill. Considerable attention is paid to other diseases, such as cancer, whereas diseases such as diabetes are often considered less serious. Now that it is clear that diabetes has become one of the major causes of death in the Mexican population, more emphasis needs to be placed on addressing the issues surrounding diabetes.
The healthcare system must implement activities to raise awareness in the population. It also should educate physicians and general healthcare professionals about the need to detect diabetes in people as early as possible in the natural course of the disease, in addition to the need to implement specific strategies to treat aggressively diabetes and prevent complications. The government is currently implementing different programs, and various institutions are enthusiastically working on these issues. However, there needs to be a more solid, collective effort in Mexico so that, ultimately, the battle against diabetes will look more favorable.

JHASiM: Despite education and treatment approaches for managing type 2 diabetes, there is still an appalling lack of controlled diabetes worldwide. Do you think that newer pharmacologic approaches will be able to rectify this situation?

Dr Caballero: I think that in the treatment of diabetes, the first approach should not always be pharmacologic interventions but rather lifestyle modifications. I would encourage everyone to try a healthy meal plan and regular physical activity as the first step in addressing diabetes and all comorbid abnormalities that usually present at the same time, including hypertension, dyslipidemia, and obesity. Unfortunately, we know that many people fail on this type of intervention and will require medications. However, we now have more options available than ever before in the history of diabetes. This is an exciting time in which the pathophysiology has led to a better understanding of how diabetes affects many patients, which has led to more options and treatment tools. It is important for physicians to obtain thorough education on the different treatment options because the proper use of these medications can lead to an improved treatment plan, better glycemic control, and, hopefully, a reduction in the rate of complications. There are now 5 classes of oral agents and there are more types of insulin. There are also newer medications that are addressing some previously untapped areas in the pathophysiology of diabetes. Specifically, the incretin pathway is an element in the pathophysiology of diabetes that has been known for more than 25 years. For the first time, medications have been developed to target some of these older concepts.

JHASiM: Given the increasing incidence of abdominal adiposity and risk for diabetes, how could incretin-based therapies contribute to stemming diabetes-related complications?

Dr Caballero: Incretin-based therapies have introduced another option to the treatment of diabetes by addressing not only glycemic control, but also by possibly targeting some of the other comorbidities that are occurring in people with diabetes, such as obesity. We know that exenatide, which is a medication that mimics the action of glucagon-like peptide-1 (GLP-1), produces 4 interesting effects that may be beneficial for many people with diabetes. It reduces postprandial hyperglycemia by stimulating the insulin production in β cells, it reduces glucagon production in α cells in the pancreas, it regulates gastric motility, and it has an effect on the central nervous system of reducing appetite and promoting satiety—all of which are beneficial effects in people with diabetes. Therefore, exenatide is a new class of treatment that should be considered seriously in many patients with diabetes, not only because of the possibility of addressing glucose control but also because of the weight-reduction benefit. This is precisely what we want to address in most of our patients with diabetes. We want to control blood sugars, but we also want to address the cardiovascular risk factors that usually happen together and, in combination, lead to the development of cardiovascular disease—the number 1 cause of death in patients with diabetes.

JHASiM: Is it possible that incretin-based therapies could impact the management of comorbid diseases, such as hypertension, cardiovascular, and cerebrovascular disease?

Dr Caballero: Unfortunately, there are no solid data yet on the incretin-based therapies showing a reduction in cardiovascular disease or cerebrovascular disease events. However, based on the data that we have seen thus far, it may be possible that, along with the beneficial effects on weight, some improvement in certain cardiovascular risk factors and markers of cardiovascular disease could be seen with these therapies in the future. It is important to remember that the treatment of diabetes requires a coordinated approach to implement nonpharmacologic interventions, in addition to the integration of a treatment plan that targets many of the pathophysiologic defects that we usually appreciate in our patients with type 2 diabetes. This includes the treatment of insulin resistance and improvement in β-cell function, the 2 main problems in patients with type 2 diabetes. Fortunately, the new
therapies that we have can act in 1 of these 2 pathophysiologic defects. When used in combination, they have a good chance of addressing the 2 most serious problems that we face when treating patients with type 2 diabetes.

**JHASiM:** Do you have any information about whether future studies of exenatide will examine any long-term cardiovascular outcomes?

*Dr Caballero:* There are no data at the present time, but ongoing studies are trying to address the effect of exenatide on cardiovascular risk factors, specifically lipids, blood pressure, and some of the markers of inflammation and vascular function, including C-reactive protein and some of the markers of endothelial activation. Ultimately, as clinicians and investigators, we would all like to see studies that address the development of cardiovascular disease or cerebrovascular disease specifically, but it is still early in this new field of diabetes treatment. It will take several years for a study to be implemented and conducted showing a reduction in cardiovascular events. It may eventually happen, but at least if the studies planned for the near future show that some of the surrogate markers of cardiovascular disease are improved with this therapy, it would be encouraging and may suggest that an impact on cardiovascular outcomes will be seen.

**JHASiM:** Studies mentioned in the second article have reported effects of incretin-based therapies on preserving or enhancing β-cell function and/or mass. What are the far-reaching implications of these data?

*Dr Caballero:* It is clear that exenatide has some beneficial effects on β-cell function and activity in the animals that have been studied. Whether there is a benefit in humans is still uncertain. However, some of the studies now being conducted may yield insight as to whether the clinical effects seen in animals have a positive clinical implication in humans. It is possible, at least from the scientific perspective, that the effects of exenatide would mimic the actions of GLP-1, which seems to also preserve β-cell function and activity. However, it is still too early to know whether the clinical trials will be able to prove that occurrence. If that is found to be the case, it would be a breakthrough finding because at the present time, the most serious problem that we see in our patients with type 2 diabetes is the inexorable decline in β-cell function, which happens for many years before diabetes develops and continues throughout the history of the disease. At this point, we don't have strong therapies to stop the β-cell functional decline, and any therapy that would stop or slow β-cell functional decline would be valuable.

**JHASiM:** What patient characteristics suggest that treatment with the GLP-based therapy exenatide would be an appropriate option?

*Dr Caballero:* I think that based on the pathophysiology of diabetes—and again, remembering that the 2 main problems are insulin resistance and β-cell dysfunction—at the present time, the medication that may stimulate β-cell function more physiologically is exenatide. The logic supporting this belief is based on the natural hormone GLP-1, which we all produce and that naturally stimulates β-cell function. Therapies that work in more physiologic ways are now being welcomed in the treatment of diabetes. The closer a therapy is to nature, the more acceptable and more logical its use is in our patients. Exenatide is, of course, a medication that only addresses 1 of the 2 problems of type 2 diabetes, β-cell dysfunction; the other is insulin resistance. There are medications that address insulin resistance, which in combination with exenatide may be a good option for the treatment of type 2 diabetes. In the United States, exenatide is approved to be used only in people with type 2 diabetes who are taking metformin, a sulfonylurea, or a combination of these 2 medications. Other studies have been initiated that examine exenatide in combination with a thiazolidinedione, or exenatide in patients on insulin. Although we do not yet have all of the data from these studies, I envision that the possibility of using exenatide in people who are taking other medications and with those who are in other stages of the disease may be feasible in the future.

It is intuitive to think that the largest benefit of exenatide would be with those patients who are still able to respond to the use of these medications and produce insulin. That is, of course, in people who have not had diabetes for a long period of time. It is difficult to precisely define what qualifies as a long duration of diabetes, but in most of the published exenatide studies, the people who have been included are those who have had diabetes for less than 10 or 15 years. But again, the current data are somewhat limited and studies of exenatide in people in later stages of the disease are needed to determine whether they respond.

The fact that this medication can lead to some weight loss makes it attractive for patients who are...
overweight. Because many patients with type 2 diabetes are overweight or obese, the weight loss effect has become another interesting effect of this medication. However, it is important to remember that exenatide is not a weight loss medication, and should not be prescribed as such. It is a medication that lowers blood sugars in patients with diabetes, and may also provide the additional benefit of weight loss.

JHAS/M: Is there a specific range of baseline hemoglobin A1c for which it is appropriate to consider exenatide therapy?

Dr Caballero: In the studies that were conducted—the AMIGO trials—the A1c was below 9% in most of the patients. Mean A1c was approximately 8.5%; however, a small fraction of people included in these studies had an A1c above 9% or even 10%. Generally speaking, this subgroup still responded well to the intervention. It is true that the closer the A1c is to the goal of less than 7%, the more important the role of postprandial hyperglycemia, which is the main target for exenatide. Therefore, the closer the A1c is to the goal, the more likely it is that a patient would respond to the medication. However, based on our recent experience and some of the subgroup analyses performed in some of these studies, an A1c level higher than 8% or 9% should not really be considered a contraindication or a factor that would preclude some people from trying the medication. This is because postprandial hyperglycemia is important at all levels of A1c, which is what we are now seeing in some of our patients. Thus, I would not recommend any specific point for A1c levels to encourage or discourage the use of exenatide.

JHAS/M: Please comment on the adverse event of nausea that you have seen in your clinical experience with exenatide.

Dr Caballero: In general, my clinical experience has been consistent with what was reported in the clinical trials, which is that approximately 1 in 3 patients who start exenatide develop nausea. My experience has also been consistent with the finding in the studies that as time goes by, the prevalence of nausea declines. Only approximately 1 in 10 people I have treated who have tried the medication have experienced severe nausea at the beginning of treatment to the point where some of them decided not to continue. In most cases, the nausea has been mild, intermittent, and usually subsided in the few weeks following initiation of treatment. Most of my patients have been able to tolerate the medication.

There are some important factors to keep in mind when treating with exenatide. One is to always start with the low dose of 5 µg twice daily as recommended. In some patients, I have had to extend the 1-month period of the low dose to 2 or 3 months before moving to the full dose of 10 µg twice daily to allow the patient to become accustomed to this medication. I have also found that when the injection is administered closer in time to the meal, the less likely it is that a patient will develop gastrointestinal side effects. I have heard about similar experiences with this medication from other investigators and clinicians.

JHAS/M: In the future, do you envision incretin-based therapies as having a therapeutic role in prediabetic states?

Dr Caballero: I am excited about this possibility because I am one of the coinvestigators for the National Diabetes Prevention Program (DPP). I have always been interested in identifying therapies that could prevent the development of type 2 diabetes because I believe prevention is the way to address the diabetes epidemic—by identifying people at risk and offering different treatment options. At this point in the field of prediabetes, several therapies that address insulin resistance—such as troglitazone or metformin, both addressed in the DPP—have shown that it is possible to reduce the progression to type 2 diabetes. In the Study to Prevent Non–Insulin-Dependent Diabetes Mellitus, a medication known as acarbose, which targets postprandial hyperglycemia, proved that the development of diabetes can be prevented. Therefore, therapies have now started to indicate that by modifying the natural history and some of the key elements of the pathophysiology of diabetes, it is possible to prevent the development of diabetes. If exenatide does work by targeting the β cell and preserving its function, it would be an excellent option for the prevention of type 2 diabetes because we know that people advance from impaired glucose tolerance to diabetes mostly due to continuously declining β cell function. Ultimately, I think that the most substantial benefit of preventing diabetes is the fact that you would thereby naturally prevent the complications of the disease and possibly also reduce cardiovascular disease rates. There are no studies at the present time, but it may be a good option to consider in the future. My
A personal approach would be the combination of a therapy such as exenatide for β-cell dysfunction and perhaps a therapy such as metformin and/or a thiazolidinedione to target the insulin resistance component. Hopefully, with that type of combination treatment, people would not develop diabetes as frequently.

We are facing an important challenge in the world with the dual epidemics of diabetes and obesity. Worldwide statistics prove that people are not doing well in their treatment plans and in the control of their diabetes state. Recent data in the United States show that only 7% of patients with diabetes reach the goal for an A1c of less than 7%, blood pressure of less than 130/80 mm Hg, or cholesterol of less than 200 mg/dL. This demonstrates that few people are achieving the goals for these well-established standards of care. The percentage of patients who achieve good glucose control may be similar in other countries, including Mexico where few people are at goal.

However, the new reality is that we now have improved type 2 diabetes treatment plans, better understanding of the disease, more knowledge about its likely course, advanced treatment options, and better medications than ever before. It is time to unite and educate each other; to participate collectively to use all of the different tools that we have and, through doing so, better serve our patient population. That is the only way in which we can begin to make an impact on this problem of diabetes and its consequences.

REFERENCES