IN THE NAME OF GOD

Insulin Therapy

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- **22 Ordibehesht 1401**

Insulin therapy

- **Agenda**
  - **Insulin preparations**
  - **Insulin therapy in Type 2 DM**
  - **Insulin therapy in Type 1 DM**

Insulin preparations

- In type 2 diabetes, insulin is generally provided in three ways:
- ***Basal supplement***
- ***Pre-meal (prandial)***
- ***Pre-mixed***

Insulin preparations

- In type 2 diabetes, insulin is generally provided in three ways:
- As a ***basal supplement*** with an intermediate-acting to long-acting preparation (NPH, glargine, detemir, or the very long-acting degludec) to suppress **hepatic glucose production** and maintain glucose levels at target in the fasting state.
- As a ***pre-meal*** (prandial) bolus dose of short-acting (regular) or rapid-acting (lispro, aspart, glulisine) insulin to cover the extra requirements **after food** is absorbed.
- As a ***pre-mixed*** combination of intermediate-acting and short-acting or rapid-acting insulin.

Pharmacokinetics of commonly used insulin preparations

(A) Prandial insulin			
Insulin type	**~ onset of action**	**Effective peak**	**~ duration of action***
Lispro, lispro-aabc aspart, faster aspart glulisine[¶]	15 to 30 minutes	1 to 3 hours	4 to 6 hours
Regular	30 minutes	1.5 to 3.5 hours	8 hours
(B) Basal insulin			
Insulin type	**Half-life[Δ]**	**Effective peak**	**~ duration of action***
NPH	4.4 hours	4 to 6 hours	12 hours
Insulin glargine			
U-100	12 hours	No pronounced peak	20 to >24 hours
U-300	19 hours	No pronounced peak	20 to >24 hours
Insulin detemir	5 to 7 hours	3 to 9 hours	6 to 24 hours◊
Insulin degludec	25 hours	No pronounced peak	>24 hours

- * Glucose-lowering action may vary considerably in different individuals or within the same individual; the duration of action is dose dependent.
  ¶ Lispro-aabc and faster aspart have quicker pharmacokinetic profiles than standard lispro and aspart.
  Δ In general, it takes 4 half-lives to reach steady state. Dose adjustments should not be made until after steady state is achieved.
  ◊ **Insulin detemir**: At higher doses (≥0.8 units/kg), mean duration of action is longer and less variable (22 to 23 hours).

TABLE 397-4 Properties of Insulin Preparations[a]

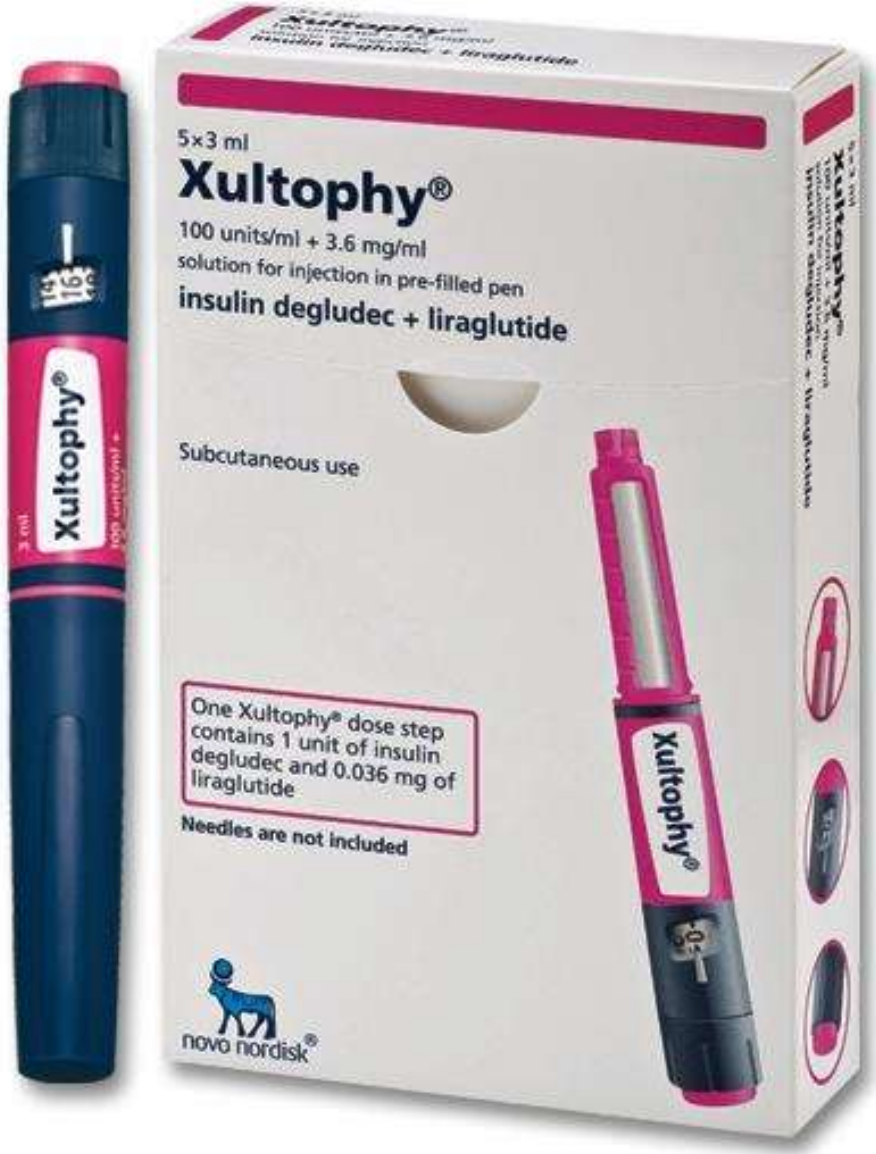
PREPARATION	TIME OF ACTION		
	ONSET, h	PEAK, h	EFFECTIVE DURATION, h
Short-acting[b]			
Aspart	<0.25	0.5–1.5	2–4
Glulisine	<0.25	0.5–1.5	2–4
Lispro[f]	<0.25	0.5–1.5	2–4
Regular[g]	0.5–1.0	2–3	3–6
Inhaled human insulin	0.5–1.0	2–3	3
Long-acting[g]			
Degludec	1–9	—[c]	42[d]
Detemir	1–4	—[c]	12–24[d]
Glargine[f]	2–4	—[c]	20–24
NPH	2–4	4–10	10–16
Examples of insulin combinations[e]			
75/25–75% protamine lispro, 25% lispro	<0.25	Dual[f]	10–16
70/30–70% protamine aspart, 30% aspart	<0.25	Dual[f]	15-18
50/50–50% protamine lispro, 50% lispro	<0.25	Dual[f]	10–16
70/30–70% NPH, 30% regular	0.5–1	Dual[f]	10–16
Combination of long-acting insulin and GLP-1 receptor agonist	See text		

[a]Injectable insulin preparations (with exception of inhaled formulation) available in the United States; others are available in the United Kingdom and Europe. [b]Formulation with niacinamide has a slightly more rapid onset and offset. [c]Degludec, determir, and glargine have minimal peak activity. [d]Duration is dose-dependent. [e]Other insulin combinations are available. [f]Dual: two peaks—one at 2–3 h and the second one several hours later. [g]Also available in concentrations >U-100.

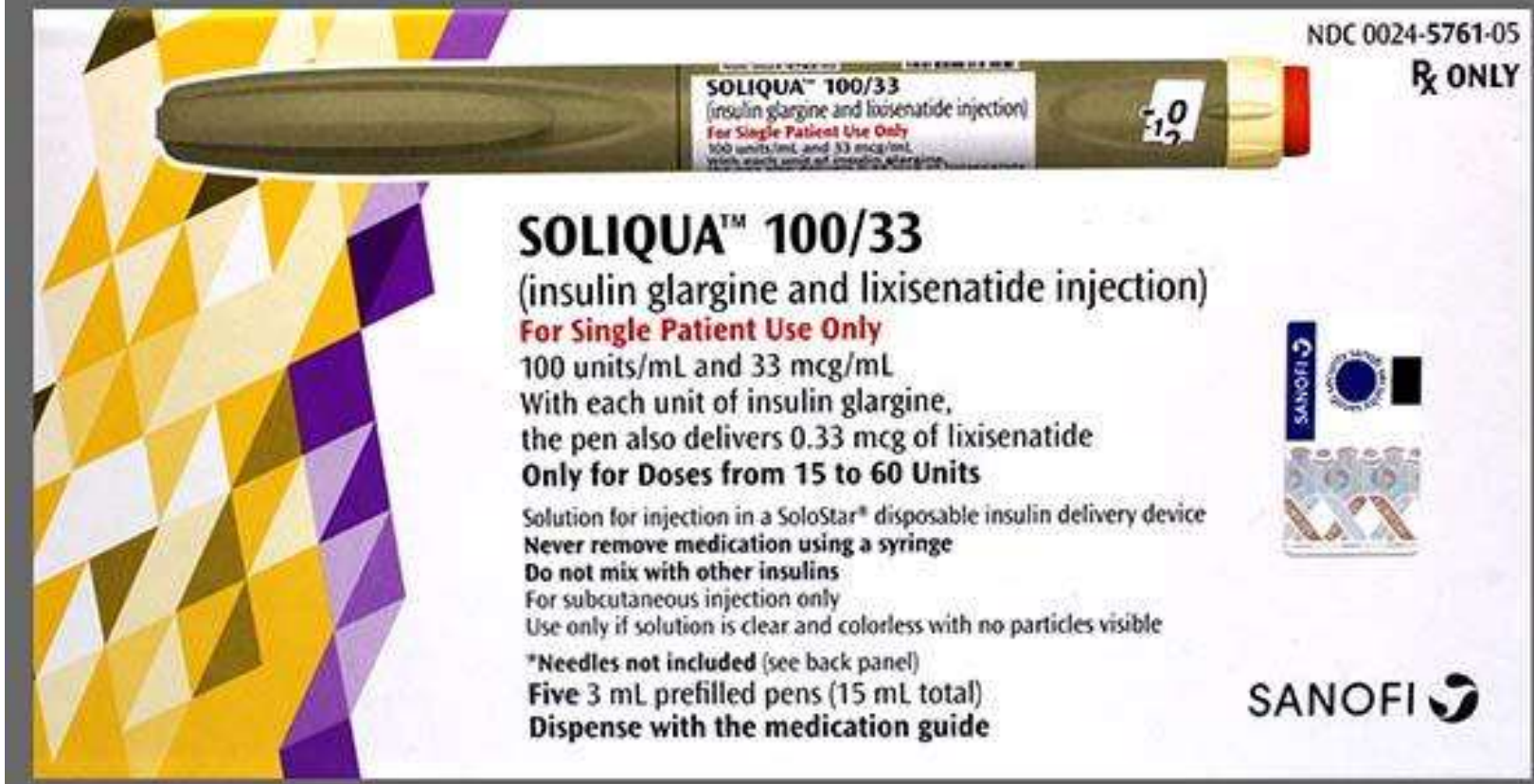
Premixed insulin/GLP-1RA products

Glargine/Lixisenatide

Degludec/Liraglutide


5×3 ml
Xultophy®
100 units/ml + 3.6 mg/ml
solution for injection in pre-filled pen
insulin degludec + liraglutide
Subcutaneous use
One Xultophy® dose step contains 1 unit of insulin degludec and 0.036 mg of liraglutide
Needles are not included
novo nordisk®
Xultophy®
Xultophy®


Xultophy® 100/3.6
(insulin degludec and liraglutide injection)
For Single Patient Use Only


NDC 0024-5761-05
℞ ONLY
SOLIQUA™ 100/33
(insulin glargine and lixisenatide injection)
For Single Patient Use Only
100 units/mL and 33 mcg/mL
With each unit of insulin glargine,
the pen also delivers 0.33 mcg of lixisenatide
Only for Doses from 15 to 60 Units
Solution for injection in a SoloStar® disposable insulin delivery device
Never remove medication using a syringe
Do not mix with other insulins
For subcutaneous injection only
Use only if solution is clear and colorless with no particles visible
*Needles not included (see back panel)
Five 3 mL prefilled pens (15 mL total)
Dispense with the medication guide
SANOFI

Concentrated Insulins

- **U-300 glargine** has a **longer duration** of action than U-100 glargine but modestly **lower efficacy** per unit administered.
- These concentrated preparations may be more *convenient* and *comfortable* for patients to inject and may **improve adherence** in those with **insulin resistance** who require **large doses of insulin**.

Insulin therapy in Type 2 DM

When Insulin therapy is necessary?

- 1- Catabolism symptoms of DM
- 2- HbA1c > 10%
- 3- BS ≥ 300 mg/dl
- 4- DM T 1

Indications for initial treatment with insulin

- **Severe hyperglycemia on presentation**
  - Symptomatic (eg, weight loss, polydipsia, polyuria) or severe hyperglycemia with ketonuria)
  - FBG >250 mg/dL, random glucose consistently >300 mg/dL, A1C >9 percent but without ketonuria or spontaneous weight loss, in whom type 1 diabetes is not likely
- **Difficulty distinguishing type of diabetes (**42 percent of cases with T1DM present after 30 years of age)
- **Pancreatic insufficiency (**cystic fibrosis, chronic pancreatitis, or after pancreatectomy)
- **Other** –Initial intensive insulin treatment for a brief period (two to four weeks) may be beneficial in patients with type 2 diabetes and may induce a remission that can last for a year or more .
- **Persistent hyperglycemia on oral agents**

- خانم 45 ساله ای مبتلاء به دیابت نوع 2 با کاهش وزن اخیر حدود 4 کیلو گرم، مراجعه کرده است. سابقه بیماری دیگری ندارد. تحت درمان با داروهای زیر می باشد:
- گلی گلازید 160 *mg*
- مت فورمین 1500 *mg*
- *امپاگلوفلوزین 10 mg*
- وزن 65 کیلوگرم و قد 160 سانتی متر دارد.
- *FBS=260 mg/dl Na=138 meq/ L*
- HbA1c= 10 % Cr= 0.8 mg/dl
- جهت بهبود کنترل قند خون وی چه روشی را توصیه می کنید؟

Diagnosis OF DKA

- (1) BS >250 mg/dL
- (2) Moderate to severe ketonemia
- (3) Acidosis (pH <7.3 or plasma bicarbonate ≤15 mEq/L)

Euglycemic DKA

- Poor oral intake
- Those treated with **insulin** prior to arrival in the emergency department
- Pregnant women
- SGLT2I

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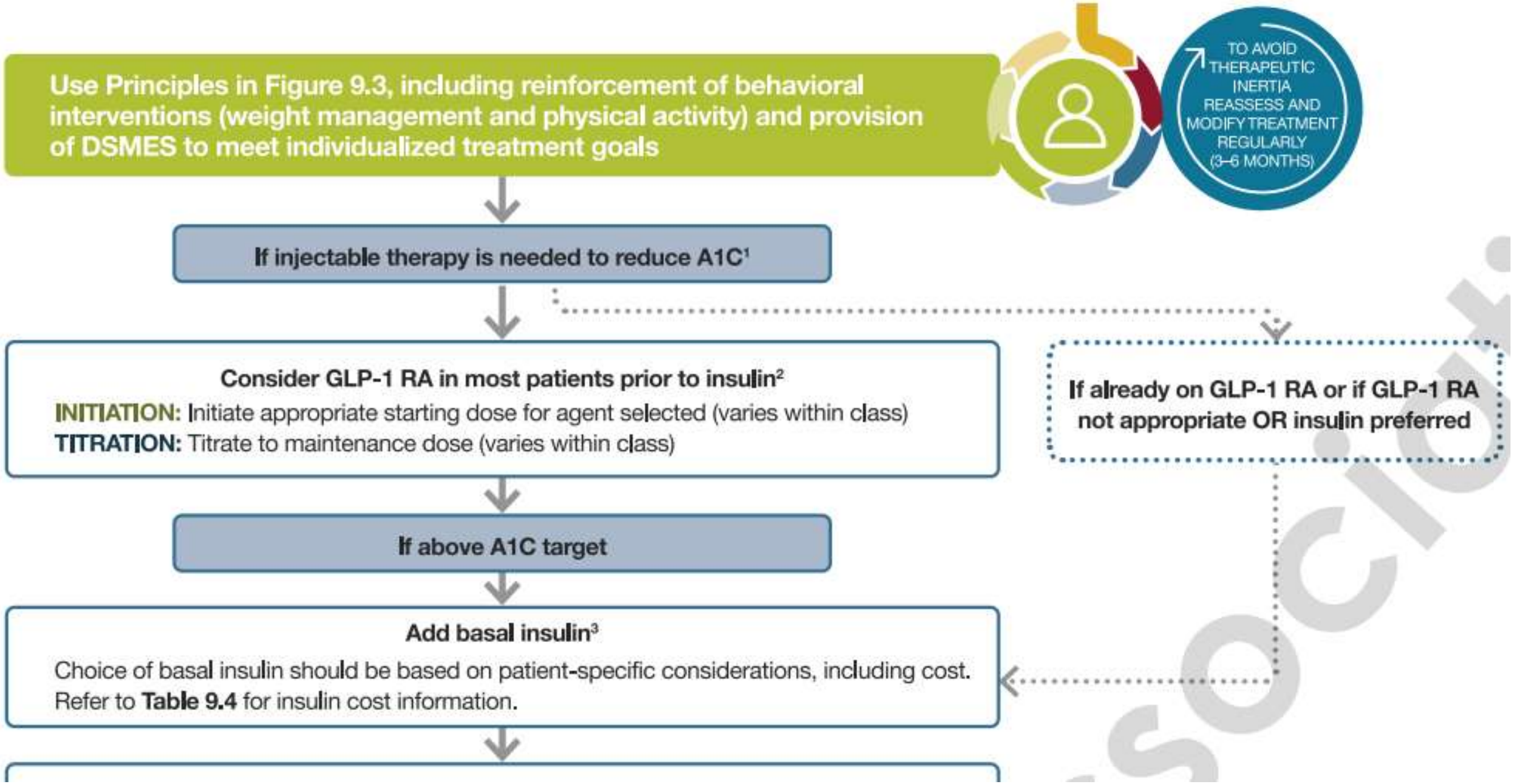
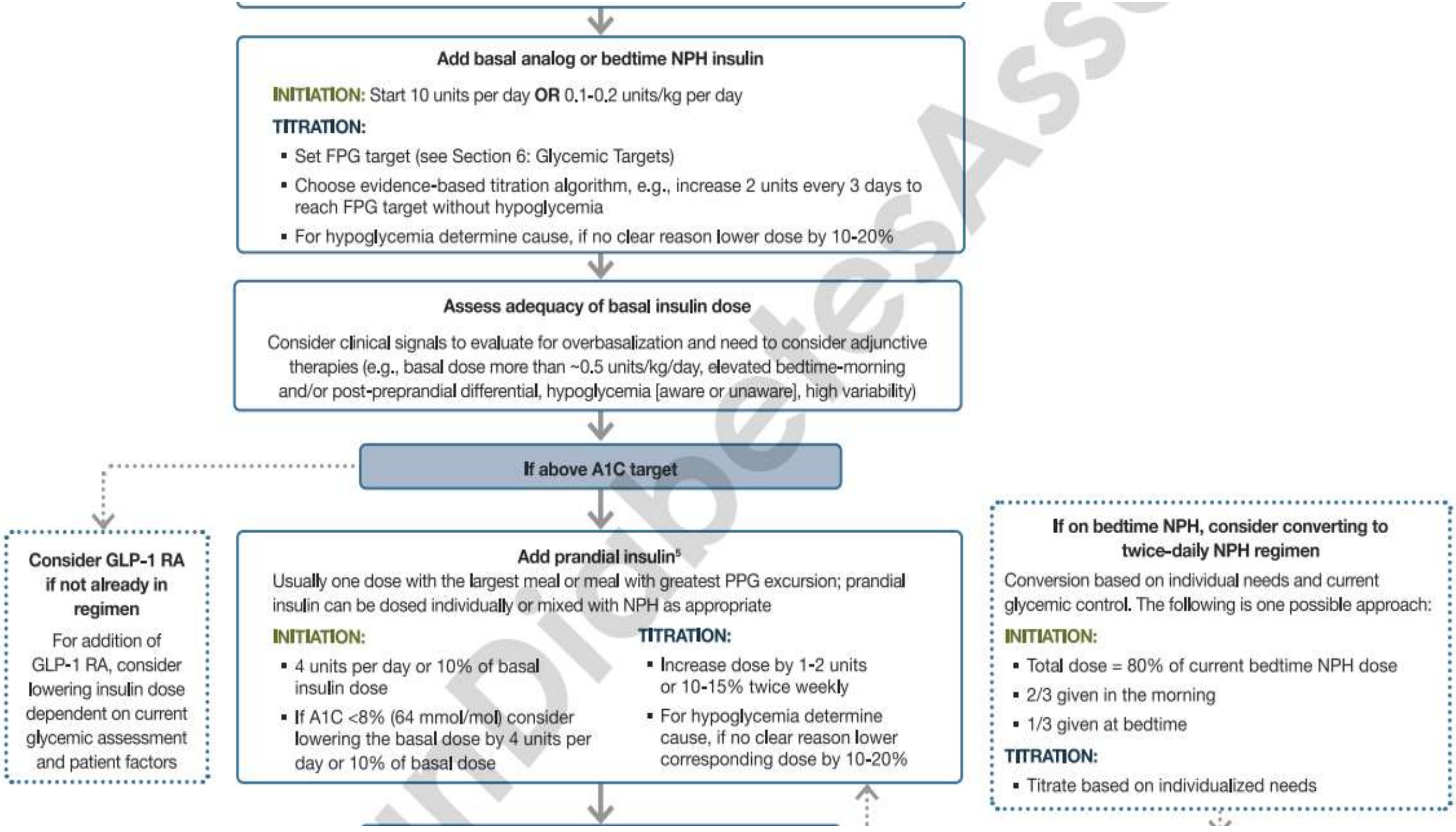
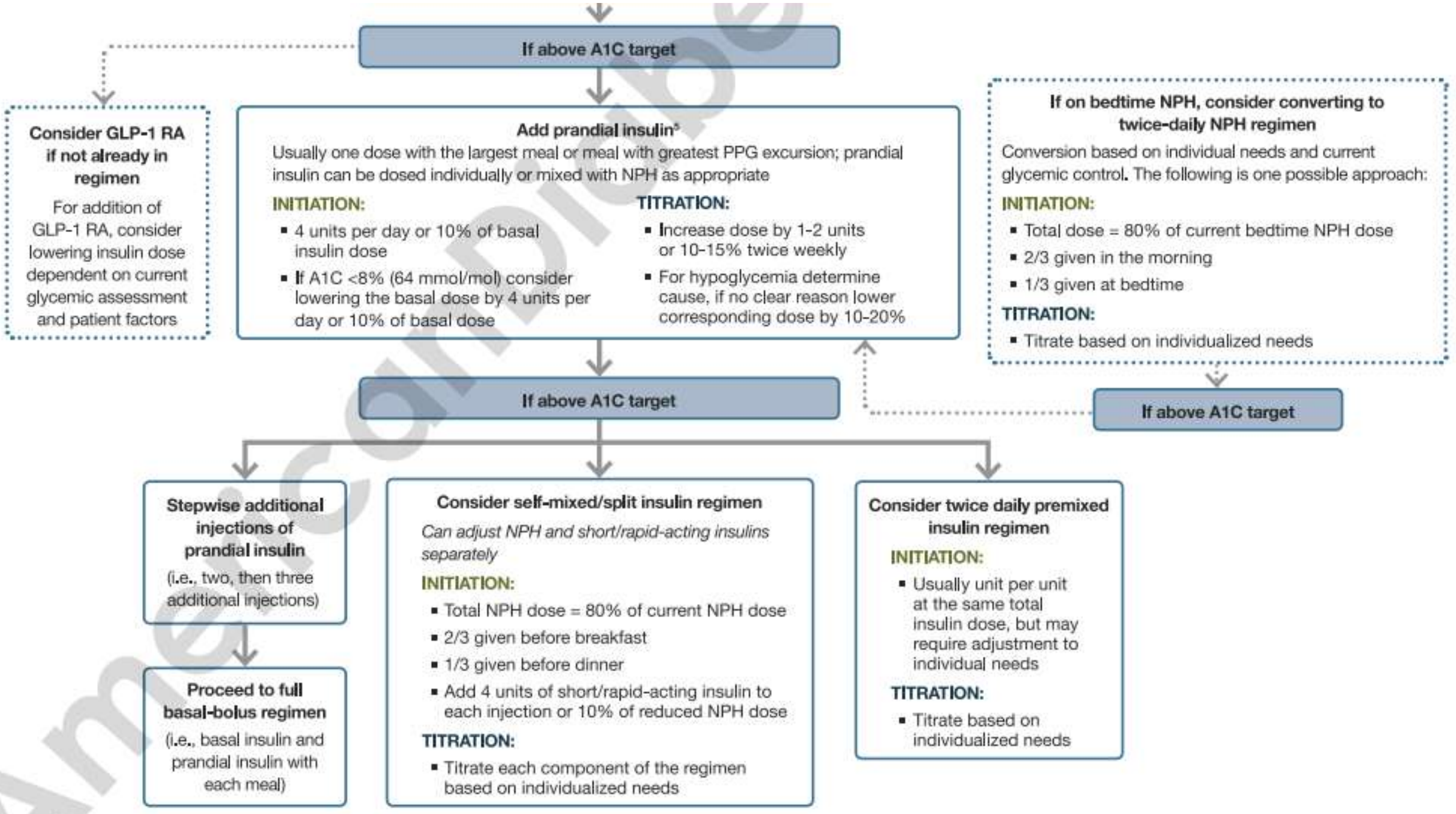
- مت فورمین 1500 *mg*
- ***امپاگلوفلوزین*** *10 mg*
- وزن 65 کیلوگرم و قد 160 سانتی متر دارد.

- *FBS=260 mg/dl* *Na=138 meq/ L*
- HbA1c= 10 % Cr= 0.8 mg/dl
- K= 4.5 meq/ L Hco3= 21 mEq/L
- Ketonuria= Neg

- جهت بهبود کنترل قند خون وی چه روشی را توصیه می کنید؟


Use Principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA in most patients prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)
If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred
If above A1C target
Add basal insulin[3]
Choice of basal insulin should be based on patient-specific considerations, including cost.
Refer to Table 9.4 for insulin cost information.


Add basal analog or bedtime NPH insulin
INITIATION: Start 10 units per day OR 0.1-0.2 units/kg per day
TITRATION:
Set FPG target (see Section 6: Glycemic Targets)
Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
For hypoglycemia determine cause, if no clear reason lower dose by 10-20%
Assess adequacy of basal insulin dose
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose more than ~0.5 units/kg/day, elevated bedtime-morning and/or post-preprandial differential, hypoglycemia [aware or unaware], high variability)
If above A1C target
Consider GLP-1 RA if not already in regimen
For addition of GLP-1 RA, consider lowering insulin dose dependent on current glycemic assessment and patient factors
Add prandial insulin[5]
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate
INITIATION:
4 units per day or 10% of basal insulin dose
If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 units per day or 10% of basal dose
TITRATION:
Increase dose by 1-2 units or 10-15% twice weekly
For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10-20%
If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is one possible approach:
INITIATION:
Total dose = 80% of current bedtime NPH dose
2/3 given in the morning
1/3 given at bedtime
TITRATION:
Titrate based on individualized needs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TITRATION:
Titrate based on individualized needs
If above A1C target
If above A1C target
Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Proceed to full basal-bolus regimen
(i.e., basal insulin and prandial insulin with each meal)
Consider self-mixed/split insulin regimen
Can adjust NPH and short/rapid-acting insulins separately
INITIATION:
Total NPH dose = 80% of current NPH dose
2/3 given before breakfast
1/3 given before dinner
Add 4 units of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
TITRATION:
Titrate each component of the regimen based on individualized needs
Consider twice daily premixed insulin regimen
INITIATION:
Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
TITRATION:
Titrate based on individualized needs

TABLE 1 When to Consider Treatment Intensification Beyond Basal Insulin

Definition of overbasalization: the titration of basal insulin beyond an appropriate dose in an attempt to achieve glycemic targets
How to identify overbasalization:
• Basal insulin dose >0.5 units/kg/day
• Postmeal blood glucose >180 mg/dL
• A1C not at goal despite target fasting blood glucose level being achieved
• BeAM differential ≥50 mg/dL

Sulfonylureas and DPP4I

- When initiating **combination injectable therapy**, metformin therapy should be maintained while sulfonylureas and DPP-4 inhibitors are typically **weaned or discontinued**.

- خانم 55 ساله ای مبتلاء به دیابت نوع 2 مراجعه کرده است. سابقه بیماری دیگری ندارد. تحت درمان با گلی گلازید 80 و مت فورمین 1500 و *امپاگلوفلوزین 10* میلی گرم و *35 واحد انسولین گلارژین میباشد*. وزن 65 کیلوگرم و قد 160 سانتی متر دارد.

- *FBS=120 mg/dl* BS 2h pp= 250 mg/dl
- HbA1c= 7.9 % Cr= 0.8 mg/dl
-

- جهت بهبود کنترل قند خون وی چه روشی را توصیه می کنید؟
- قطع گلی کلازید
- 4 واحد انسولین سریع الاثر در کاملترین وعده غذائی (یا وعده غذائی که بیشترین قند خون PP را دارد
- 4 واحد از انسولین بیزال کم کنید

Simplify complex insulin regimens

- As people with type 2 diabetes **get older**, it may become necessary to **simplify complex insulin** regimens because of a decline in self-management ability.

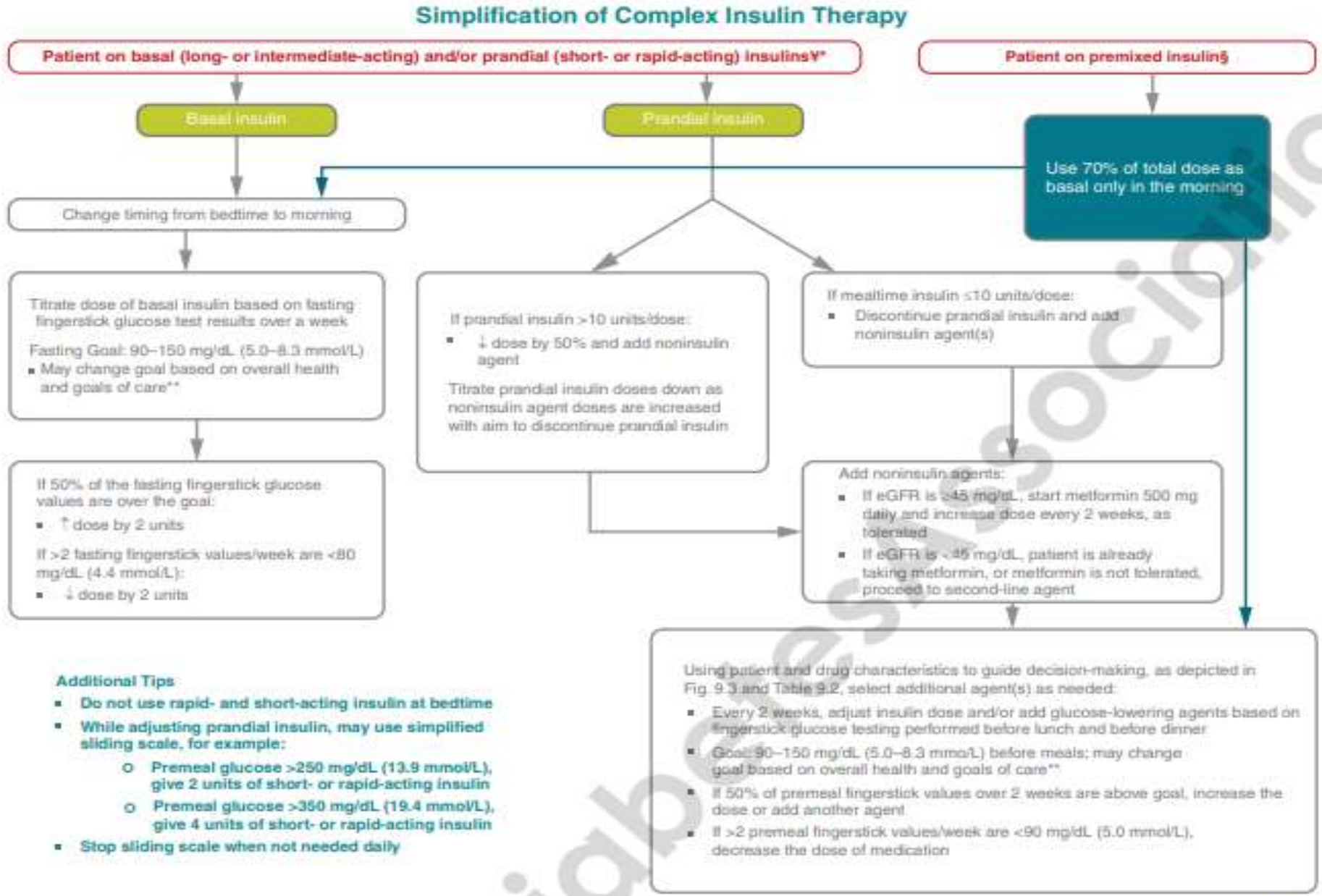


Figure 13.1—Algorithm to simplify insulin regimen for older patients with type 2 diabetes. eGFR, estimated glomerular filtration rate. *Basal insulins: glargine U-100 and U-300, detemir, degludec, and human NPH. **See **Table 13.1**. ¥Prandial insulins: short-acting (regular human insulin) or rapid-acting (lispro, aspart, and glulisine). §Premixed insulins: 70/30, 75/25, and 50/50 products. Adapted with permission from Munshi and colleagues (85,123,124).

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

- ۱-آقای ۳۲ ساله با شکایت پرنوشی و پرادراری به درمانگاه داخلی مراجعه نموده است. وی از کاهش وزن ۶ کیلوگرمی طی ۲ هفته گذشته شاکی است. اشتهای وی خوب است ولی مدتی است به دنبال غذا خوردن دچار درد شکم می شود ولی خفیف است و به تازگی اشتهای وی کم شده است. در حال حاضر قد ۱۷۰ سانتی متر، وزن ۷۹ کیلوگرم دارد. در معاینه تب ندارد و در لمس شکم تندرنس خفیف روی اپی گاستر دارد. فشارخون ۱۲۰/۸۰ mmHg دارد.
- آزمایشات **مربوط به ۲ روز قبل** وی به شرح زیراست:
- FBS= 220 mg/dl HbA1C= 7.6% Cr= 1.3 mg/dl
- در برخورد با وی کدام گزینه صحیح است؟
- الف) شروع مت فورمین
- ب) تجویز لیراگلوتاید
- ج) تجویز توام لیراگلوتاید و انسولین
- د) درخواست کتون ادرار و بلاد گاز وریدی اورژانسی

TYPE 1 DIABETES

- **Multiple daily** injections of prandial and basal insulin, or **continuous subcutaneous insulin infusion**
- **Rapid-acting insulin** analogs →↓hypoglycemia risk

- Patients with type 1 diabetes should be trained to match prandial insulin doses to **carbohydrate intake**, **premeal blood glucose**, and anticipated **physical activity**.

Insulin Therapy

- The hallmark of type 1 diabetes is absent or near-absent ß-cell function
- Hypertriglyceridemia
- Ketoacidosis
- Tissue catabolism

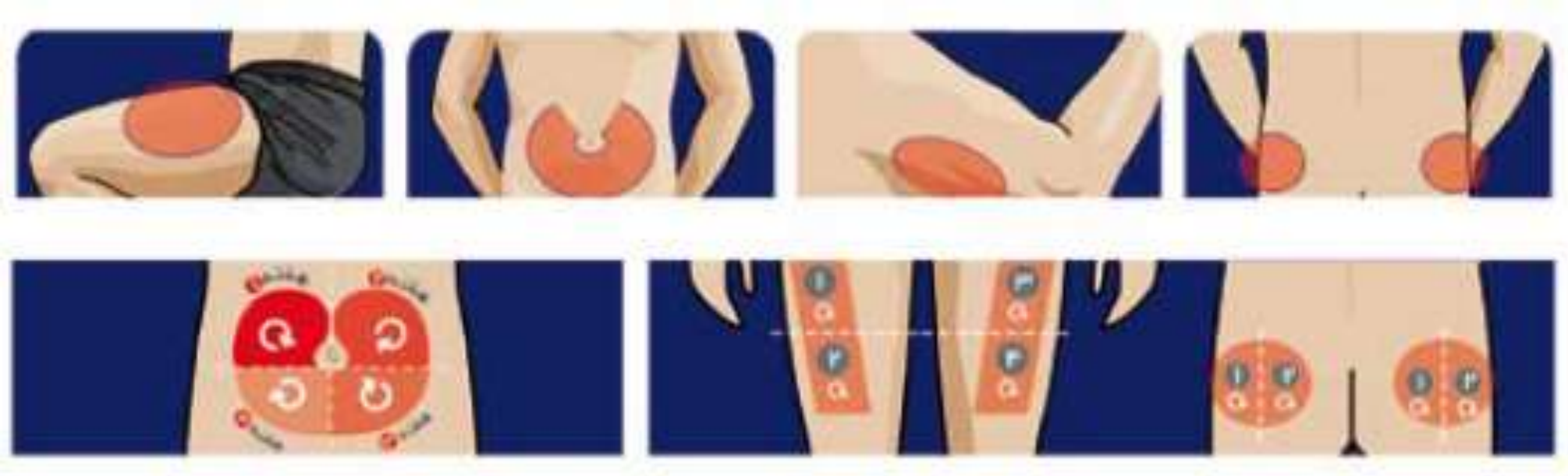
TYPE 1DIABETES

- In general, patients with type 1 diabetes require **50%** of their daily insulin as **basal** and 50% as **prandial.**

TYPE 1DIABETES

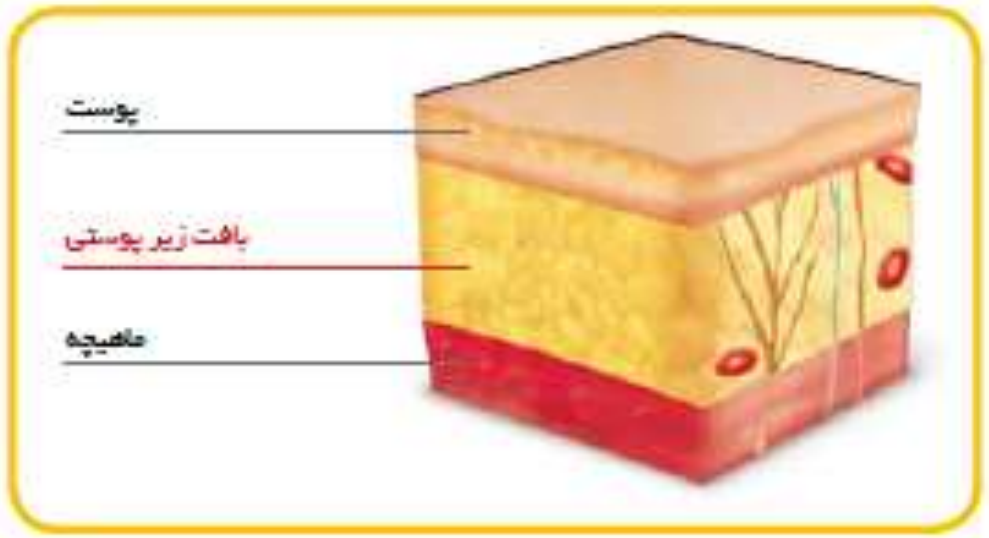
- Total daily insulin requirements can be estimated based on weight, with typical doses ranging from **0.4 to 1.0 units/kg/day**.
- Higher amounts are required during:
- **Puberty**
- **Pregnancy**
- **Medical illness**

Recommended sites for insulin injection



Injection site rotation

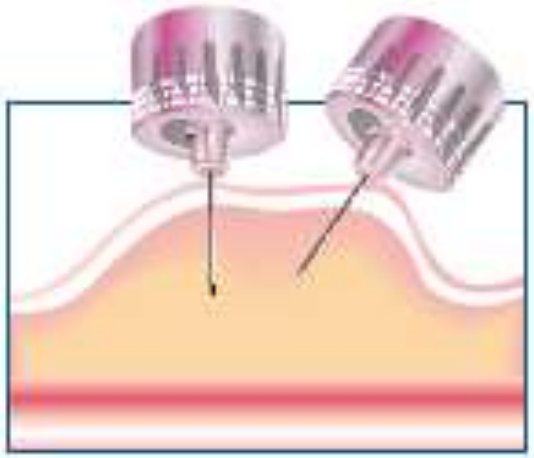
Insulin Injection Technique



برای اطمینان از این امر:

۱- پوست را با یک نیشگون بگیرید.

۲- سوزن را ترجیحا به صورت عمودی (با زاویه ۹۰ درجه) وارد کنید.



۳- پوست را رها کنید و انسولین را تزریق کنید.


Thanks for your attention