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EDITORIAL

Using Insulin in Type 2 Diabetes: In Need of a Renaissance?

David Kerr, M.D., and Tolulope Olateju, M.B., B.S., MRCP

Introduction

At the time of discovery in 1921, insulin was aptly described as a "force of magical activity," as the subsequent impact on the lives of people with diabetes has been nothing short of miraculous.[1] Nowadays, the usual approach to managing adults and children with type 1 diabetes is early introduction of multiple daily injections (MDIs) of insulin or use of continuous subcutaneous insulin infusion (insulin pump therapy) as part of a package of "intensive" care.[2] Based on experiences from the Diabetes Control and Complications Trial, it is generally accepted that intensive insulin therapy requires patients to perform regular self-monitoring of blood glucose (SMBG) levels and make adjustments of their mealtime insulin doses based on the carbohydrate content of meals ("carb counting"), with appropriate corrections in the dose for the prevailing and target blood glucose levels, with the aim of tight glycemic control almost immediately from diagnosis.[3]

In contrast, the current approach to pharmacologic therapy in type 2 diabetes is one of escalation as glycemic targets are not met.[4] There are now potentially multiple combinations and permutations of therapies for this type of diabetes, although the impact of combination therapy is rarely assessed in randomized-controlled clinical trials.[5] In reality, for patients with type 2 diabetes, the greatest risk is the development of premature cardiovascular disease rather than microvascular complications.[6] Evidence has suggested that intensified glucose lowering (which is not necessarily the same as intensive insulin therapy) is less effective in reducing the risk of premature cardiovascular disease than lowering blood pressure or cholesterol and that the impact on diabetes-related complications diminishes with age and life expectancy. In particular, use of insulin in type 2 diabetes is associated with important acute complications such as hypoglycemia and weight gain, and there has been debate about the role of insulin in the areas of cancer and dementia promotion.[7] There are also controversies related to the cost–benefit equation for newer long-acting insulin analogs compared with older types of insulin preparation.[8] With the availability of glucagon-like peptide-1-type therapies, these appear to have displaced insulin as the first-line injectable, at least where obesity is a coexistent condition.[9] Therefore, in the hierarchy of therapies for type 2 diabetes, insulin more and more is perceived as a "last resort."

Where insulin is initiated in type 2 diabetes, it is usually as a once-daily dose of basal insulin rather than offering MDI therapy.[10] In clinical trials, insulin initiation in type 2 diabetes using once-daily basal insulin appears to have the same impact on hemoglobin A1c (HbA1c) levels and weight, irrespective of the basal insulin used (**Figure 1**).

Author Affiliation: Bournemouth Diabetes and Endocrine Centre, Royal Bournemouth Hospital NHS Foundation Trust, Bournemouth, Dorset, United Kingdom

Abbreviations: ((HbA1c) hemoglobin A1c, (MDI) multiple daily injection, (SMBG) self-monitoring of blood glucose

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Corresponding Author: Tolu Olateju, M.B., B.S., MRCP, Bournemouth Diabetes and Endocrine Centre, Royal Bournemouth Hospital NHS Foundation Trust, Bournemouth, Dorset, UK BH7 7DW; email address tolu.olateju@rbch.nhs.uk

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Within the first few weeks after starting insulin, HbA1c levels fall precipitously to an acute nadir in approximately 3 months. Subsequently, over the following 12 months, there is only a further modest reduction in HbA1c levels, albeit still a sustained improvement compared with preinsulin levels, but this is associated with significant weight gain linked to progressive increases in daily insulin doses.[11]

In studies assessing the impact of adding once- or twice-daily basal insulin to oral agents, dose titration of the insulin has usually been based on fasting SMBG levels, although some studies have also corrected for the subject's starting weight[12,13] or degree of hyperglycemia.[14] Although some studies recommend a frequency of testing adherence, this is not always reported. Others simply adopt a pragmatic approach with general rather than specific recommendations (**Table 1**).

In previous trials of adding mealtime rapid-acting insulin, the starting dose has not always been stated. Some studies have used a fixed dose regime or based starting amounts on the subjects' weight, with others incorporating a specific algorithm based on a combination of the study participants' weight, height, and fasting glucose levels (**Table 1**). Other studies involving patients already exposed to insulin have calculated the initial insulin doses based on fractions of prestudy insulin requirements.[23] Some have left the initial insulin dose completely to the investigators' discretion based on "clinical assessment," which is invariably undefined.[20,21] In others, dose titration algorithms have been used to target blood glucose measurements at specific times, usually based on values at 90–120 minutes after a meal. Relevant clinical events, mainly occurrences of hypoglycemia, are usually also taken into consideration with regards to further dose titration. Although studies may report that subjects had participated in an education/training program focusing on intensive insulin therapy, the extent and depth of education undertaken in the trials has not always been included in the final reports. Individual subject factors, including use of insulin-to-carbohydrate ratios, correction factors for blood glucose levels, or consideration of the duration of insulin action for a given bolus ("insulin on board") as an element in dose calculation algorithms, are also rarely, if ever, reported.

Based on experience with insulin pump therapy, there is a move to introduce bolus calculators to reduce the burden of performing complex calculations associated with choosing an accurate and safe dose of rapid-acting insulin for a meal. If effective, the potential impact of such a technology for insulin-treated type 2 patients may be anticipated as

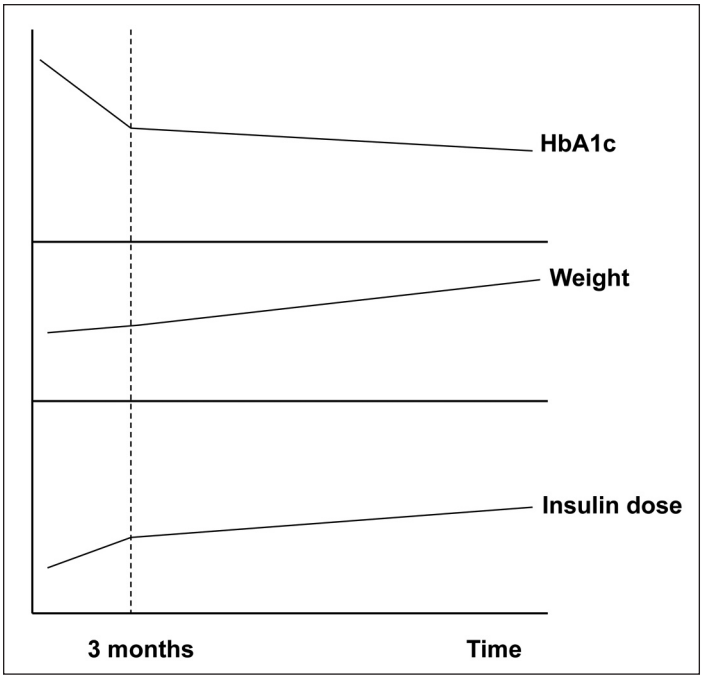

Figure 1. A representation of the changes in levels of HbA1c, body weight, and insulin doses in trials of insulin initiation in type 2 diabetes.

- Earlier introduction of mealtime rapid-acting insulin;
- Fewer patients using fixed-dose MDI regimens, where they do not count carbohydrates or factor in correction doses for the prevailing and target glucose levels, or twice-daily premixed insulin; and
- Better compliance with insulin therapy.

For patients, this will hopefully result in (1) better control of blood glucose levels, (2) a reduction in excess weight gain, and (3) less hypoglycemia, but this remains to be determined by appropriate clinical trials. The key will be the impact of using these devices on patient adherence to their prescribed insulin and SMBG regimen. However, practical use of this type of technology will be dependent upon the user interface as much as the mathematical wizardry producing effective algorithms. Here it may be appropriate to consider using the lessons from successful consumer electronic companies in terms of their approach to user engagement. Price will remain relevant as will patient selection. The question for health care educators is whether it is important to teach patients about the theory of intensive insulin therapy or whether it is enough to ask them to accept the result. As an analogy, few people know the engineering behind an internal

Table 1.
Addition of Insulin in Type 2 Diabetes[a]

Study/first author	Insulin initiation regimen	Insulin naïve	Dose initiation	SMBG regimen	Dose titration	Detailed information about prestudy education received
4T (Holman[11])	Prandial/biphasic/basal	Yes	FBG-, Wt-, and Ht-based formula. Patient specific and algorithm derived	Premeal and postprandial; eight-point profiles at intervals	Online trial management system; investigators and patients encouraged to vary suggested doses as clinically appropriate	Not stated
Kann[12]	Biphasic/basal	Yes	Wt based	Premeal and postprandial; seven-point profiles at intervals	By participants; algorithm based	Not stated
PREFER Study (Liebl[13])	Basal bolus/biphasic	Some	Prestudy insulin requirements or fixed doses with body mass index consideration	FBG, premeal, and postprandial	Algorithm based for basal and biphasic; at investigator's discretion for bolus	Not stated
INITIATE (Raskin[14])	Biphasic/basal	Yes	Fixed doses but FBG taken into account	FBG and premeal	Algorithm based	Not stated
DURABLE Trial (Buse[15])	Biphasic/basal	Yes	Fixed doses	Prebreakfast and predinner; seven-point profiles at intervals	By participants; algorithm based	Not stated
APOLLO (Bretzel[16])	Prandial/basal	Yes	Fixed doses	FBG, premeal, and postprandial; eight-point profiles at intervals	Algorithm based	Training on SMBG and injection techniques
Malone[17]	Biphasic/basal	Yes	Not stated	FBG, premeal, and postprandial; four- and seven-point profiles at intervals	No algorithm; at investigator's discretion to glycemic target	Instruction on SMBG and insulin administration
Malone[18]	Biphasic/basal	No	Based on insulin requirements in lead-in period	FBG, premeal, and postprandial; four- and eight-point profiles prerandomization	No algorithm; at investigator's discretion to glycemic target	Not stated
Kazda[19]	Prandial/ prandial mix/basal	Yes	Not stated	FBG and postprandial; eight-point profiles at intervals	No study algorithm; at investigator's discretion to glycemic target	Not stated
IONW (Jacober[20])	Prandial mix/ basal	Yes	Not stated	FBG and postprandial; eight-point profiles at intervals	No study algorithm; at investigator's discretion to glycemic target	Training on SMBG; signs, symptoms, and treatment of hypoglycemia; and insulin injection techniques
JDDM (Hirao[21])	Bolus (±basal)/ biphasic	Yes	Not stated	Not stated	No study algorithm; at investigator's discretion to glycemic target	Not stated
1001 (Robbins[22])	Prandial mix/ basal	Some	Based on insulin requirements in lead-in period	FBG and postprandial; seven-point profiles at intervals	By investigators; algorithm based	Verbal and written instructions on diet and exercise, SMBG, and signs, symptoms, and treatment of hypoglycemia
Rosenstock[23]	Prandial mix/ basal bolus	No	Based on prestudy insulin requirements	FBG and preprandial	Algorithm based	Not stated

[a]FBG, fasting blood glucose; Ht, height; Wt, weight.

combustion engine, but most are quite happy simply to switch the engine on.

Nevertheless, there is an opportunity for this type of technology to offer patients more personalized intensive insulin therapy rather than simply attempting to lower glucose levels without considering the collateral impact on the individuals and their families. It will also depend upon the approach of engineers in creating these new technologies, as summed up in an article by Shaywitz:[24] "Most engineers and computers scientists conceptualize medicine as primarily a rational, evidence-based, problem-solving enterprise focused on well-defined conditions, rather than a discipline that owes more to scientism than science, is far more ambiguous than most engineers tend to recognize and is founded on relationships, connectedness, trusted advice, reassurance and frequently the off-loading of significant responsibilities from patient to doctor."

Disclosures:

David Kerr has received research funding from Roche and Abbott Diabetes Care, manufacturers of blood glucose monitoring equipment and bolus calculators for insulin-treated patients; has had consultancy agreements with Roche and Abbott Diabetes Care; and has received research funding and honoraria for participating in advisory boards from Novo Nordisk, Lilly, and Sanofi-Aventis. David Kerr is also founder of VoyageMD.com, a service for insulin-treated travelers with diabetes.

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