EDITORIAL

Ever-Increasing Insulin-Requiring Patients Globally

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PREVALENCE OF DIABETES continues to increase worldwide and now involves about half a billion people globally.^{1–3} The majority of this increase involves patients diagnosed with type 2 diabetes (T2D).³ Unfortunately, even today about 40%–50% of patients are undiagnosed.⁴ Recent data from the Centers for Disease Control and Prevention (CDC) show a slight increase in the prevalence of diabetes in the United States to be about 9% with about 84 million people with prediabetes.⁴ Type 1 diabetes (T1D) is also increasing worldwide at a rate of ~3%–5% annually.^{5–8} This increase in patients with T1D involves not only the Western world but also emerging economies.³ Since there is a significant delay in diagnosing and initiating effective treatment for T2D, there is an ever-increasing number of patients requiring insulin. The total number of insulin-requiring patients today is expected to be around 150–200 million (by all means this is an underestimate). Thirty millions of these are patients with T1D⁶ of which 1.5–3 million are in the United States, a number that is likely to triple in the next three decades.^{8,9} About 10%–20% of patients with T2D are misdiagnosed (antibody positive), which makes about 40–80 million patients requiring insulin.^{10,11} Another 20%–30% of patients with T2D will require insulin therapy during the course of T2D due to significant beta cell loss over time and delays in diagnosing and initiating necessary treatments on time.^{10,12} Thus, cumulatively we have about 150–200 million people requiring insulin therapy worldwide.

The majority of patients with diabetes (T1D and T2D) do not achieve target A1cs (<7% or 6.5%) as recommended by the American Association of Clinical Endocrinologists (AACE), American Diabetes Association (ADA), European Association of Study for Diabetes (EASD), and other local/national diabetes organizations.^{13–15} It is also unfortunate that about two-third of the patients with T1D are overweight or obese,¹⁶ and, of course, the majority of patients with T2D are either overweight or obese.¹ Patients, especially those with T1D, also face morbidity and mortality risks from severe hypoglycemia and diabetic ketoacidosis.^{17,18}

Recent guidelines by American College of Physicians published in *Annals of Internal Medicine*¹⁹ were ill-conceived

and make no sense in recommending A1c goals to be 8% from 7% as recommended by global diabetes organizations. It adds confusion to a general practitioner for diabetes care.

Because of this tremendous increase in the number of patients, especially those requiring insulin therapy, the cost of healthcare related to diabetes and its complications is ever increasing.^{4,20} Global economic burden related to diabetes is expected to increase to 2.5 trillions of dollars annually by 2030.²¹ It is estimated that global costs for all insulins alone have escalated to about 30 billion U.S. dollars,²² which is likely to continually increase.^{23,24} Part of this increase in the cost of all insulins is a disproportionate increase in costs (sometimes it is 5–10 times higher) in the United States.^{25–29}

Total mortality rate in T1D and T2D is significantly higher than that in nondiabetic volunteers.^{4,29} Fortunately, the rate of almost all long-term complications of diabetes has been decreasing in the past two decades^{4,30}; however, the total number of patients with those complications has been increasing because of the global increase in the prevalence of diabetes.³⁰ The decrease in the rate of complications has been largely attributed to small but significant improvements in glycosylated hemoglobin, availability of several new therapies (new classes of drugs such as new longer acting and rapid-acting insulin analogues, Dipeptidyl peptidase IV (DPP IV) inhibitors, newer once a day or weekly Glucagon-like polypeptide-1 (GLP-1) analogues, and Sodium-glucose transport protein 2 (SGLT-2) inhibitors) for managing diabetes effectively.^{31–34} In addition, the availability of several insulin analogues (insulin lispro, aspart, glulisine, Flasp, glargine, detemir, U300 glargine, and U100 and U200 degludec)^{35–43} allows effective intensive insulin therapy in insulin-requiring patients with no further increase in hypoglycemia despite improving glucose control, (which has usually been the hurdle to intensify insulin therapy).^{35,36,39} Last, but not least, the availability of new technologies such as continuous glucose monitors (CGMs), insulin pumps, and hybrid closed-loop systems has further advanced diabetes management without increase in hypoglycemia while achieving target A1cs.^{44–47}

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It is important to keep in mind that new technologies may not be the answer for the majority of the insulin-requiring patients because of increasing cost and difficulties in implementing these technologies in clinical practice.⁴⁸ Currently, <1% of insulin-requiring patients are using either insulin pumps alone and/or CGMs or hybrid closed-loop systems.^{11,49,50} The majority of patients using pumps are in the United States or in Western Europe. However, the need for insulin-requiring patients is far higher in the rest of the world,⁵¹ where cost is a major issue in implementing CGM or pump therapy.²⁶ Thus, the majority of the insulin-requiring patients would benefit from an alternative platform that uses insulin-delivery pens that have memory functions (in development) in them, along with data being transmitted to a mobile device on an app. The patient's CGM/self-monitoring of blood glucose (SMBG) data would also transmit to the same app and thus advise them on day-to-day diabetes management.

In this supplement, Welsh focuses on the role of CGM in insulin-requiring patients, especially in T2D.⁵² They emphasize that the use of CGMs effectively improves glucose control without increasing hypoglycemia. In fact, it is important to note that the majority of the recent studies they included show that a large number of patients continue to use CGMs. In part, this may be due to improvement (accuracy) in technologies such that the majority of the currently available CGMs have an Mean Absolute Relative Difference of <10%.⁵² In his review, Bob Ratner underscores the importance of hypoglycemia in diabetes care and how, in the near future, some of the newer insulin analogues might even get a favorable label change by the Food and Drug Administration (FDA).⁵³

Helena Rodbard and Thomas Danne highlight the role of new GLP analogues, especially the those that can be used once a week (dulaglutide and semaglutide), and the new SGLT1 and SGLT2 inhibitors in diabetes care, respectively.^{54,55} Thomas Danne also highlights the possible adjunctive use of SGLT inhibitors in T1D (not yet approved by the FDA or European Medicines Agency (EMA)), in addition to their role in T2D.⁵⁵ H. Kaan Akturk highlights the ways to improve postprandial glucose, especially using technosphere insulin (Afrezza, Mannkind, Inc., CA) due to the rapid onset of action (recent FDA label change).⁵⁶

Weaver and Hirsch summarize the results of small studies related to different artificial pancreas systems showing no increase in hypoglycemia or ketoacidosis while emphasizing we are far from a system that replicates islet cell function in a fully automated multihormonal system.⁵⁷

Lal et al. present emerging technologies including novel insulin, insulin delivery devices, glucose monitoring technology, and decision support systems that may be applicable for the majority of the insulin-requiring patients.⁵⁸ Although SGLT1 and 2 inhibitors sound promising for patients with T1D, the proper mitigation plan for reducing the risk of diabetic ketoacidosis (DKA) is needed.⁵⁵

Messer et al. discuss skin issues with the chronic use of insulin-delivery devices and CGMs.⁵⁹ In addition to addressing these concerns, they offer prophylactic and alternative ways to reduce skin issues with these devices.⁵⁹ David Rodbard emphasizes differences in glucose variability (GV) parameters in T1D and T2D, and the difficulties in implementing GV in clinical practice.⁶⁰ He also gives us a view into the future for new indices for possible GV.⁶⁰ It is possible that in the near future, we will start quantifying glucose

control not only by HbA1c but also by time-in-range, which may become a more important marker for day-to-day diabetes management.⁶¹ However, A1c measurements may be more important for population health and determining long-term complications of diabetes. Even though GV has never been proven to be an independent risk factor for long-term complications of diabetes, both patients and providers strongly believe that if GV can be effectively reduced, the quality of patients' life who require insulin therapy significantly improves. Tim Bailey, while stressing emerging technologies in diabetes care, also emphasize realistic expectations regarding artificial pancreas systems and the challenges in implementing the new technologies in daily clinical practice.⁶²

I hope that you will enjoy and learn by reading this supplement. I sincerely want to thank all the authors who contributed in a timely manner to the supplement and the sponsors for providing an unrestricted educational grant to make this possible. We collectively need to have a clear message for the providers even though we might disagree. I strongly believe that the future is bright for patients with diabetes as they will continue to live longer with all the advances in the field. Unfortunately, the price of living longer that nobody talks about is the burden to the society that needs to be dealt appropriately.

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