Clinical Overbasalization Revisited

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Cowart and Carris recently wrote a commentary in *Clinical Diabetes* (1) defending their definition of overbasalization as occurring in patients with A1C levels >8.0% who are receiving >0.5 units/kg of a basal insulin. Their commentary was written in response to an earlier commentary by me that was also published in this journal (2), in which I challenged their definition, although they did not mention my earlier article in theirs. I had made the case that the appropriate definition of overbasalization is a clinical situation in which basal insulin doses are increased even further after fasting plasma glucose (FPG) targets have been achieved in an attempt to control postprandial glycemia during the day (2). This practice often results in hypoglycemia, usually overnight. Cowart and Carris agreed with that definition describing overbasalization but stated that it was uncommon (not in my experience) and went on to defend their own definition (1).

They support their definition by considering two post hoc studies of clinical trials evaluating glargine insulin 100 units/mL (U-100) that had been carried out by glargine manufacturer Sanofi. The first of these studies (3) showed that patients receiving >0.5 units/kg had significantly greater absolute decreases in FPG and A1C than those receiving ≤0.5 units/kg. This was acknowledged by Cowart and Carris, who then went on to state that "the incremental response of increasing basal insulin to >0.5 units/kg/day was diminished versus the incremental response at lower doses" (1). This conclusion was based on the percentage of patients achieving target FPG (<130 mg/dL) and A1C (<7.0%) levels. Regarding FPG targets, 65.5% and 60.2% of patients receiving ≤0.5 units/kg and >0.5 units/kg, respectively, achieved them. Regarding A1C targets, 49.7% and 48.0% of patients receiving ≤0.5 units/kg and >0.5 units/kg, respectively, achieved them. *P* values for these two comparisons were 0.26 and 0.73, respectively (3).

The second post hoc study (4) was a pooled analysis of 15 randomized treat-to target trials, which included the three in the first post hoc analysis. Cowart and Carris pointed out that there was a smaller A1C reduction over the 24 weeks of the study in patients receiving >0.5 units/kg compared with those receiving a lesser dose (1). However, this difference was only 0.12%, which only achieved statistical significance because of the very large numbers of patients in each group (1,075 and 1,762, respectively), a difference that is hardly of clinical significance.

Regarding hypoglycemia, there was no difference in hypoglycemia in patients receiving ≤0.5 units/kg and >0.5 units/kg in the study (5) on which the first post hoc analysis was based (3). There was also no difference during the entire 24-week period in overall and nocturnal hypoglycemia in these two groups in the second post hoc study (4). In patients receiving >0.5 units/kg, there was an increase of 2.9 hypoglycemic events per patient per year after the dose exceeded 0.5 units/kg (4). This finding would be expected, however, because 82% were taking sulfonylureas, and as they approached their FPG target, their risk for hypoglycemia might increase. Clinically, if hypoglycemia did occur, the dose of the sulfonylurea should be reduced or the drug discontinued altogether. As part of their argument, Cowart and Carris mentioned that patients receiving >0.5 units/kg gained significantly more weight. However, the mean difference was only 1.2 kg in the first post hoc study (3) and 1.0 kg in the second (4), again hardly of clinical significance.

Cowart and Carris correctly pointed out that "as A1C is lowered from >10 to ~7.3%, the relative cause of glucose exposure transitions from being predominantly FPG to being predominantly PPG" (1). They then recommend that, when basal insulin doses reach 0.5 units/kg, clinicians consider treating postprandial hyperglycemia regardless of whether FPG targets have been achieved. Because postprandial glucose concentrations are mostly determined by the preprandial glucose value (6–8), the most effective way of treating postprandial hyperglycemia is to lower preprandial values. This strategy entails

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achieving FPG targets, as fasting values are a major determinant of subsequent preprandial values.

A large number of patients receiving basal insulin alone require doses >0.5 units/kg. In a clinical trial in which glargine U-100 insulin was introduced in patients failing noninsulin drugs whose baseline A1C levels were 10.2%, 46% achieved an A1C <7.0% with a mean basal insulin dose of 0.55 units/kg (9). Thus, more than half of these patients were receiving >0.5 units/kg. In a meta-analysis of five randomized BEGIN research program trials, one-third of patients taking a basal insulin alone received >60 units/day (10). Thus, the dose for patients weighing <220 lb (100 kg) was >0.6 units/kg.

There are two arguments against stopping basal insulin doses at 0.5 units/kg before achieving FPG targets and embarking on treatment of postprandial hyperglycemia. First, higher basal insulin doses will continue to lower FPG levels (3), and when targets are achieved, up to half of patients will also achieve A1C targets (9). Why expose them unnecessarily to preprandial insulin, with its attendant increased risks of hypoglycemia, increased requirements for blood glucose testing, and reduced lifestyle flexibility regarding eating and exercise? Second, preprandial insulin will have little effect on reaching FPG targets, so basal insulin doses will have to be increased even further to reach this goal.

I do agree with two of the recommendations by Cowart and Carris. They recommend considering treatment of hyperglycemia if "residual fasting hyperglycemia is not present" (i.e., if FPG targets have been met). They also recommend trying a glucagon-like peptide 1 (GLP-1) receptor agonist before preprandial insulin when considering treatment of postprandial hyperglycemia. A number of studies have shown little difference in A1C improvement between adding preprandial insulin or adding a GLP-1 receptor agonist to basal insulin (11). One study even showed that a GLP-1 receptor agonist could be successfully substituted for preprandial insulin in 54% of patients on a basal/bolus insulin regimen (12).

In conclusion, my view is that a clinical definition of overbasalization is warranted—not one that is based on arbitrary values of basal insulin doses and A1C levels. Clinical overbasalization occurs when basal insulin doses are increased even further after FPG targets have been achieved in an attempt to correct postprandial hyperglycemia. This practice often leads to hypoglycemia, mostly overnight, but also persistent postprandial hyperglycemia because the peakless action of basal insulin cannot provide the increased postprandial action necessary to dispose of meal-related blood glucose.

DUALITY OF INTEREST

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

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