Insulin Tactics in Type 2 Diabetes

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KEYWORDS

• Type 2 diabetes • Insulin secretion • Exogenous insulin profiles
• Insulin administration • Insulin adjustment • Noninsulin therapy

KEY POINTS

- Type 2 diabetes is a multifactorial disease comprising insulin resistance, relative insulin deficiency, increased hepatic glucose output, and increased renal glucose reabsorption, which together result in failure to maintain normal glucose homeostasis.
- Therapeutic interventions for Type 2 diabetes include lifestyle modifications, noninsulin drugs, and insulin therapy.
- Although insulin can be used as stand-alone therapy, it is more commonly used as add-on to other noninsulin agents.
- Insulin treatment in Type 2 diabetes is generally instituted with basal insulin alone and intensified to basal plus bolus insulin regimens if glycemic goals are not achieved.
- Self-monitored blood glucose (SMBG) testing is critical in guiding the titration of insulin treatment.
- The addition of newer noninsulin drugs to previous insulin treatment may allow for partial or complete reduction of the insulin.
- Patient education by a multidisciplinary treatment team that includes diabetes educators is helpful in maximizing efficacy and minimizing adverse events related to the use of insulin.

INTRODUCTION

Type 2 diabetes (T2D) is a heterogeneous disorder in which multiple pathophysiologic defects result in an imbalance between the rate of glucose production (which is increased) and its disposal (which is decreased) resulting in hyperglycemia (Fig. 1). Among the defects is insulin resistance, leading to decreased glucose uptake by peripheral tissues (predominantly the muscles) and an increase in hepatic glucose production (gluconeogenesis). Compounding this are defects in incretin hormones,

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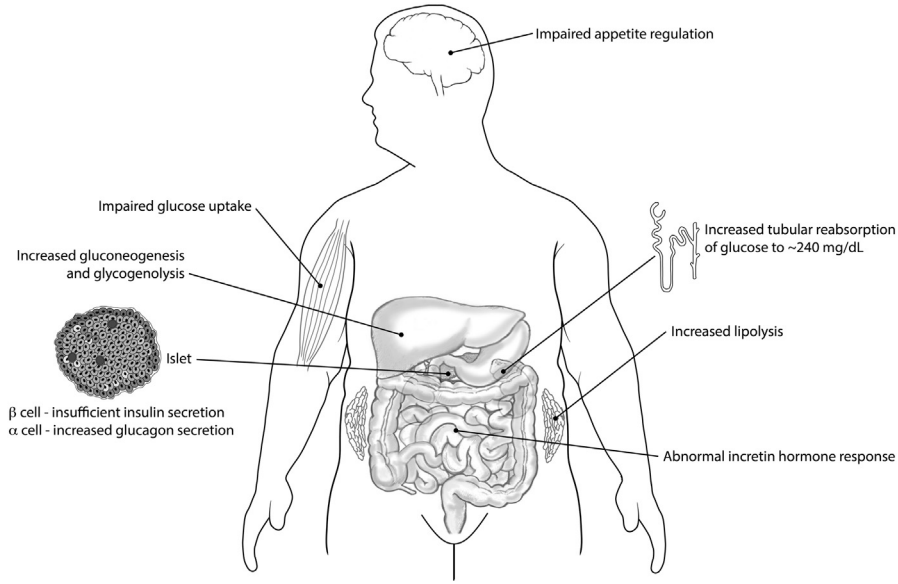

Fig. 1. Pathophysiologic defects in T2D.

resulting in decreased postprandial insulin release by the beta (β) cells accompanied by a failure to suppress glucagon by the alpha (α) cells, resulting in postprandial hyperglycemia and continued release of glucose from hepatic glycogen stores (glycogenolysis).[1] Furthermore, there is increased renal tubular reabsorption of glucose due to upregulation of sodium glucose co-transporters-2 (SGLTs-2) and a β-cell deficiency secondary to a decrease in its numbers, mass, and function.[1,2] All these factors together increase the workload of the β cell, which can, over time, lead to its exhaustion, implying that insulin therapy might be an inevitable consequence of longstanding T2D.[3–5]

Therapy with insulin, however, has challenges, because unlike most other drugs, it needs to be dosed in synergy with the peaks and troughs of glucose. Commercially available insulin, however, does not share the physiologic properties of endogenous insulin. It is therefore important to understand the pharmacokinetic properties of insulin preparations and to time the dose of the insulin to meet the needs of the patient. In this article, we discuss strategies of how to introduce insulin as a treatment option in patients with T2D and how to decrease it when other noninsulin drugs are added to the treatment.

Physiology of Insulin Production

Insulin secretion in the nondiabetic individual

Following an overnight fast, the liver of nondiabetic individuals produces glucose at a rate of approximately 2.0 mg/kg/min (**Fig. 2**).[1] The kidneys reabsorb most of this glucose, based on a physiologically set renal threshold of approximately 180 mg/dL, resulting in less than 0.5 g of glucose being excreted per day.[1,6] This glucose (referred to as basal glucose) is metabolized by a steady production of basal insulin by the β cell and euglycemia is maintained. With an oral load of glucose, such as during a meal, additional bolus (also referred to as prandial) insulin is secreted by the β cells (**Fig. 3**) to help in its metabolism.

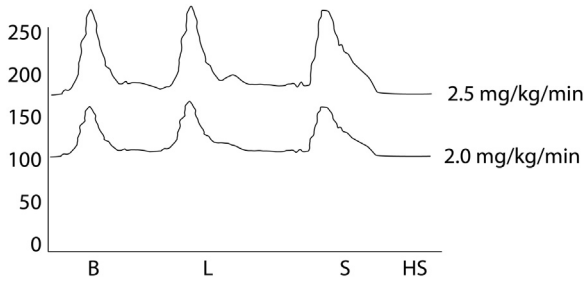

Fig. 2. Endogenous glucose production of the nondiabetic and the diabetic individual. Compared with nondiabetic individuals who produce glucose at a rate of 2.0 mg/kg/min, hepatic glucose output in diabetic individuals is increased to a rate of 2.5 mg/kg/min. In addition, in response to an oral glucose load, diabetic individuals experience a greater rise in glucose related to insufficient insulin production. B, breakfast; L, lunch; S, supper/dinner; HS, bedtime.

As seen in **Fig. 4**, insulin (along with C-peptide) packaged in membrane-bound storage granules in the pancreatic β cell, is released into the portal circulation in a pulsatile and biphasic manner when stimulated by rising glucose.[7] The first phase of insulin release (FPIR) is steep, with an onset in 1 minute and lasting 5 to 10 minutes.[8] It is believed that this FPIR reflects the immediate discharge of primed and docked insulin from secretory vesicles due to direct stimulation by glucose and indirectly through the production of intestinal incretin hormones.[1] This first phase is followed by a second phase of insulin release, which is gradual, and most likely requires mobilization of secretory insulin granules to the cell membrane before their discharge.[7] Once released, insulin enters the portal circulation and is cleared by the liver. The concentration of insulin in the portal vein therefore is twofold to fourfold higher than in the peripheral circulation.[9] This higher concentration of insulin in the portal vein is important in suppressing hepatic glucose production; an important attribute of endogenously produced insulin. When administered exogenously (ie, as a drug), insulin enters the peripheral circulation directly, bypassing the portal circulation, creating an insulin gradient in which peripheral hyperinsulinemia is necessary to suppress hepatic

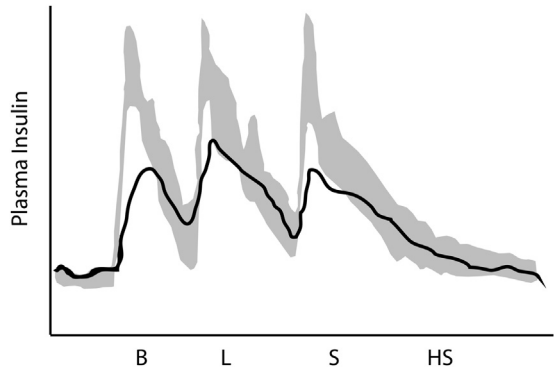

Fig. 3. Endogenous insulin production of the nondiabetic and the diabetic individual. Pulsatile endogenous insulin production in the nondiabetic individual (*gray shaded areas*) closely maintains euglycemia during and between meals. In the diabetic individual (*black lines*), FPG is elevated, as there is insufficient basal insulin production by the pancreatic β cell. In addition, there is insufficient mealtime insulin production due to a blunted FPIR and incretin hormone defects. B, breakfast; L, lunch; S, supper/dinner; HS, bedtime.

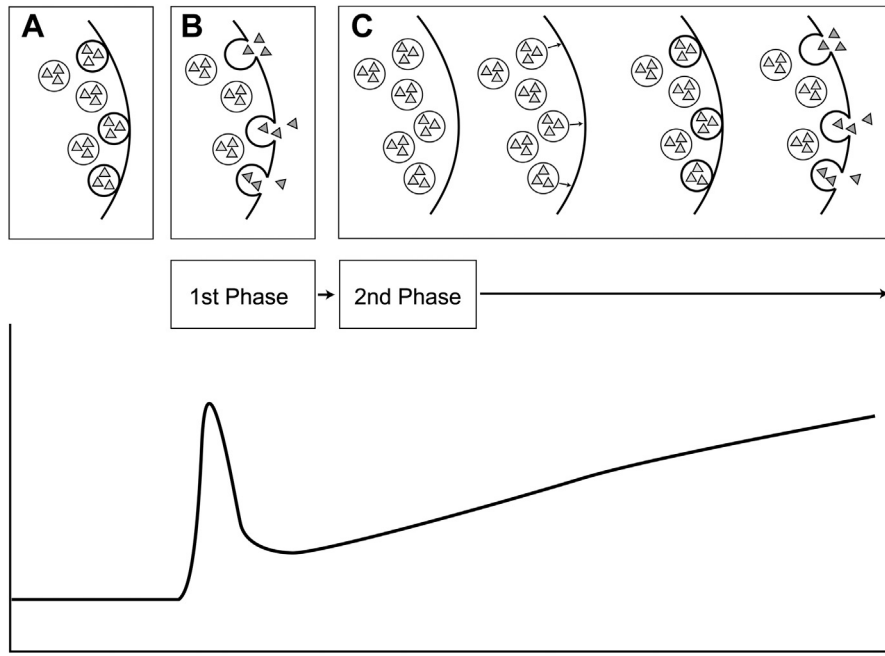

Fig. 4. The first and second phases of insulin secretion. Insulin (Δ) is packaged in membrane-bound insulin secretory granules in the pancreatic β cell. (*A, B*) The steep first-phase insulin response reflects the immediate discharge of primed and docked insulin from secretory vesicles due to direct stimulation by glucose and indirectly through intestinal incretin hormones. The second phase of insulin release is gradual and requires mobilization of insulin secretory granules to the cell membrane before their discharge (*C*).

glucose production.[9] This explains why high doses of exogenous insulin are often required in patients with insulin resistance.

Insulin secretion in individuals with type 2 diabetes

In patients with T2D, hepatic glucose output is increased to 2.5 mg/kg/min secondary to multiple defects, as discussed previously (see **Figs. 2** and **3**).[1] In addition, the renal threshold in T2D can be increased up to 240 mg/dL due to upregulation of SGLT-2 transporters,[6,10] resulting in the kidneys reabsorbing excessive amounts of glucose (see **Fig. 1**), further adding to the hyperglycemia.

Normally, the β cell responds to an increment change in glucose (ΔG) with an increment change in insulin (ΔI). With increasing insulin resistance, the β cell increases its secretion. This changing insulin response to changing insulin sensitivity forms a hyperbolic relationship termed the disposition index and can be used to provide an assessment of β-cell function (**Fig. 5**).[11–13] At any given insulin sensitivity, the capacity of the β cell can be measured by exposing it to an intravenous glucose challenge: the Acute Insulin Response to Glucose ($AIR_{glucose}$). As seen in **Fig. 5**, patients who can maintain adequate β-cell secretion, such as those with polycystic ovarian syndrome might not progress to hyperglycemia despite substantial insulin resistance.[12,13] If, however, the $AIR_{glucose}$ decreases with increasing insulin resistance, patients progress from normal glucose tolerance to impaired glucose tolerance and eventually T2D. Relative insulin deficiency is therefore a key pathophysiological defect in T2D and exogenous insulin therapy becomes a therapeutic option for all patients.

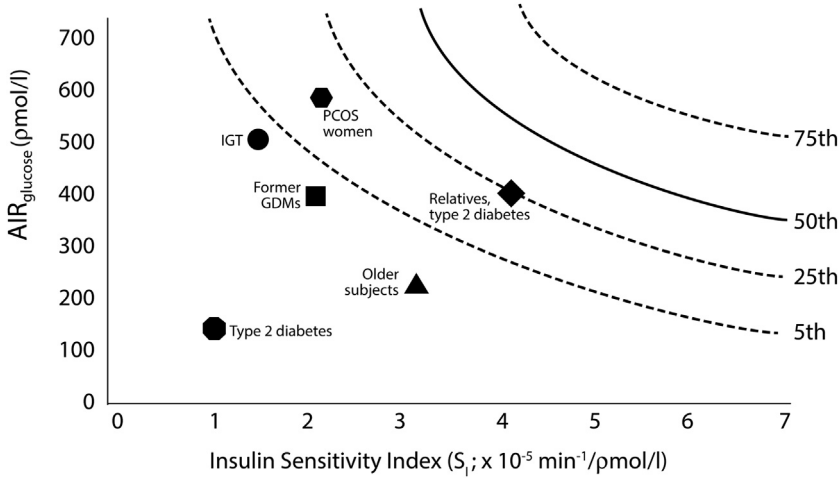

Fig. 5. Insulin sensitivity and insulin secretion. At any given insulin sensitivity, the residual capacity of the β cell can be measured by exposing it to an intravenous glucose challenge called the Acute Insulin Response to Glucose (AIRglucose). If the AIRglucose decreases with increasing insulin resistance, patients progress from normal glucose tolerance to impaired glucose tolerance, and eventually T2D. Patients who can maintain adequate β-cell secretion, such as those with polycystic ovarian syndrome, might not progress to hyperglycemia despite substantial insulin resistance. (*From* Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia 2003;46(1):7; with permission.)

GUIDELINES FOR INITIATION OF INSULIN IN TYPE 2 DIABETES

Before one can initiate insulin (or any drug therapy) in a patient with diabetes, it is critical that goals of treatment are established. The first of these goals is the trigger for initiation of a new drug. The second goal is to set parameters under which therapy needs to be advanced either with the same drug or with the addition of new agents.

The trigger to initiate drug therapy can be either the hemoglobin A1c (HbA1c) or self-monitored blood glucose values (SMBG). In general, it is easiest to use HbA1c as the trigger for initiation of therapy; a parameter used by most guidelines. SMBG can then be used to modify the initiated therapy.

The most commonly used guidelines for the treatment of T2D used in the United States come from the American Diabetes Association (ADA) (**Fig. 6**)[14] and the American Association of Clinical Endocrinologists (AACE) (**Fig. 7**).[15] The ADA guidelines recommend a target HbA1c of 7.0% or lower in most patients. More stringent HbA1c targets of 6.0% to 6.5% are recommended in patients with short disease duration, long life expectancy, and no significant history of cardiovascular disease; provided these goals can be achieved without adverse effects (particularly hypoglycemia). Less-stringent HbA1c targets of 7.5% to 8.0% are recommended in patients with long disease duration, short life expectancy, history of severe hypoglycemia, advanced complications, extensive comorbid conditions, and in patients difficult to control despite intensive education (see **Fig. 6**). With these guidelines, following metformin (MET) monotherapy as first line, the addition of a second drug is recommended if HbA1c is not at goal after 3 months. Importantly, besides HbA1c-lowering ability, the ADA guidelines recommend consideration to cost, effect on weight, hypoglycemia risk, and potential for side effects when making the choice of second agent, with basal

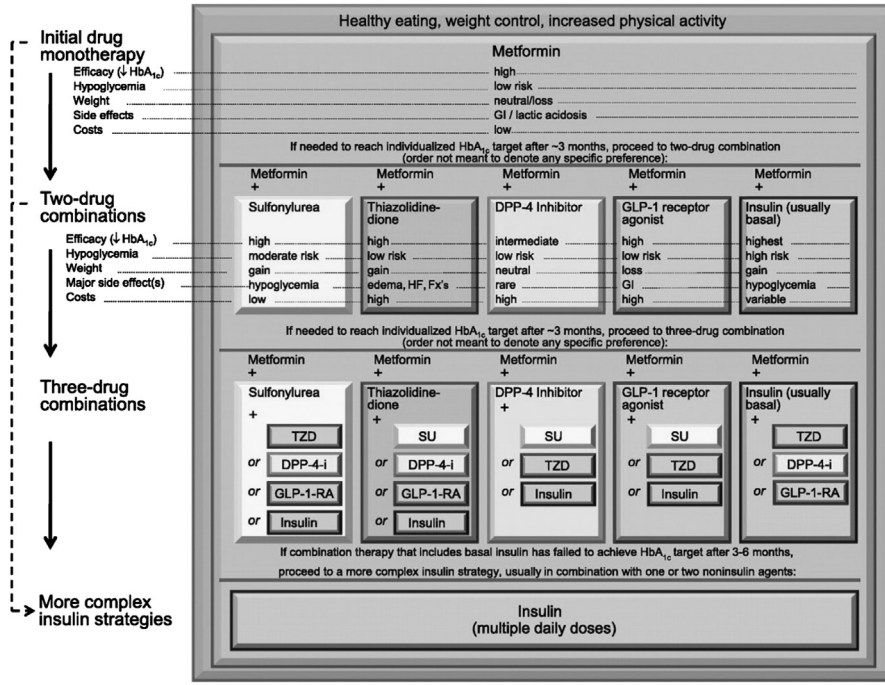

Fig. 6. The ADA treatment algorithm for T2D. These guidelines recommend MET monotherapy followed by addition of agents every 3 months if HbA1c is not at goal. Basal insulin can be used as a second-line agent. The guidelines recommend taking into consideration efficacy, hypoglycemia risk, effect on weight, side-effect profile, and cost when making a choice of drug. (*From* the American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014;37(Suppl 1):S14; with permission.)

insulin being one of the choices (see **Fig. 6**). After 3 to 6 months of a 2-drug regimen, if HbA1c targets are still not achieved, the guidelines recommend addition of a third noninsulin agent or intensification of insulin therapy if already initiated.[14]

The AACE treatment algorithm also uses HbA1c as a guide to therapy; however, they recommend a more stringent goal of 6.5% or lower for most patients. In addition, these guidelines use baseline HbA1c itself as *the trigger for choosing the number of drugs* with which to start therapy (see **Fig. 7**). With the AACE guidelines, for patients with baseline HbA1c less than 7.5%, monotherapy with any of the approved noninsulin agents is considered appropriate. For patients with baseline HbA1c between 7.5% and 9.0%, these guidelines recommend a 2-drug approach with MET plus another agent from a different class, including basal insulin. For patients with a baseline HbA1c higher than 9.0%, the AACE guidelines recommend initiating therapy with an aggressive 2-drug or in some cases even a 3-drug approach, and in severely symptomatic patients they recommend having insulin be one of these agents. Once treatment is initiated, these guidelines go on to recommend an aggressive 3-monthly up-titration of therapy with the addition of additional drugs if HbA1c targets of 6.5% or lower are not achieved.[15]

Our own approach is a hybrid of the ADA and AACE guidelines. As initial therapy, we prefer a "MET Plus" approach; maximizing MET over a period of 1 month to 2000 mg per day or the maximum tolerated dose followed by the addition of a second noninsulin agent in 1 to 3 months irrespective of HbA1c. If MET is contraindicated or not tolerated,

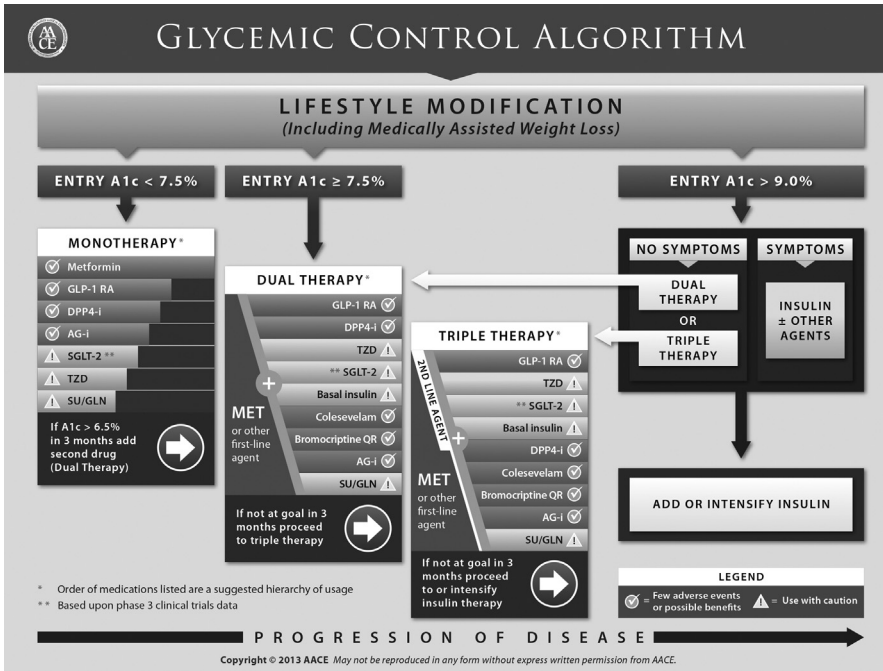

Fig. 7. The AACE treatment algorithm for T2D. These guidelines make recommendations on the choice and number of agents based on baseline HbA1c. (*From* American Association of Clinical Endocrinologists. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm. Endocr Pract 2013;19:6; with permission.)

we use one of the other noninsulin oral agents from the AACE guidelines as first line.[15] We use this approach to address the multiple pathophysiological defects of T2D[1] because we have found that single-drug approaches generally fail to maintain HbA1c over time similar to what has been observed in the UK Prospective Diabetes Study and A Diabetes Outcome Progression Trial (ADOPT) Study.[16,17] Our choice of second drug is based on the criteria of cost, hypoglycemia risk, weight-losing properties, and side-effect profiles as proposed by the ADA (**Fig. 8**).[14] If a 2-drug regimen is ineffective in maintaining HbA1c, a third drug from a different class can be added. We, however, wait 6 to 12 months before proceeding from a 2-drug to a 3-drug regimen. Waiting for this period is particularly helpful when using agents that can result in weight loss; therapies that have the potential to continue to modify the diabetes disease process by reducing insulin resistance. In addition, it can take up to 6 months or longer for a newly diagnosed patient to truly affect lifestyle changes, which may also alter the need for additional medications. Unless there is severe and symptomatic hyperglycemia, we try different combinations of noninsulin agents for a period of 12 to 24 months before considering insulin. We initiate insulin therapy earlier if weight loss has stabilized but hyperglycemia persists or if weight loss continues in the setting of sustained hyperglycemia, indicating an insulin-deficient, catabolic state. We also consider insulin as a treatment option at the time of diagnosis of T2D for those patients who have severe symptoms of polyuria and polydipsia and especially those with excessive weight loss. In these individuals and in patients who do not manifest the typical features of metabolic syndrome, such as low high-density lipoprotein levels, high triglycerides, or hypertension, it may be appropriate to test for immune markers of Type 1 diabetes,

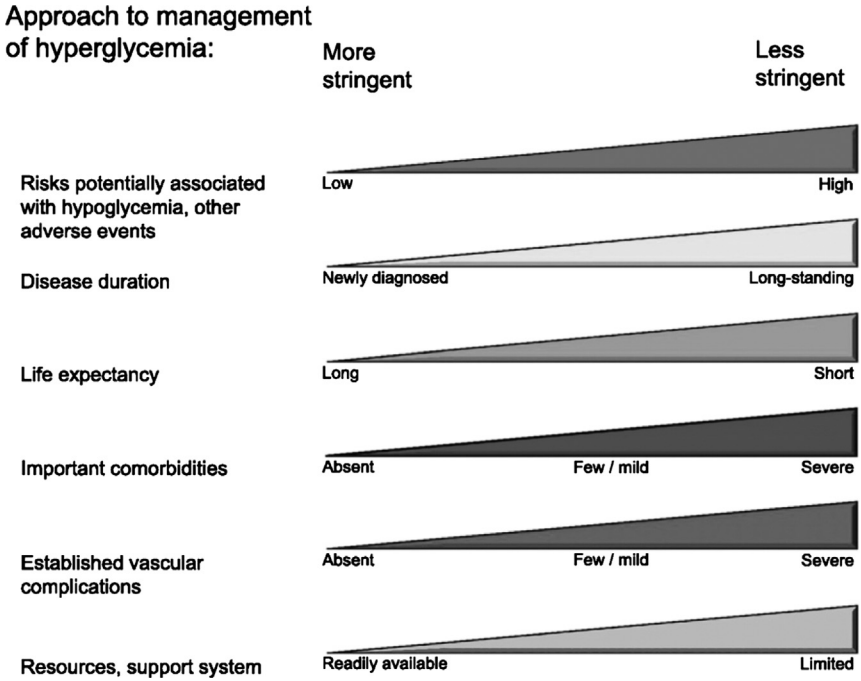

Fig. 8. ADA approach to management of hyperglycemia. Multiple factors contribute to the decision of which therapy to add to the therapeutic regimen in the treatment of T2D. Elements toward the left justify more stringent glycemic efforts, whereas those toward the right justify less-stringent efforts. (*From* the American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014;37(Suppl 1):S12; with permission.)

such as Glutamic Acid Decarboxylase (GAD) antibodies, to rule out the possibility of Latent Autoimmune Diabetes of the Adult (LADA), a condition not typically prone to ketoacidosis that can be managed initially with noninsulin therapy but may, in 6 to 12 months after diagnosis, require insulin to maintain glycemic goals.[18,19]

ROLE OF SELF-MONITORED BLOOD GLUCOSE IN ACHIEVING GLYCEMIC GOALS

Although HbA1c is typically measured every 90 days, it can be checked every 30 days in the early stages of therapy to monitor response. However, once insulin (or any noninsulin therapy) has been initiated, we find SMBG to be most helpful in guiding titration. Particularly in the early stages of insulin therapy, it is helpful for patients to monitor glucose fasting, before meals, and at bedtime to gauge an understanding of glycemic control. The ADA guidelines recommend a goal fasting plasma glucose (FPG) of less than 130 mg/dL and 2-hour post-prandial glucose (2h-PPG) less than 180 mg/dL[14] whereas the AACE guidelines recommend a goal FPG less than 110 mg/dL and 2h-PPG less than 140 mg/dL,[15] if these goals can be achieved safely without hypoglycemia. Once glycemic goals have been achieved, then checking SMBG 2 to 3 times daily (one must be fasting) may be adequate. PPG testing may be helpful in individuals on basal-bolus insulin therapy to help assess the adequacy of the chosen insulin-to-carbohydrate ratio (ICR) (discussed later).

It is important to keep in mind that SMBG goals chosen for the patient must be congruent with HbA1c targets for that patient. As seen in **Table 1**, for every 29-mg/dL

Table 1
Estimated average blood glucose (eAG) and hemoglobin A1c (HbA1c)

Hemoglobin A1c, %	Blood Glucose (range), mg/dL	Blood Glucose (range), mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Adapted from Nathan DM, Kuenen J, Borg R, et al. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31(8):1473–8.

increase in blood glucose (BG), HbA1c goes up by approximately 1%.[20] This relationship between HbA1c and BG is referred to as the estimated Average Glucose (eAG), and most validated laboratory assays for HbA1c now report an eAG result as well. Explaining this relationship to patients is helpful, because they can correlate their SMBG data with HbA1c goals.[20]

CHOOSING AN INSULIN PREPARATION

Because the basis of insulin therapy is to try to match the onset of insulin action, its peak, and duration with the onset, peak, and duration of its need to metabolize glucose, if there is a mismatch between glucose levels and the actions of the injected insulin, either hyperglycemia persists or hypoglycemia can result. Because the pharmacokinetic properties of exogenously administered insulin (when the insulin peaks) do not always match the pharmacodynamic needs of the body (when the insulin should peak), it is critical to understand the properties of different insulin preparations and choose a product based on the glycemic needs of the patient (**Fig. 9**, **Tables 2** and **3**).[21–23]

Human Insulin Preparations

The earliest insulins were derived from animal pancreas. These extracts had significant variability in their onset, peak, and duration of action depending on purification

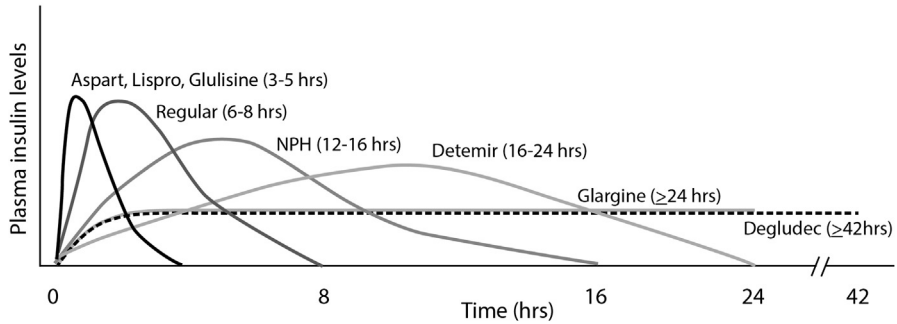

Fig. 9. Pharmacokinetics of exogenous insulin preparations.

Table 2
Pharmacokinetics of insulin preparations

Insulin	Onset	Peak	Duration of Action	Trade Name	Shelf Life (Days) After Opened	Manufacturer
Short-acting						
Human Regular	30–60 min	2–4 h	6–8 h	Humulin R	Vial (31) ΩΨ	Eli Lilly
				Novolin R	Vial (42) ΩΨ	Novo Nordisk (Bagsvaerd, Denmark)
Rapid-acting						
Lispro	5–15 min	0.5–1.5 h	3–5 h	Humalog	Vial (28)ΩΨ Pen (28)Ψ	Eli Lilly (Indianapolis, USA)
Aspart				NovoLog	Vial (28)ΩΨ Pen (28)Ψ	Novo Nordisk (Bagsvaerd, Denmark)
Glulisine				Apidra	Vial (28)ΩΨ Pen (28)Ψ	Sanofi (Bridgewater, USA)
Intermediate-acting						
NPH	1–2 h	6–12 h	12–16 h	Humulin N	Vial (31)ΩΨ Pen (14)Ψ	Eli Lilly (Indianapolis, USA)
				Novolin N	Vial (42)ΩΨ Pen (14)Ψ	Novo Nordisk (Bagsvaerd, Denmark)

Long-acting						
Glargine	1 h	Peakless	≥24 h	Lantus	Vial (28)ΩΨ Pen (28)Ψ	Sanofi (Bridgewater, USA)
Detemir	1 h	Peakless	16–≥24 h	Levemir	Vial (42)ΩΨ Pen (42)Ψ	Novo Nordisk (Bagsvaerd, Denmark)
Degludec[a]	0.5–1.5 h	Peakless	>42 h	Tresiba	Not Available in the US	Novo Nordisk (Bagsvaerd, Denmark)
Premixed						
70/30 NPH/Regular	30–60 min	Dual	10–16 h	Humulin 70/30	Vial (31)ΩΨ Pen (10)Ψ	Eli Lilly (Indianapolis, USA)
				Novolin 70/30	Vial (42)ΩΨ Pen (10)Ψ	Novo Nordisk (Bagsvaerd, Denmark)
75/25 NPL/Lispro	5–15 min	Dual	12–20 h	Humalog Mix 75/25	Vial (28)ΩΨ Pen (10)Ψ	Eli Lilly (Indianapolis, USA)
50/50 NPL/Lispro	5–15 min	Dual	12–20 h	Humalog Mix 50/50	Vial (28)ΩΨ Pen (10)Ψ	Eli Lilly (Indianapolis, USA)
70/30 NPA/Aspart	5–15 min	Dual	12–20 h	NovoLog Mix 70/30	Vial (28)ΩΨ Pen (14)Ψ	Novo Nordisk (Bagsvaerd, Denmark)
70/30 Degludec/Aspart[a]	5–15 min	Dual	>24 h	Degludec Plus 70/30	Not Available in the U.S.	Novo Nordisk (Bagsvaerd, Denmark)

Abbreviations: NPA, neutral protamine aspart; NPH, neutral protamine Hagedorn; NPL, neutral protamine Lispro; Ω, refrigerate; Ψ, room temperature.

[a] Insulin Degludec and Degludec/Aspart are not approved for use in the United States.

Adapted from Skyler JS. Insulin treatment. In: Lebovitz HE, editor. Therapy for diabetes mellitus and related disorders. 5th edition. Alexandria (Egypt): American Diabetes Association; 2009. p. 273–89.

Table 3
Important facts and caveats regarding insulin preparations

Insulin	US Trade Name	Insulin Type	Timing or Frequency of Injection	Characteristics
Short-acting insulin				
Regular	Humulin R Novolin R	Human	30–60 min before each meal	• Tends to self-associate into hexameric aggregates but subsequent to subcutaneous injection, disassociates in the interstitium to dimers, then monomers, which explains delayed absorption[25] • Activity profile is dose-dependent • Provides some basal coverage because still has activity after food has been absorbed • Can result in postprandial hypoglycemia due to sustained action
Rapid-acting insulin				
Lispro Aspart Glulisine	Humalog NovoLog Apidra	Analog	15 min before meal up to 15 min after meal	• Forms hexameric aggregates in solution; however, subsequent to subcutaneous injection, quickly disassociates into the active monomeric form[25] • No change in dose needed if switching among the rapid-acting insulins
Intermediate-acting insulin				
NPH	Humulin N Novolin N	Human	Daily-twice a day	• Delayed absorption due to the addition of protamine and zinc • Can be mixed with prandial insulins • Activity profile is dose-dependent, meaning the higher the dose, the broader the peak, and the longer the duration of action • Greater risk of afternoon and nocturnal hypoglycemia
Long-acting insulin				
Glargine	Lantus	Analog	Daily	• Solubilized in acidic pH; precipitates in neutral subcutaneous tissue pH once injected forming hexamers, which slowly disassociate, thereby prolonging action • Can sting on injection due to acidic pH (pH 4)
Detemir	Levemir	Analog	Daily-twice a day	• Omission of threonine at position B30 and acylation with a 14-carbon fatty acid to lysine at position B29 facilitates albumin binding, which prolongs action • Dose-dependent duration of action thus dosed twice daily at smaller doses (<20–30 units) but once daily at larger doses (>0.4 U/kg) • Reduced insulin receptor affinity and metabolic potency, thus slightly higher doses may be required[26]
Degludec[a]	Not available in the US	Analog	Daily	• Omission of threonine at position B30 and acylation with a 16-carbon fatty acid to lysine at position B29 facilitates albumin binding, which prolongs action[27] • Exists as dihexamers; however, forms long multihexamers subsequent to subcutaneous injection with subsequent slow release of monomers into the circulation[22] • Has displayed flexibility in that time of injection can vary from day to day[22]

[a] Insulin Degludec is not approved for use in the United States.

techniques. They also had a propensity to induce anti-insulin antibodies[24] and have since been phased out in the United States. Now, with recombinant DNA technology, the human insulin gene can be introduced into yeast or *Escherichia coli*, which then secrete insulin with the same amino acid sequence as native human insulin; this is the predominant form of insulin in the world. These recombinant DNA–produced insulins are collectively referred to as *Human Insulin* and broadly, there are 2 types: a short-acting product called human regular insulin (Regular) and an intermediate-acting product called neutral protamine Hagedorn (NPH) insulin (see **Fig. 9**, **Tables 2** and **3**).

Short-acting human regular insulin

Human regular insulin is a short-acting insulin that, when injected, tends to self-associate to form hexameric aggregates in the presence of zinc.[25] These hexamers slowly disassociate into dimers, then monomers, which are the active form of the insulin (**Fig. 10**). This disassociation takes time, which explains the need to administer this insulin approximately 30 to 45 minutes before meals. The typical activity profile of human regular insulin is displayed in **Fig. 9**. However, it is important to keep in mind that the activity profile of human regular insulin is also dose-dependent; the higher the dose, the slower is the onset of action (sometimes up to 60 minutes), the broader the peak (2–3 hours), and the longer the duration of action (up to 3–6 hours). Because the time to peak and duration of action do not replicate endogenous bolus insulin secretion, it is a disadvantage for most patients when used at mealtimes.

Intermediate-acting neutral protamine Hagedorn insulin

NPH is an intermediate-acting insulin that has delayed absorption kinetics due to the addition of protamine and zinc. It has an onset of action in 1 to 2 hours, broad peak at 6 to 12 hours, and duration of action of 12 to 16 hours. It is a cloudy suspension and, to prevent variability in its absorption, it must be gently rolled in the palms of the hands 15 to 20 times to resuspend it before injection.

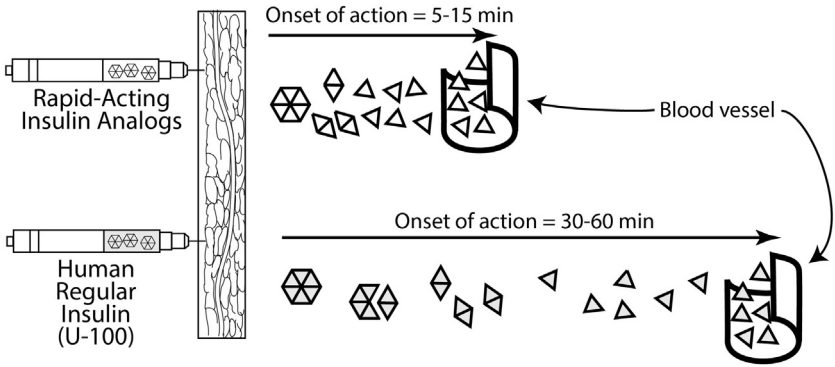

Fig. 10. Dissociation and absorption of human regular compared with rapid-acting analog insulin. Human regular insulin tends to self-associate to form hexameric aggregates in the presence of zinc. After subcutaneous injection, these hexamers slowly disassociate into dimers, then monomers, which are the active form of insulin. The onset of action is slow and human regular insulin must be administered approximately 30 to 45 minutes before meals. Rapid-acting insulin analogs also exist in hexameric aggregates in solution; however, have a low tendency to self-aggregate subsequent to subcutaneous injection. Once injected, they quickly disassociate into the active monomeric form. The onset of action is therefore quick, allowing this insulin to be given approximately 15 minutes before and up to approximately 15 minutes after the meal is consumed.

NPH should typically be dosed twice daily, once with breakfast and again with dinner or at bedtime to provide continuous basal coverage, although it is sometimes used only once a day in clinical practice. When used twice a day, the morning dose peaks in the afternoon, which can result in hypoglycemia, particularly if lunch is delayed or skipped. The dinner or bedtime dose peaks during sleep. This nocturnal peak is a reason to recommend SMBG testing at approximately 3 AM, especially when a dose change is made.

Analog Insulin Preparations

Because recombinant human insulins do not replicate physiologic insulin production, with amino acid substitutions in the human insulin molecule, insulin pharmacokinetics can be modified to facilitate more physiologic action profiles. These modified peptides are called analog insulins, of which there are 2 types: rapid-acting analogs, generally used for meal coverage (and insulin pump therapy), and long-acting products for basal coverage (see **Fig. 9**, **Tables 2** and **3**).

Rapid-acting analog insulins

The main objective with a rapid-acting analog insulin is to make the onset of action quick. This allows the insulin to be injected closer to the meal or in some cases even immediately after the meal has been consumed. Unlike human regular insulin, with rapid-acting analogs, active monomers are formed quickly after subcutaneous injection, allowing this insulin to be given approximately 15 minutes before and up to approximately 15 minutes after the meal is consumed, (see **Fig. 10**). This profile better matches the time course of carbohydrate absorption from the gut thus overcoming the main disadvantage of human regular insulin, which needs to be dosed well in advance of the meal. There are 3 rapid-acting analog products available in the United States, which are interchangeable with each other (see **Tables 2** and **3**).

Long-acting (basal) analog insulins

For basal insulin coverage, a key requirement is to have an insulin that does not have a peak and lasts at least 24 hours. Two analog basal insulin products are available in the United States: glargine and detemir.[26] With amino acid changes that are made to create insulin glargine, it has to be solubilized at an acidic pH of 4.0. This creates microprecipitates of the insulin when injected into neutral pH subcutaneous tissue, slowly releasing monomeric insulin, thus prolonging and flat lining its action over 24 hours (see **Fig. 9**). Detemir on the other hand is acylated with a 14-carbon fatty acid, facilitating albumin binding, which prolongs its action.[27] An ultra-long-acting basal insulin analog, degludec, with a duration of action greater than 24 hours, is also available in some countries, but is currently not approved for use in the United States (see **Tables 2** and **3**).[22,27]

Other Insulin Preparations

Premixed insulin

Premixed insulin is a combination product of intermediate-acting insulin with human regular or a rapid-acting analog in fixed proportions. The main advantage of these insulins is the convenience of fewer injections in patients on basal-bolus therapy. However, titration is not easy because changes occur in both the intermediate and short/rapid-acting insulin when doses are titrated. Human insulin containing premixed products must be injected 30 to 40 minutes before a meal, whereas the analog insulin containing premixed products can be injected in the 15-minute window around the meal (see **Table 2**).[28,29]

Highly concentrated (U-500) insulin

When first isolated from animal pancreatic extract in 1922, 1 unit of insulin (US Pharmacopeia) was defined as the amount of insulin that will lower the glucose of a healthy 2-kg (4.4-lb) rabbit that has fasted for 24 hours to 45 mg/dL (2.5 mmol/L) within 4 hours.[30] When first commercialized in 1923, the concentration of insulin was 20 units in 1 mL (U-20). Subsequently, more concentrated insulins were produced: U-40, U-80, and currently U-100, which is the most common concentration worldwide. A U-200 concentration of degludec is also available, but not in the United States.[22]

For patients with severe insulin resistance, very high doses of insulin could be needed. The large volume of U-100 insulin required for such patients may be painful and impractical. In such a circumstance, a highly concentrated insulin containing 500 units/mL (Humulin R U-500; Eli Lilly and Company, Indianapolis, USA) is available. This preparation is made from human regular insulin and should be reserved for patients requiring more than 200 units of insulin per day and those with a good understanding of self-management principles. It should be prescribed only by providers who are trained in its safe use. Special caution is required for this insulin to be used in the hospital due to the possibility of an error.

INSULIN-DELIVERY DEVICES

Insulin can be dispensed in vials, pens, or with pumps. When dispensed in a vial, there is usually 1000 units/10 mL; whereas in pens, 300 units per device. **Table 4** summarizes the advantages and disadvantages of the various insulin-administration devices.[31,32]

INITIATING INSULIN THERAPY IN TYPE 2 DIABETES

The overarching goal with insulin therapy is to mimic physiologic insulin profiles, with basal insulin to suppress overnight and between-meal hepatic glucose production and bolus insulin to account for meal excursions (**Figs. 11–17**).[33] Much of the actual insulin tactics discussed here are anecdotal, although more recently some guidelines are evolving from experience in clinical trials.[14,15,34,35]

Approaches Using Basal Insulin

We generally follow the ADA guidelines for the introduction of basal insulin after failure of 2 or more noninsulin agents, as discussed previously, and AACE guidelines on titration/intensification, as shown in **Fig. 11**.[14,15] These guidelines have been developed from studies such as the treat-to-target trial, which showed that the addition of a single dose of basal insulin (NPH or glargine) was effective in achieving a target HbA1c of less than 7.0%. One critical element of the treat-to-target trial was a forced titration algorithm,[36] which highlighted the importance of regular and sustained efforts at adjusting doses of the insulin to predetermined glycemic goals. We prefer a long-acting basal analog over NPH insulin because of its sustained action over 24 hours and less risk of afternoon and nocturnal hypoglycemia (see **Figs. 12** and **13**). If there is concern for nocturnal hypoglycemia, 3 AM SMBG values should be checked, especially when using NPH insulin. In most circumstances, at the time of basal insulin initiation, ongoing noninsulin therapies are not discontinued. Although there is some controversy whether secretagogues, especially sulfonylureas should be continued when insulin is started, our approach is to stop these medications only when we introduce bolus insulin.

Numerous studies have shown that glycemic goals can be achieved when patients are given guidance and autonomy in managing their own insulin dose titration.[37–39] We strongly endorse such empowerment. We however feel the 2-day to 3-day schedule suggested in the AACE guidelines (see **Fig. 11**)[15] is too aggressive for self-titration

Table 4
Advantages and disadvantages of insulin delivery devices

Delivery Device	Advantages	Disadvantages	Additional Information
Vials/Syringes	• Least-expensive insulin delivery device	• Patient has to draw up insulin before injection with a syringe, which requires good visual acuity and dexterity	• U-100 vials are available in 10 mL (containing 1000 units of insulin) or less commonly in 3 mL (containing 300 units). The latter is primarily for hospital use • Syringe sizes: 3/10 mL (30 units) with $^1/_2$-unit markings, 3/10 mL (30 units) with 1-unit markings, $^1/_2$-mL (50 units) syringe with 1-unit markings, and 1-mL (100 units) syringe with 1-unit markings • Needle lengths: 5 mm, 8 mm, 12 mm
Pens	• Easy to use, dose set by turning the dial, more consistent subcutaneous insulin delivery than syringe • Preferred device for most patients	• More expensive than insulin vials	• U-100 pens are available in 3 mL (containing 300 units of insulin) • Pen needle lengths: 4 mm, 5 mm, 8 mm, 12 mm • Maximum dose of insulin per injection is 60–80 units (depending on pen)
Insulin pump	• Useful for patients who desire very tight control of BG • Fewer injections	• No basal insulin depot, so high risk of DKA if pump fails requires meticulous monitoring of BG and self-management skills on the part of the patient	• Some pumps connect to the body with tubing (such as Medtronic, Animas, Accu-check); however, a tubeless pump is available (OmniPod)[32]
Insulin patch	• Disposable, 24-h use • No batteries, syringes, or needles needed	• Fixed doses, therefore tight glycemic control may not be possible	• Only 1 product V-Go produced by Valeritas[31] • Available in 3 preset basal insulin devices: the V-Go 20 (20 units/24 h or 0.83 U/h), the V-Go 30 (20 units/24 h or 1.25 U/h), and the V-Go 40 (40 units/h or 1.67 U/h) • Each push of the bolus button releases 2 units of insulin with a maximum of 36 units per use

Abbreviations: BG, blood glucose; DKA, diabetic ketoacidosis.

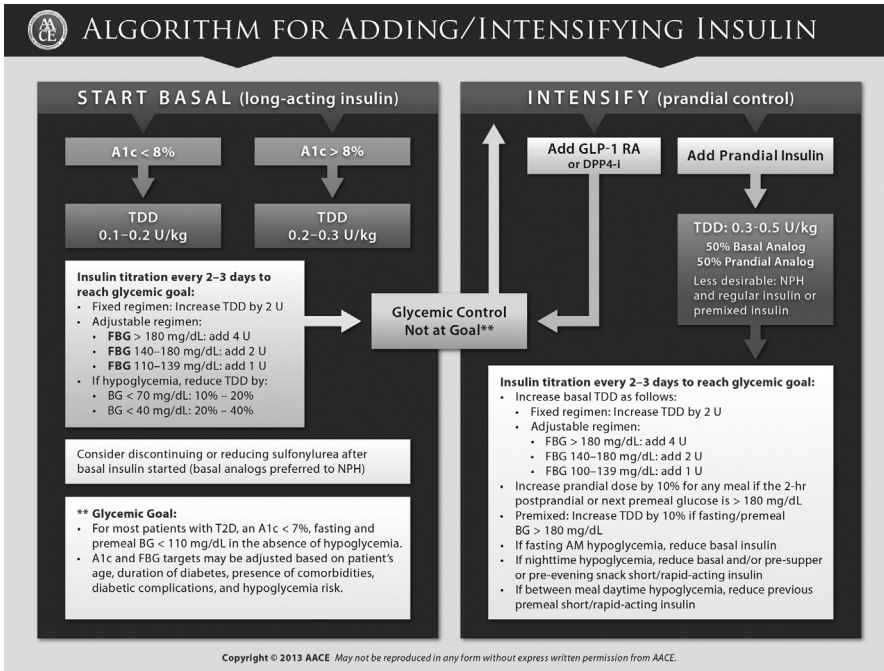

Fig. 11. AACE algorithm for initiation and modification of insulin therapy. These guidelines provide guidance on the starting dose of basal insulin based on body weight. In the event of hypoglycemia, a decrease of the total daily dose is recommended. If glycemic goals are being achieved, intensification to a basal-bolus regimen with titration based on SMBG is the next step. (*From* American Association of Clinical Endocrinologists, Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm. Endocr Pract 2013;19:7; with permission.)

and prefer a 5-day to 7-day schedule instead. Like the treat-to-target trial, we use a mean of the last 3 days of FPG as a guide to dose adjustment.[36] Once insulin is initiated, it is important for the physician to monitor the patient's progress every 1 to 2 weeks for the first month and then biweekly for the next 1 to 2 months, at which time the patient should be reevaluated in the clinic. We pick a maximum daily basal insulin dose, generally 30 to 40 units a day, at which time if FPG goals have not been achieved, we ask the patient to return to the clinic for an evaluation. At the visit, we reassess the patient's understanding of self-management, with particular attention to insulin-injection techniques and compliance. We then determine if therapy needs to be modified with the addition of or changes to noninsulin drugs or if the addition of bolus insulin is necessary.

Approaches Using Bolus Insulin

It is uncommon to use bolus insulin alone in the treatment of T2D; such therapy is usually added on to basal insulin. Some of the triggers[15,40,41] that can be used to consider adding bolus insulin include 50% of the total daily dose of insulin (TDD) is reached with basal insulin alone but before-meal targets are still not being achieved; FPG is at target, however HbA1c is still above target; FPG is at target, but 2h-PPG after breakfast is elevated; there is sustained bedtime hyperglycemia (BG >180 mg/dL); or high-dose glucocorticoid therapy is added in individuals with uncontrolled T2D (see **Fig. 14**).

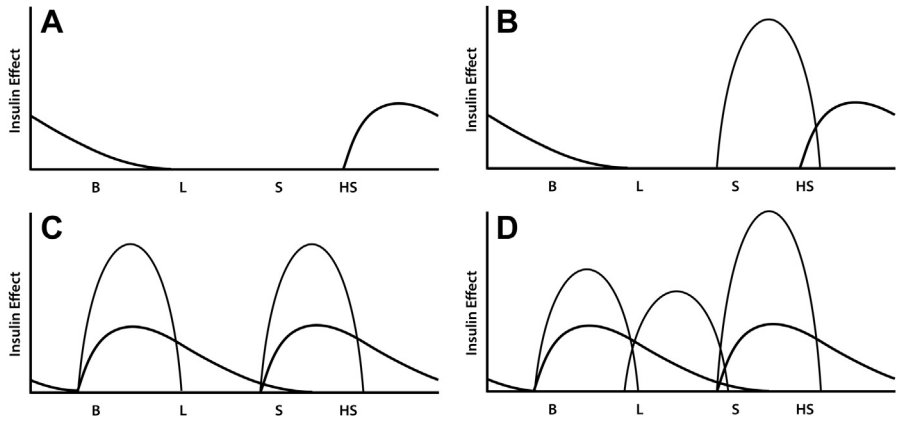

Fig. 12. Basal and basal-bolus insulin regimens using human insulin preparations. B, breakfast; L, lunch; S, supper/dinner; HS, bedtime. (*A*) NPH insulin alone at bedtime. As seen in this figure, NPH alone has the potential to cause nocturnal hypoglycemia at its peak action and it does not provide coverage for the entire 24-hour period. (*B*) Addition of 1 dose of human regular insulin with the largest meal to bedtime NPH. This regimen helps cover dinner and also helps with bedtime targets. However, the human regular insulin must be dosed 30 to 45 minutes before the meal. (*C*) Addition of 2 fixed doses of human regular insulin with NPH before breakfast and supper. As seen in the figure, this regimen produces a gap in coverage if the patient were to consume lunch. In addition, because the dose of the mealtime insulin is fixed, the amount of carbohydrate consumed also needs to be fixed to match the injected insulin dose. (*D*) Addition of flexible (carbohydrate-based) doses of human regular insulin with each meal with NPH before breakfast and supper. Although this regimen allows for variable amounts of carbohydrates with each meal, the protracted duration of action of the regular insulin results in an overlap (stacking) of the insulin doses. Patients also need to learn to count carbohydrates.

Generally, the total daily dose consists of 50% basal and 50% bolus insulin. With the initiation of bolus insulin, therefore, the basal insulin may need to be decreased by 10% to 20% to prevent fasting hypoglycemia. If FPG is already at target, a greater reduction in the basal insulin may be necessary.

There are 2 broad approaches to bolus insulin therapy in T2D. The first approach is to start with fixed doses of mealtime insulin and then adjust based on 2h-PPG or the blood glucose immediately before the next meal. For this fixed dose approach, we follow AACE guidelines for initiation, as shown in **Fig. 11**. The second approach is based on counting carbohydrates, which is more complex but provides more precise mealtime insulin dosing and allows patients the flexibility to adjust insulin to varying amounts of carbohydrates (see **Figs. 12**D and **13**D). Although the complexity of the carbohydrate-counting approach has been called into question in patients with T2D, in our clinical experience it remains a valuable tool for patients and both this approach and the fixed-dose approach can achieve similar glycemic goals.[42] With either approach it is important to assess meal patterns so as to choose the best initial regimen.

Dose with largest meal or high carbohydrate-containing meals

For patients who consume 1 large meal or 1 carbohydrate-rich meal, a single dose of prandial insulin can be added to the meal with the greatest glucose excursion (see **Figs. 12**B and **13**B).

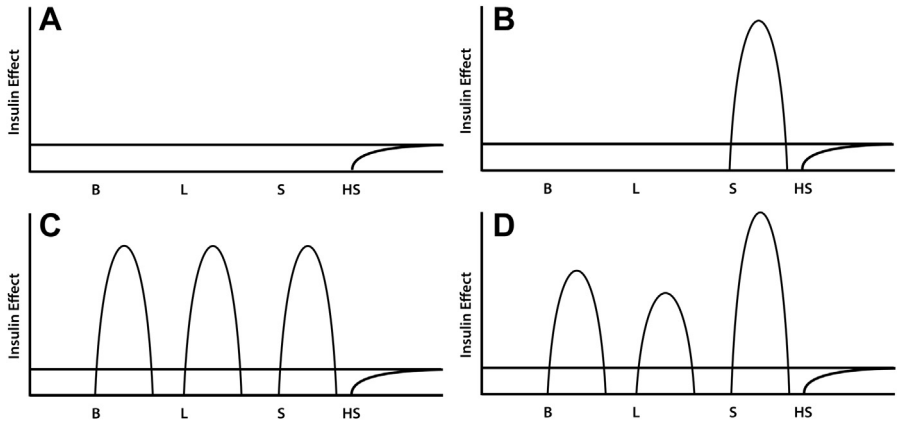

Fig. 13. Basal and basal-bolus regimens using analog insulin preparations. B, breakfast; L, lunch; S, supper/dinner; HS, bedtime. (*A*) Long-acting basal insulin analog alone at bedtime. As seen in this figure, unlike with NPH insulin (see Fig. 12A), a single dose of a long-acting analog insulin given once a day has the potential to provide consistent basal insulin coverage for the entire day. (*B*) Addition of 1 dose of rapid-acting analog insulin with the largest meal to bedtime long-acting analog insulin. Unlike with human regular insulin (see Fig. 12B), a rapid-acting analog can be administered with the meal and also helps achieve bedtime targets. (*C*) Addition of fixed doses of rapid-acting analog insulin with each meal to bedtime long-acting analog insulin. Due to the shorter duration of action of rapid-acting analogs, this regimen highlights the need for continuous basal insulin coverage. There is, however, less potential for insulin stacking. (*D*) Addition of flexible (carbohydrate-based) doses of rapid-acting analog insulin with each meal to bedtime long-acting analog insulin. This is the ideal basal-bolus insulin regimen with multiple daily injections. The analog rapid-acting insulin can be dosed with meals based on carbohydrates consumed again with little risk for insulin stacking. However, this regimen does require the patient to be well versed with self-management skills, including carbohydrate counting.

Fixed dose with each meal

This regimen is ideal for patients who consume meals similar in size and carbohydrate content. Because the doses of insulin are fixed in this regimen, hyperglycemia could result if patients eat more than they usually do or hypoglycemia if less food is consumed (see Figs. 12C and 13C).

Carbohydrate-counting approach

The patient learns how to count carbohydrates using an Insulin:Carbohydrate Ratio (ICR). An ICR is calculated using the formula 500/TDD of insulin. For example, if the TDD is 50 units, 1 unit of rapid-acting analog insulin is required for every 10 g of carbohydrates consumed (500/50 = 10). Another method is to use TDD/3 to approximate the amount of bolus insulin for each meal. This is particularly helpful for patients who eat fixed amounts of carbohydrates with each meal.

With the addition of rapid-acting insulin, a correction dose, known as the Insulin Sensitivity Factor (ISF) should be added to the insulin regimen. The ISF is a dose of rapid-acting insulin *given at meal times* along with the meal dose of the same rapid-acting insulin to account for glucose that is out of target before the meal is consumed. This corrective dose of insulin is calculated using the "1800 rule," (1800/TDD) for rapid-acting analogs, or the "1500 rule" (1500/TDD) for human regular insulin. The actual calculation can be written for the patient as follows: X – (Target BG)/ISF; X

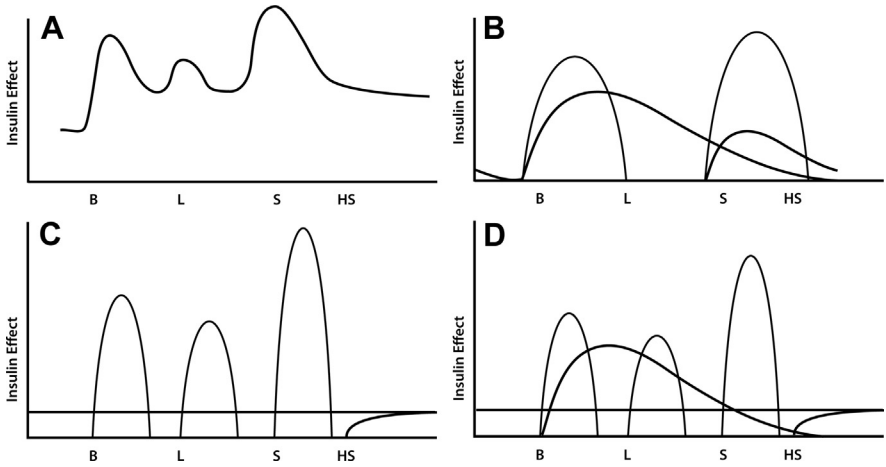

Fig. 14. Insulin regimen for exogenous glucocorticoids. B, breakfast; L, lunch; S, supper/dinner; HS, bedtime. (*A*) The addition of exogenous glucocorticoids leads to postprandial hyperglycemia, thus more insulin is required with meals. (*B*) One solution with human insulin preparations is to use NPH and regular insulin with breakfast and dinner. In this regimen, 60% of the NPH dose is administered with breakfast and 40% with dinner. For the regular insulin, the proportions are reversed, with 40% of the dose given 30 to 45 minutes before breakfast and 60% of the dose 30 to 45 minutes before dinner to try to match the expected glucose excursions, as seen in (*A*). (*C*) Another solution with analog insulin is to give 1 dose of long-acting analog basal insulin with breakfast and mealtime analog rapid-acting insulin with each meal, the highest dose administered with dinner again to match glucose excursions, as shown in (*A*). We prefer to administer the long-acting basal with breakfast in patients on steroids, because their glucose nadir occurs in the morning just before breakfast. (*D*) For patients already on a basal-bolus insulin with analog long-acting basal insulin at bedtime and mealtime, analog rapid-acting insulin, insulin NPH can be added at breakfast to account for the afternoon BG rise that occurs with glucocorticoids.

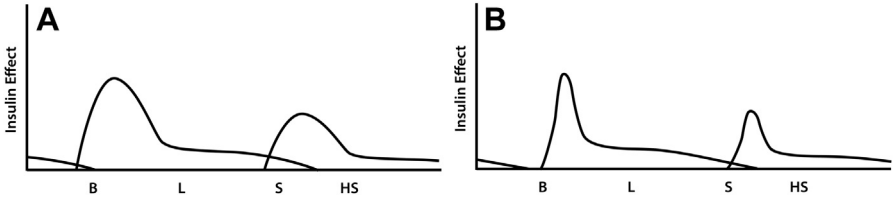

Fig. 15. Premixed insulin-based regimens. B, breakfast; L, lunch; S, supper/dinner; HS, bedtime. (*A*) Human premixed insulin products administered twice a day, 30 to 45 minutes before breakfast and supper. Typically 60% of the dose is administered before breakfast and 40% before supper. As seen in this figure, there is inadequate coverage in the middle of the day, with some stacking at dinner. The risk for nocturnal hypoglycemia persists from the evening dose of the NPH. (*B*) Analog premixed insulin products administered twice a day with breakfast and supper. Typically 60% of the dose is administered with breakfast and 40% with supper. Although this insulin offers the advantage of mealtime administration, the shorter duration of action of the rapid-acting analog manifests itself as longer periods of insulin deficiency during the day.

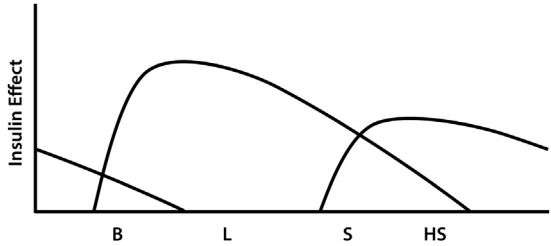

Fig. 16. Humulin R U-500 insulin-based regimens. As seen in the figure, U-500 insulin injected twice has the effect of overlapping of the doses. In effect, therefore, the pharmacokinetic profile of this insulin is similar to basal insulin. Typically 60% of the dose is administered before breakfast and 40% before supper. B, breakfast; L, lunch; S, supper/dinner; HS, bedtime.

represents the patient's BG. For example, with a premeal BG of 230 mg/dL, target BG of 130 mg/dL, and an ISF of 50, the patient will require (230 − 130)/50 = 2 units of rapid-acting insulin added to the meal dose.

Titration of bolus insulin

With either the fixed-dose approach or a carbohydrate-counting–based approach, bolus insulin is titrated based on the 2h-PPG or preprandial BG at the following meal (eg, breakfast bolus insulin dose is adjusted based on the 2h-post breakfast BG or prelunch BG) (see **Fig. 11**). It is important to emphasize that insulin doses in general, and prandial insulin in particular, should not be titrated based on HbA1c values, which proved a long-term measure of glycemic control and is not useful for the purpose of titrating a medication on a weekly or more frequent basis. As discussed earlier, we prefer to titrate every 5 to 7 days instead of 2 to 3 days, as recommended by the AACE guidelines. If correction doses are required for almost all meals, it would suggest that the basal insulin dose needs to be increased or the ICR needs to be changed or both. One strategy is to add up all the corrective doses used for a day and incorporate all or a significant proportion of the total into the basal insulin dose and then reassess patient response after another 5 to 7 days.

Insulin stacking

Insulin stacking refers to situations in which a previously injected insulin still has a residual effect due to its protracted duration of action. It is generally a problem with short-acting human regular insulin (see **Fig. 12**C, D), because these are dosed more

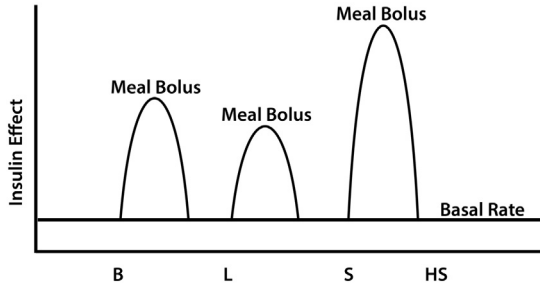

Fig. 17. Insulin regimen with CSII, using a pump. B, breakfast; L, lunch; S, supper/dinner; HS, bedtime. CSII therapy uses only rapid-acting analog insulin, delivered at preset "basal" rates with a mealtime "bolus" based on the ICR plus the ISF.

frequently, although it can occur with any type of insulin. If a subsequent short-acting insulin injection does not take the residual insulin from the previous dose into account, the two can add on to each other, resulting in hypoglycemia.[43] For this reason, short-acting insulins are typically administered at least 4 hours apart.

Approaches Using Premixed Insulin

As discussed earlier, premixed insulin has numerous drawbacks. However, it could be an option in poorly controlled T2D in patients poorly compliant with multiple daily injections, in elderly individuals who need assistance with injections, and those with less-stringent HbA1c goals (see **Fig. 15**). We generally follow the AACE calculation guidelines for the initiation of bolus insulin to dose premixed insulins (see **Fig. 11**)[15] with 60% of the TDD before breakfast and 40% of the TDD before supper. The breakfast dose of premixed insulin is titrated based on presupper BG values and the supper dose is titrated based on FPG.

Approaches Using Highly Concentrated (U-500) Insulin

The triggers, advantages, and disadvantages of Humulin R U-500 insulin (U-500) have been described earlier. Typically, the initial U-500 dose is calculated based on the U-100 insulin requirements. **Table 5** shows the U-500 dose in units (with a U-100 syringe) and in milliliters (with a tuberculin syringe).[44] Initial dosing includes administration of 60% of the TDD 30 minutes before breakfast and 40% of the TDD 30 minutes before supper (see **Fig. 16**).[44] For example, an individual on 300 units of U-100 would be transitioned to 0.36 mL (180 units) of U-500 insulin 30 minutes before breakfast and 0.24 mL (120 units) of U-500 insulin before supper. Carbohydrate counting is not done with this insulin unless used in a pump, but an ISF can be added typically in intervals of 5 units (0.01 mL). Except sulfonylureas and meglitinides, other noninsulin agents are generally continued when treating with U-500 insulin. When dosed twice daily, the breakfast dose of this insulin is titrated based on presupper BG values and the supper dose is titrated based on FPG.

Given that there is no special device for its injection, special precautions must be undertaken when using this insulin. It can be dispensed with either a U-100 insulin

Table 5
Calculating U-500 insulin dose (mL) based on U-100 insulin dosage (Units)

U-500 Regular Insulin Dose, Units	U-100 Syringe, Markings in Units	Tuberculin Syringe, Volume in mL
25	5	0.05
50	10	0.1
75	15	0.15
100	20	0.2
125	25	0.25
150	30	0.3
175	35	0.35
200	40	0.4
225	45	0.45
250	50	0.5

Adapted from Lane WS, Cochran EK, Jackson JA, et al. High-dose insulin therapy: is it time for U-500 insulin? Endocr Pract 2009;15(1):71–9.

syringe or a tuberculin syringe. Care should be taken in using only 1 of these 2 injection devices and patients should be retrained in the use of the device even if they have used a U-100 syringe before. *The prescription for U-500 insulin should always clearly state the device type to be used*. If prescribed with a U-100 insulin syringe, the amount of insulin drawn into the syringe should be written in units and if prescribed with a tuberculin syringe the amount should be written in milliliters (see **Table 5**). In the case of the patient described previously who is transitioning from 300 units of U-100 to U-500 insulin, the prescription should read: Humulin R U-500 (500 units/mL), inject 36 units 30 minutes before breakfast and 24 units before supper with an insulin syringe. If using a tuberculin syringe, the same prescription should read: Humulin R U-500 (500 units/mL), inject 0.36 mL 30 minutes before breakfast and 0.24 mL before supper with a tuberculin syringe. Our preferred administration device is the tuberculin syringe with dose written in milliliters so there is no confusion of the actual insulin dose administered with the unit markings of an insulin syringe.

Approaches Using Continuous Subcutaneous Insulin Infusion

For the highly motivated patient who frequently monitors BG, is on at least 2 daily insulin injections, and requires tighter control and fewer injections, continuous subcutaneous insulin infusion (CSII) may be an option (see **Fig. 17**).[45] It is, however, important that patients have a full evaluation with diabetes educators addressing all aspects of self-management skills before initiating pump therapy to maximize its success. An initial 1:1 dose switch from multiple daily injections to CSII can be used in patients switching to CSII.[45] We usually recommend starting with 1 basal rate, 1 ISF, and 1 ICR. These can then be modified based on response. It is prudent to follow-up with the patient either in-clinic or on the phone on a weekly basis for the first month of therapy.

ADVERSE EFFECTS OF INSULIN THERAPY

Although insulin is the most powerful agent to correct hyperglycemia, its use is not without risk. Besides weight gain, treatment with insulin can produce lipohypertrophy (deposition of fat) at the site of injections due to local anabolic effects of the drug. The absorption, and hence the kinetics, of insulin action can become erratic if the drug is injected into these hypertrophied areas. It is, therefore, important to rotate injection sites.

By far, however, the greatest risk associated with insulin use is that of hypoglycemia. Individuals should be counseled on the clinical manifestations of hypoglycemia, as well as treatment. We educate patients on “the rule of 15”; on noting the symptoms of hypoglycemia, the patient performs a BG to confirm hypoglycemia. If hypoglycemia is confirmed, the patient is to consume 15 g of carbohydrates (eg, 3 glucose tablets, 4 oz fruit juice) and then recheck BG 15 minutes later to ensure BG is trending up. The process should be repeated until the BG is greater than 100 mg/dL. Because of the potential risk of hypoglycemia with insulin therapy, we believe that all patients prescribed this drug should be given a prescription for glucagon and a family member or person who has close and constant contact with the patient should be trained in its use. All patients on insulin therapy should also be encouraged to wear a medical alert bracelet and always check their BG before driving and frequently when driving for long periods of time. In certain high-risk occupations (eg, drivers of commercial vehicles, pilots, and those operating dangerous machinery), workers who use insulin must provide detailed glucose logs and paperwork from their physicians regarding their history of diabetes and its management. Awareness of the risk of hypoglycemia

is also important when using combination therapy with multiple medications in patients with T2D as discussed later in this article.

DEESCALATING INSULIN THERAPY IN TYPE 2 DIABETES

There are circumstances in which a need to deescalate previously started insulin therapy might arise. One such circumstance is following a new diagnosis of T2D with glucose toxicity, where insulin was initiated at the time of diagnosis. As glucose toxicity abates with treatment, it may be possible to taper off insulin while at the same time introducing other noninsulin therapy. Similarly, insulin-sparing agents, such as incretin mimetics or SGLT-2 inhibitors, might be introduced in patients already on insulin. The introduction of these agents could precipitate hypoglycemia if the insulin (or sulfonylurea) doses are not adjusted downward. Because there are no published guidelines on strategies for reducing insulin in such circumstances, we present our approach to insulin adjustment in the presence of such agents.[16,46–63] The approach presented is an amalgamation of our clinical experience and insulin dose titrations used in clinical trials where new therapeutic agents were used on a background of insulin therapy. We have summarized the mechanism of action of drugs from different therapeutic classes used for T2D in **Table 6** to help determine when insulin deescalation might be appropriate to consider.

For patients on basal insulin alone:

In such circumstances, our strategy is to reduce the basal insulin as follows:

- HbA1c $\leq$8%: Basal insulin is reduced by 20% on initiation of the new agent.
- HbA1c >8%: Basal insulin is reduced by 0% to 10% on initiation of the new agent.

The patient continues to monitor SMBG, and if any 2 values in 1 week are less than 100 mg/dL (or <80 mg/dL if tighter control is desired), basal insulin should be reduced by another 10% to 20%. Such reductions occur weekly until the patient is taking less than 10 to 20 units of basal insulin. At this time, the need for continuing basal insulin needs to be reassessed. For the management of hyperglycemia, if 3 BG values in 1 week are greater than 250 mg/dL, we recommend the patient contact the physician to assess if the dose of the newly introduced agent or insulin needs modification.

For patients on basal + bolus insulin (or bolus insulin alone):

In such circumstances, our strategy is to reduce the bolus insulin first, as follows:

- HbA1c $\leq$8%: Bolus insulin is reduced by 30% to 50% on initiation of the new agent.
- HbA1c >8%: Bolus insulin is reduced by 0% to 20% on initiation of the new agent.

The patient continues to monitor SMBG, and if any 2 values in 1 week are less than 100 mg/dL (or <80 mg/dL if tight control is desired), bolus insulin should be reduced by another 30% to 50%. Such reductions occur weekly until adequate glycemic control is achieved or the bolus insulin is tapered off entirely. Once bolus insulin has been tapered off completely and if the patient continues to have any 2 SMBG values in a week less than 100 mg/dL, we recommend basal insulin reductions as described previously. For the management of hyperglycemia, if 3 SMBG values in 1 week are greater than 250 mg/dL, we recommend that the patient contact the physician to assess if therapy with the noninsulin agent or insulin needs modification.

For patients on premixed insulin, we generally follow the parameters for basal insulin alone. For patients on insulin plus a sulfonylurea, our approach is to try to reduce the insulin before the sulfonylurea, because in our experience patients prefer to remain on oral agents over injectable ones.

Table 6
Mechanisms of action of currently available agents for type 2 diabetes

		Mechanism of Action							Effect on Glycemia		Adverse Effects	
Class	Agents	Decrease Hepatic Glucose Production	Increase Insulin Secretion	Increase Peripheral Insulin Intake (Insulin Sensitizer)	Slows Gastric Emptying	Decrease Renal Glucose Absorption	Decrease Intestinal Glucose Absorption	Evidence Supporting Improvement in β-Cell Function	Decrease Fasting Plasma Glucose (FPG)	Decrease 2-h Postprandial Plasma Glucose (2h-PPG)	Weight Effect	Risk of Hypoglycemia as Monotherapy
Biguanide	Metformin	+++	0	+	0	0	0	0[16]	+++	+	Neutral	No
Sulfonylurea	Glyburide Glipizide Glimepiride	0	+++	0	0	0	0	0[46,47]	+++	+	Gain	Yes
Meglitinide	Repaglinide Nateglinide	0	++	0	0	0	0	0	++	++	Gain	Yes
Thiazolidinedione	Pioglitazone Rosiglitazone	++	0	+++	0	0	0	+[51,52]	++	++	Gain	No
GLP-1 receptor agonist	Short-acting: exenatide Long-acting: liraglutide, exenatide-QW	++	++	0	+++	0	0	+[52–54]	+ ++	+++ +	Loss	No
DPP-IV inhibitor	Sitagliptin Saxagliptin Linagliptin Vildagliptin[a] Alogliptin	++	++	0	0	0	0	+[55]	++	+	Neutral	No
SGLT-2 inhibitor	Canagliflozin Dapagliflozin	0	0	0	0	+++	+	+[56]	+	+++	Loss	No
α-Glucosidase inhibitor	Acarbose Miglitol	0	0	0	0	0	+++	+[60]	+	+++	Neutral	No
Amylinomimetic	Pramlintide	+	0	0	+++	0	0	0	+	+++	Loss	N/A
Bile acid sequestrant	Colesevelam	0	0	0	0	0	+++	0	0	++	Neutral	No
Dopamine agonist	Bromocriptine	Unknown[61]							+[62]	+[62]	Neutral	No

N/A, not used as monotherapy; 0, no effect; +, small effect; ++, moderate effect; +++, marked effect.
[a] Vildagliptin is not yet approved for use in the United States.

THE ABCS OF DIABETES CARE AND THE DIABETES CARE T.E.A.M. APPROACH

When managing the patient with diabetes, it is important to not only emphasize glycemic goals as measured by Hb*A*1c, but also *B*lood Pressure and *C*holesterol targets, collectively referred to as the ABCs of diabetes.[64] Addressing these helps reduce the risk of both microvascular and macrovascular complications. This is best accomplished using what we call the T.E.A.M. approach. The most critical member of the T.E.A.M. is the patient; other members include the physician, a certified diabetes educator (CDE) dietician, nurse CDE, pharmacist, optometrist/ophthalmologist, podiatrist, behavioral psychologist, social worker, and the family of the patient. All members of the team help in achieving goals for diabetes. The T.E.A.M. approach itself consists of the following:

- *T*alking with the patient: Clearly communicating goals and roles and responsibilities of each member of the team with the patient is key in overcoming barriers to optimal glycemic control. This communication should occur with and from all team members.
- *E*xercise and nutrition: Addressing pertinent lifestyle issues.
- *A*ttitude: Help the patient deal with psychological, social, and financial issues that could become barriers to achieving control.
- *M*edications: Choosing the correct medications *in discussion with* the patient.

SUMMARY

Insulin is the most powerful glycemic control agent available. However, its use as a therapeutic modality requires education of the patient and regimentation of food intake, exercise, and frequent glucose monitoring. Such regimentation is particularly important when using a basal-bolus therapy approach.

The introduction of many novel noninsulin drugs in the past decade has resulted in better glycemic control and often a need to reduce previously instituted insulin therapy. Although many of these novel therapies by themselves do not cause hypoglycemia, by reducing the overall glycemic burden through a myriad of mechanisms, they function in an insulin-sparing fashion. The doses of exogenously administered insulin may therefore need to be reduced in the presence of these new drugs to mitigate hypoglycemia.

For insulin therapy (or any other drug treatment) to be successful, it is critical that the physician not only establish glycemic goals, but communicate these goals to the patient. The measurement of HbA1c helps in achieving a long-term goal, but on a day-to-day basis, patients need to be cognizant of their own BG goals and what they need to do if falling outside of target. The patients' understanding of self-management skills and empowerment are therefore foundational to insulin therapy.

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