

Physicians' Corner

The Ever-Expanding Universe

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COSMOLOGY AND DIABETES

I've just finished reading a wonderful book titled, "A Short History of Nearly Everything."¹ It's an engaging walk through science and theories relating to our universe, from "the very beginning" to the current time. Although I'm certainly no cosmologist, I admit that I am fascinated with the fabulous theories relating to the origin of the universe and its magnitude. Maybe I just like things to remain stable and unchanging, but the concept of a rapidly expanding, massive universe is hard for me to grasp and equally hard for me to ignore.

Over a year ago, Nathan published a commentary in *The New England Journal of Medicine* titled, "Finding New Treatments for Diabetes—How Many, How Fast...How Good?"² In this thought-provoking piece he suggested that, "in the beginning," we had few choices for treating diabetes—primarily insulin, secretagogues, and, in some locations, metformin. From this small collection of tools, we have experienced in recent years a suddenly expanding universe of therapies for diabetes: 9 classes of drugs, including over 30 different products.²

Choices are usually good, but evidence has shown that this galaxy of choices didn't translate into immediate improvements in diabetes care.³ Nathan indicated that perhaps we are better off relying on tried and true medications that have been around for 50 years—ie, insulin, secretagogues, and metformin.² He didn't seem to embrace the rapidly expanding universe of diabetic therapies any more than I naturally embrace the complexity of our rapidly expanding physical universe.

The consensus algorithm for type 2 diabetes mellitus (DM) developed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), first published in 2006,⁴ has provided a sensible framework for initiating and advancing treatment. It cut through the expanse of therapies and concentrated on getting the job done—reducing glycosylated hemoglobin (A1C) levels to <7.0%, primarily using a small universe of therapies: metformin, sulfonylureas, basal insulin, and, perhaps, thiazolidinediones (TZDs). In other words, this algorithm looked at the "big bang" of new diabetic therapies in the prior decade and shrunk that universe down to a few agents aimed at a single target—lowering the A1C to <7.0%. In an uncanny way, this sequence mirrors the theories of many cosmologists that our universe started small, expanded rapidly, and will become small again (pulsatile expansion and contraction).⁵ Certainly, the simplicity and straightforwardness of the ADA/EASD algorithm offers a great deal of utility and appeal. In my conversations with colleagues, I'm impressed that this "small universe" of choices seems to have been widely accepted by primary care practitioners.

And then, BANG! At the ADA's 68th Scientific Sessions in San Francisco, California, DeFronzo challenged the notion of addressing just the A1C in a simple, stepwise fashion.⁶ He urged consideration of some therapies that are quite new and suggested addressing underlying physiology as the way to lower A1C. He challenged the newly contracted notion of a simplistic treatment paradigm (the ADA/EASD consensus algorithm) and introduced new concepts, new targets, and new treatments. In an instant, the universe of treatments for type 2 DM was suddenly expanding again to include newer agents that enhance the effects of the incretin system. Just as the sheer vastness of our physical universe lures individuals to become students of the cosmology process, the expanding universe of diabetes care should pull all practitioners into more serious study of this fascinating world. Quite frankly, I find this subject to be fun and fascinating reading.

GOAL-FOCUSED VERSUS PHYSIOLOGY-FOCUSED

One concern expressed in DeFronzo's lecture was that the ADA/EASD algorithm is a stepwise approach to lowering the A1C solely, rather than addressing underlying pathophysiologic disturbances. Clearly, it is hard to argue with this concern. Recent analyses of data from the Action to Control Cardiovascular Risk in Diabetes trial certainly suggest that cardiovascular outcomes are tied to more complex processes than simply forcing the A1C down to a low number.⁷ For some time, there has been a sense of frustration that our best efforts to control A1C levels aren't having more of an effect on the devastating macrovascular complications of type 2 DM.⁸ My son, Mark, has often reminded me not to "look at the world through a paper towel tube," and perhaps simply lowering A1C is just that. By focusing on this one isolated

detail and blinding ourselves to the surrounding milieu of physiologic derangements, we may be missing a wealth of benefit that could come from a broader approach aimed at addressing these basic physiologic problems.

THE OMINOUS OCTET

What are these basic physiologic defects? DeFronzo somewhat poetically referred to them as the “ominous octet” (Table)—8 pathophysiologic derangements that contribute to the development of type 2 DM.⁶ At the heart of the matter, always, is the failure of β -cells in type 2 DM. Most readers are familiar with that fact, but what causes the β -cells to fail?

Several members of this ominous octet are well known. First on our list, the process of insulin resistance leads to decreased glucose uptake by muscle cells in the periphery, causing hyperglycemia that is toxic to β -cells.

Second on this list is impaired insulin secretion. Generally, by the time type 2 DM is diagnosed, as much as 80% of insulin secretion by β -cells has been lost.⁹ This loss of β -cell function is a core defect in type 2 DM. Autopsy studies have shown that $\geq 50\%$ of β -cell mass is gone by the time of diagnosis.¹⁰ Factors such as age, genetics (eg, transcription factor TCF7L2), glucose and free fatty acid (FFA) toxicity, abnormal deposition of amyloid-like deposits in the pancreas, impaired incretin activity, and the higher insulin production demands created by insulin resistance all lead to failure of β -cells.⁶

Another familiar problem in type 2 DM is enhanced hepatic production of glucose. Most of the elevation in fasting blood glucose levels comes from overnight excessive hepatic glucose production.¹¹ However, other factors are at work, contributing to the failure of β -cells and the rising incidence of type 2 DM.

Perhaps considered less often is the fact that resistance to the effects of insulin leads to increased lipolysis. This creates an environment of increased FFA toxicity that impairs insulin secretion by β -cells. In susceptible individuals, even 48 hours of exposure to such an environment will suppress both first- and second-phase insulin secretion.¹²

We know that the physiologic problems of type 2 DM extend beyond β -cells. Pancreatic α -cells overproduce glucagon in type 2 DM.⁶ This, in turn, leads to pathologic increases in glucose that contribute to worsened β -cell function. Increases in glucose to as little as 113 mg/dL have been shown to impair glucose-mediated insulin secretion by β -cells.¹³

The kidney also contributes to the pathophysiology of type 2 DM. The maximal renal tubular resorption capacity for glucose is increased in these patients.¹⁴ What does this mean? The kidney avidly holds on to what needs to be dumped—glucose. The net effect is that this contributes to the toxicity problems of excessive glucose.

Another unsuspected player in this octet is the brain. An area within the hypothalamic region behaves abnormally in response to glucose ingestion.¹⁵ This leads to overeating, obesity, and the accompanying worsening insulin resistance.

To round out the octet, we must consider alterations of the incretin effect that are typical in type 2 DM. Glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), the 2 most prominent incretins in humans,¹⁶ have been shown to have a significant role in insulin secretion in response to meals.¹⁷ GLP-1 clearly enhances first-phase insulin secretion in a glucose-mediated fashion.¹⁷ In type 2 DM, β -cells are resistant to the insulin-stimulating effect of GIP.¹⁸ Also, patients with type 2 DM underproduce GLP-1 in response to oral glucose challenge (ie, meals).¹⁷ Because this incretin effect is diminished in type 2 DM, insulin secretion suffers.¹⁷ Studies suggest that incretin action slows the loss of β -cell function.¹⁹ Incretins also have an effect on the brain, favorably impacting the satiety center.¹⁷ Furthermore, incretins suppress glucagon, which is produced in overabundance in type 2 DM.⁶ It is no wonder that lack of incretin effect in type 2 DM is a significant contributor to the pathophysiologic problems that worsen diabetes.

THE BEGINNING OF A NEW ALGORITHM?

In making his case for a new, broader treatment paradigm, DeFronzo touted addressing physiologic areas of disturbance rather than just stepwise reduction of A1C.⁶ He suggested that early use of basal insulin for type 2 DM is not an option that is likely to be chosen by most primary care providers, or even endocrinologists. I'm not sure my experience leads me to this same conclusion, but the reasons given were that insulin therapy is time consuming to initiate and that lowering the A1C to $< 7.0\%$ is difficult using insulin without triggering hypoglycemia or weight gain (2 undesirable complications of therapy).⁶ He suggested that these issues tend to push practitioners toward oral therapies such as metformin plus sulfonylurea, a combination that is likely to induce hypoglycemia and weight gain. In addition, this particular oral approach may hasten β -cell failure, causing most patients to need insulin quickly.⁶

Table. The ominous octet.⁶

1. Insulin resistance
2. Impaired insulin secretion
3. Hepatic glucose overproduction
4. Increased lipolysis
5. Overproduction of glucagon (by pancreatic α -cells)
6. Renal hyperresorption of glucose
7. Central nervous system (brain)
8. Lack of incretin effect

What does DeFronzo suggest we do? He would start all patients at the time of diagnosis of type 2 DM on lifestyle changes plus metformin, pioglitazone, and exenatide.⁶ This approach is designed to address the problems of hepatic glucose overproduction (metformin + TZD), insulin resistance and peripheral glucose disposal (TZD + metformin), tendency toward lipolysis and FFA toxicity (TZD), decline of β -cell function (TZD + exenatide), excessive glucagon secretion by α -cells (exenatide), and weight gain (exenatide). This combination-therapy approach should address these problems without increasing the likelihood of hypoglycemia or weight gain. DeFronzo suggested that a target A1C of <6.0% could be achieved by such an approach. At first I wondered why so low, and then it sunk in: If basic physiology is somewhat restored, one would expect the A1C to return to normal (<6.0%). This concept clearly offers a new initial therapeutic pathway.

Does this mean that diabetes care just got harder? Not at all! In fact, what could be easier than addressing core physiologic defects one by one with tools designed to specifically address those needs? Does this mean that insulin therapy will vanish? Certainly not! Insulin therapy remains the primary treatment for type 1 DM; there is no substitute. In type 2 DM, lack of sufficient basal insulin secretion remains a fundamental defect and will have to be replaced in many patients.²⁰ The algorithm proposed by DeFronzo⁶ is aimed primarily at early care, when β -cell preservation will be most beneficial and insulin secretory deficits least critical.

Will this new method work? DeFronzo provided compelling evidence that it should. However, it is untested in widespread clinical practice, so no one really knows about the day-in/day-out clinical utility of this type of scheme. From a practical standpoint, the cost of such a triple-therapy regimen certainly poses some financial challenges compared with the ADA/EASD algorithm, which focuses on an efficient and cost-effective treatment strategy. However, the ADA has allocated research funds for a clinical trial of DeFronzo's triple-therapy concept, which should eventually provide comparative data to evaluate the relative utility of this new approach.

COMPLEX OR COMPLICATED?

What are the implications of this novel proposal for providers of diabetes care? First and foremost, we have an obligation to understand what is being proposed here, for it is really a review of pertinent diabetes pathophysiology and how it relates to treatment strategy. We need to thoroughly understand the therapeutic role of metformin, TZDs, incretins, and insulin. I devoted my commentary to this subject, in part, to challenge readers to re-examine their knowledge of physiology and pharmacology and consider what can be done to best benefit our type 2 DM patients.

As I said, I like things to be simple and unchanging; but diabetes is complex and continues to change as our knowledge expands. As DeFronzo stated,⁶ type 2 DM derives from complex interactions of a number of factors, circumstances, and hormones. The principle for patient care that I've used for a number of years still stands: "Give them what they are missing." I used to believe that this meant basal insulin after metformin. DeFronzo, however, has introduced us formally to the fact that "what's missing" touches on a variety of physiologic areas, many of which we can treat. Therapeutic considerations touch on everything from β -cell health and insulin, to gut cells and GLP-1 and GIP, to addressing lipid needs, to controlling excessive glucagon production, to improving insulin sensitization, to controlling adiposity and avoiding hypoglycemia. Admittedly, this is complex, but it is not complicated.

CONCLUSIONS

Finally, what does this novel strategy mean for a journal titled *Insulin*? Does the concept proposed by DeFronzo impact the utility of a publication so titled? Just as insulin remains the core issue in diabetes, *Insulin* should, and will, remain a central, knowledge-based resource for diabetes practitioners, covering all modalities of diabetes care. *Insulin* is committed to continually providing cutting-edge information to the community of health care professionals serving patients with diabetes.

Let me encourage you to consider all the possibilities for your diabetic patients: new concepts of pathophysiology, new treatments, and new management strategies. Take the time to develop a working understanding of the major therapeutic agents now available and how they fit into a proven, effective treatment strategy that you are comfortable using. Type 2 DM is not only a rapidly expanding epidemic, but also an area of rapidly expanding knowledge and treatment options. Above all, be assured that your best efforts can change your patients' lives. Nowhere, to my knowledge, does conscientious, preventive, goal-oriented care pay off better than in well-managed type 2 DM patients.²¹

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