Practicable Measurement and Identification of Overbasalization

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In the March 2020 issue of *Clinical Diabetes*, our Practical Pointers article (1) outlined a definition for overbasalization as the titration of basal insulin beyond an appropriate dose in an attempt to achieve glycemic targets. Although there is consensus in this general definition, it does not offer clinicians a practicable marker to identify overbasalization. Indeed, the only clear-cut case of overbasalization would be an increase in the basal insulin dose of a patient with controlled fasting plasma glucose (FPG) to treat postprandial hyperglycemia. As we expect such an event to be uncommon, why, then, is overbasalization a growing concern?

The primary role of basal insulin in type 2 diabetes is to control fasting hyperglycemia by replacing a patient's insulin production lost secondary to diminished β-cell function (2). The amount of insulin required to achieve this "replacement" is affected by insulin resistance; a higher insulin dose is required to achieve the desired effect of basal insulin on FPG in patients with versus those without insulin resistance. However, the impact of insulin resistance and diminished β-cell function is also seen as impaired glucose tolerance, noted by postprandial glucose (PPG) excursions. The goal of better defining "overbasalization" is, therefore, to identify patients with residual or extended postprandial hyperglycemia who can be better treated with agents targeting PPG excursions to facilitate overall glucose control.

In our recent cross-sectional analysis published in *Clinical Diabetes* (3), we defined overbasalization as a situation in which a person has an A1C >8% while using >0.5 units/kg/day of basal insulin. This definition was selected based on guidance from the American Diabetes Association's (ADA's) *Standards of Medical Care in Diabetes* to identify patients with residual hyperglycemia whose treatment regimen was targeted at further escalation of FPG therapies versus PPG therapies. It is well known that, as A1C is lowered from >10% to ~7.3%, the relative cause of glucose exposure transitions from being predominately FPG to being predominately PPG (4). However, basal insulin directly targets this pathophysiology at higher A1C levels, thus shifting the relative contribution to A1C elevation toward PPG as it is titrated.

Supporting this relationship in basal insulin–treated patients, a post hoc study by Umpierrez et al. (5) evaluated the dose-response relationship between glargine insulin 100 units/mL (U100 glargine) and glycemic control. Absolute changes in FPG and A1C were significantly greater with higher (i.e., >0.5 units/kg/day) versus lower basal insulin doses. However, although the greater total response with higher basal insulin doses was expected, the incremental response of increasing basal insulin to >0.5 units/kg/day was diminished versus the incremental response at lower doses (6). Umpierrez et al. (6), with which we concur, noted the continued, although diminished, effect of continuing to titrate basal insulin above 0.5 units/kg/day and the limited ability to measure insulin resistance in standard practice. Thus, a basal insulin dose of 0.5 units/kg/day can be best viewed as a landmark highlighting a need to reassess insulin therapy overall, rather than as a "line in the sand" (6). Indeed, a full assessment of insulin therapy is likely to benefit patients. A pooled analysis of 15 randomized treat-to-target trials of patients with type 2 diabetes starting U100 glargine showed a smaller A1C reduction (with or without oral antidiabetic drugs) over ≥24 weeks when patients' doses exceeded 0.5 units/kg/day (7). Moreover, these patients experienced additional weight gain. Although the overall and nocturnal hypoglycemic event rates were lower in patients with higher basal insulin doses compared with those with lower doses, the authors postulated that this finding may have been driven by significantly increased hypoglycemia event rates in the subgroup using sulfonylureas. It is important to also note that the authors analyzed mean hypoglycemia event rates before and

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after exceeding basal insulin dose cutoffs of >0.5, 0.7, and 1 unit/kg/day. Among patients exceeding each cutoff, overall and nocturnal hypoglycemia event rates were higher after exceeding the cutoff compared with before exceeding the cutoff.

Therefore, we propose that a detailed assessment of therapies and glycemia is prudent before increasing basal insulin beyond 0.5 units/kg/day, and primary care providers cannot singularly rely on FPG in making this determination. The principal determination in deciding whether to titrate basal insulin above 0.5 units/kg/day is to confirm residual fasting hyperglycemia. However, clinicians should be wary of additional clinical signals suggestive of overbasalization. As supported by the ADA's most recent Standards (8), these clinical signals may involve a basal insulin dose >0.5 units/kg/day, high bedtime-to-morning or postprandial-to-preprandial glucose differential (e.g., bedtime-to-morning glucose differential ≥50 mg/dL), hypoglycemia (with or without awareness), and high glycemic variability. Indeed, high variability, including nocturnal hypoglycemia, can lower A1C while postprandial excursions remain significantly uncontrolled.

Continuous glucose monitoring (CGM) is needed to evaluate many of these variables and can be particularly useful in identifying detailed glycemic patterns, which can be evaluated to determine whether overbasalization is occurring. Thankfully, CGM is becoming more available to patients with type 2 diabetes, and primary care providers can use it to identify high variability, bedtime-to-morning or postprandial-to-preprandial glucose differential, and the presence of hypoglycemia. If residual fasting hyperglycemia is not present, an agent targeting postprandial hyperglycemia should be considered to reach the A1C goal.

The selection of an agent to address PPG excursions should be done carefully, with particular attention to potential for weight gain and hypoglycemia (8). Additional factors may involve cost, efficacy, and cardiovascular risk reduction (8). Two common options for treatment intensification are prandial insulin and glucagon-like peptide 1 (GLP-1) receptor agonists (9–12). Prandial insulin is associated with weight gain, whereas GLP-1 receptor agonists facilitate weight loss. Prandial insulin is associated with hypoglycemia, whereas gastrointestinal symptoms are common with GLP-1 receptor agonists. However, GLP-1 receptor agonists offer additional advantages over prandial insulin, including their injection frequency (once daily to once weekly versus one to three times daily), their favorable impact on cardiovascular risk (13–15), and their ability to address both FPG and PPG (16).

Fixed-ratio combination formulations of basal insulin and a GLP-1 receptor agonist offer a new approach with great potential to limit overbasalization and simplify the diabetes regimen. However, limiting factors to this approach are the inability to titrate agents individually and to reach basal insulin doses >60 units daily, which may be clinically necessary (17). Once combination injectable therapy is initiated, CGM readings can help to ensure appropriate GLP-1 receptor agonist or prandial insulin dose titration.

Presently, there is no widely accepted clinical definition for "overbasalization," and no prospective studies have investigated the maximum dose of basal insulin at which alternative drug therapy should be initiated. Until more evidence is available, we propose that clinicians can take the approach of using A1C >8% with >0.5 units/kg/day of basal insulin as a marker for potential overbasalization. We propose that this approach has clinical relevance and can be easily implemented in practice as a landmark to reevaluate diabetes therapy and consider CGM, thus allowing clinicians to judiciously select a patient-specific treatment intensification strategy.

Although limitations to this approach exist, including its omission of patients with an A1C of 7–7.5% with near-goal FPG and unidentified nocturnal hypoglycemia, we recommend this approach to aid in optimizing patients' antihyperglycemic therapy regimen. Although we expect future studies to refine this definition, we found when using it the presence of overbasalization in 38% of patients with an A1C >8% (3). Thus, overbasalization is a major concern in need of an actionable definition, with a practicable method of measurement to further optimize the use of basal insulin in patients with type 2 diabetes.

DUALITY OF INTEREST

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

AUTHOR CONTRIBUTIONS

K.C. developed the concept for this article, and both authors wrote and reviewed/edited the manuscript. K.C. is the guarantor of this work and, as such, had full access to all the data presented and takes responsibility for the integrity of the commentary.

REFERENCES

1. Cowart K. Overbasalization: addressing hesitancy in treatment intensification beyond basal insulin. Clin Diabetes 2020;38:304–310

2. American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2021*. Diabetes Care 2021;44(Suppl. 1): S15–S33

3. Cowart K, Updike WH, Pathak R. Prevalence of and characteristics associated with overbasalization among patients with type 2 diabetes using basal insulin: a cross-sectional study. Clin Diabetes 2021;39:173–175

4. Hershon KS, Hirsch BR, Odugbesan O. Importance of postprandial glucose in relation to A1C and cardiovascular disease. Clin Diabetes 2019;37:250–259

5. Umpierrez GE, Skolnik N, Dex T, Traylor L, Chao J, Shaefer C. When basal insulin is not enough: a dose-response relationship between insulin glargine 100 units/mL and glycaemic control. Diabetes Obes Metab 2019;21:1305–1310

6. Umpierrez GE, Skolnik N, Dex T, Traylor L, Chao J, Shaefer C. When basal insulin is not enough: response to M Davidson. Diabetes Obes Metab 2020;22:711–712

7. Reid T, Gao L, Gill J, et al. How much is too much? Outcomes in patients using high-dose insulin glargine. Int J Clin Pract 2016;70:56–65

8. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2021*. Diabetes Care 2021;44(Suppl. 1): S111–S124

9. Balena R, Hensley IE, Miller S, Barnett AH. Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. Diabetes Obes Metab 2013;15:485–502

10. Rosenstock J, Fonseca VA, Gross JL, et al.; Harmony 6 Study Group. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. Diabetes Care 2014;37:2317–2325

11. Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. Drugs Context 2015;4:212283

12. Carris NW, Taylor JR, Gums JG. Combining a GLP-1 receptor agonist and basal insulin: study evidence and practical considerations. Drugs 2014;74:2141–2152

13. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322

14. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844

15. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–130

16. Huthmacher JA, Meier JJ, Nauck MA. Efficacy and safety of short- and long-acting glucagon-like peptide 1 receptor agonists on a background of basal insulin in type 2 diabetes: a meta-analysis. Diabetes Care 2020;43:2303–2312

17. David J, Fonseca V. When should fixed ratio basal insulin/glucagon-like peptide-1 receptor agonists combination products be considered? J Diabetes Complications 2019;33:107473