MAYO CLINIC

COMMENTARY

Diabetes Mellitus: A Perspective on the Post-Insulin Era

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The year 2021 will mark 100 years since the discovery of insulin. The discovery of insulin and the start of insulin therapy represent a marvelous multidisciplinary team effort that profoundly transformed the lives of people with diabetes mellitus (DM). Insulin treatment substantially extended the very short life span and health span of patients with type 1 diabetes (T1D). It was further shown that insulin action is lower (insulin resistance [IR]) in obesity and that IR in combination with insufficient insulin secretion is the underpinning of type 2 diabetes (T2D) stimulated momentous research on ways to enhance insulin action. The ramification of the discovery of insulin and its actions in different tissues stimulated not only technological advances in devices to monitor glucose and deliver insulin, but also novel oral and injectable therapies to treat T2D. Today we have unprecedented options in treating all patients with DM that substantially reduce the burden of debilitating diabetic complications. This is an appropriate time and context for an overview of the transformative impact of insulin discovery in treating a widely prevalent global disease that causes substantial morbidity and mortality around the world. In the next 18 months, *Mayo Clinic Proceedings* will publish insightful reviews offering an opportunity for readers to look back and also look forward to the future of treatment, prevention, and potential cure of DM.

DEVELOPMENT OF INSULIN THERAPEUTICS

Insulin extracts were used initially to treat patients with T1D and a single type of preparation was used and administered multiple times daily.[1] Realization of the need for higher throughput, the preparation of insulin extracts from porcine and beef pancreas, crystallization of insulin, and soluble insulin were developed by pharmaceutical organizations. After the early years of regular insulin therapy with each meal, the imperative need for a longer-acting insulin to achieve better glucose control in the post-absorptive period and overnight prompted the development of longer-acting insulin preparations. Therefore, the pharmacokinetics of insulin was altered by the presence of other molecules in the solution starting with the development of longer-acting protamine zinc insulin in 1936[2,3] and neutral protamine Hagedorn or isophane insulin (in 1946) and Lente further advanced the goal to better glycemic control. The recognition that these and subsequent animal (porcine and beef) insulin preparations contained impurities that result in lipoatrophy and immunogenicity led to the development of more purified insulin preparations such as monocomponent insulins for clinical practice in the 1970s.[4] Insulin was the first molecule to be manufactured using recombinant insulin technology and was approved for human use in 1982.[5,6] More recently, further engineering of the insulin molecule has resulted in the development of better meal time and basal insulin with the preparations referred to as insulin analogs.[7] The ideal insulin therapy should achieve relatively stable glycemic pattern and body composition mimicking normal physiology while inducing no hypoglycemia and weight gain. Thus, analog insulin preparations continue to advance with the goal of acting rapidly after meal ingestion, extending the duration of basal insulin and resulting in stable biologic effects.

THE ROAD TO CLOSED LOOP THERAPY OR THE ARTIFICIAL PANCREAS

Monitoring glucose is a simple way to assess insulin action, and measurements of blood glucose several times per day are used routinely to guide insulin therapy. Basal-bolus insulin therapy, also called complex insulin therapy, using multiple daily insulin injections and continuous subcutaneous insulin infusion or conventional insulin therapy consisting of one to two insulin injections were tested in smaller studies followed by the landmark Diabetes Control and Complications trial[8] which demonstrated the efficacy of improved glycemic control achieved with complex insulin therapy in preventing or delaying the progression of microvascular complications.

Hypoglycemia experienced by patients increased with complex insulin therapy and emphasized the need to monitor glucose continually. Continuous glucose monitoring (CGM) in ambulatory settings started in 1998, and several more advanced generations of these devices have been developed since then. Control algorithms to modify insulin delivery based on the glucose signal from CGM have been developed, tested, and refined in the past 15 years.[9] Automated insulin delivery systems starting with low glucose insulin suspend systems have been approved since September 2013 with a hybrid closed loop (HCL) insulin system approved since September 2016 and in clinical practice since March 2017.[10] More systems have been tested and are expected to become available over the next few years.[11] With the maturation of CGM, glucose control outcomes based on metrics developed for CGM are being reported and time in optimal range (TIR) of 70 to 180 mg/dL and time less than 70 mg/dL have emerged as key outcomes in clinical trials and an important outcome in clinical practice.[12,13] HCL achieves greater than 70% TIR and less than 4% time less than 70 mg/dL compared with about 60% TIR and greater than 4% time less than 70 mg/dL in patients on sensor-augmented insulin pump or multiple daily insulin or continuous subcutaneous insulin infusion therapy. However, time greater than 180 mg/dL continues to be a challenge everyday, even with HCL, occurring mostly in the postprandial period, and hypoglycemia continues to be experienced by patients with T1D serving as a barrier to regular health-promoting exercise. This has stimulated the development of non-glucose signals such as physical activity measurement for incorporation into automated insulin delivery and also the development of dual hormone insulin and glucagon artificial pancreas to prevent hypoglycemia and promote exercise.

TRANSPLANTATION THERAPY FOR DIABETES

Solid organ transplantation has transformed management of end-stage renal disease (ESRD) in diabetes. Kidney transplantation developed in the 1950s changed the natural history of patients with both type 1 and type 2 DM with ESRD. Subsequently, technical aspects of pancreas transplantation were addressed by the 1980s and simultaneous kidney-pancreas transplantation has been performed mainly for patients who have T1D with ESRD since the 1980s and is an extremely transformational therapy for such patients. The importance of kidney transplantation being performed before initiating dialysis has been recognized with an increasing number of pre-emptive transplantations.[14] More forms of beta cell transplantation have been pursued for patients with high glucose variability and acceptable kidney function. Pancreas transplantation alone has been available for such patients over the past 30 years, and islet transplantation alone (ITA) has been evaluated in prospective studies. However, ITA has many factors limiting application in the United States; thus, a pathway to clinical practice application of the therapy remains to be established as a standard of care treatment.[15] ITA is being pursued in certain regions of the world with Canada and France providing the best such examples to date. A few centers in the world continue to pursue islet xenotransplantation with wild-type pigs or genetically manipulated pigs serving as organ donors. Stem cell—based islet products have been

Mayo Clin Proc. ■ January 2020;95(1):15-21 ■ https://doi.org/10.1016/j.mayocp.2019.11.016
www.mayoclinicproceedings.org

pursued. The ViaCyte studies use an encapsulated pancreatic endocrine precursor cell product and phase 1/2 trials have not shown function of this product in patients with T1D in good health. A second-generation product with encapsulation but blood vessel formation from the embryonic stem cell product necessitates immunosuppressant use and is being pursued at multiple US and Canadian sites at present in patients with T1D and hypoglycemia unawareness.[16] The development of induced pluripotent stem cell (iPSC) technology raised hopes of autologous stem cell—based therapy, but this technology is labor intensive, time consuming, inefficient, and expensive at this time. Thus, the first iPSC product is likely to be derived from a single iPSC line requiring encapsulation for human studies.[17]

IMPACT OF THERAPY ON COMPLICATIONS ASSOCIATED WITH T1D

The Diabetes Control and Complications Trial (DCCT) was designed to evaluate the impact of tight glucose control on retinopathy. The retinopathy endpoint was a 2-step progression based on fundus photographs. The DCCT showed that tight glucose control decreased the progression of retinopathy but also increased the risk of mild and severe hypoglycemia. A small subset of patients experienced much more severe hypoglycemia compared with others in the experimental cohort. Laser photocoagulation to treat proliferative retinopathy decreased the risk of severe vision loss but also increased the risk of isolated defects in the field of vision. The development of angiogenesis inhibitors has transformed management of diabetic retinopathy. Subjects enrolled in the DCCT were offered enrollment in the Epidemiology of Diabetes Interventions and Complications study and more than 80% are being followed. Tight glucose control during the DCCT has been shown to decrease the risk of target organ complications including microvascular complications and major acute cardiovascular events (MACE).

INSULIN RESISTANCE

Harold Himsworth proposed a classification of diabetes into two types[3]: insulin-sensitive and insulin-resistant. More sophisticated techniques to quantify insulin action were developed subsequently and IR was shown in patients with T2D.[18] Extensive work has been performed to understand mechanisms of IR at the molecular level and to develop therapies that decrease IR, improve glycemic control, and impact target organ damage favorably.[19] It is well known that both caloric restriction and exercise training (aerobic and resistance) significantly improve insulin sensitivity that not only improves glycemic control but also has a positive impact in preventing T2D and its complications. Results of gastric bypass surgery that significantly improves insulin action clearly supports the notion that in most cases T2D and related metabolic problems can be ameliorated with significant intentional weight loss. It is likely that mitigation of IR in multiple organs by interventions is a logical approach in preventing T2D and its complications.

PHARMACOTHERAPY FOR T2D AND IMPACT ON TARGET ORGAN COMPLICATIONS

In the 1970s, therapeutic trials were started to show the impact on diabetes-associated complications. The UK Prospective Diabetes Study included testing of blood pressure and glucose control and showed an impact on microvascular complications. There was no significant impact on macrovascular complications with glycemic control, but blood pressure control was shown to play a critical role in improving morbidity. The results of the Action to Control Cardiovascular Risk in Diabetes trial, which unexpectedly increased mortality in the intensive therapy group, led to a US Food and Drug Administration (FDA) recommendation that trials of new antihyerglycemic agents include assessment of cardiovascular safety.[20] The past 15 years have seen the testing and publication of results from trials designed to test the safety of a therapeutic approach including

impact on cardiovascular and renal endpoints. Currently, several classes of agents have been approved for diabetes management, and certain classes include FDA labels for impact on diabetes-associated complications. Guidelines to achieve better glucose control and simultaneously decrease target organ complications have been published and now undergo periodic updating.[21] A detailed evaluation of the pharmacologic agents to treat T2D is beyond the scope of the current commentary. New classes of drugs, particularly GLP1 Receptor agonists (GLP-1 RAs) and SGLT2 inhibitors, have been shown to impact target organ complications in T2D

Recognition of the incretin effect led to the development of GLP-1 RAs that use this effect to improve glycemic control and decrease weight in overweight and obese patients and T2D. Multiple GLP-1 RA and SGLT2 inhibitors have been tested in large multinational trials. Some GLP-1 RAs decrease the risk of MACE. Agents which act on the GLP1 system may belong to the exendin category or the GLP1 category.[22] The latter may or may not be associated with albumin to prolong action. Currently, it appears that GLP1 agonists decrease the risk of MACE, with the main impact on cardiovascular events, and they may have some impact on renal outcomes, an effect that is not seen with exendin category agents. SGLT2 inhibitors decrease the risk of MACE, heart failure, and renal endpoints.[23]

Somewhat Unexpected Adverse Events With Antihyperglycemic Therapies

There are also less-expected adverse events that have emerged from large clinical trials in both T1D and T2D. Rapid improvement in glucose control has been shown in the DCCT and the Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN6) to be associated with an increased risk of macular edema. An improvement in hemoglobin (A1c) of greater than 2% within 3 months has been identified as a risk factor for macular edema.[24] A1c reduction of greater than 3% to 5% in 3 months has also been shown to be associated with neuropathy in cohort studies, and based on extensive clinical practice, this seems to be real.[25] Fournier gangrene, a severe cellulitis affecting the perineum, has been reported with SGLT2 inhibitors in case reports and adverse event reporting to the FDA. The a priori identification of patients at risk for these adverse events is important for future clinical practice and research. With the ability to improve glucose control and impact target organ complications, more thought must be directed towards improving A1c without increasing adverse events associated with rapid improvement. Research is needed to study whether clinical phenotype, pharmacogenomics, or environmental factors can predict the complications related to effective pharmacotherapeutic agents.

These large multinational trials have also clarified concerns raised about possible adverse events associated with these agents. The risk of pancreatitis and pancreatic neoplasia with GLP-1 agonists has been studied extensively. Although the risk is not increased with these agents, there is agreement that these agents are best not prescribed in individuals with past history of pancreatitis and pancreas neoplasia. Increased risk of lower extremity amputations associated with canagliflozin was a concern with early reports but this has since been clarified as not an issue.[21]

Need to Consider Normal Physiologic Insulin Milieu in Diabetic Patients

Insulin treatment by peripheral insulin administration results in alteration of normal insulin milieu. In people without diabetes, more than 50% of the insulin secreted from the pancreas is extracted by the liver, causing a liver:periphery ratio of insulin of 2:1. The potential impact of this altered insulin concentration remains to be determined. For example, evidence in preclinical studies suggests that direct administration of insulin to portal vein versus via peripherally is associated with less decline in energy expenditure,[26] potentially explaining weight gain on insulin treatment. High insulin has also

Mayo Clin Proc. ■ January 2020;95(1):15-21 ■ https://doi.org/10.1016/j.mayocp.2019.11.016
www.mayoclinicproceedings.org

been shown to prevent the degradation of proteome, and maintaining proteostasis by degrading irreversibly damaged protein and replacing it with de novo synthesized protein is important for maintaining all cellular functions.[27] It remains to be determined whether delivery of insulin via the portal route will have a beneficial effect over peripheral insulin delivery.

Diabetes and Dementia

There is increasing realization that diabetic patients in general have substantially higher prevalence of Alzheimer disease and other dementias. Although insulin action is not necessary for glucose metabolism in the brain, there are specific areas of the brain with an abundance of insulin receptors.[28] Preclinical studies indicate that IR adversely affects energetics and increases oxidative stress of brain areas involved in memory and cognition[29] that could contribute pathologies that adversely affect cognition. Studies performed during an insulin-deficient state suggest the potential role of ketones and lactate in ameliorating oxidative stress,[30] but this protective effect does not occur when insulin levels are high. The respective contributions of vascular lesions, hypoglycemia, and altered energetics and oxidative stress to the pathogenesis of dementia in diabetes remain to be fully understood. Greater understanding of these questions could potentially result in the development of therapeutic approaches to prevent of the high incidence of dementia in patients with DM.

PERSONALIZED MEDICINE (PRECISION MEDICINE) FOR DIABETES

Although personalization of therapy is part of clinical encounters in all fields of medicine including DM, the quest to improve this especially using genetic information and other high throughput assays continues. An increasing number of monogenic disorders associated with diabetes have been described and may involve defects in genes associated with glucose metabolism referred to as maturity-onset diabetes of the young (MODY) genes or those associated with lipid metabolism that result in lipodystrophy and insulin resistant diabetes.[31] Establishing the correct diagnosis of MODY helps to individualize therapy for the disorder. Pharmacogenetic testing to individualize therapy for T2D currently has a small effect size. Predicting what will not work may be an approach with a bigger clinical impact.[31] This is an area of active and exciting research.

IMMUNOTHERAPY FOR DIABETES

The development of various immunosuppressant agents starting in 1950 has led to the testing of such therapies in autoimmune disorders including T1D. However, these studies have shown modest C-peptide preservation when used in T1D early after clinical diagnosis. A recent phase 2 study in high-risk young individuals with normoglycemia has reinvigorated this field and phase 3 trials are currently being conducted to evaluate this approach further.[32] Patients had a 59% decrease in risk of development of clinical T1D. Median follow-up was 745 days and onset of diabetes was delayed by about 2 years. Certain human leukocyte antigen haplotypes and the presence of antibodies to zinc transporter 8 protein show promise as biomarkers that may identify success for such intervention. A phase 3 trial of this approach is currently being conducted.

COST OF INSULIN AND OTHER THERAPIES IN DM

The cost of many medications has increased in the past 2 decades. However, somewhat unexpected and frustrating has been the increase in the cost of insulin, even after expiration of the patent and the availability of generic preparations. This issue appears complex and concern has been expressed by various subspecialty medical organizations. The American Diabetes Association developed a multidisciplinary task force called the Insulin Access and Affordability Working Group to evaluate the extent of this issue and propose solutions. Much work lies ahead to address this important issue if patients are to experience the benefits of clinical evidence generated.[33] Although many novel therapeutic agents to

treat T2D are effective, their cost is a major impediment to their wide use.

CONCLUSION

As the centenary celebration of the discovery of insulin approaches, we have attempted in this commentary to draw attention to key milestones and areas of research in the development of therapy for DM. There is an imperative need to address several gaps in our understanding of diabetes. Although glucose is the seminal biomarker of insulin deficiency and insulin resistance, insulin effect on a multitude of other areas, especially energy metabolism, oxidative stress, fatty acid, and protein metabolism remains to be fully understood. Advances in these areas potentially will have substantial impact in preventing diabetes and its debilitating complications. Over the next 18 months, several of the milestones described will be addressed in insightful, clinically relevant, reviews in *Mayo Clinic Proceedings* by experts in each area.

ACKNOWLEDGMENTS

The authors thank Dr Ravinder Jeet Kaur and Ms Melissa Aakre for their assistance.

Potential Competing Interests: Dr Kudva is supported by NIH Grants UC4 DK108483, R01 DK120358, and R01 DK122603. Dr Nair is supported by R21 AG060139, R01 AG062859, and U24 DK112326.

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