



Overbasalization: Addressing Hesitancy in Treatment Intensification Beyond Basal Insulin

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The proportion of patients with type 2 diabetes achieving recommended treatment goals remains suboptimal despite advances in diabetes care (1). Only 30% of patients with type 2 diabetes who use basal insulin achieve an A1C <7%, with the probability of doing so diminishing greatly if not achieved within 1 year of insulin initiation (2–6). Factors underlying these delays are complex and may involve therapeutic inertia, which is defined as failure to intensify or deintensify therapy when appropriate (7).

Rationale for Basal Insulin

The clinical course of type 2 diabetes is characterized by a progressive decline in β -cell mass and function, as well as insulin resistance (8). Early in the course of the disease, the addition of basal insulin addresses decreasing β -cell function and is an efficient step in controlling fasting blood glucose but has little effect on controlling postprandial blood glucose (9). In patients with type 2 diabetes and elevated A1C, the relative contribution of fasting hyperglycemia is dominant with higher A1C, and postprandial hyperglycemia is a larger contributor when A1C is closer to 7% (10). Thus, titration of basal insulin when A1C is close to 7% will have minimal effect on postprandial hyperglycemia or on attainment of the A1C goal (11). Basal insulin is not designed to address postprandial hyperglycemia; its role is mainly to suppress hepatic glucose production, address insulin resistance, and correct fasting hyperglycemia.

What Is the Appropriate Basal Insulin Dose?

In theory, the ideal basal insulin dose should allow a patient with type 2 diabetes to fast for 24 hours without hypoglycemia. Once basal insulin has been initiated, appropriate titration is necessary to avoid “overbasalization,” or titration of basal insulin beyond an appropriate dose in an attempt to achieve glycemic targets. Several evidence-based titration algorithms exist (12–14); however, no particular algorithm has been shown to provide superior clinical benefit over others (15). One example that may be easy for patients to remember is the “2 \times 3 rule,” which requires patients’ self-titration of their basal insulin by 2 units every 3 days (with the upper dose limit being 0.5 units/kg/day) until fasting blood glucose is between 80 and 130 mg/dL (13) or <110 mg/dL (16). If hypoglycemia occurs as basal insulin is titrated to a fasting blood glucose goal, the clinician should consider a 10–20% basal insulin dose reduction if no clear reason for the hypoglycemia can be identified (13).

Basal insulin has a “ceiling effect,” whereby fasting blood glucose reductions become proportionally smaller with increasing doses (17). This ceiling-effect response has been shown to occur at a basal insulin dose of 0.5 units/kg/day, with ranges in the literature suggesting that it may occur at as low as 0.3 units/kg/day and as high as 1 unit/kg/day in some patients (13,18,19). In one pharmacokinetic study among obese patients with type 2 diabetes, doses of insulin glargine ≥ 0.5 units/kg/day resulted in only modest effects on glycemia (20). Additionally, in a pooled analysis of 15 randomized treat-to-target trials in insulin-naïve patients with type 2 diabetes who were treated with insulin glargine with or without oral anti-diabetic drugs for ≥ 24 weeks, there was only a small change in A1C from baseline with a higher likelihood of weight gain and hypoglycemia with daily insulin glargine doses >0.5 units/kg (21).

A recent post hoc analysis of three insulin glargine treat-to-target trials found a linear response with greater glycemic control at basal insulin doses <0.3 units/kg/day and a nonlinear, diminishing response with basal insulin doses between 0.3 and 0.5 units/kg/day (18). Additionally, this analysis found that basal insulin efficacy

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plateaus at doses >0.5 units/kg/day (18). Contrary to findings from other pharmacokinetic studies of insulin glargine, there was a similar incidence of hypoglycemia across insulin doses (18). This post hoc analysis raises an important consideration to begin evaluating the need for treatment intensification with postprandial coverage once the basal insulin dose is ≥ 0.3 units/kg/day if patients are still not meeting their A1C goal (18). A summary of when to consider treatment intensification beyond basal insulin is shown in Table 1.

The American Diabetes Association (ADA) *Standards of Medical Care in Diabetes—2020* (13) and the 2019 “Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm” (16) recommend considering combination injectable therapy to address postprandial hyperglycemia at basal insulin doses >0.5 units/kg/day if a patient’s A1C remains above goal (13). However, this recommendation is based on expert opinion (12); no prospective studies to date have investigated the maximum dose of basal insulin at which additional drug therapy should be initiated.

Beyond Basal Insulin

A summary of pharmacologic treatment intensification strategies is shown in Table 2, and these options for intensifying type 2 diabetes therapy beyond basal insulin are discussed in more detail below.

Prandial Insulin

When treatment intensification is warranted, clinicians may be most familiar with adding prandial insulin in a stepwise manner to basal insulin, usually by starting with a patient’s largest meal of the day. The addition of prandial insulin is associated with a higher incidence of weight gain and hypoglycemia than the addition of a

glucagon-like peptide 1 (GLP-1) receptor agonist to basal insulin (22–24).

If prandial insulin is used, a rapid-acting insulin formulation (i.e., lispro, glulisine, or aspart) should be considered over regular or short-acting insulin because of its faster rate of absorption, higher maximum concentration, shorter duration of action, lower incidence of hypoglycemia, and action profile that more closely resembles that of meal-stimulated endogenous insulin release (25,26). Ultra-rapid-acting insulin aspart is also available and contains the addition of vitamin B3 (niacinamide) and an amino acid (L-arginine) to stabilize the formulation (27). Compared with rapid-acting insulin aspart, the ultra-rapid-acting formulation has a quicker onset of action and a faster offset of exposure and can be dosed at mealtime or within 20 minutes after starting a meal (27,28). For select patients (Table 2), a rapid-acting human Technosphere insulin is available and administered via a breath-powered oral inhaler (29). Compared with injectable prandial insulin, this inhaled insulin has a faster onset and shorter duration of action (30).

The use of prandial insulin requires extensive patient education on topics such as meal timing and the relationship between insulin doses and carbohydrate intake and also requires increased glucose monitoring. The additional injection burden and necessary patient education may explain in part why clinicians sometimes continue titrating basal insulin beyond appropriate doses rather than adding prandial insulin to the regimen.

Premixed Insulin

Premixed insulin (e.g., NPH/regular 70/30) is administered either before the largest meal of the day or, more commonly, as two injections per day before breakfast and dinner (31). Therefore, its use allows for less flexibility in dosing than a basal-bolus insulin regimen. Although premixed insulin is less costly than insulin analogs, patients must eat regular meals and may be at greater risk for hypoglycemia than with a basal-bolus regimen (31,32). The choice of whether to initiate a basal-bolus or premixed insulin regimen should be patient specific, accounting for eating habits, preferences, convenience, and cost (13).

GLP-1 Receptor Agonists

A GLP-1 receptor agonist should be considered before basal insulin therapy for most patients and can also be considered as add-on therapy in patients needing treatment intensification beyond basal insulin (13,16). This recommendation is based on evidence demonstrating

TABLE 1 When to Consider Treatment Intensification Beyond Basal Insulin

Definition of overbasalization: the titration of basal insulin beyond an appropriate dose in an attempt to achieve glycemic targets

How to identify overbasalization:

- Basal insulin dose >0.5 units/kg/day
- Postmeal blood glucose >180 mg/dL
- A1C not at goal despite target fasting blood glucose level being achieved
- BeAM differential ≥ 50 mg/dL

TABLE 2 Pharmacologic Treatment Intensification Strategies Beyond Basal Insulin

Generic (Brand)	Favorable Effects	Unfavorable Effects/Cautions	Clinical Pearls for Drug Selection and Management Beyond Basal Insulin
Metformin (Glucophage)	<ul style="list-style-type: none"> • High efficacy • Low hypoglycemia risk • Weight neutral/modest loss • Low cost 	<ul style="list-style-type: none"> • Long-term use associated with vitamin B12 deficiency (monitor if peripheral neuropathy, anemia) • Contraindicated when eGFR <30 mL/min/1.73 m² • Rare/serious safety concerns: lactic acidosis 	<ul style="list-style-type: none"> • Should be continued, if tolerated and not contraindicated • May require basal insulin dose reduction upon initiation • Consider metformin XR if previous GI intolerance to metformin IR
Thiazolidinediones Pioglitazone (Actos) Rosiglitazone (Avandia)	<ul style="list-style-type: none"> • High efficacy • Low hypoglycemia risk • Low cost • Benefit in NASH 	<ul style="list-style-type: none"> • Weight gain • Fluid retention/edema (among those with heart failure) • Bone fractures (among postmenopausal females and elderly males) • Bladder cancer (pioglitazone) • Increased LDL-C (rosiglitazone) 	<ul style="list-style-type: none"> • May require basal insulin dose reduction upon initiation • May cause weight gain when used in combination with insulin
Sulfonylureas Glipizide (Glucotrol) Glimepiride (Amaryl) Glyburide (Diabeta)	<ul style="list-style-type: none"> • High efficacy • Low cost 	<ul style="list-style-type: none"> • High risk of hypoglycemia • Weight gain 	<ul style="list-style-type: none"> • May cause weight gain when used in combination with insulin • Consider discontinuing when initiating combination injectable therapy
GLP-1 receptor agonists Liraglutide (Victoza) Exenatide ER (Bydureon) Dulaglutide (Trulicity) Semaglutide injection (Ozempic) Semaglutide oral (Rybelsus) Lixisenatide (Adlyxin)	<ul style="list-style-type: none"> • High efficacy • Low hypoglycemia risk • Weight loss (semaglutide> liraglutide>dulaglutide> exenatide>lixisenatide) • CV benefits (liraglutide>dulaglutide> semaglutide injection) • Renal benefits seen with liraglutide (LEADER) and injectable semaglutide (SUSTAIN-6) 	<ul style="list-style-type: none"> • High cost • Avoid in setting of gastroparesis • GI intolerance (nausea, vomiting, diarrhea) • Rare/serious safety concerns: MEN2 or thyroid C-cell tumors, acute pancreatitis, worsening of diabetic retinopathy complications (semaglutide oral and injection) 	<ul style="list-style-type: none"> • Consider prior to basal insulin in most patients • May require a lower insulin dose when initiating a GLP-1 receptor agonist • Shorter-acting agents have greater PPG reduction vs. longer-acting agents
SGLT2 inhibitors Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance) Ertugliflozin (Steglatro)	<ul style="list-style-type: none"> • Intermediate efficacy • Low hypoglycemia risk • Weight loss • CV benefits (empagliflozin and canagliflozin) • Renal benefits seen with canagliflozin in CREDENCE; ongoing trials with dapagliflozin (DAPA-CKD) and empagliflozin (EMPA-KIDNEY) • Modest decrease in blood pressure 	<ul style="list-style-type: none"> • High cost • Genitourinary infections • Volume depletion/hypotension • Rare/serious safety concerns: amputation risk (canagliflozin and ertugliflozin), eDKA, bone fractures (canagliflozin), urinary tract infections, Fournier's gangrene 	<ul style="list-style-type: none"> • May require basal insulin dose reduction upon initiation
DPP-4 inhibitors Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta) Alogliptin (Nesina)	<ul style="list-style-type: none"> • Intermediate efficacy • Low hypoglycemia risk • Weight neutral 	<ul style="list-style-type: none"> • High cost • Joint pain • Potential risk for heart failure exacerbation (saxagliptin, alogliptin) • Rare/serious safety concerns: acute pancreatitis, joint pain 	<ul style="list-style-type: none"> • Consider discontinuing DPP-4 inhibitor when initiating a GLP-1 receptor agonist

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TABLE 2 Pharmacologic Treatment Intensification Strategies Beyond Basal Insulin (continued)

Generic (Brand)	Favorable Effects	Unfavorable Effects/Cautions	Clinical Pearls for Drug Selection and Management Beyond Basal Insulin
Fixed-ratio combinations (basal insulin plus GLP-1 receptor agonist) Insulin degludec plus liraglutide (Xultophy) Insulin glargine plus lixisenatide (Soliqua)	<ul style="list-style-type: none"> • Once-daily regimen • Less hypoglycemia and weight gain compared with intensive insulin regimens • Greater reduction in BeAM differential glucose as compared with insulin glargine monotherapy • Reduced GI side effects vs. GLP-1 receptor agonist alone 	<ul style="list-style-type: none"> • High cost • Less flexibility in dosing • GI side effects 	<ul style="list-style-type: none"> • For initiation, if currently on GLP-1 receptor agonist, use 10–16 dose steps (Xultophy) or 10–15 units (Soliqua) • Dose adjustments should be made based on target FBG every 3–4 days
Prandial insulin (rapid-acting analogs) Insulin lispro (Humalog) Insulin glulisine (Apidra) Insulin aspart (Novolog) Ultra-rapid-acting insulin aspart (Fiasp) Inhaled human insulin (Afrezza)	<ul style="list-style-type: none"> • Highest efficacy • Greater flexibility in dosing vs. premixed insulin • Inhaled option available for select patients desiring less injections 	<ul style="list-style-type: none"> • High cost • Weight gain • Multiple daily injections 	<ul style="list-style-type: none"> • Mimics physiological meal-stimulated insulin release • Consider rapid-acting over short-acting insulin for less risk of hypoglycemia • Fiasp has a quicker onset of action and faster offset of exposure and can be dosed at mealtime or within 20 minutes after starting a meal • Initial dose of lispro, glulisine, or aspart should be 4 units or 10% of the basal dose with the largest meal • Titrate lispro, glulisine, or aspart by 1–2 units or 10–15% twice weekly • Afrezza is available in three cartridge strengths (4, 8, and 12 units) and is contraindicated in patients with chronic lung disease (asthma, COPD) and is not recommended in patients who smoke or recently quit smoking
Premixed insulin NPH/regular 70/30 (Humulin 70/30) Lispro 50/50 (Humalog 50/50) Lispro 75/25 (Humalog 75/25) Lispro 75/25 (Humalog 75/25) Aspart 70/30 (Novolog 70/30)	<ul style="list-style-type: none"> • Lower costs compared with basal insulin analogs • Fewer injections compared with basal-bolus regimens • Simplified regimen vs. basal-bolus 	<ul style="list-style-type: none"> • High incidence of nocturnal hypoglycemia and glycemic variability • Less flexibility in dosing 	<ul style="list-style-type: none"> • May be initiated in insulin-naïve patients and those already receiving insulin requiring treatment intensification

COPD, chronic obstructive pulmonary disease; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-CKD, A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; eDKA, euglycemic diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; FBG, fasting blood glucose; GI, gastrointestinal; IR, immediate release; LDL-C, LDL cholesterol; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes; MEN2, multiple endocrine neoplasia syndrome type 2; NASH, nonalcoholic steatohepatitis; PPG, postprandial glucose; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects with Type 2 Diabetes; XR, extended release.

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high efficacy, lower risk of hypoglycemia, and greater weight reduction of GLP-1 receptor agonists compared with insulin (33–35). Additionally, GLP-1 receptor agonists have been found to decrease major adverse cardiovascular (CV) events and mortality in patients with atherosclerotic cardiovascular disease (ASCVD) and those with increased ASCVD risk (36–38).

Fixed-Ratio Combination Products

A newer pharmacologic option, which uses a fixed-ratio combination of basal insulin and a GLP-1 receptor agonist, harnesses great potential to address overbasalization in clinical practice. Fixed-ratio combination products have been shown to reduce the bedtime-morning (BeAM) differential more than monotherapy with insulin glargine (39). The BeAM differential is the difference between bedtime and pre-breakfast blood glucose values and can be calculated by subtracting the morning blood glucose value from the previous night's bedtime blood glucose value (40). The BeAM is clinically relevant, allowing clinicians to assess when it is appropriate to initiate prandial therapy (40). A BeAM value ≥ 50 mg/dL in patients with type 2 diabetes using basal insulin has been shown to be indicative of a need for prandial coverage (39,40).

Oral Antidiabetic Agents

Dipeptidyl peptidase 4 (DPP-4) inhibitors or sodium–glucose cotransporter 2 (SGLT2) inhibitors, if not already prescribed, may also be considered as add-on therapy to basal insulin because drugs from both classes address postprandial hyperglycemia. When added to basal insulin, SGLT2 inhibitors are associated with greater A1C and weight reduction, systolic blood pressure reduction, a lower incidence of hypoglycemia, and evidence of CV benefit (in select populations) compared with DPP-4 inhibitors (41). Therefore, an SGLT2 inhibitor should be considered as an additional agent before a DPP-4 inhibitor in this setting. This recommendation is supported in a 2018 consensus report from the ADA and the European Association for the Study of Diabetes (42).

Semaglutide is the first-in-class oral GLP-1 receptor agonist approved for the treatment of type 2 diabetes. When added to basal insulin in patients with uncontrolled type 2 diabetes, oral semaglutide demonstrated improved glycemic control and superior reduction in body weight compared with placebo (43). Additionally, oral semaglutide led to a reduction in total daily dose (TDD) of insulin without an increase in hypoglycemia compared with placebo (43). Oral semaglutide has not

demonstrated CV benefit, which was shown with the injectable formulation of the drug, although its non-inferiority to placebo for CV safety has been shown (44).

It is worth noting that metformin should be continued in combination with insulin therapy unless otherwise contraindicated (16).

Thiazolidinediones directly reduce insulin resistance and have high efficacy and a low risk of hypoglycemia (16). However, side effects such as weight gain, increased bone fracture risk, and risk of edema in patients with heart failure may limit their use (16).

As treatment is intensified beyond basal insulin, sulfonylureas may increase the risk of weight gain and hypoglycemia. Therefore, the dose of sulfonylurea should be gradually decreased until discontinued (13,16).

For patients who are already on a basal-bolus insulin regimen and still above their A1C goal, the drug regimen should be reevaluated. In such situations, the insulin TDD should be calculated, and basal insulin should not comprise $>50\%$ of the TDD (45).

Role of Glucose Monitoring

Patients with diabetes who use insulin should be instructed on appropriate self-monitoring of blood glucose (SMBG) (46). Continuous glucose monitoring (CGM) is an alternative to SMBG and allows patients to evaluate and react to glycemic patterns and trends. Such data can help to inform food intake, physical activity, and insulin titration, if necessary (46). Glucose monitoring, whether through SMBG or CGM, allows patients to evaluate their responses to drug therapy and to assess whether their glycemic targets are being met. An increase in available glycemic data may also better position clinicians to appropriately intensify treatment when warranted, which may help to avoid overbasalization.

Areas for Future Research

The prevalence of overbasalization in clinical practice has not been reported in the literature. Given the large proportion of people with type 2 diabetes who are not reaching treatment goals, and the even larger proportion of those on insulin therapy who are not reaching their goals, there is a clear need to 1) understand the prevalence of overbasalization, 2) investigate the maximum effective dose of basal insulin at which treatment intensification is warranted, and 3) develop strategies to overcome

overbasalization and hesitancy with regard to treatment intensification beyond basal insulin.

Conclusion

In summary, overbasalization can be defined as titration of basal insulin beyond an appropriate dose in an attempt to achieve glycemic targets. Overbasalization can be identified by a basal insulin dose >0.5 units/kg/day, postmeal blood glucose levels >180 mg/dL, A1C not at goal despite attainment of the fasting blood glucose target, or a BeAM differential \geq 50 mg/dL. Pharmacologic characteristics to consider when treatment intensification beyond basal insulin is necessary include patient preferences, tolerability, cost, safety, glycemic efficacy, risk of hypoglycemia, potential for weight loss, and CV risk reduction (13).

DUALITY OF INTEREST

No potential conflicts of interest were reported.

AUTHOR CONTRIBUTIONS

K.C. is the sole author and guarantor of this work.

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