The Clinical Definition of Overbasalization

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This commentary will discuss the issue of overbasalization. To focus the discussion clinically, let us consider two similar patients whose glycemia has not been well managed on noninsulin drugs and who are both started on basal insulin but have different responses.

Case 1

This is an obese man who has had diabetes for 15 years, with a BMI of 36 kg/m^2. His diabetes has not been controlled with maximal doses of metformin, a dipeptidyl dipeptidase 4 (DPP-4) inhibitor, and pioglitazone, and his A1C is 9.2%. He is kept on these oral agents, and a basal insulin is initiated and titrated upward. Six months later, the majority of his fasting plasma glucose (FPG) readings are in the range of 140–180 mg/dL, and he is taking 0.7 units/kg of basal insulin. His before-dinner glucose readings range from 160 to 220 mg/dL, and his A1C is 8.1%. Preprandial bolus doses of insulin are started to control his daytime hyperglycemia.

Case 2

This is an obese man who has had diabetes for 9 years with a BMI of 36 kg/m^2. His diabetes has not been controlled with maximal doses of metformin, a DPP-4 inhibitor, and pioglitazone, and his A1C is 9.2%. He is kept on these oral agents, and a basal insulin is initiated and titrated upward. Six months later, the majority of his FPG readings are in the range of 100–130 mg/dL, and he is taking 0.7 units/kg of basal insulin. His before-dinner glucose readings range from 160 to 220 mg/dL, and his A1C is 8.1%. His basal insulin dose is titrated upward to 0.9 units/kg to control his daytime hyperglycemia, but he begins to complain of hypoglycemia, occurring mostly overnight but sometimes during the day when he misses or delays a meal.

Cowart (1) defined "overbasalization" in an article about clinical inertia as the titration of basal insulin beyond an appropriate dose to achieve glycemic targets. In a subsequent article describing the prevalence and characteristics of patients who experience overbasalization, he and his colleagues define it as an A1C >8.0% plus a basal insulin dose of >0.5 units/kg/day (2). These two definitions of overbasalization are inconsistent because, in the latter, basal insulin has not been titrated beyond an appropriate dose.

The dose restriction of not titrating to 0.5 units/kg is based on a post-hoc analysis of three prospective, randomized, treat-to-target studies evaluating the glycemic responses to glargine insulin 100 units/mL (U-100) in people with type 2 diabetes who were also taking metformin and a sulfonylurea (3). The outcomes in that analysis were the changes in FPG and A1C per 0.1 units/kg of insulin. As would arithmetically be expected, these changes became progressively smaller as the insulin dose was increased, which would (erroneously) suggest that doses exceeding 0.5 units/kg are less effective. Calculating the glycemic outcomes in this manner is a self-fulfilling prophecy, as the higher insulin doses simply reflect more insulin resistance (i.e., more insulin being required to accomplish the same response). A more valid approach would have been to compare the effects of lower and higher insulin doses on the *absolute* changes in FPG and A1C and the proportion of patients who achieved the American Diabetes Association (ADA)-recommended FPG and A1C targets.

The author wrote to the journal in which the post-hoc analysis had been published asking for a comparison of these valid clinical responses to the lower and higher insulin doses (4), which was eventually provided (5). As can be seen in Table 1, absolute changes from baseline in FPG and A1C were actually significantly greater with the higher doses of insulin. Furthermore, there were no differences in the proportion of patients who achieved the ADA-recommended targets among the different insulin doses. Importantly, there were also no differences in hypoglycemia between patients receiving ≤0.5 and those receiving >0.5 units/kg of insulin (3).

These results are consistent with other treat-to-target studies. In 15 phase 3 studies using U-100 glargine

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TABLE 1 FPG and A1C Changes From Baseline With Different Doses of Basal Insulin

	Dose 1: ≤0.3 units/kg	Dose 2: ≤0.5 units/kg	Dose 3: >0.5 units/kg	*P* (Dose 1 vs. Dose 2)	*P* (Dose 2 vs. Dose 3)
N	145	287	171	–	–
Mean FPG change, mg/dL	−58.8	−70.6	−90.1	<0.0001	0.0013
Patients achieving FPG <130 mg/dL, %	64.9	65.5	60.2	0.3945	0.2569
Mean A1C change, %	−1.48	−1.59	−1.79	0.0031	0.0237
Patients achieving A1C <7.0%, %	52.4	49.7	48.0	0.4323	0.7274

insulin (including the three studies described above), 38% of patients required >0.5 units/kg (6). At the end of those studies, the mean FPG concentrations were 116.6 and 120.7 mg/dL in patients receiving ≤0.5 and >0.5 units/kg, respectively. The final A1C levels were 7.16 and 7.28%, respectively. In all 15 studies, hypoglycemia (both glucose concentrations <70 mg/dL and those <56 mg/dL) was significantly lower in patients receiving >0.5 units/kg of insulin, probably reflecting the increased insulin resistance in the patients receiving the higher doses of insulin (Table 2). These significant differences in hypoglycemia event rates held for patients also receiving metformin alone, a sulfonylurea alone, or both. Note that the overall hypoglycemia event rates were much higher than the nocturnal event rates. This probably reflects the fact that 78% of the patients were taking a sulfonylurea. As the FPG values approached their target values, sulfonylurea-induced daytime hypoglycemia occurred, especially in patients with irregular eating patterns. These data clearly indicate that higher doses of basal insulin are just as effective and safe as lower ones.

The most important determinant of postprandial glucose concentrations is the preprandial value (7–9). This fact underscores the importance of lowering the FPG to target levels before evaluating daytime glycemia for possible insulin intensification. In a seminal article, Cusi et al. (7) studied people with type 2 diabetes whose glycemia was not controlled with a sulfonylurea (metformin was not available in the United States at that time). They discontinued the medication for 4 weeks before starting bedtime NPH insulin, which was aggressively titrated upward. The baseline FPG concentration of 263 mg/dL fell to 95 mg/dL, and the rise in postprandial glucose concentrations over preprandial values was similar before and after insulin treatment. The mean A1C decreased from 10.9 to 7.2% in 16 weeks. The mean bedtime NPH insulin dose to accomplish this was 0.86 units/kg (range 0.3–1.3 units/kg).

One-third of people with type 2 diabetes who are treated with basal insulin require >60 units daily (10). For patients who weigh ≤l00 kg, this translates to >0.6 units/kg. Thus, a large number of people with type 2 diabetes will require basal insulin doses >0.5 units/kg to achieve FPG targets. After starting glargine insulin in

TABLE 2 Hypoglycemia Event Rates

	Insulin Dose, units/kg					
	≤0.5	>0.5	≤0.7	>0.7	≤1.0	<1.0
Patients, *N*	1,762	1,075	2,384	453	2,726	111
Plasma glucose <70 mg/dL						
Nocturnal hypoglycemia	0.85	0.60*	0.82	0.39*	0.76	0.34*
Overall hypoglycemia	4.70	3.40*	4.49	2.67*	4.28	1.87*
Plasma glucose <56 mg/dL						
Nocturnal hypoglycemia	0.34	0.22*	0.33	0.13*	0.30	0.08*
Overall hypoglycemia	1.44	1.06*	1.40	0.73*	1.32	0.45*

Event rates are per patient year. **P* <0.05 for being significantly lower in patients exceeding the cutoff dose compared with those not exceeding it. Adapted from ref. 6.

a randomized controlled trial in patients receiving noninsulin drugs whose mean baseline A1C was 10.2%, aggressive titration achieved an FPG target of 70–109 mg/dL at a mean dose of 0.55 units/kg. Forty-six percent of these patients also achieved the ADA's A1C target of <7.0% and did not require insulin intensification (11). In a large observational study in 10 countries involving 17,374 patients receiving noninsulin drugs with a mean baseline A1C of 8.9% whose 3,219 physicians decided to initiate detemir insulin, 33% achieved an A1C <7.0% (12). The final mean insulin dose was only 0.3 units/kg; if higher doses had been used, it is likely that even more patients would have achieved the ADA's A1C target of <7.0%.

If patients who would require insulin doses >0.5 units/kg to meet FPG targets do not receive those appropriate amounts, many would unnecessarily be prescribed preprandial insulin with its attendant increased risks of hypoglycemia, increased injections, and increased blood glucose monitoring requirements, as well as its inconvenient impact on their lifestyles. Additionally, preprandial insulin will have relatively little effect on meeting FPG targets. These patients will need higher preprandial insulin doses because of their fasting hyperglycemia.

Once FPG targets have been achieved by appropriate doses of basal insulin, clinicians must determine whether intensification of the insulin regimen is necessary. There are two ways to do this. The first is to wait 3 months and make a decision based on the next A1C measurement. The increase in the relative risk of microvascular complications is small with A1C levels between 7.0 and 7.5% (13). Patients taking preprandial bolus doses of short- or rapid-acting insulins face a major disruption in their lifestyles, as described above. Given the cost-to-benefit ratio of this decision, the author uses a value of ≥7.5% to initiate intensification.

A faster way to make this decision is to monitor glucose readings during the day. With consistent preprandial dinner values >180 mg/dL, it is unlikely that target A1C levels will be achieved 3 months later. The author intensifies the insulin regimen in that situation. This is a variation of the BeAM method (14). In that approach, intensification of the insulin regimen is recommended if differences between bedtime and fasting glucose readings exceed 55 mg/dL. Because the FPG target has been achieved, this difference reflects high bedtime readings. The author uses preprandial dinner readings instead to avoid the varying effects of the carbohydrate content of the evening meal and the time between the end of the meal and bedtime.

The author agrees with the first definition of overbasalization offered by Cowart (i.e., the titration of basal insulin beyond an appropriate dose to achieve glycemic targets) (1). The appropriate dose, however, is one that allows patients to reach FPG targets—not one arbitrarily limited by a dose maximum. On the other side of the coin, inappropriate dosing also occurs when the appropriate basal insulin dose is increased even further in an attempt to control daytime hyperglycemia. This often leads to hypoglycemia, especially overnight. Moreover, increasing doses of basal insulin are not very effective in controlling postprandial hyperglycemia, which requires acute increases in insulin (either endogenous or exogenous) that basal insulin cannot provide. This situation defines "clinical overbasalization" (i.e., basal insulin doses that are increased even further after FPG targets have been achieved, leading to hypoglycemia with persistent postprandial hyperglycemia in a basal-only insulin regimen).

Let us return to the two cases described above. The first certainly does not represent overbasalization, as the appropriate amount of basal insulin has not been prescribed. Further dose increases are necessary to achieve target FPG values, with the possibility that preprandial bolus doses of insulin might not be needed. The second case represents clinical overbasalization, as the stable, peakless blood insulin levels after basal insulin injections cannot rise to dispose of the postprandial increase of glucose into tissues.

In conclusion, an appropriate basal insulin dose is the amount necessary to achieve the FPG target. After starting basal insulin, doses should be gradually increased until the FPG target is met. At that point, further increases are inappropriate and can lead to clinical overbasalization. Because preprandial glucose concentrations are a major determinant of postprandial values, only when FPG targets are reached should daytime glycemia be evaluated to determine whether insulin intensification is necessary. If insulin intensification occurs when FPG concentrations remain high, a number of patients will be denied the opportunity to meet the recommended A1C target on basal insulin alone and will unnecessarily face an increased risk of hypoglycemia, increased glucose testing requirements, more injections, and lifestyle disruption.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTION

As the sole author, M.B.D. is the guarantor of this work and takes responsibility for the integrity of its content.

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