

DDTP Advancement in Diabetes  
April 20, 2022

# Insulin Management in Patients with Diabetes Mellitus

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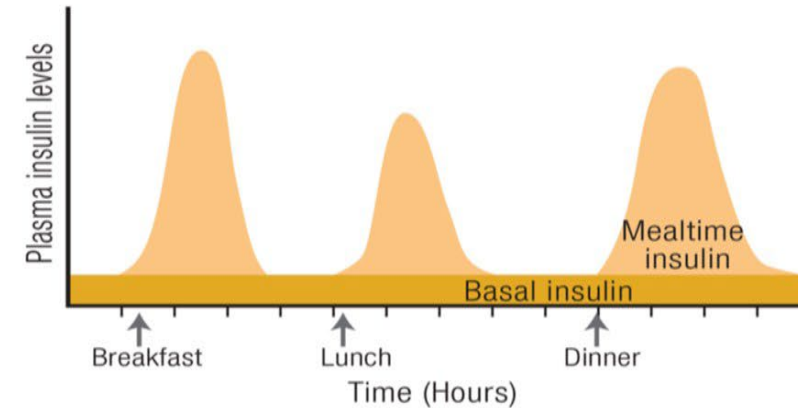
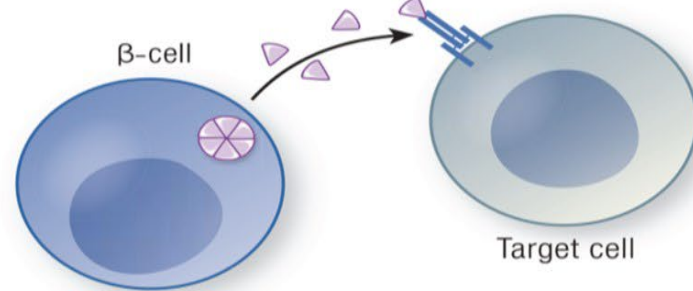
Speaker has no financial disclosures

# Insulin Management in Patients with Diabetes Mellitus – Objectives

- Describe the different types of insulin and the types of patients with diabetes for whom they are best suited.
- Review common adverse effects of insulin therapy in managing blood glucose.
- Determine how SMBG or CGM can be best utilized to improve glucose management.

# Insulin Physiology

Endogenous  
insulin



- Beta cells synthesize and secrete insulin in response to ambient glucose and certain amino acid concentrations, and modulated by GLP-1 activation
- Insulin molecules are coupled with zinc to form hexamers in granules of beta cells
- Liver receives first pass of insulin release from the pancreas, extracting 50% of release
- Insulin interacts with receptors of responsive cells, primarily liver, muscle, and fat cells and stimulate glucose and amino acid uptake
- Inadequate basal and prandial insulin production result in fasting and prandial hyperglycemia

# Administration of Exogenous Insulin Therapy

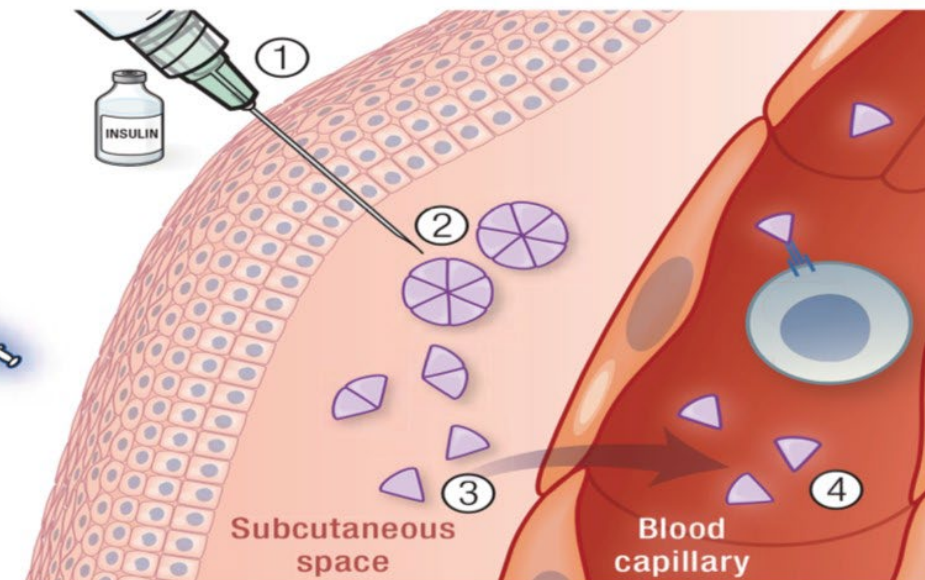
- Unregulated insulin application; not responsive to changing glucose levels (high or low) and once given, cannot take it back.
- Subcutaneous injection or inhaled administration does not provide first pass liver extraction.
- Many factors impact subcutaneous and inhalation absorption for bioavailable insulin.

What's in this 10 ml vial of Novolin R U-100?

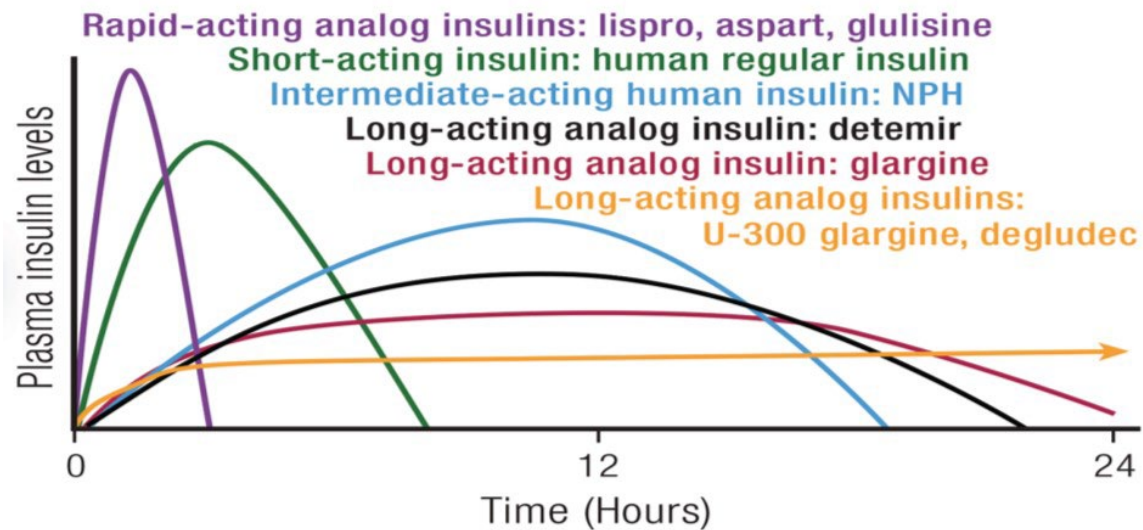


1. 100 units/ml of Recombinant Insulin
2. Zinc Acetate
3. Saline-pH 7.0
4. Excipients:  
Metacresol (preservative)  
Glycerol, absorption/osmotic monosaccharide

Exogenous insulin

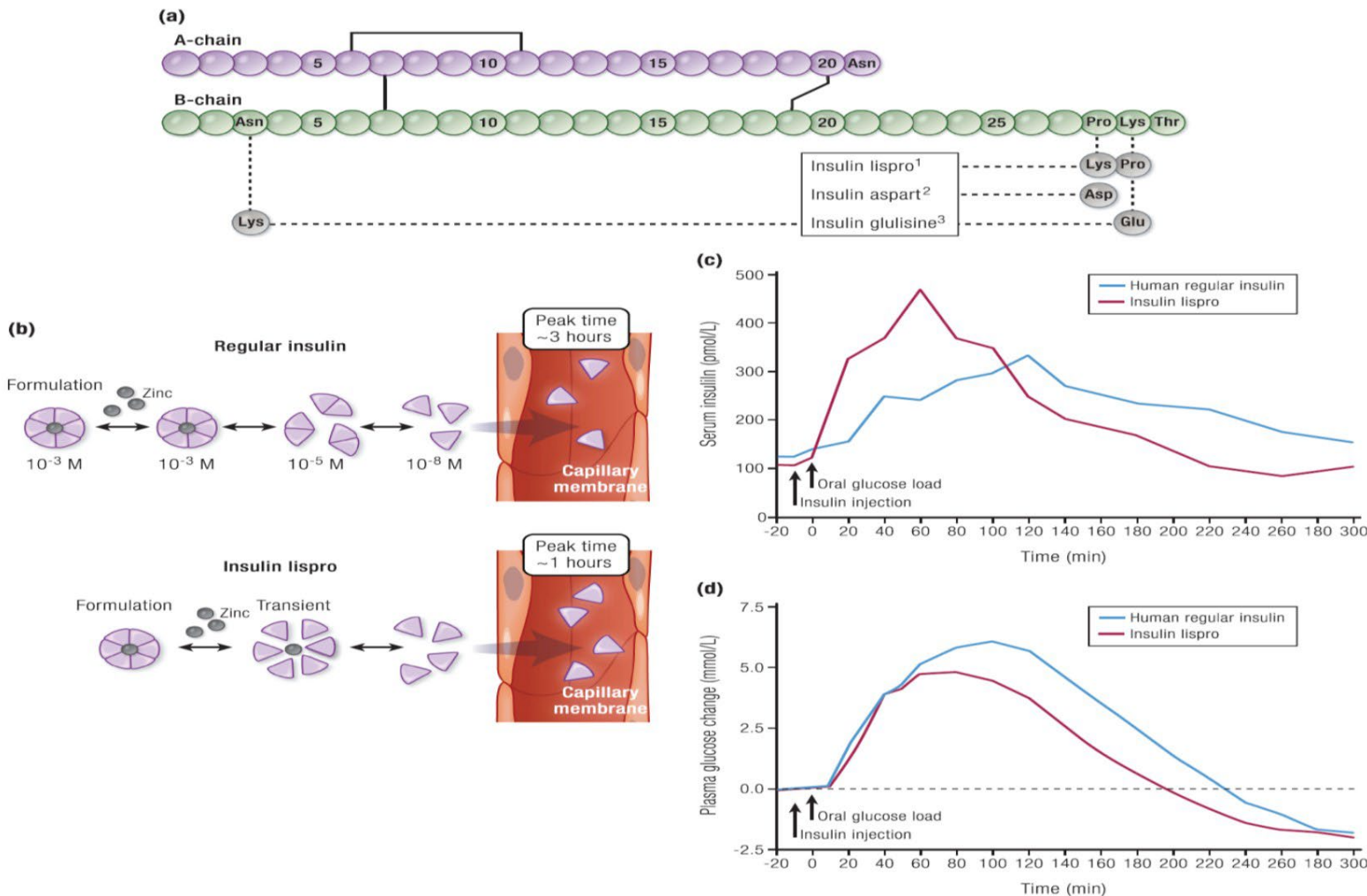


There ARE limitations of exogenous insulin therapy.  
What has been done to enhance insulin application for clinical care?



Why Do we have so many insulins?

# Insulin Structure



Hirsh IB, Juneja R, Beals JM, Antalis CJ, Wright, Jr EE. *The Evolution of Insulin and How it Informs Therapy and Treatment Choices. Endocrine Reviews* 2020;41(5):733-755. <https://doi:10.1210/endrev/bnaa015>

# Insulin Prescribing Information

## Faster Analogs: Excipients

- Faster aspart: inactive ingredients: arginine (as L-arginine hydrochloride), USP (3.48 mg); disodium phosphate dihydrate, USP (0.53 mg); glycerol, USP (3.3 mg); metacresol, USP (1.72 mg); niacinamide, USP (20.8 mg); phenol, USP (1.50 mg); zinc (as zinc acetate), USP (19.6 mcg) and water for injection, USP
- Lispro-aabc: inactive ingredients: glycerol (12.1 mg), magnesium chloride hexahydrate (1.02 mg), metacresol (3.15 mg), sodium citrate dihydrate (4.41 mg), treprostinil sodium (1.06 mcg), zinc oxide (content adjusted to provide 39 mcg zinc ion)



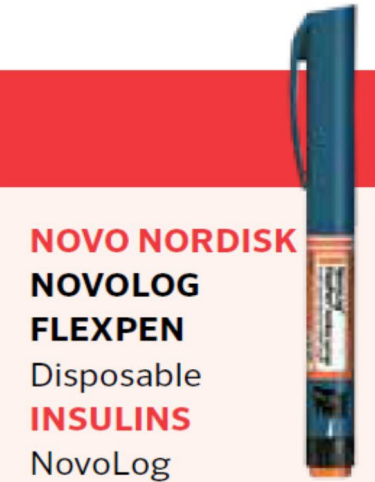
## Inhaled Regular Insulin

Afrezza offers insulin administration via lung alveoli and absorption profile best matches consumption glucose profiles. However, there are some limitations. Afrezza is contraindicated in patients who smoke or have stopped smoking within the past 6 months or have chronic lung disease. Patients should have lung function assessed with spirometry (FEV1) prior to initiating inhaled insulin.

# Prandial Insulins: Pharmacokinetics

Short-Acting Insulin	Administering with meals	Peak (hrs..)	Duration (hrs..)
Regular U-100 (Novolin R, Humulin R)	30 minutes before	2-4	6-12

Rapid-Acting Insulin	Administering with meals	Peak (hrs..)	Duration (hrs..)
Aspart U-100 (Novolog)	Within 5-10 min before	1-2	5-7
Faster Aspart U-100 (Fiasp)	At the start or within 20 min after starting	1	3-5
Glulisine U-100 (Apidra)	Within 15 min before or within 20 min after starting	1-2	3-6
Lispro (Humalog U-100, U-200; Admelog U-100)	Within 15 min or immediately after	1-2	3-5
Lispro-aabc U-100, U-200 (Lyumjev)	At the start or within 20 min after starting	1	2-4



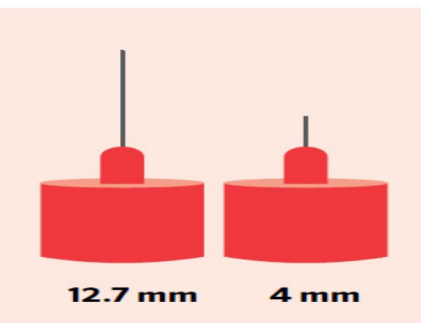
**NOVO NORDISK**  
**NOVOLOG**  
**FLEXPEN**  
 Disposable  
**INSULINS**

NovoLog  
 NovoLog Mix 70/30

**DOSE DELIVERY**

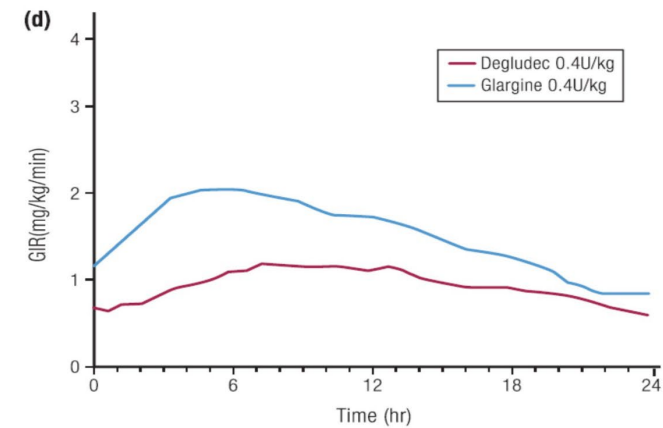
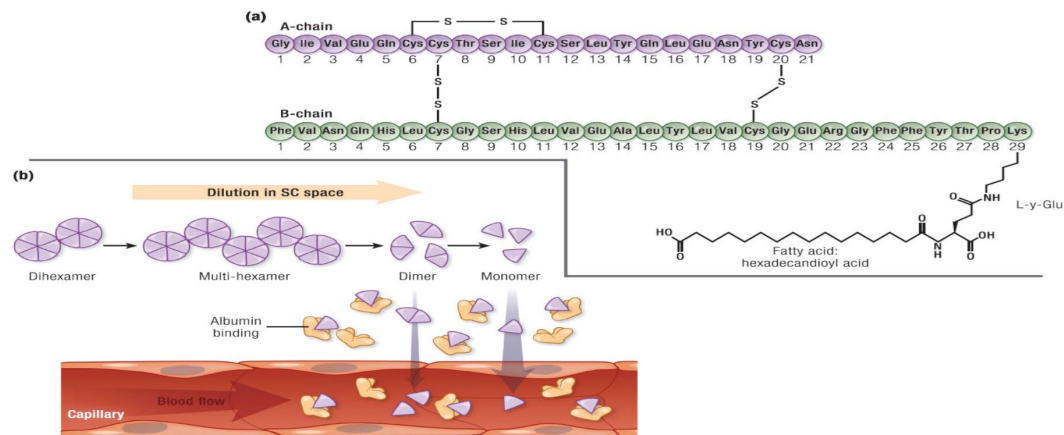
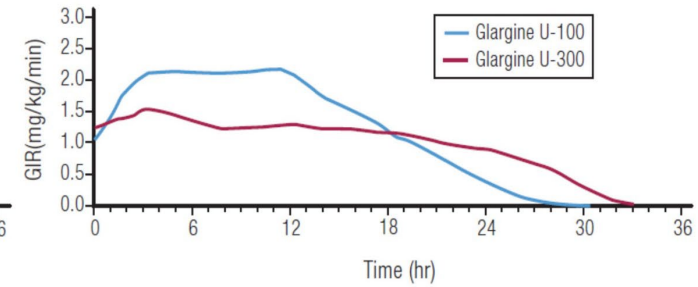
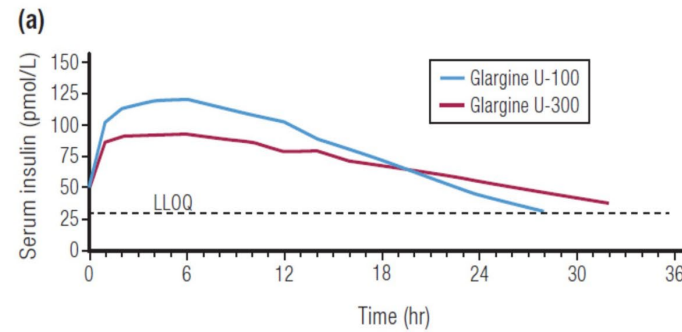
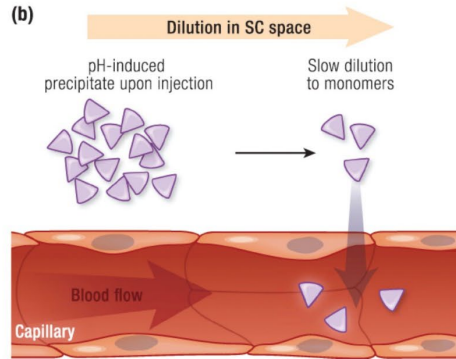
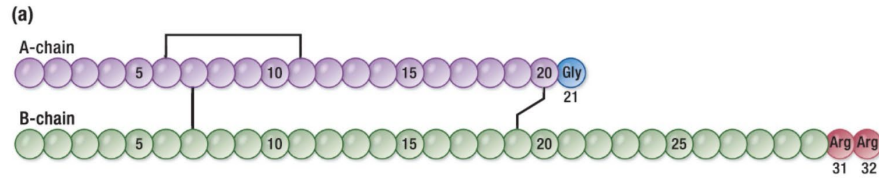
1-unit increments,  
 up to 60 units at a time

**TOTAL CAPACITY**  
 300 units





# Insulin Glargine



# Basal Insulins: Pharmacokinetics

Long-Acting Insulin	Administration	Duration (hrs.)
Detemir U-100 (Levemir)	Onset of action is slower and no pronounced peak Administer once a day and at the same time every day	8-24
Glargine U-100 (Lantus, Semglee*, and Basaglar)	Onset of action is slower and no pronounced peak Administer once a day and at the same time every day	Up to 24
Glargine U-300 (Toujeo)	Onset of action is slower and no pronounced peak Administer once a day and at the same time every day	24-36
Degludec U-100, U-200 (Tresiba)	Onset of action is slower and no pronounced peak Administer once a day and at the same time every day	Up to 42

Intermediate-Acting Insulin	Onset	Peak	Duration
NPH U-100 (Novolin N, Humulin N)	1-2 hrs.	2-8 hrs.	14-24 hrs.

diabetesforecast.org



**SANOFI**  
**LANTUS**  
**SOLOSTAR**  
Disposable  
**INSULIN**  
Lantus  
**DOSE DELIVERY**  
1-unit increments, up to 80 units at a time  
**TOTAL CAPACITY**  
300 units



12.7 mm    4 mm

diabetesforecast.org



**NOVO NORDISK**  
**TRESIBA**  
**FLEXTOUCH**  
Disposable  
**INSULINS**  
Tresiba U-100  
Tresiba U-200  
**DOSE DELIVERY**  
For U-100: 1-unit increments, up to 80 units at a time.  
For U-200: 2-unit increments, up to 160 units at a time.  
**TOTAL CAPACITY**  
For U-100: 300 units  
For U-200: 600 units

- \*Semglee is the first interchangeable biosimilar insulin and can be substituted for Lantus by the pharmacy without physician orders.
- American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2022*. *Diabetes Care* 2022;45(Suppl 1):S125-S143. <https://doi.org/10.2337/dc22-S009>.

# Premixed and Concentrated Insulins

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Pre-Mixed Insulin	Administering with meals	Peak (hrs.)	Duration (hrs.)
NPH/Regular U-100 (Novolin70/30)	Determined by Regular or rapid-acting insulin components	2-12	18-24
NPA/Aspart U-100 (Novolog Mix 70/30)	Determined by Regular or rapid-acting insulin components	1-4	12-24
NPL/Lispro U-100 (HumalogMix75/25, Mix50/50)	Determined by Regular or rapid-acting insulin components	1-4	6-12
Degludec/Aspart U-100 (Ryzodeg 70/30)	With largest meal	1-3	> 24

Concentrated Insulin	Administering with meals	Peak (hrs.)	Duration (hrs.)
Regular U-500 (Humulin R U-500 Kwikpen)	30 minutes before	0.5-8	13-24



**ELI LILLY  
HUMULIN  
KWIKPEN**  
Disposable  
**INSULINS**  
Humulin N  
Humulin 70/30  
Humulin R U-500  
**DOSE DELIVERY**  
For all except U-500:  
1-unit increments, up to 60 units at a time.  
For U-500: 5-unit increments, up to 300 units at a time.  
**TOTAL CAPACITY**  
For all except U-500: 300 units. For U-500: 1,500 units.

- Patients with severe insulin resistance requiring > 200 units per day of insulin are candidates for Regular U-500. Total daily dosing may be started BID split 50-50 with meals or TID split 40-30-30 with breakfast, lunch, and dinner meals respectively.
- American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2022*. *Diabetes Care* 2022;45(Suppl 1):S125-S143. <https://doi.org/10.2337/dc22-S009>.

# Insulin Indications and Therapy Recommendations

- Patients with Type 1 diabetes; multiple daily injections (MDI) with basal and bolus insulin or continuous subcutaneous insulin infusion (CSII)
- Patients with pregestational and gestational diabetes mellitus unable to attain glycemic targets with nutrition therapy alone
- Patients with type 2 diabetes unable to achieve glycemic targets with lifestyle intervention and/or oral and/or injectable non-insulin therapies
- Hospitalized patients (with or without diabetes) requiring treatment to maintain glycemic targets of 140 to 180 mg/dL
- Patients with diabetes and recovering from surgical procedures
- Patients with diabetes and severe hypertriglyceridemia (> 1000 mg/dL) unable to achieve triglyceride goals with anti-lipid therapy

American Diabetes Association. 9. Pharmacologic Approach to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care e222;045(Suppl. 1):S125-S143. <https://doi.org/10.2337/dc22-S009>.

# Insulin Therapy: Side Effects and Complications

- Hypoglycemia (worse with short or rapid acting insulins)
- Weight gain (more with short or rapid acting and/or concentrated insulins)
- Retinopathy (transient worsening with initiation or intensification)
- Edema
- Muscle cramps
- Acanthosis nigricans (skin condition of insulin resistance)
- Lipohypertrophy (non-rotation of injection sites)
- Injection site pain and reactions (glargine in acidic solution)

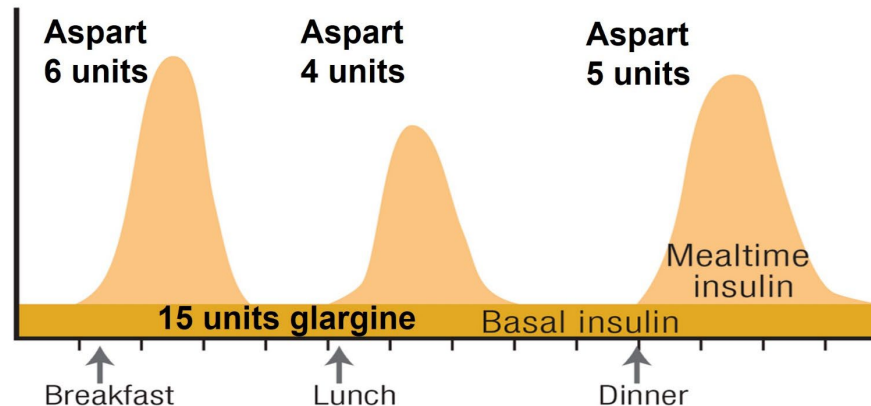
American Diabetes Association. 9. Pharmacologic Approach to Glycemic Treatment: *Standards of Medical Care in Diabetes-2022*. *Diabetes Care* e222;045(Suppl. 1):S125-S143. <https://doi.org/10.2337/dc22-S009>.

# INSULIN TREATMENT IN PATIENTS WITH TYPE 1 DIABETES – Calculations

1. Start with calculation of total daily insulin dosage based on weight using a range of 0.25–0.75 units/kg/day.
2. Divide total daily dose to approximately 50% basal and 50% prandial distributed with meals.

For example: A patient weighs 60 kg, total daily insulin dose range is 15 to 45 units/day; basal and prandial doses range 7.5 to 22.5 units/day. Prandial coverage can be divided 2–3 units to 7–8 units three times a day before meals.

If we select 0.5 unit/kg/day, total daily dose = 30 units a day



# INSULIN TREATMENT IN PATIENTS WITH TYPE 1 DIABETES – Adjustments

1. Glucose targets and correction factors:
  - A. 1800 rule:  $1800/\text{total daily dose (TDD) of Rapid-Acting insulin} = \text{Insulin Sensitivity Factor (ISF)}$ ; 1 unit of insulin to lower BS (1500 rule for Regular insulin)
  - B. Correction dose:  $\text{Current Glucose} - \text{target glucose} / \text{ISF} = \text{dose}$
2. Insulin coverage for carbohydrate consumption:
  - A. Insulin to Carbohydrate ratio (ICR) = 500 rule:  $500/\text{TDD of insulin}$  (usually 1unit:5 to 20 gm)
3. Other adjustments: snacks, exercise, trends
4. Example: Patient taking 14 units glargine daily and 6 units aspart TID ac with a prebreakfast BS level of 165 mg/dL and plans to consume toast/OJ = 60 gms of carbs. What's the aspart dose?
  - A.  $\text{ICR} = 500/32$  (TDD) or 15 gm:1 unit insulin. Breakfast dose is  $60/15 = 4$  units.
  - B.  $\text{ISF} = 1800/32$  or 56 mg/dL per 1 unit aspart. Target glucose is 100 mg/dL so correction dose is  $165 - 100 / 56 = 1.2$  units + 4 units, so 5 units for breakfast.

# A Patient with Diabetes

- 40 yo gentleman diagnosed in 2018 with diabetes during a 20-day admission for diverticulitis with complications. He was treated with sliding scale insulin therapy.
- He was discharged on glipizide/metformin/DPP-4 inhibitor. Over the next few months, he was given basal insulin treatment to reduce his BS levels.
- By late 2020, his treatment regimen progressed to basal-bolus therapy with glargine daily and lispro three times a day with meals. His A1C in March 2021 was 11.2%.
- His work schedule made it difficult for him to follow up in the clinic, but based on his SMBG profiles, his insulin treatment regimen was adjusted.
- Clinic visit on 10/2/2021 revealed a lean individual weighing 132# (60kg) with BMI of 20.7, HR of 82/min, BP 126/78 mmHg, and an unremarkable examination for diabetes complications.
- Laboratory tests: A1C 9.2%; C-peptide of 0.9 ng/ml (NL 0.5 – 2.0 ng/ml) with a BS of 412 mg/dL; Anti-GAD antibody titer was positive (NL < 5.0 units/ml)



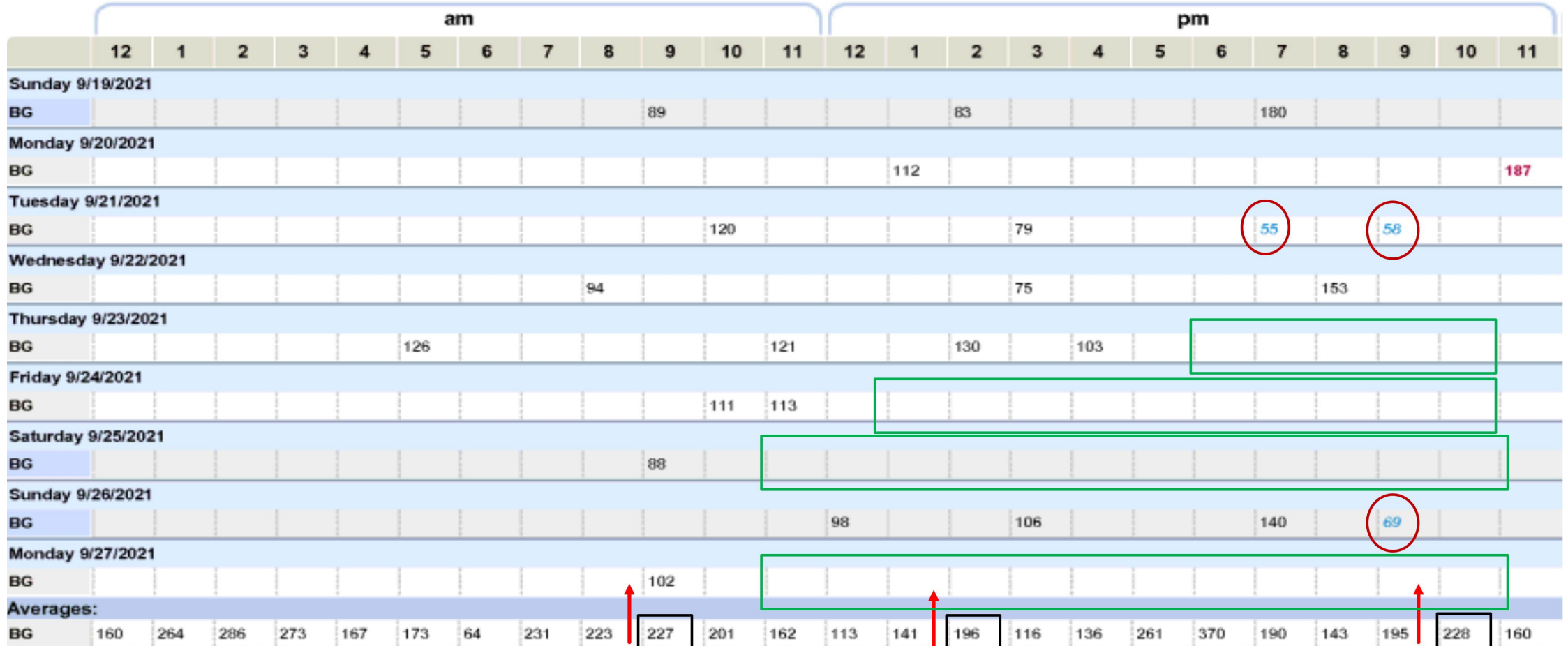
# Blood Glucose Monitoring (BGM)

## Recommendations from the ADA Professional Practice Committee

- 7.7 People who are on insulin using BGM should be encouraged to check when appropriate based on their insulin regimen. This may include checking when fasting, prior to meals and snacks, at bedtime, prior to exercise, when low blood glucose is suspected, after treating low blood glucose levels until they are normoglycemic, and prior to and while performing critical tasks such as driving. B
- 7.8 Providers should be aware of the differences in accuracy among blood glucose meters- ... use with unexpired strips... E
- 7.9 Although BGM in individuals on noninsulin therapies has not consistently shown clinically significant reductions in A1C, it may be helpful when altering diet, physical activity, and/or medications (particularly medications that can cause hypoglycemia) in conjunction with a treatment adjustment program. E

American Diabetes Association. 7. Diabetes Technology: *Standards of Medical Care in Diabetes-2022*. *Diabetes Care* 2022;45(Suppl. 1):S97-S112. <https://doi.org/10.2337/dc22-S007>.

# Patient's SMBG Profiles (July–Sept 2022)



Glargine 14 units,  
lispro 2-6 units

lispro 2-6 units

lispro 2-6 units

# Continuous Glucose Monitoring



**Table 7.3—Continuous glucose monitoring devices**

Type of CGM	Description
rtCGM	CGM systems that measure and store glucose levels continuously and without prompting
isCGM with and without alarms	CGM systems that measure glucose levels continuously but require scanning for storage of glucose values
Professional CGM	CGM devices that are placed on the patient in the provider’s office (or with remote instruction) and worn for a discrete period of time (generally 7–14 days). Data may be blinded or visible to the person wearing the device. The data are used to assess glycemic patterns and trends. These devices are not fully owned by the patient—they are clinic-based devices, as opposed to the patient-owned rtCGM/isCGM devices.

CGM, continuous glucose monitoring; isCGM, intermittently scanned CGM; rtCGM, real-time CGM.

# Continuous Glucose Monitoring metrics



**FIGURE 1**

Sample display of continuous data provided by FCGM.

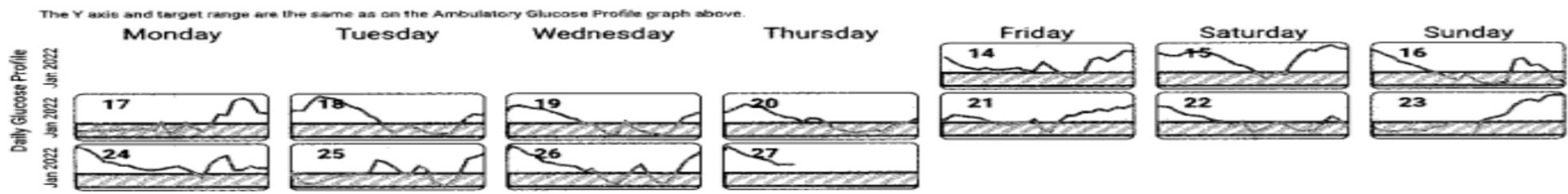
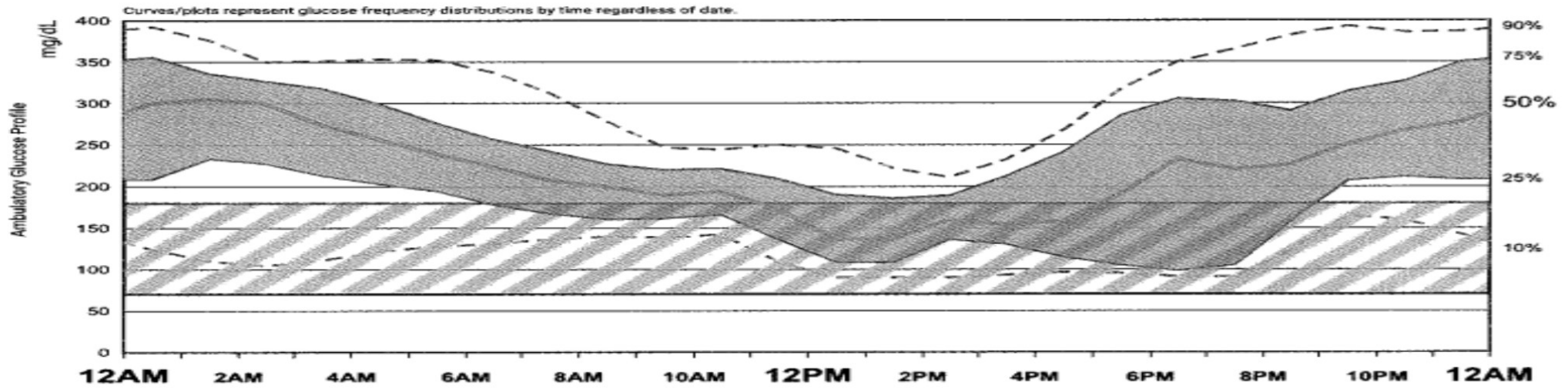
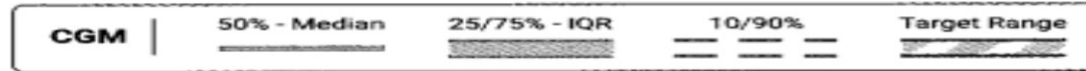
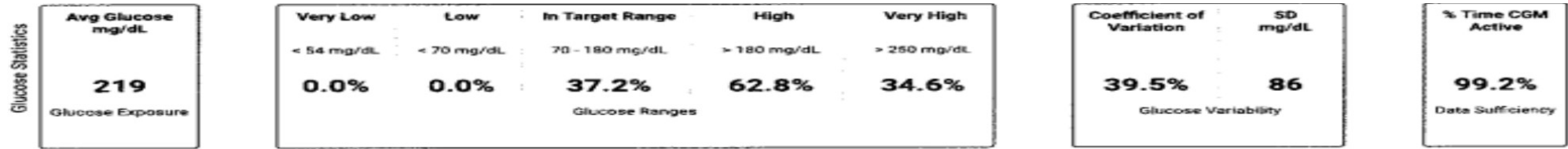
**Table 6.2—Standardized CGM metrics for clinical care**

1. Number of days CGM device is worn (recommend 14 days)	
2. Percentage of time CGM device is active (recommend 70% of data from 14 days)	
3. Mean glucose	
4. Glucose management indicator	
5. Glycemic variability (%CV) target $\leq 36\%^*$	
6. TAR: % of readings and time $>250$ mg/dL ( $>13.9$ mmol/L)	Level 2 hyperglycemia
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia
10. TBR: % of readings and time $<54$ mg/dL ( $<3.0$ mmol/L)	Level 2 hypoglycemia

CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range. \*Some studies suggest that lower %CV targets ( $<33\%$ ) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. Adapted from Battelino et al. (34).

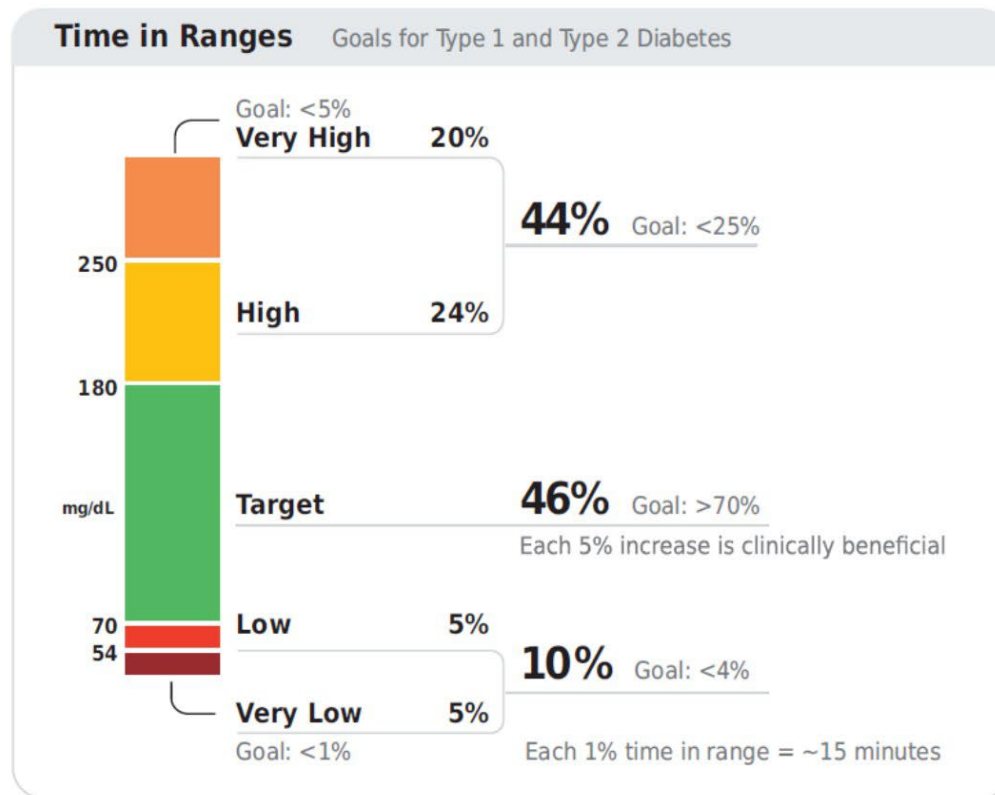
- American Diabetes Association. 6. Glycemic Targets: *Standards of Medical Care in Diabetes-2022*. *Diabetes Care* 2022;45(Suppl. 1):S83-S96. <https://doi.org/10.2337/dc22-S006>
- Hirsch IB, Battelino T, Peters AL, Chamberlain JJ, Aleppo G, Bergenstal RM. *Role of Continuous Glucose Monitoring in Diabetes Treatment*. Arlington, Va., American Diabetes Association, 2018

# Patient's CGM Profiles



# AGP Report

## AGP Report: Continuous Glucose Monitoring



**Test Patient** DOB: Jan 1, 1970

**14 Days: August 8-August 21, 2021**

**Time CGM Active: 100%**

### Glucose Metrics

**Average Glucose** ..... **175 mg/dL**  
Goal: <154 mg/dL

**Glucose Management Indicator (GMI)** ..... **7.5%**  
Goal: <7%

**Glucose Variability** ..... **45.5%**  
Defined as percent coefficient of variation  
Goal: ≤36%

# GENERAL CONSIDERATION FOR INSULIN TREATMENT IN PATIENTS WITH TYPE 2 DIABETES

- Common situation to start insulin is a patient on multiple medications but still not at targeted goal (crossroads of management).
- Initiation of insulin should be accompanied by reinforcement of SMBG and lifestyle therapy (nutrition counseling, physical activity, and weight loss).
- Revisit diabetes self-management education with insulin treatment; review benefits and side effects.
- If considering multiple daily injection treatment, regimen similar to type 1 DM except to accommodate insulin resistance with higher doses.
  - TDD estimate based on weight is between 0.4 units-1.0 unit per kg per day.
  - 50 % of TDD is basal and 50% is prandial divided into two or three meals.
  - Metformin therapy is continued (if possible); reduces insulin dose, mitigates weight gain.

# INSULIN TREATMENT IN PATIENTS WITH TYPE 2 DIABETES – General Recommendations

## Initiating Insulin Treatment (General Recommendations)

1. Start long-acting, 10 units or 0.1-0.2 units/kg daily, usually at bedtime.
2. Titrate by 2-4 units or 10-15% every 3-4 days until FPG falls to target range (optimally 80-130 mg/dL but should be individualized).
3. Long-acting insulin may be changed to BID dosing for some patients.
4. Patients should continue other antidiabetes therapies however, consider stopping or reducing TZD to decrease risk of excessive weight gain and CHF hospitalization.
5. Reduce dose by 10-20% if hypoglycemic event occurs or FPG falls below target range.



# INSULIN TREATMENT IN PATIENTS WITH TYPE 2 DIABETES – Advancing Treatment

If A1C not within individualized goal AND

FPG at target with basal insulin dose  $< 0.5$  units/kg OR

FPG not at target and basal insulin dose exceeds 0.5 units/kg

It's time to advance insulin treatment

# INSULIN TREATMENT IN PATIENTS WITH TYPE 2 DIABETES

## Advancing Insulin Treatment

1. Start rapid-acting or short-acting insulin 2-4 units or 10% of long-acting insulin dose before largest meal. (Reduce long-acting insulin dose by 10% if A1C < 8% or FPG within target range).
2. Titrate by 1-2 units or 10-15% every 3-7 days until premeal glucose levels of the next meal falls within target range (optimally 80-130 mg/dL but should be individualized).
3. Patients should discontinue sulfonylurea or meglitinide to reduce the risk of hypoglycemia and more weight gain.
4. Reduce dose by 10-20% if hypoglycemic event occurs or if glucose levels falls below target range.

Intensify insulin therapy to other meals following the protocol above.

# A Patient with Type 2 Diabetes

- 51 yo gentleman initially presented with symptoms of diabetes in 2015 and had high BS levels with an A1C level of 14%. He was started on metformin and sulfonylurea, and was provided self-management training along with dietary counseling.
- Later, DPP-4 inhibitor was added and later replaced by GLP-1 agonist and SGLT-2 inhibitor.
- In 2017, he had a NSTEMI that required 3 stent insertions.
- His current anti-diabetes medications are metformin/empagliflozin 1000/5 mg BID; glipizide 10 mg BID; and oral semaglutide (Rybelsus) 14 mg QD.
- His other medications include metoprololER 200 mg daily, atorvastatin 80 mg QD, fenofibrate 200 mg daily, losartan 100 mg QD, spironolactone 50 mg QD, chlorthalidone 25 mg daily, ASA 81 mg daily.
- Clinic visit revealed an obese individual weighing 248# (111kg) with BMI of 38, HR 124/min, BP 130/74 mmHg. His examination was remarkable for tachycardia, acanthosis over neck, LE dermopathy, and absent ankle reflexes on foot exam.
- Laboratory tests: A1C 11.9%; Triglyceride 3,058 mg/dL, HDL cholesterol 39 mg/dL, creatinine 1.2 mg/dL (eGFR 70), UACR 478 mg/g, LFTs WNL.

# A Patient with Type 2 Diabetes (2)

- Patient admits to not taking oral semaglutide, but has been compliant with other meds.
- He denies alcohol use and his TSH level is NL. His hypertriglyceridemia has been a problem over the past 3 years.
- He is reticent to start any injectable, especially insulin or consider BGM.
- (Laboratory tests: A1C 11.9%; Triglyceride 3,058 mg/dL, HDL cholesterol 39 mg/dL, creatinine 1.2 mg/dL (eGFR 70), UACR 478 mg/g, LFTs WNL)
- The patient's treatment options are insulin, insulin, insulin!
- No restarting oral semaglutide or adding another oral agent; and he refused another session with the dietitian.
- He started glargine 10 units at HS (convincing him required his wife's intervention).
- Dose of glargine increased based on clinic POV fingerstick; later switched to degludec.
- Combination basal insulin/GLP-1 RA is an option once A1C and triglyceride levels improve OR he could move on to covering meals with rapid-acting insulin (he'll gain more weight).

# Resources and References

## Resources

1. DDTP Standards of Diabetes Care and Resources for Clinicians and Educators: Glycemic Control
2. DDTP Diabetes Treatment Algorithm: Insulin Therapy for Type 2 Diabetes and Insulin Concentrations
3. Diabetes Forecast, 2019-cg-insulin pens <http://main.diabetes.org/dforg/pdfs/2019/2019-cg-insulin-pens.pdf>

## References

1. Hirsh IB, Juneja R, Beals JM, Antalis CJ, Wright, Jr EE. *The Evolution of Insulin and How it Informs Therapy and Treatment Choices*. *Endocrine Reviews* 2020;41(5):733-755. <https://doi.org/10.1210/edrv/bnaa015>
2. Holt RIG, DeVries JH, Hess-Fischl A, et al. Management of Type 1 Diabetes in Adults: *Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)*. *Diabetes Care* 2021;44(11):2589–2625. <https://doi.org/10.2337/dci21-0043>
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# Diabetes Discoveries and Practice Blog

How can you help your patients use new technologies?



Link- [https://www.niddk.nih.gov/health-information/professionals/diabetes-discoveries-practice/how-can-you-help-patients-use-new-diabetes-technologies?utm\\_medium=email&utm\\_source=rasa\\_io](https://www.niddk.nih.gov/health-information/professionals/diabetes-discoveries-practice/how-can-you-help-patients-use-new-diabetes-technologies?utm_medium=email&utm_source=rasa_io)