DIABETES: INITIATING AND MANAGING INSULIN

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Week 3

Educational Objectives:

1. Describe clinical and patient considerations related to initiation of insulin therapy
2. Weigh the risks and benefits of starting a patient with type 2 diabetes on insulin
3. Develop an initial insulin treatment plan for a patient with type 2 diabetes
4. Discuss the spectrum of available insulin products and the indications for using them

CASE ONE:

MX (they/them) is a 47-year-old civil engineer who you have been caring for since they moved to the area five years ago. They have a 12-year history of type 2 diabetes, HTN, and a persistent intention tremor in the left hand following a motor vehicle accident two years ago. Despite paying close attention to diet and exercise, their hemoglobin A1c has been creeping up since the accident.

MX is highly motivated to control their glucose but was unable to tolerate both dulaglutide and oral semaglutide due to abdominal discomfort and persistent nausea. Additionally, they live alone, and have been concerned about being able to take insulin given the tremor. You review their chart prior to the visit and are reminded that their diabetes medications include combination metformin XR 1,000 mg/empagliflozin 12.5 mg twice daily, glipizide 20 mg twice daily, and pioglitazone 30 mg daily. After receiving the results of bloodwork from last week with an HbA1c of 9.7% (average blood glucose 232 mg/dL), you no longer feel this is adequate, as you have mutually agreed on an HbA1c goal of 7.0%.

MX checks their fasting blood glucose daily, so the elevated HbA1c level is not a surprise. You have talked in the past about the natural history of type 2 diabetes and its complications, and the eventuality of starting insulin, however they have been reluctant to do so.

Questions:

1. **Should this patient be started on insulin? Why or why not?**
   The decision to initiate insulin therapy in patients with type 2 diabetes is a complex one and, importantly, one that cannot be made without the buy-in of the

patient. To help guide these decisions, there are two professional organizations in the U.S., the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE), whose evidence-based recommendations provide benchmarks (based on hyperglycemic symptoms, HbA1c, and blood glucose values) that are useful in practice:

- The **ADA** recommends consideration of early introduction of insulin if blood glucose is ≥ 300 mg/dL, HbA1c ≥ 10%, if the patient has hyperglycemic symptoms, or if there is evidence of ongoing weight loss related to hyperglycemia (ADA, 2023). Here, "early" introduction of insulin refers to either using basal insulin as the initial treatment or the addition of a basal insulin as the first medication added in combination with a medication from another drug class as part of a stepwise approach to therapy. The rationale is that early introduction of insulin more effectively reduces pancreatic beta-cell gluco- and lipotoxicity, thereby preserving (and in some cases, improving) beta-cell function and slowing the progression of glucose intolerance. The 2022 Joint Consensus statement from the **ADA** and European Association for the Study of Diabetes (**EASD)** includes a figure (Figure 5, page 22) which nicely summarizes current expert opinion on the role of insulin in diabetes management (Davies, 2022) noting that, in addition to the four above mentioned criteria for early insulin introduction, providers should also consider insulin in the event of ketonuria/ketosis or acute glycemic dysregulation (e.g., during hospitalization, surgery, or acute illness); in underweight people (given the insulin side effect of weight gain); or when the diagnosis of type 1 diabetes is suspected, given the limited utility of using non-insulin therapies in patients with type 1 diabetes.

- On a similar note, the **American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Statement** (Samson, 2023) has two frameworks to guide the selection of glucose control medications, a *Complications-Centric Algorithm* and a *Glucose-Centric Algorithm*. While the former focuses on the selection of specific non-insulin therapies that have demonstrated disease-modifying benefits for patients with chronic kidney disease, atherosclerotic cardiovascular disease, stroke/TIA, and heart failure (with insulin incorporated as a potential fourth-line treatment), the *Glucose-Centric Algorithm* recommends incorporation of insulin therapy as second-line treatment (following metformin) in patients with severe hyperglycemia – defined as HbA1c > 10% and/or blood glucose ≥ 300 mg/dL **PLUS** hyperglycemic symptoms.

At this point, we are no longer talking about "early" introduction of insulin – the addition of insulin to the patient's treatment regimen is the best of a limited number of remaining medication options. Regardless of the framework that one chooses, we know from the vignette that MX has not previously wanted to start

insulin, which is how they ended up on a four-drug regimen. Thus, it is critical to understand their hesitancy prior to talking more about starting insulin therapy. Some patients may have concerns related to the use of needles or, in this case, about navigating insulin injections in the setting of physical limitations. They may also have concerns based on the prior experiences of friends or family members who have diabetic complications and/or take insulin. Other patients may have feelings of frustration, failure, or shame about needing to start on insulin therapy. For more information about the psychosocial impact of diabetes and, specifically, the concept of diabetes distress, please refer to the *Psychosocial Issues* section on page 10 in Additional Reference 3 (ADA, 2023). The success of insulin therapy is dependent on how well these concerns are solicited, validated, and addressed by the provider/team of providers. Providing education about the natural history of type 2 diabetes (emphasizing insulin resistance ultimately gives way to progressive impairment in insulin secretion) may be enough to help some patients realize that the need for insulin is not a reflection of failure on their part.

Once the patient's willingness to take insulin has been addressed, it will be important to discuss the risks and benefits of insulin therapy. Their HbA1c remains above goal despite adhering to lifestyle changes and optimized doses of four different antihyperglycemic medications; thus, if MX agrees, it is now time to start insulin therapy.

2. **What issues related to insulin therapy (including risks and benefits) will you need to discuss with MX?**
   The decision to initiate insulin therapy should only occur after a discussion with the patient of the associated risks and benefits, determining the target HbA1c (using a patient-centered approach), and addressing any additional concerns the patient may have about insulin therapy. In addition to the patient's willingness to consider insulin therapy, the key issues to be addressed include:
   - Physiologic risks and benefits of insulin therapy
   - Hypo- and hyperglycemia risk factors, symptoms, assessment, and treatment
   - The commitment required on the part of the patient to follow through with the recommended treatment regimen

   The most significant risks of insulin therapy include weight gain (1-3 kg over 24 weeks) (ADA, 2023) and hypoglycemia (particularly as the insulin dose is titrated and if the patient has inconsistent eating habits). The development of pain, localized bruising, and subcutaneous nodule formation at injection sites is another concern; these can be ameliorated, however, by using a new needle with each injection and rotating injection sites. The most significant benefit of insulin therapy to individuals with long-standing type 2 diabetes, however, is improved HbA1c control, which is correlated with a decrease in the risk of developing microvascular complications of diabetes (including retinopathy and nephropathy).

Finally, this is also an opportunity for continuing the discussion of risk factors for extreme blood sugar values, focusing on how to detect and respond to hypo- and hyperglycemia. This is a conversation which should have started at the time of diabetes treatment initiation; however, insulin therapy has an additional degree of risk. In this case, the patient has been glipizide (sulfonylurea), which can lead to hypoglycemia. Therefore, the clinician should already be in the habit of routinely asking about symptoms of hypo- and hyperglycemia at each visit.

CASE ONE CONTINUED:

In talking with MX about their reluctance to start insulin therapy, you realize that they have been focused on concerns related to the injection equipment. Specifically, MX is worried about being able to safely be able to draw up the appropriate insulin dose in a syringe and self-administer it correctly, given their tremor. You pull up an image of an insulin pen on the computer in the exam room and describe this as an alternate mode of delivery that may feel safer to them. Fortunately, you have a demonstration insulin pen and pen needles in your office and show MX how to assemble the set, dial up the dose, and inject into an injection pad. You then hand over the materials and they are successfully able to demonstrate the assembly and injection steps in under two minutes! "That was much easier than I thought it would be," says MX, and agrees that this is the best next step forward.

They have normal renal function with an eGFR > 60 mL/min. Additionally, their height is 5' 8", weight 69 kg, and BMI 23.1 kg/m^2.

3. **What are their basal insulin options? What is the significance of the different insulin concentrations (U-100, U-200, U-300, and U-500)?**
   As of November 2023, there are seven options for basal insulin (including alternate concentrations) that are available in the U.S., under 12 brand names:

Insulin	Concentration	Onset	Peak	Duration	Cost
Insulin NPH (Novolin N, Humulin N, ReliOn N)	U-100	1-2 h	4-8 h	12-24 h	$24-$105 per 10 mL vial **or** $300 per 5 x 3 mL pens
U-500 insulin regular	U-500	30 min	4-8 h	14-15 h	$1,450 per 20 mL vial
Insulin glargine (Basaglar, Lantus, Rezvoglar, Semglee)	U-100	2-4 h	None	20-24 h	$100 (L) or $50-100 (S) per 10 mL vial **or** $100 (L/S/R) or $250 (B) per 5 x 3 mL pens

Insulin glargine (Toujeo)	U-300	1-4 h	None	24-36 h	$350 per 3 x 1.5 mL pens
Insulin detemir (Levemir)	U-100	1-3 h	6-8 h	18-20 h	$300 per 10 mL vial **or** $450 per 5 x 3 mL pens
Insulin degludec (Tresiba)	U-100	1-9 h	None	> 42 h	$110 per 10 mL vial **or** $160 per 5 x 3 mL pens
Insulin degludec (Tresiba)	U-200	1-9 h	None	> 42 h	$190 per 3 x 3 mL pens

(All basal insulin formulations available in the United States as of September 2023 per *Lexicomp* database. Pharmacokinetic information from "Insulins for Type 2 Diabetes." *The Medical Letter on Drugs and Therapeutics.* 2019 May 6;61(1571):65-68. Information about Semglee and Rezvoglar added to table from *Lexicomp* database.) [*Cost estimates from www.goodrx.com; Accessed 11 September 2023.*]

Certainly, insulin NPH is the least expensive option. Despite the fact that insulin NPH and the insulin analogs (detemir, glargine, and degludec) have been demonstrated to be equally effective in terms of glycemic control, NPH can be associated with increased risk of hypoglycemic events due to peak concentrations that may result in nighttime low blood sugar values. The concern for hypoglycemia is particularly important in the case of patients who are unable to eat regularly, whether due to inconsistent access to food, concomitant medical issues leading to poor appetite, or self-imposed dietary restrictions related to lack of appropriate nutrition education (none of which is the case for this patient). Additionally, NPH comes as a cloudy suspension that must be mixed well (vial or pen rolled between the hands until the liquid appears uniformly white and cloudy) immediately prior to every use. Insufficient mixing can alter the effectiveness of an NPH dose by rolling the insulin pen an inadequate number of times, or by attempting to resuspend the insulin when it is not yet warmed to room temperature.

Insulin glargine, detemir, or degludec would all be appropriate options, and do not require resuspension prior to administration. The glargine and degludec formulations are relatively peakless and, thus, less likely to cause hypoglycemia in a patient who is eating inconsistently. Importantly, all three are available in pen delivery systems (which need to be used with pen needles that are prescribed separately) or in 10 mL vials that are used with syringes. Of note, insulin does not automatically come with delivery devices, so is critical that the clinician prescribes the correct one (e.g., insulin syringes to go with vials or pen needles to go with the insulin pens) along with the insulin.

The designation U-100 indicates that the insulin concentration is 100 units per mL; almost all insulin types that are commercially available for human use in the U.S. (whether rapid, short, intermediate, or long acting) are manufactured in this concentration. Patients who have severe insulin resistance (requiring > 200 units of insulin daily) may benefit from transitioning to a concentrated insulin as larger

volumes of insulin (> 0.8mL of fluid, equivalent to > 80 units of a U-100 concentration insulin) are variably absorbed, preventing patients from realizing the full benefit of their dose. As MX is just starting on basal insulin, they do not require a concentrated insulin. Therefore, the U-200 option (Tresiba), U-300 option (Toujeo), and hyper-concentrated U-500 insulin regular are not appropriate considerations at this time.

4. **What initial regimen would you recommend, and what changes (if any) would you make to their other diabetes medications?**
The literature includes a variety of insulin starting dose recommendations; however, they do not differ dramatically from each other. This patient does not have a low (< 20 kg/m^2) BMI, they are relatively young (age < 65 years), and their GFR is > 45 mL/min, so it would be appropriate to start the basal insulin dose for this 69 kg patient at any of the following:

    - ADA: basal insulin (+/- metformin and other non-insulin medications) at a dose of 10 units daily OR 0.1-0.2 units/kg/day = ***(7-14 units/day)***
    - AACE/ACE: since the HbA1C is > 8%, start with an initial basal insulin dose of 0.2-0.3 units/kg/day = ***(14-21 units/day)*** (if the HbA1C were < 8%, the starting dose should be 0.1-0.2 units/kg/day)
    - Wallia article: 10 units daily. If the patient had severe hyperglycemia (defined in the article as fasting glucose > 250 mg/dL or HbA1C > 10%), this article suggests a starting dose of 0.25 units/kg/day basal insulin dose = ***22 units/day***. (This is calculated based on the assumption of an initial total daily insulin dose [TDD] requirement of 0.5 units/kg/day, and the understanding that typically one-half of a person's TDD is needed to address their basal insulin needs.)

    Importantly, these dosing schemes hold true for any basal insulin. The choice of basal insulin may, unfortunately, often be heavily influenced by health insurance formularies or the availability of insulin through drug company or retail pharmacy discount programs. Of note, two of the basal insulin options (NPH and insulin detemir) are dosed twice daily—in these cases, the calculated starting basal insulin dose would be split in half. With respect to our patient, however, insurance coverage is not an issue, and they do not want to take two injections per day; thus, a good option would be to start on insulin glargine at 14 units once daily in the morning.

    Patients with BMI of 20 kg/m^2 or less, age > 65 years, or GFR < 45 mL/min are likely to be more sensitive to small amounts of exogenous insulin, and so should be started on more conservative doses to avoid hypoglycemia. As noted in the Wallia article, the recommended TDD for a patient who meets one of these criteria would be 0.25 units/kg (with 50% of that as basal insulin and, if starting on pre-prandial rapid-acting insulin as well, the remaining 50% divided into three equal bolus doses).

From an initial basal dose once per day (as noted in Figure 9.4 of the Primary Reference article [ADA, 2023]), some patients may be able to titrate their own basal insulin dose, using the rough guide of increasing the dose by two units every three days until the desired fasting glucose level is achieved (typically 80-130 mg/dL). Depending on the resources in your practice, there may be other members of the care team (e.g., pharmacist, nurse) who can assist with this titration. Many patients, however, will either prefer to have their primary clinician titrate the insulin dose or may not be able to do it safely on their own. Potential barriers may be related to the patient's educational level, degree of health literacy, or issues with hand-eye coordination.

It is important to note that although patients may be managed on basal insulin with three times daily mealtime insulin when admitted to the hospital, a four-injection per day regimen may be challenging for many patients to follow at home, especially when first starting on insulin. This is why the ADA and AACE both recommend a stepwise approach to adding prandial insulin, starting with one rapid- or short-acting insulin dose at the time of the largest meal of the day.

Given that MX has had type 2 diabetes mellitus for 12 years and their HbA1c remains elevated despite optimal dosing of metformin, glipizide, pioglitazone, and empagliflozin, it is likely that the sulfonylurea has lost some of its effectiveness due to progressive pancreatic beta-cell dysfunction and decreased insulin secretion. While their blood glucose is not well-controlled and it is reasonable to continue all four medications at the time that the insulin is being added (allowing the patient an opportunity to become comfortable with/practiced at insulin administration), the glipizide should be discontinued as soon as feasible. In general, sulfonylureas should not be continued once insulin is added to a diabetic treatment regimen, due to concerns for an increased risk of hypoglycemia. Otherwise, metformin, TZDs, and SGLT-2 inhibitors, as well as GLP-1 receptor agonists, GIP/GLP-1 receptor agonists, and DPP-4 inhibitors, are all safe to continue along with insulin therapy.

It would be appropriate to instruct MX to continue checking their fasting blood sugar once per day, as well as to provide them with enough extra glucometer test strips to be able to check a fingerstick if they develop symptoms of hypo- or hyperglycemia. A fasting blood sugar level will help to assess whether the combination of medications includes a high enough dose of basal insulin (irrespective of diet). If the fasting blood sugar is in the target range (80-130mg/dL for most situations) and the A1c is not at goal, this would indicate the likely presence of meal-related/post-prandial hyperglycemia. At this point it would be appropriate to have MX begin checking their blood sugar at other times of day as well – for example, checking a fasting glucose plus a fingerstick before and one hour after their largest meal. This will give additional information about the adequacy of the basal insulin dose, as well as preparing for the likely initiation of mealtime rapid- or short-acting bolus dose insulin (+/- a sliding scale correction).

5. **How would you assess whether MX is appropriately self-administering the insulin?**
   Regardless of the delivery system (syringe or pen), it is important to review the steps for insulin administration with the patient. The following chart contains the steps and potential problems that can arise at each point (Rabin, 2013). You can also refer to the *Insulin Injection Techniques* section (page S142) in ADA, 2023. Steps 1-3 below are common to all injectable diabetes medications, and the need to rotate injection sites and avoid intramuscular injection is even more critical when a patient is taking multiple injectable doses in the same day. *Facilitators may wish to practice these steps with the learners using demonstration pens/syringes, if available.*

Steps for Insulin Administration	Potential Complications (if step not followed)
Review potential injection sites (including the stomach, thigh, upper arm, or hip) and assess frequency of site rotation	Development of lipohypertrophy Inadvertent intramuscular injection leading to hypoglycemia
Assess for lipohypertrophy or infection	Decreased/delayed absorption Increased pain at injection site
Clean or disinfect injection site	Risk of infection if unclean skin or patient in an institutional setting
Re-suspend medication (only if NPH or pre-mix containing NPH)	Variable NPH concentration leading to hypoglycemia
Select appropriate length needle (pen or syringe) for subcutaneous delivery	Inadvertent intramuscular injection leading to rapid absorption and hypoglycemia
Use new pen needle with each dose (if using pen delivery system)	Increased pain or bruising at injection site Entry of air in or insulin leakage out of pen
Prime pen with two units of insulin for each new needle	Blockage of medication flow Loss of medication in needle dead space
Use new insulin syringe with each dose (no need to prime syringes)	Increased pain or bruising at injection site
Pinch skin fold, insert needle/syringe at 90º angle	Inadvertent intramuscular injection leading to rapid absorption, hypoglycemia
Leave needle in skin for 10 seconds after medication has been injected	Medication leakage from injection site (suboptimal dosing)
Withdraw needle/syringe, release skin fold	
Dispose of needle/syringe according to local regulations	

6. **Although MX has been taking a sulfonylurea and has already been at risk for hypoglycemia, it will be important to reinforce their understanding of hypoglycemia warning signs and treatment now that they are taking insulin. What do they need to know?**
   Regardless of the duration of diabetes treatment, clinicians should be in the habit of routinely:
   - Asking about hypoglycemic symptoms at every clinical visit

- Noting the pattern of hypoglycemic symptoms/episodes and how they relate to the pharmacokinetics of the different types of insulin or other medications
- Concurrent activity levels (increased exercise/activity levels may result in hypoglycemia due to increased glucose utilization) and/or food intake

Symptomatic hypoglycemia occurs when a patient has typical symptoms of hypoglycemia (e.g., shakiness, diaphoresis, visual disturbances) in the context of a measured blood glucose ≤ 70 mg/dL and in the absence of another more probable cause of the symptoms. It is important to remind patients to check their blood glucose level if they feel any of these symptoms or otherwise feel unwell, and to ensure that they have enough glucose testing supplies to be able to do so. It is also important to be aware of the potential over time for *asymptomatic hypoglycemia*, which is noted when a patient has a documented blood glucose level ≤ 70 mg/dL, but no associated symptoms of hypoglycemia.

In cases of hypoglycemia, the treatment would follow the "15-15 rule," in which the patient should consume 15 grams of carbohydrate, and then recheck their blood sugar after 15 minutes. Examples of a 15-gram serving of carbohydrates would include four ounces of orange or apple juice, one tablespoon of honey, three sugar packets (not artificial sweetener packets), or three to four glucose tablets. It is helpful to remind patients to carry the equivalent of a 15-gram serving of carbohydrate with them at all times. Importantly, candy that contains fats (e.g., chocolate) will not be as helpful in responding rapidly to hypoglycemia, as fats delay the absorption of associated glucose. If the blood sugar remains below 70 mg/dL (or if symptoms persist), then patients should repeat the treatment cycle. Once the symptoms have resolved and the blood sugar is > 70 mg/dL, the patient should follow the acute treatment with a snack that includes both carbohydrate and protein (e.g., crackers with peanut butter, sandwich with hummus or deli meat, rice and beans). Keeping in mind the duration of action of whichever medicine(s) that caused the hypoglycemia, this additional snack will keep the blood sugar out of the hypoglycemic range, thus preventing a rebound episode of hypoglycemia.

In contrast, *severe hypoglycemia* requires intervention from another person, whether administering glucagon or carbohydrates and/or contacting emergency medical personnel. Importantly, this is characterized by complete neurological recovery along with return to normoglycemia. *Relative hypoglycemia* occurs when a patient experiences typical symptoms of hypoglycemia, but the concurrent documented blood glucose level is > 70mg/dL. This occurs in patients with diabetes who have chronically elevated blood glucose levels; in such cases, their bodies have "reset" the level below which they experience hypoglycemic symptoms (which are caused by an autonomic surge in response to low blood sugar). Thus, these patients experience symptoms of hypoglycemia when the measured blood glucose is in the "normal" range. Given how uncomfortable and frightening the experience of relative hypoglycemia can be, it is often helpful to

work to lower the blood glucose more gradually in patients who have chronically very elevated levels. Importantly, a more gradual approach to HbA1c targets that does not precipitate these symptoms may also help keep the patient engaged as they achieve incremental successes on their way to a more ideal target.

CASE ONE CONTINUED:

Eight months later: Working together, you and MX have decided to discontinue both the glipizide and pioglitazone. Although they subsequently tried to tolerate both a DPP-4 inhibitor and another GLP-1 receptor agonist, MX was unable to continue with either medication due to side effects. Thus, you have been focusing on titrating the dose of their once daily insulin glargine (in combination with the previously optimized metformin/empagliflozin) to achieve consistent fasting glucose numbers in the 80-130 mg/dL target range.

7. **Planning ahead, how would you use the HbA1c to guide the decision about a future need to add mealtime insulin doses? How would you approach that next step?**
   It is important to keep in mind that the HbA1c goal should be individualized for each patient, generally targeting a value between 6.5% and 8% depending on specific patient- and disease-related factors. (For specific recommendations regarding HbA1c goals, refer to the *Glycemic Goals* section on page 11 in Additional Reference 2 (ADA, 2023).

   Considering a stepwise approach to treatment intensification, we have already eliminated the possibility of this patient of adding a DPP-4 inhibitor, GLP-1 receptor agonist, or GIP/GLP-1 receptor agonist (which tend to have more side effects than GLP-1 receptor agonists alone). If the patient's HbA1c remains above goal despite achieving the target fasting glucose level, then it is appropriate to discuss adding mealtime (also known as *prandial*) insulin to the regimen. The addition of one mealtime insulin injection at a time avoids overwhelming the patient with a dramatic increase in the number of daily injections. And typically, one would start by adding a prandial insulin dose immediately prior to the largest meal of the day. (See Figure 9.4 in the Primary Reference [ADA, 2023] for specific guidance on initiating prandial insulin – generally as a once daily injection and aiming for a dose of 4 units or 10% of basal insulin dose). When adding a prandial insulin, patients should be counseled to check their glucose levels both before and one-hour after the largest meal of the day. This information will allow the clinician to evaluate the adequacy of the prandial insulin dose and adjust as needed. As a reminder, at this point our patient is already on:

   - Goal doses of metformin and empagliflozin – this patient takes them as combined tablets (two pills per day) but, depending on insurance

coverage, patients may need to take these pills separately (up to five pills per day); and
- An optimized once-daily insulin glargine dose

In general, prandial insulin can either be dosed as a separate injection of a rapid- or short-acting insulin or may be available already mixed in the same syringe or insulin pen as a "fixed dose combination." *Fixed dose combinations* are products that include two types of insulin combined according to a specific ratio; the longer acting insulin type makes up the greater proportion of the product. Importantly, certain basal insulins (insulin glargine and insulin detemir) cannot be mixed together in the same syringe or pen with a rapid- or short-acting insulin, as the mixture will alter the activity of the basal insulin. Examples of available fixed dose combinations include mixes of **insulin NPH + insulin regular** (available in a 70%:30% ratio and a 50%:50% ratio), **insulin lispro protamine [NPH] + insulin lispro** (available in a 75%:25% ratio or a 50%:50% ratio), and **insulin aspart protamine [NPH] + insulin aspart** (available only in a 70%:30% ratio). To better understand premixed insulins, consider that a dose of 30 units of 70/30 insulin NPH + insulin regular is the equivalent of injecting 21 units of insulin NPH (30 units x 70%) and nine units of insulin regular (30 units x 30%) at the same time. The benefit is that this can be done in one injection instead of two. Additionally, there are two once-daily fixed-dose combination products on the market that contain a basal insulin mixed with a GLP-1 receptor agonist. (For a list by generic names of the available insulins and insulin combination products, please refer to Table 9.4 in ADA, 2023.)

Primary Reference:

1. American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes – 2023. Diabetes Care 2023; 46(Supplement 1): S140-S157. **https://doi.org/10.2337/dc23-S009** [Pay particular attention to pages S151-S154, as well as Figure 9.4 on page S150 – *Intensifying to injectable therapies in type 2 diabetes.*]

Additional References:

1. Davies MJ, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;45(11):2753–86.
2. Samson SL, et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm - 2023 Update. Endocrine Practice 2023 Jan; 29:305-40.
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Knowledge Questions:

1. **Mr. Q, a 47-year-old graphic designer with a nine-year history of type 2 diabetes (weight 120 kg, BMI 42 kg/m^2, HbA1c 11.7%) presents to the clinic with concerns about his inability to improve his HbA1c despite perfect adherence to the regimen of metformin 1000 mg PO twice daily and semaglutide 2 mg SC once weekly. He also reports frustration with increased thirst and urinary frequency over the past two weeks. What would be the most appropriate starting dose of insulin for him?**

    a. 24 units daily of insulin glargine
    b. 24 units daily of insulin detemir
    c. 12 units daily of insulin glargine
    d. 8 units of insulin detemir, given three times daily before meals
    e. 8 units of insulin lispro, given three times daily before meals

2. **A 32-year-old lawyer with a seven-year history of type 2 diabetes (hemoglobin A1c 10.3%; goal 7.0%), presents to the clinic for routine follow-up. She was started on a basal insulin regimen two weeks ago. She takes metformin 1000 mg PO twice daily, sitagliptin 100 mg daily, and is currently on insulin glargine 10 units daily in the morning. What risks/benefits of insulin therapy would be important to discuss with her prior to insulin initiation?**

    a. Potential for hypoglycemia, and how to recognize and manage it
    b. Potential for weight loss
    c. Decrease in microvascular complications of diabetes with improved glucose control
    d. a and c
    e. a, b, and c

2. **Ms. G is a 48-year-old woman with a six-year history of type 2 diabetes who you would like to start on basal insulin. Despite maximal doses of metformin, glipizide, and dulaglutide, her HbA1C continues to climb above her goal. She does not fit the typical phenotype of a patient with type 2 diabetes—she weighs 50 kg and is petite with a BMI of 19 kg/m^2. What instructions about starting insulin glargine are INCORRECT?**

    a. Continue to check fasting blood sugar each morning
    b. Rotate insulin administration sites on a regular basis
    c. Insulin pen needle tips can be re-used up to 10 times
    d. Avoid intramuscular insulin delivery

Answers:

1. **a** *As this patient has poorly controlled glucose values and does not have a low BMI, age > 65 years, or chronic renal insufficiency (GFR < 45 mL/min), there is no need to be conservative with the insulin starting dose (answer **c** would represent a conservative weight-based dose of 0.1 units/kg/day). Note that insulin detemir does not last for 24 hours and should only be prescribed once daily under specific circumstances (answer **b**); however, it is considered a long-acting basal insulin and should never be dosed three times a day (answer **d**), Additionally, insulin lispro is a rapid acting insulin and should not be used in place of a basal insulin (answer **e**). Thus, answer **a** is the best option, as this represents an appropriate starting dose of 0.2 units/kg/day of a once daily basal insulin.*
2. **d** *Answers **a** and **c** describe documented risks and benefits of using insulin therapy. Insulin leads to weight gain, not weight loss; therefore, answers **b** and **e** are incorrect.*
3. **c** *Answers **a**, **b**, and **d** are all components of a successful insulin regimen. Each of these three answers describes a critical step in the proper administration of insulin via a pen delivery system. Importantly, intramuscular injection of insulin should be avoided as it can lead to unpredictable insulin absorption and increase the risk of hypoglycemia (answer **c**).*