Therapeutic Options for the Management of Postprandial Glucose in Patients With Type 2 Diabetes on Basal Insulin

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IN BRIEF For patients with type 2 diabetes who require add-on therapy to metformin plus basal insulin, GLP-1 receptor agonists may be a favorable option because they effectively manage postprandial glucose, reduce body weight, and have an overall favorable safety profile compared to other agents. Given the wide range of treatment combinations available for type 2 diabetes management, health professionals must partner with patients to determine the best choices based on patients' individual lifestyle, resources, and treatment goals.

Providing patients with optimal strategies for the management of hyperglycemia associated with type 2 diabetes is challenging. This is especially true as type 2 diabetes progresses and patients require two- and three-drug combinations or complex insulin regimens to achieve glycemic targets (1). Current consensus guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), as well as the 2015 diabetes management algorithm of the American Association of Clinical Endocrinologists, recognize that many different drug combinations can be used to achieve A1C goals (Figure 1) (1,2). Given this range of available therapeutic options, ADA/EASD guidelines emphasize the importance of individualized, patient-centered care (1). If patients are able to be involved with treatment decisions, health care professionals (HCPs) must use a shared decision-making process to increase patient satisfaction and adherence to treatment (3). HCPs should emphasize treatment outcomes that are also important to the patient (3). Factors to consider in such individualized type 2 diabetes treatment plans include patients' attitudes and willingness to make lifestyle changes and risk factors for hypoglycemia and other adverse events. HCPs should also consider patients' body weight, duration of disease, life expectancy, comorbidities, established vascular complications, overall level of support, and economic burdens of treatment (1). All treatment plans should include strategies for controlling obesity, blood pressure, and hyperlipidemia and emphasize smoking cessation, regular exercise, and healthy eating habits (4).

Targeting Fasting Plasma Versus Postprandial Plasma Glucose

The effects of different treatments on fasting plasma glucose (FPG) versus postprandial plasma glucose (PPG) have to be considered when determining an appropriate treatment regimen. Normalization of both FPG and PPG levels is usually necessary for patients to achieve A1C goals (4,5).

In patients with A1C levels >7.0% who are taking oral antidiabetic drugs (OADs), elevated FPG is the major contributor to overall hyper-

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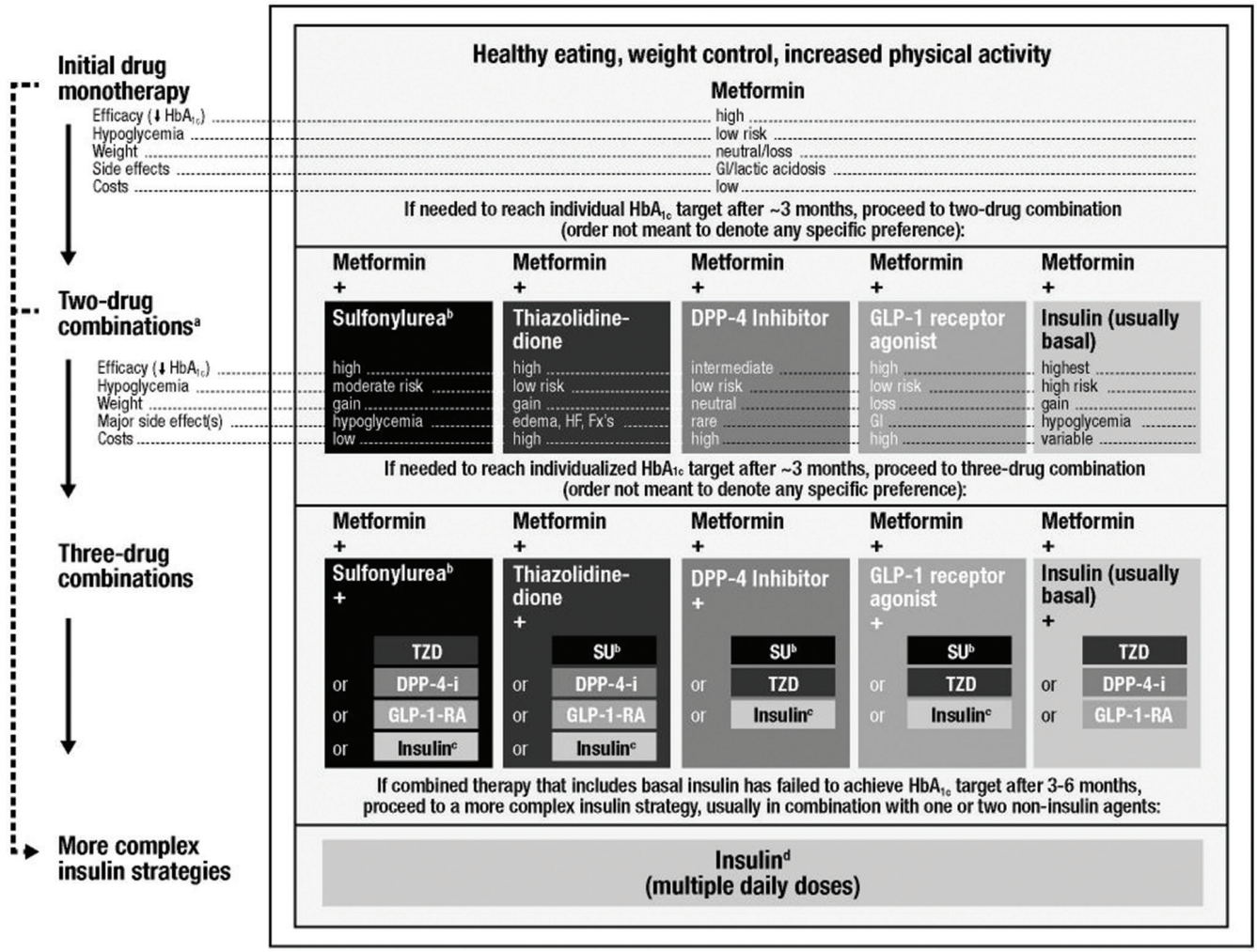

FIGURE 1. ADA/EASD general recommendations for type 2 diabetes management (1). DPP-4-i, DPP-4 inhibitor; Fx's, fractures; GLP-1-RA, GLP-1 receptor agonist; HF, heart failure; SU, sulfonylurea.

[a]Consider beginning at this stage in patients with a very high A1C level (e.g., ≥9%).

[b]Consider rapid-acting, nonsulfonylurea secretagogues (meglitinides) in patients with irregular meal schedules or who develop late postprandial hypoglycemia on sulfonylureas.

[c]Usually a basal insulin (NPH, glargine, or detemir) in combination with noninsulin agents.

[d]Certain noninsulin agents may be continued with insulin. Consider beginning at this stage if patient presents with severe hyperglycemia (≥300–350 mg/dL; A1C level ≥10.0–12.0%) with or without catabolic features (e.g., weight loss or ketosis).

glycemia (5,6). Although metformin is the traditional initial OAD therapy in type 2 diabetes, it is often not enough to maintain glycemic control for the long term. Additional OADs and noninsulin injections are added, and progressive β-cell failure often results in the need for insulin injections.

Initiation of basal insulin is often the first step in insulin therapy. When optimized, basal insulin therapy improves FPG but usually will not provide adequate PPG control (5). Therefore, when patients fail to reach glycemic goals on basal insulin, it is reasonable to consider adding a treatment that selectively targets PPG. Therapies such as mealtime insulin, thiazolidinediones (TZDs), DPP-4 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and meglitinides (or glinides) provide exogenous insulin, stimulate endogenous insulin, increase insulin secretion, and/or suppress postprandial glucagon, thus improving PPG levels (1,7–11). α-Glucosidase inhibitors also improve PPG levels by slowing intestinal carbohydrate digestion and absorption; however, they are currently used infrequently in clinical practice, possibly because of their associated gastrointestinal (GI) effects (1,12).

Case Study

Presentation

A 54-year-old white woman presents with a 9-year history of type 2 diabetes and a BMI of 27.2 kg/m^2. Her LDL cholesterol level is 135 mg/dL, and

her blood pressure is 148/86 mmHg. The patient's social history involves a hectic daily routine, with skipped or late meals, frequent fast-food dinners, and irregular exercise. Her medications include extended-release metformin 1,000 mg twice daily, glimepiride 4 mg once daily, lisinopril 10 mg once daily, atorvastatin 10 mg once daily, and glargine 34 units at bedtime. Laboratory testing shows her A1C level is 7.9%, up from 7.6% 3 months ago. When she was first prescribed insulin, her A1C level was 9.8%. It decreased to 7.1% after starting and titrating basal insulin but is now increasing again.

Management

Because this patient did not reach an A1C goal in the range of 6.5–7.0% on a multidrug regimen that included basal insulin, additional antihyperglycemic therapy is necessary. ADA/EASD guidelines recommend TZDs, DPP-4 inhibitors, sodium–glucose cotransporter 2 (SGLT2) inhibitors, or GLP-1 receptor agonists in patients whose type 2 diabetes is uncontrolled on basal insulin (1). Direct progression to more complex mealtime-plus-basal or premixed insulin regimens may be appropriate in patients with severe hyperglycemia (i.e., A1C ≥9.0%).

As with all type 2 diabetes treatment decisions, the choice of therapy for this patient should be based on individual factors, including risks of side effects, drug-drug interactions, cost, and likelihood of adherence to therapy (1). Choosing drugs with complementary mechanisms of action is also important to maximize glycemic benefits (1). Because basal insulin primarily targets FPG, patients such as this one who fail to achieve glycemic goals on basal insulin may benefit from drugs that target PPG (5). Additionally, steps should also be taken to improve control of the patient's high blood pressure and cholesterol levels (e.g., by titrating lisinopril to 20 mg and atorvastatin to 40 mg once daily). It is also crucially important to note that this patient may benefit from comprehensive diabetes education, with a focus on lifestyle interventions that include better food choices, modest portion sizes, consistent carbohydrate intake, and increased physical activity (1).

Possible Additions to Basal Insulin Therapy

TZDs

TZDs, now usually prescribed as pioglitazone, have been recommended for use in combination with insulin because they improve insulin sensitivity and are associated with a low risk of hypoglycemia (1,2,13). TZDs are appropriate options for patients with insulin resistance, metabolic syndrome, or nonalcoholic fatty liver disease (13). However, most of the antihyperglycemic effects associated with TZDs are the result of lowered FPG; these agents have only mild effects on PPG (13).

Risk-to-benefit analysis does not always support the use of TZDs. For patients who are already overweight, similar to the patient in the case presented above, a TZD added to basal insulin might increase weight and edema without providing a powerful postprandial benefit (2,13). Thus, it may not be an appropriate treatment option. The concomitant use of TZDs and insulin can also lead to fluid retention, increased risks of congestive heart failure, and increased fracture risk for postmenopausal women. More recent concerns about bladder cancer have not held up under further investigation (2,13,14).

DPP-4 Inhibitors

DPP-4 inhibitors may be a good option as initial or add-on therapy to basal insulin because they act predominantly to reduce PPG (10,15). In a recent study of the DPP-4 inhibitor linagliptin added to basal insulin with or without metformin and/or pioglitazone, linagliptin resulted in a statistically significant placebo-adjusted mean change in A1C from baseline of −0.65% (P <0.0001) (16). Although predicting an individual's response to therapy based on clinical trial averages is often problematic, the expected decrease in A1C from the DPP-4 drug class is ~0.5–0.7%, which would be insufficient to get the patient in our case to goal. More clinical studies of DPP-4 inhibitors as add-on agents to basal insulin are needed to develop a more complete efficacy profile for this class of drugs (17).

DPP-4 inhibitors are generally well tolerated, with a low incidence of hypoglycemia and neutral effects on body weight (16,18–20). For some DPP-4 inhibitors such as sitagliptin, saxagliptin, and alogliptin, dose reductions are required when treating patients with advanced chronic kidney disease (CKD) (18,19).

Meglitinides (or Glinides)

Meglitinides act by closing ATP channels on β-cell membranes, thereby increasing insulin secretion (1). Meglitinides have the advantage of flexible dosing, which is attractive for some patients with irregular meal schedules, because of their rapid onset and short duration of action. However, this profile is also a disadvantage because it requires more frequent dosing (1,21–23). Although meglitinides are effective in controlling PPG levels (22,23), a meta-analysis found a more modest decrease in A1C with meglitinides than with most other antidiabetic drug classes (24).

As with TZDs, weight gain has been reported with meglitinides. Therefore, this class is not an ideal treatment option for overweight patients such as our case (1,25). Meglitinides are also associated with a risk of hypoglycemia (1,25). However, they are associated with less weight gain (25) and hypoglycemia than sulfonylureas (26).

SGLT2 Inhibitors

SGLT2 inhibitors are a class of diabetes medications that lower the renal threshold and allow the kidneys to excrete excess glucose instead of "recirculating" it (27). This effect is

seen in the proximal tubule, well beyond the glomerulus, and results from blocking SGLT2-mediated glucose reabsorption, which accounts for ~90% of glucose normally reabsorbed (27). This loss of glucose provides significant reduction in A1C level (–0.78%) and, to some extent, FPG improvements (–0.70 mg/dL), as well as modest body weight loss (–0.59 kg) and reduction of systolic (–0.27 mmHg) and diastolic (–0.24 mmHg) blood pressure compared to placebo (27,28).

GLP-1 Receptor Agonists

Used in combination with basal insulin, with or without metformin or a sulfonylurea, GLP-1 receptor agonists can provide additional A1C and PPG lowering with a minimal risk of hypoglycemia and often allow for reduced basal insulin doses (9,29–32). Note that GLP-1 agonists have differential glycemic effects depending on their pharmacokinetic properties: whereas short-acting prandial compounds (e.g., exenatide and lixisenatide) primarily lower PPG via inhibition of gastric emptying, long-acting nonprandial compounds (e.g., exenatide extended-release, liraglutide, and albiglutide) have a stronger effect on FPG via their enhanced endogenous insulin and suppressed glucagon properties (33). Dulaglutide replaces both first- and second-phase insulin release and so would potentially affect both FPG and PPG.

GLP-1 receptor agonists are associated with clinically meaningful weight loss (~1–4 kg or 2–9 lb) because they increase satiety (34–36). For example, twice-daily exenatide added to basal insulin resulted in a significant body weight decrease of 1.8 kg (4.0 lb) compared to a 1.0-kg (2.2-lb) weight increase with placebo (between-group difference 2.7 kg or 6 lb) (30).

Although GLP-1 receptor agonists can cause mild to moderate GI side effects (e.g., nausea and vomiting), these usually subside and can be minimized with slower titration strategies (1,34,35). GLP-1 receptor agonists are generally well tolerated and have a low risk of hypoglycemia (34). Twice-daily exenatide is contraindicated in patients with GI disease (gastroparesis) or stage 4 or 5 CKD (37). Rare but serious adverse cases of pancreatitis have been observed with GLP-1 receptor agonists (35). Prescribing information for liraglutide, dulaglutide, albiglutide, and exenatide extended-release (once-weekly formulation) contains a black-box warning about relatively rare thyroid C-cell cancer (medullary thyroid carcinoma) and multiple endocrine neoplasia syndrome type 2 (38,39).

Overall, GLP-1 receptor agonists provide A1C lowering that is superior to DPP-4 inhibitors and have more favorable effects on body weight (17). Therefore, addition of a GLP-1 receptor agonist to our patient's current regimen would be a logical therapeutic option to consider. Although these agents are injectable, they are delivered subcutaneously using very short needles.

Prandial Insulin

The patient presented in our case has longstanding type 2 diabetes. Therefore, it is likely that her β-cell function is compromised (minimal), and additional insulin therapy may provide the most robust A1C response (1). If basal insulin has been titrated to a dose that effectively controls FPG but the patient is experiencing significant PPG excursions (>180 mg/dL), the addition of mealtime insulin in the past was the traditional option (40). Now other options are available that may increase simplicity while reducing the risk of hypoglycemia and weight gain.

Indeed, a basal-bolus regimen using rapid- and long-acting analog insulins remains the gold standard for insulin therapy. Premixed insulin formulations do not allow for flexibility in meal times (41–43). Basal-bolus therapy also offers individualization of treatment based on regularity of eating habits, risk of hypoglycemia, patient dosing preferences, and cost (1,40). Also, basal-bolus regimens allow insulin doses to be adjusted more easily to optimize glycemic control (43). However, they do have some inherent disadvantages. These include a significantly increased risk of hypoglycemia, the addition of extra calories to treat low glucose levels, and the need for frequent self-monitoring of blood glucose (40). Also, the potential for clinically significant weight gain from such a regimen is especially undesirable for most patients with type 2 diabetes who are already overweight (44).

For these reasons, adding mealtime insulin may not be a preferred strategy for our patient. Furthermore, hypoglycemia is particularly dangerous for patients with other complicating factors such as older age (45,46) or cardiovascular comorbidities (e.g., coronary artery disease) (47). Patients with type 2 diabetes and comorbid CKD are also at an increased risk of severe hypoglycemia (48).

Discussion

To get patients to glycemic goal, both their FPG and PPG must be controlled. Basal insulin may effectively control FPG levels, but it will have little effect on PPG (4,5). Quite often in clinical practice, when patients are overweight and afraid of hypoglycemia, an SGLT2 inhibitor, DPP-4 inhibitor, or GLP-1 receptor agonist may be the best option as add-on therapy to basal insulin.

GLP-1 receptor agonists more effectively reduce A1C compared to DPP-4 inhibitors, significantly reduce body weight, and have more favorable safety profiles than other antihyperglycemic agents (e.g., TZDs, meglitinides, and additional mealtime insulin) (36). In a recent study, lixisenatide, a once-daily GLP-1 receptor agonist, resulted in an additional placebo-adjusted 0.4% reduction in A1C from baseline versus placebo on a background of basal insulin with or without metformin (9). Another trial conducted in

patients with type 2 diabetes uncontrolled on insulin glargine showed that adding twice-daily exenatide reduced A1C from baseline by a placebo-adjusted 0.7% (30). Thus, our patient could reasonably achieve a goal A1C level of 6.5–7.0% with optimization of her current regimen and addition of a GLP-1 receptor agonist.

If our patient loses weight after starting a GLP-1 receptor agonist, her overall condition may markedly improve because even a modest weight loss of ~5–10% can result in better glucose control and reduced cardiovascular risk (1). With improved glycemic control and weight loss, this patient's quality of life may ultimately improve, likely as a result of a reduction in the anxiety that is often associated with weight gain (49). The lower risk of hypoglycemia with GLP-1 receptor agonists and basal insulin compared to a basal-bolus insulin regimen will be an added advantage. Appropriate modifications in lisinopril and atorvastatin dosages, along with better food choices and increased physical activity, may also reduce this patient's blood pressure and lipid levels.

In clinical practice, consistent with the 2015 ADA/EASD guidelines for the management of type 2 diabetes, GLP-1 receptor agonists can be introduced at multiple stages throughout type 2 diabetes treatment (1). GLP-1 receptor agonists are a versatile class of antihyperglycemic agents because they can be used as initial monotherapy when metformin is contraindicated, as add-on therapy to metformin, or as part of three- or four-drug combinations that exclude DPP-4 inhibitors. For example, a GLP-1 receptor agonist could have been introduced in our patient's regimen before moving to basal insulin. Data on randomized clinical studies investigating this approach are generally limited. However, one recent study (50) evaluated a treatment intensification sequence of adding a GLP-1 receptor agonist to metformin, followed by further intensification with systematically titrated basal insulin in patients with an A1C level ≥7%. The study found that this strategy yielded good glycemic control and substantial weight loss, with very low hypoglycemia rates and acceptable tolerability.

Given the wide range of treatment combinations available for managing type 2 diabetes, HCPs must work with patients to determine the best treatment choices for their individual lifestyle and treatment goals (1). For successful long-term management, patients should actively participate in decisions about their treatment and daily self-management (1). Patients' active involvement will facilitate better adherence to therapeutic regimens (1). Diabetes education is essential for all treatment plans and must include ongoing support from and engagement with educators and clinicians (1).

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Duality of Interest

The author serves on speaker's bureaus for Boehringer Ingelheim, AstraZeneca, Eli Lilly and Company, Janssen, PamLab, and Sanofi, as well as various medical education companies and serves on advisory boards for Abbott, Boehringer Ingelheim, CeQur, Eli Lilly and Company, Janssen, Roche, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

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