Insulin's Role in Diabetes Management: After 90 Years, Still Considered the Essential "Black Dress"

William T. Cefalu,[1] Julio Rosenstock,[2] Derek LeRoith,[3] and Matthew C. Riddle[4]

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It has been 93 years since Banting and Best extracted insulin in Scottish physiologist J.J.R. Macleod's laboratory and, with the help of their fellow Canadian chemist James B. Collip, used it to successfully treat a cachectic boy, Leonard Thompson, who suffered from life-threatening diabetes. Since that time, insulin therapy has become the mainstay of treatment for patients with type 1 diabetes and a cornerstone therapy for many individuals with type 2 diabetes.

Over the years, many changes in insulin therapy have occurred, including new formulations, new delivery systems, and additional therapeutic tactics. We are on the brink of a new and exciting era with increasingly reliable and easy-to-use continuous glucose monitoring as part of a closed-loop delivery system. This new "artificial pancreas" system, with its carefully modulated insulin (which remains *the* key component), may soon be ready for clinical use. In addition, an impressive array of new oral and injectable agents for type 2 diabetes has been developed over the past 20 years. Many thought that these could replace injected insulin in a therapeutic regimen, or at least delay its use. Yet, the reality is that insulin will always be needed for type 1 diabetes until a cure is found and progressive insulin deficiency is a fundamental defect of type 2 diabetes.

Furthermore, supplementation of endogenous insulin continues to be necessary for large numbers of individuals with type 2 diabetes. Meanwhile, the other classes of therapeutic agents are vying for a strategic position alongside insulin in clinical regimens for type 2 diabetes, and there is an unmet need for adjuvant therapies to mitigate the treatment challenges in type 1 diabetes as well.

To dramatize the continuing role of insulin in the management of diabetes, we propose an analogy from the world of clothing and fashion: Insulin is and will remain the simple "black dress" that will never be out of fashion, can go with almost anything, and remains the basis of one's wardrobe—something we learned from our wives! Just like the "black dress," by simple additions or modifications it can be adapted to nearly all occasions. To illustrate this point, our editorial team is featuring a collection of articles that displays the diversity of and recent innovations in the clinical use of insulin in this issue of *Diabetes Care*. These selected articles touch on the versatility of insulin in general, as well as new concepts regarding older formulations, new formulations, the advantages of using insulin in combination with the newer agents both in type 1 and type 2 diabetes, and new insulin delivery systems.

This issue's review of insulin begins with articles evaluating an old classic, NPH insulin. Whereas this insulin has been used for decades, it might be asked whether anything new about it can possibly be demonstrated. Yet a simple study by Lucidi et al. (1) provided quantitative support for an old clinical observation that has direct relevance to clinical efficacy. The authors described how NPH insulin comes in a two-phase solution, including both soluble and crystalline components that require adequate mixing (resuspension of the crystalline phase) prior to injection to provide consistent results. In this pharmacokinetics/pharmacodynamics study, lack of resuspension profoundly altered the action profiles of human NPH insulin (1). Given the continuing widespread use of NPH throughout the world, either alone or in premixed formulations with rapid insulins, this modest but elegant study reminds us that attending to resuspension of NPH before injection may improve day-to-day glycemic stability.

Another study in this issue also evaluated an older formulation for in-hospital insulin management. In an inpatient setting, Bellido et al. (2) evaluated premixed insulin (30% regular and 70% NPH insulin [Mixtard 30; Novo Nordisk]) as compared with a basal-bolus regimen with insulin glargine once daily (Lantus;

[1]*Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA*
[2]*Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX*
[3]*Division of Endocrinology, Diabetes and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, NY*
[4]*Division of Endocrinology, Diabetes & Clinical Nutrition, Oregon Health & Science University, Portland, OR*

Corresponding author: William T. Cefalu, cefaluwt@pbrc.edu.

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Sanofi) together with rapid-acting insulin glulisine before meals (Apidra; Sanofi). The rationale for the study was that premixed insulin is commonly prescribed for outpatient management of patients with type 2 diabetes, yet the safety and efficacy of premixed insulin versus basal-bolus formulations in a hospital setting had not been previously studied in a randomized controlled fashion. In this prospective open-label trial, the investigators randomly assigned general medicine and surgery patients to a basal-bolus regimen or to premixed insulin twice daily (2). They concluded that inpatient treatment with premixed human insulin resulted in similar glycemic control, but the study had to be prematurely terminated because of significantly more hypoglycemia occurring with the premixed insulin compared with basal-bolus treatment. This outcome is consistent with findings of ambulatory studies, but, as is needed in an era of evidence-based medicine, it provides the scientific basis for health care providers working in hospital settings to choose the proper insulin regimen. Who would have thought we could learn anything new on the use of NPH insulin or at least could confirm in a scientifically rigorous fashion what we knew or suspected after all these years? Fortunately, these investigators have brought us helpful, new, validated information to consider when caring for patients.

Our review of insulin continues with data on the new long-acting insulins. In the search for good glycemic control with less risk of hypoglycemia, there is renewed interest in basal insulins with slightly flatter and longer pharmacological profiles. Home et al. (3) compared the pharmacological profile of insulin glargine 100 units/mL (Gla-100) to insulin glargine 300 units/mL (Gla-300) in an open-label study in subjects with type 1 diabetes. They reported that the change in HbA_{1c} was equivalent in the two treatment groups, with Gla-300 meeting the statistical criterion for noninferiority (3). However, nocturnal confirmed or severe hypoglycemia over the first 8 weeks was lower with Gla-300, as was slightly less weight gain. It was concluded that in long-duration type 1 diabetes, Gla-300 provides similar glucose control to Gla-100, with lower risk of hypoglycemia initially after transfer from other insulins, independent of time of injection.

An important aspect for the study of the long-acting insulins now involves the new "biologics." In this regard, Linnebjerg et al. (4) provided an excellent background and rationale for this topic. They stated that a therapeutic protein molecule ("biologic") is one that is "highly similar to a previously marketed product, with no clinically meaningful difference in safety or efficacy" (4) and is commonly referred to as a "biosimilar," but also stated that a "biosimilar" is essentially a regulatory designation. In their article, they presented the results of three pharmacokinetics/pharmacodynamics studies conducted in healthy subjects as part of the LY2963016 (LY IGlar) development program and stated that these findings contributed evidence to support the approval of the first biosimilar insulin analog in the European Union (September 2014). To provide a critique of this field, two thoughtful commentaries are also published in this issue. In the first commentary, Dr. Home provided an insightful narrative about the approach, value, benefits, and limitations of the clamp technique as required to assess biosimilar insulins (5). In this case, he stated that for the Lilly insulin glargine, when based on other available information (e.g., fasting blood glucose and hypoglycemia), the complete package of clinical data lends credence to Lilly's claim of biosimilarity rather than the clamp data in isolation (5). In the second commentary, Porcellati et al. (6) also agreed that the conclusions reached by the studies of Linnebjerg et al. (4) are "correct in the specific conditions examined in this study," but they felt that "one should be cautious ... when extrapolating to the general population of 'users' of basal insulin." Thus, adaptations and modifications to the metabolic techniques to assess the pharmacokinetics/pharmacodynamics of the biosimilar insulins reflected in properly conducted, randomized, controlled clinical trials will be required as we move forward to adequately evaluate the longer-acting formulations.

Our idea that insulin therapy is like a basic "black dress" includes the concept that both can go well with additional accessories—in the case of insulin, other therapies used in combination. As a case in point, Giorgino et al. (7) reported on the use of oral agents in combination with either basal insulin or a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist competing with insulin glargine for basal glucose control. In a 78-week, open-label study, the authors compared the efficacy and safety of once-weekly dulaglutide with daily basal insulin glargine. Both agents were combined with maximally tolerated doses of metformin and glimepiride in patients with type 2 diabetes. Dulaglutide 1.5 mg, when compared with a relatively low dose of daily insulin glargine used without forced titration, demonstrated greater HbA_{1c} reduction and weight loss, with higher incidence of gastrointestinal adverse events and lower risk of hypoglycemia. In this case, it appears that the newer agent had some advantages, but it should be noted that the decision to limit titration deprived basal insulin of one of its leading attributes: the opportunity to seek the optimally effective dose for each individual. This has been shown in numerous treat-to-target trials that achieved significantly lower HbA_{1c} levels than what was achieved in the study by Giorgino et al. Whereas this study was in subjects with type 2 diabetes and compared the GLP-1 receptor agonist directly to insulin, data are now available on the new approach of combining a GLP-1 receptor agonist with insulin therapy in type 1 diabetes. Frandsen et al. (8) reported a very innovative study of the efficacy and safety of once-daily liraglutide versus placebo as an add-on to insulin treatment in patients with poorly controlled type 1 diabetes. They demonstrated that liraglutide had no significant effect on HbA_{1c}, but it reduced body weight with a slight reduction in insulin requirements. However, with this type of result, one wonders if the reduction in weight and insulin requirements (but without benefits in glucose control and hypoglycemia) would be enough to consider this option for individuals with type 1 diabetes? The possible answer can be inferred from the company's recent announcement of the decision not to pursue the liraglutide indication in type 1 diabetes after having conducted two large randomized controlled trials that have not been reported yet in scientific settings (9).

In a similarly innovative approach to the study of combination regimens with adjuvant therapy in type 1 diabetes, Henry et al. (10) assessed the efficacy

and safety of canagliflozin, a sodium–glucose cotransporter 2 inhibitor, when added to insulin in adults with type 1 diabetes. Strengths of this study include the large number of subjects ($n = 351$) and the fact that the intervention was done in a double-blind fashion. The participants were either using multiple daily insulin injections or continuous subcutaneous insulin infusion to which canagliflozin 100 mg, canagliflozin 300 mg, or placebo was added. Canagliflozin provided significant reductions in HbA_{1c}, body weight, and insulin dose with no increase in hypoglycemia, all very relevant findings for this cohort of patients. However, as reported elsewhere for this class of agents (11,12), increased rates of ketone-related adverse events were noted, including ketoacidosis. A commentary by Rosenstock and Ferrannini (13) published in the September issue of *Diabetes Care* provided insight on the association of ketoacidosis with use of sodium–glucose cotransporter inhibitors. The authors reviewed the mechanisms of action of this class of drugs and the way ketosis can occur and offered suggestions on how to limit the risk and consequences of this effect by early detection and prompt intervention to prevent the development of euglycemic diabetic ketoacidosis.

Finally, we revisit the pulmonary delivery of insulin. The potential for pulmonary delivery of insulin, as an alternative to injection, has been suggested before. Indeed, a formulation was commercially available at one time but was discontinued for commercial and not for safety reasons. In this issue, we present articles evaluating a newer inhaled insulin formulation (Technosphere insulin [TI]) that has a very rapid onset (14,15). In a type 1 diabetes cohort, Bode et al. (14) compared its efficacy and safety with that of insulin aspart in patients with type 1 diabetes in an open-label noninferiority design. They concluded that in patients with type 1 diabetes receiving basal insulin, HbA_{1c} reduction with TI was noninferior to that of aspart, with less hypoglycemia and less weight gain but with increased incidence of dry cough that subsided over time. In an insulin-naïve cohort of people with type 2 diabetes not well controlled with oral agents, Rosenstock et al. (15) investigated the efficacy and safety of prandial TI. TI significantly reduced HbA_{1c} by -0.8% (-9.0 mmol/mol) from a baseline of 8.3% (66.8 mmol/mol) compared with Technosphere inhaled placebo -0.4% (-4.6 mmol/mol). More TI-treated subjects achieved an $HbA_{1c} \leq 7.0\%$ (53.0 mmol/mol) (38% vs. 19%; $P = 0.0005$). The authors concluded that prandial inhaled insulin added to ≥ 1 oral antidiabetes agent is an effective treatment option for patients with inadequately controlled type 2 diabetes who may be reluctant to initiate injectable insulin. The potential clinical relevance of these new findings is addressed in a critique by Leahy (16). He concluded that the ultrafast profile of TI is novel and offers several possibilities. He noted the intensive but easier mealtime insulin coverage with less hypoglycemia and suggested that inhaled insulin may still be a convenience product rather than a substantive advance in insulin therapy. He further offers that TI "is at the forefront of several faster insulins that are in development" (16). Obviously, more studies are needed to better define the role of premeal TI and also its potential to easily control interprandial "glycemic spikes" detected by the increasing use of continuous glucose monitoring. Moreover, several new injectable insulins that are similarly ultrafast acting are in development and may soon be available, and this discussion is very likely to continue.

With this collection of insulin articles in this issue of *Diabetes Care*, our editorial team is once again honored to present a high-level set of studies centered on a theme of ongoing interest. From these studies, it is apparent that insulin has come a long way in over 90 years. Although it has always been the mainstay of type 1 diabetes treatment, we recognize now its effectiveness and safety in type 2 diabetes and continue to learn to use it in new ways. To a great extent, the newer classes of glucose-lowering agents are being studied as "add-on" tactics on a background of insulin rather than as a replacement for insulin in subjects with type 2 diabetes. Thus, we think insulin is and will continue to hold the place of the "black dress" among therapies ... meeting a basic need, never out of fashion, and always adaptable to everyday needs.

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