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Commentary

Beyond basal-bolus insulin regimen: Is it still the ultimate chance for therapy in diabetes?

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1. Introduction

All people with type 1 diabetes (T1D) need insulin to survive, with the hope to cut or slow down the devastating long-term micro and macrovascular complications. About one fourth of people with type 2 diabetes (T2D) uses insulin, either as the only antyhyperglycemic drug, or in combination with other glucose-lowering medications [1,2]. Every day, about 6 million diabetic people in the U.S. inject insulin to control their hyperglycemia.

2. Which is the best insulin regimen?

It is a general belief that the so called basal-bolus (B-B) insulin regimen represents the golden standard for people with T1D and the best final insulin option for people with T2D. The American Diabetes Association (ADA) [3] strongly (A level of evidence) recommends that most people with T1D should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. The B-B insulin regimen tries to mimic the physiological kinetics of endogenous insulin release, composed by a basal secretion upon which are superimposed secretory peaks in response to meals. In T1D, the boluses are usually made up of three shots of insulin at breakfast, lunch and dinner; the continuous subcutaneous administration through an insulin pump is based on the same principle. In T2D, ADA [3] suggests starting with basal insulin at bedtime added to metformin and other oral agents; advancement to combination injectable therapy is considered when the appropriate dose of basal insulin fails to maintain hemoglobin A1c (HbA1c) within target. This intensification approach can use either a GLP-1 receptor agonist (GLP-1RA) or doses of prandial insulin added to the ongoing basal insulin; both strategies may offer the same glycemic control, with the advantage for the combination of basal insulin and GLP-1RA of less weight gain and hypoglycemia compared with intensified insulin regimens [4–6]. However, if HbA1c remains above the target, the full basal-bolus insulin regimen is still considered the ultimate therapeutic option for patients with T2D [3].

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3. Does basal-bolus always achieve glycemic target?

About 80% of patients enrolled in the T1D Exchange Clinic Network are not at their glycemic goal (HbA1c < 7%) despite the use of a full B-B insulin regimen or an insulin pump [7]. Although insulin is not need to survive for people with T2D, the progressive nature of the disease makes insulin necessary for optimizing glycemic control in the long run, especially after multiple drug failure. In T2D, glycemic targets are achieved by about one half of the population using the B-B regimen [8]. In general, it appears that the diabetes care cascade (defined as diabetes diagnosis, linkage to care, and achievement of individual and combined treatment targets) in the United States has not significantly improved between 2005 and 2016 [9], despite the launch of new antihyperglycemic drugs and increasing insulin use [1]. Moreover, hospitalization for major diabetes complications (acute myocardial infarction, stroke, lower-extremity amputation, and end-stage kidney disease) has shown a substantial increase between 2010 and 2015 [10].

4. Is basal-bolus easy to manage?

Once B-B is started, adjustments of doses are usually needed in both mealtime and basal insulins. If HbA1c does not improve, there is the need to consider additional diabetes self-management education and support. In this context, use of real-time continuous glucose monitoring can help improve blood glucose control in people with T1D whether they use an insulin pump or a basal-bolus regimen [11]. Although there is no consensus to guide choosing which form of insulin administration is best for a given patient with T2D [3], comfortability with more frequent injections or more glucose monitoring, coupled with good patients ability to inject (cognitive ability, manual dexterity, need for carer) favors the B-B regimen. However, simplification of complex insulin regimens may be necessary because of a decline in self-management ability in the older people with T2D. This may be particularly important, as both clinical inertia and medication non-adherence remain significant barriers to optimal glycemic targets in type 2 diabetes [12].

5. What's beyond basal-bolus?

For adults with T1D who are struggling to control their blood glucose levels despite a full B-B insulin regimen, various newer oral drugs have been proposed as add-on to insulin, including GLP-1RA and sodium glucose co-transporter-2 inhibitors. At this time, these adjunctive agents are not approved in the context of T1D, except for dapagliflozin and sotagliflozin in the E.U., if the body mass index is of 27 kg/m^2 or more [13,14]. In the T1D Exchange Clinic Registry [7], the proportion of patients with T1D who have become overweight or obese in the course of the disease continues to rise.

Insulin is still regarded as the last chance of antihyperglycemic therapy in T2D, and the progressive intensification of insulin therapy to a full B-B regimen is practically unavoidable, and continues lifelong [3]. However, despite the four daily insulin injections, the glycemic control of these patients is often suboptimal [8] and may be managed by increasing insulin doses. However, this may lead to the vicious circles of rising insulin in the attempt to improve glycemic control (Fig. 1): ironically, more insulin is associated with increased risk of hypoglycemia and increased body weight, which, in turn, may get glycemic control worse.

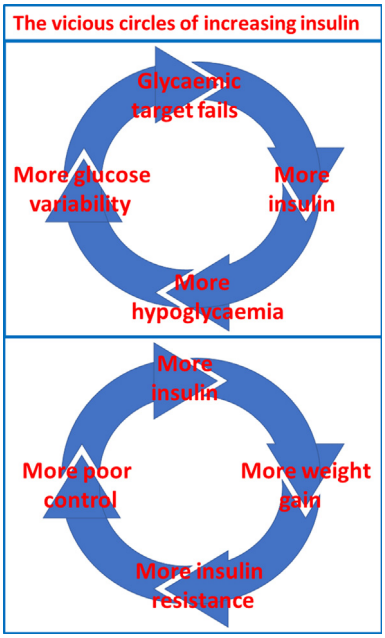

Fig. 1 – Rising insulin doses in the attempt to control hyperglycemia in both type 1 and type 2 diabetic patients may lead to unintended consequences that paradoxically deteriorate further glycemic control.

6. Conclusions

There is an urgent need to find a solution for the many patients who fail to achieve their glycemic target despite the use of a full B-B insulin regimen. For adults with T1D, adding a SGLT-2 inhibitor (at the present time dapagliflozin only in the E.U.) may help reduce HbA1c and hypoglycemia, offering a treatment possibility in addition to a full B-B regimen. For adults with T2D, there are no reported studies specifically designed to reverse the full B-B to a less complex therapy (i.e. combining basal insulin with a GLP-1RA or a SGLT-2 inhibitor). The increase of the cost of combined treatments may be mitigated by detracting the cost of saving insulin doses and by the improved quality of life, which is perceived by patients as the worst in relation to the intensive insulin treatment [15]. Whatever the near future holds for the diabetic patient, the B-B insulin regimen should no more be considered as the ultimate chance for therapy in both T1D and T2D.

Author contribution

D.G. wrote the manuscript. M.I.M., G.B., and K.E. made important contributions to all aspects of the manuscript. All authors approved the manuscript.

Declaration of Competing Interest

D.G. received honoraria for speaking at meetings from Novartis, Sanofi-Aventis, Lilly, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Mundi Pharma. M.I.M. received honoraria for speaking at meetings from Astra-Zeneca, Sanofi-Aventis, Novo Nordisk. K.E. received honoraria for speaking at meetings from Novartis, Sanofi-Aventis, Lilly, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Mundi Pharma. G.B. declares no conflict of interest.

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