# ECHO Diabetes

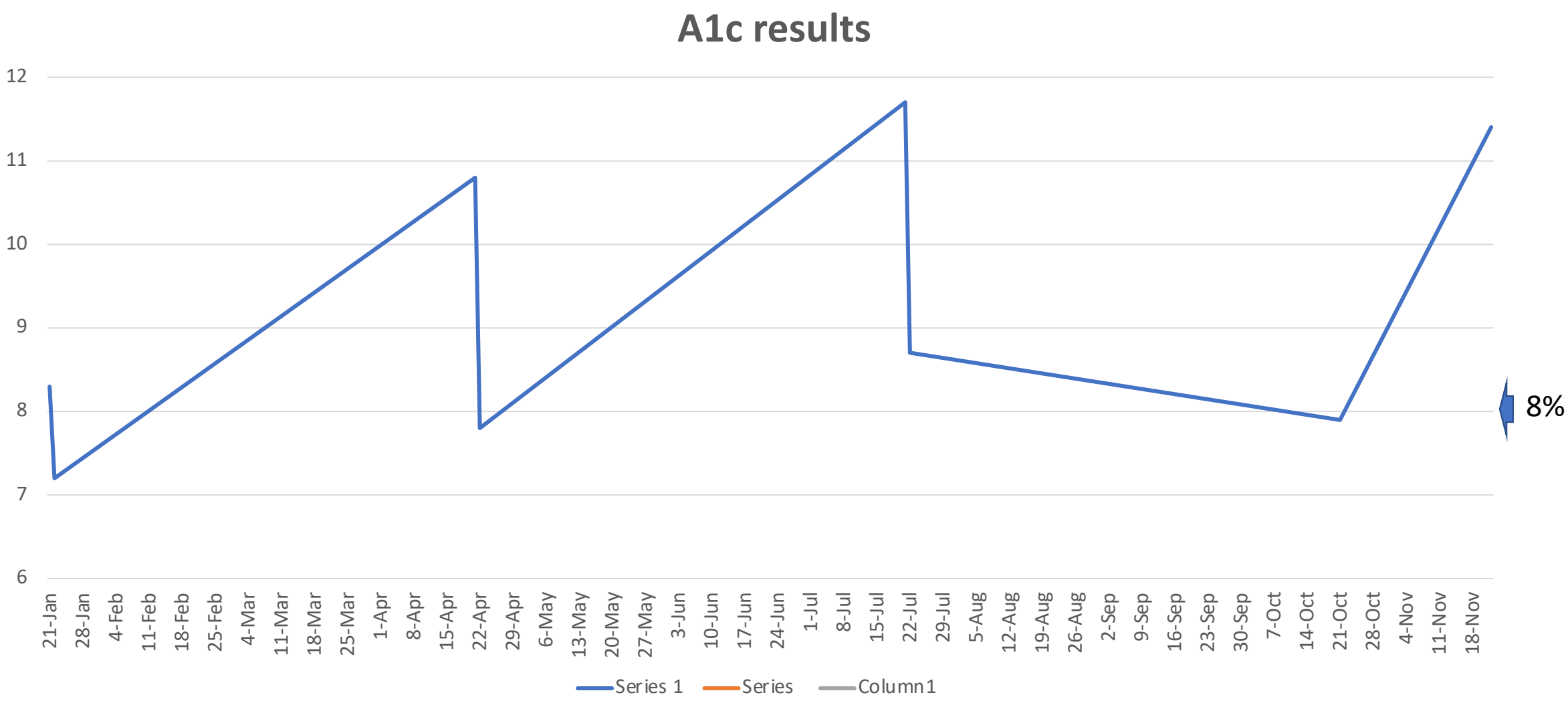
## Case Discussion

December 15, 2022

Carol Greenlee MD

# *"Pt to begin Trulicity and would like recommendation on how/when to start titrating insulin(s)"*

- **A1c 11.37%** (11/2022) - average BG on CGM ~261
- FBS 238 CGM - **TIR (70-180) = 18%** -- no low BG (TBR)
  - 68% of BG above 240, 14% 181-240
  - Any pattern of what time of day higher vs lower BGs?
- Weight 250# (~100 kg) (increase from 229# past year)
- Levemir insulin: 60u qAM – 8u qPM
- Novolog insulin:  3 units for every 50 points above 150 (1/16.6) TID
- Metformin 500 mg BID
- Pioglitazone 15 mg QD
- *Patient goals – improve glycemia, lose weight, avoid CKD & dialysis*
  - *Works long hours, often skips lunch, high stress level*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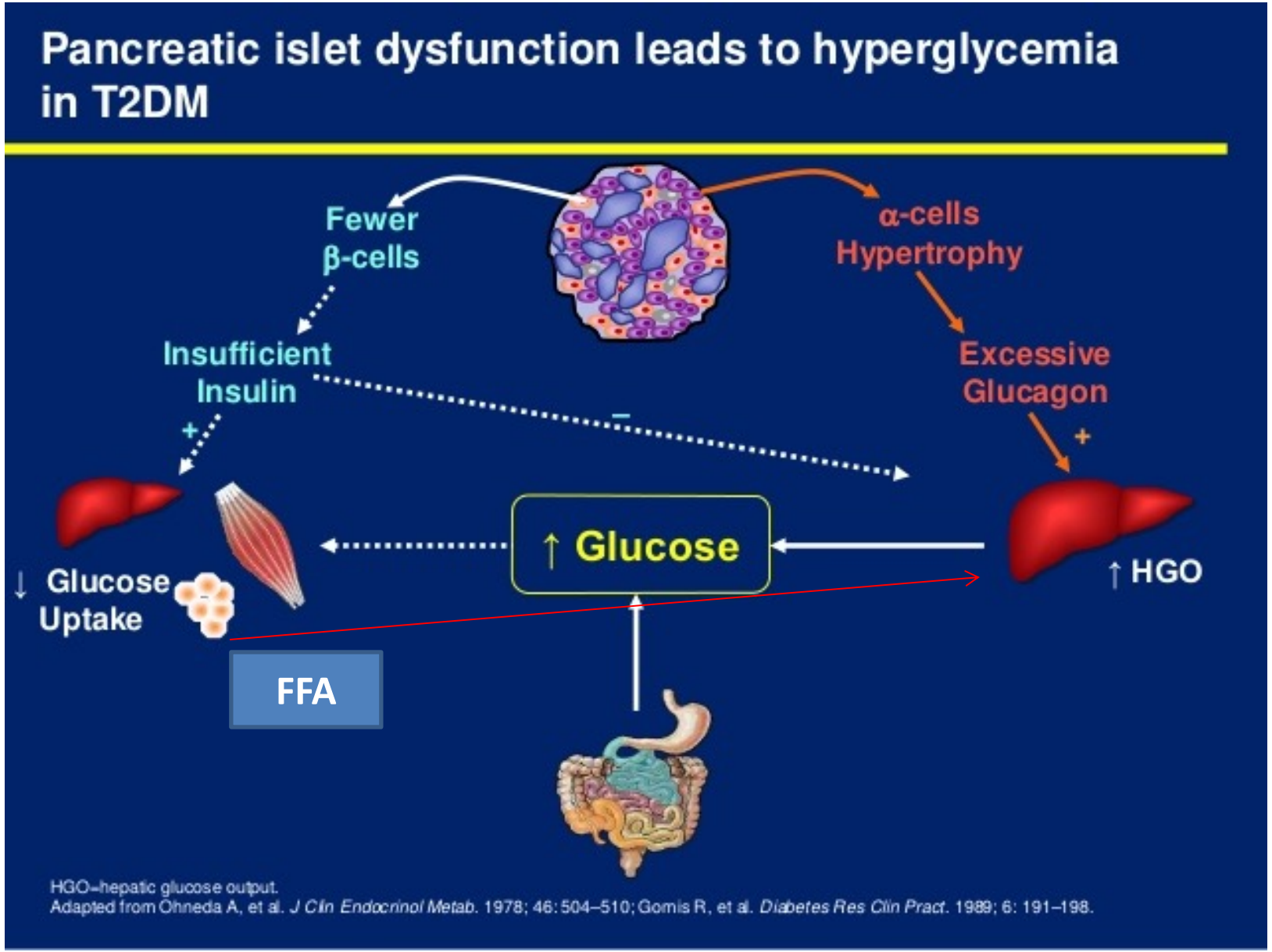
# Assessment

- Typically, if A1c is >8% and/or if TIR is <66% - high BG is due to too much basal glycemia → target basal glucose
  - If A1c <8% and/or TIR >66% - target postprandial glucose

- Her A1c pattern shows that she can get BGs down with current meds
  - High BGs due to missed meds and /or stress eating +/- stress???
    - Overeat at night? (note 21# weight gain over past year)
  - Trulicity might reduce stress eating

- Glucotoxicity might be present (reduced insulin secretion & increased insulin resistance – "desensitization")
  - Need to "break" glucotoxicity to restore responsiveness to meds – need to get BGs down
    - Large doses of insulin
    - SGLT2i medications
    - GLP1 RA (?)

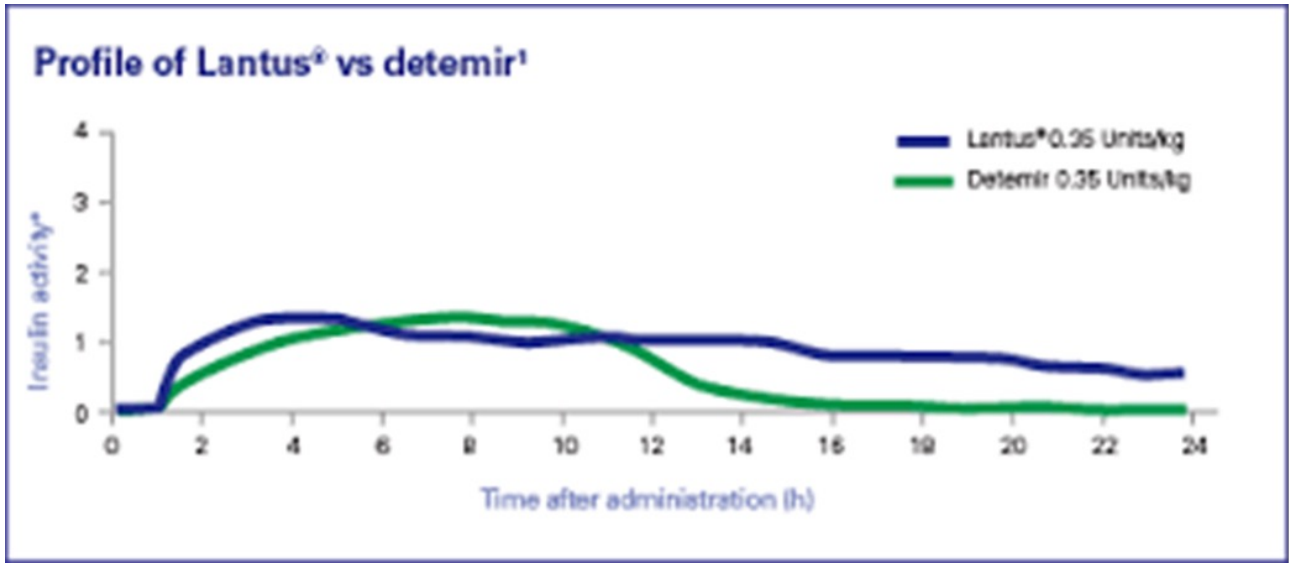
# Basal (fasting) Hyperglycemia



# Target Basal Glucose

- **Basal insulin** is designed to *suppress hepatic glucose production* and ***improve basal (fasting) hyperglycemia***
- **GLP-1 receptor agonists** provide improvements in ***both PPG and FPG*** levels, complementing the effects of basal insulin – GLP1 RA
  - stimulate glucose-dependent insulin secretion
  - Inhibit glucose-dependent glucagon secretion
  - slow gastric emptying
  - increase satiety

# Levemir (insulin detemir) basal insulin




**Smaller doses** → shorter duration of action, may not adequately suppress Hepatic glucose output (HGO)
**Larger doses** → exceed basal levels and partially cover meals, in addition large dose can impair absorption

# Any Pattern to Glycemia?

- Stress during day might increase BG
- Skipping meals during the day might have lowest BGs midday to late afternoon – especially with higher dose of detemir insulin in AM
- Eating more in evening might result in higher bedtime, overnight & fasting BGs –
- Lower dose of only 8 units in PM may not be enough to control hepatic glucose output overnight

# Suggestions

- Stress reduction at work
  - Stand up every 20 minutes x 1-2 minutes* (metabolic effects -postural muscles)
  - Parasympathetic breathing
- Utilize CGM to help guide insulin adjustments while titrating up Trulicity
- Hold rapid acting (mealtime) correction insulin
- Redistribute basal detemir insulin?
  - Consider 30u BID using CGM to titrate down as titrate up Trulicity dosage if BGs drop
    - Her response to Trulicity will determine if she needs less insulin or if Trulicity just helps the adequacy of her current dose
- If Trulicity does not result in significant decrease in BGs (either non-responder or persistent glucotoxicity), consider
  - SGLT2i
  - High dose insulin temporarily – requires close contact with patient
- Once basal glycemia controlled, if need mealtime insulin – start with Basal-Plus (vs Basal- Bolus)**
  - Include meal/carb coverage (“small”, “medium” or “large”) + correction coverage

# Basal-Plus vs Basal-Bolus

- Full **basal-bolus therapy** *comprises* ***basal insulin plus three short-acting insulin injections per day*****.**
- The term '**basal-plus therapy**' is usually used to describe a regimen comprising ***one basal insulin injection and the stepwise addition of one to three preprandial short-acting insulin injections*** per day
  - The progressive nature of Type 2 diabetes suggests that stepwise intensification of insulin therapy would be a more logical and simpler approach to treatment, and, also, the most acceptable to both patients and physicians .

# Review of *basal-plus* insulin regimen options for simpler insulin intensification in people with Type 2 diabetes mellitus

D. Raccah, et al Diabet Med. 2017 Sep; 34(9): 1193–1204.

Review: Compare progressive intensification of a basal insulin regimen to a **basal-plus** regimen (one basal insulin injection plus stepwise addition of one to three preprandial short-acting insulin injections/day) vs **a basal-bolus** regimen (basal insulin plus three short-acting insulin injections per day) in people with Type 2 diabetes.

Results: A basal-plus regimen can provide glycemic control equivalent to that obtained with a full basal-bolus regimen, with fewer injections of prandial insulin.

Conclusions: Compared with a basal-bolus regimen, a **basal-plus insulin regimen is as effective but more practical and has the best chance of acceptance and success** in the real world.

**For people with Type 2 diabetes on basal insulin who require intensification, is a *stepwise approach* to addition of prandial insulin an effective alternative to a *full* basal-bolus approach?**

- of all participants who received prandial insulin:
  - 19–50% received **one** prandial injection per day
  - 34–47% received two prandial injections per day
  - 13–44% received 3 prandial injections per day.

These results suggest that a *full basal-bolus regimen is probably not necessary* for the majority of patients at the time of insulin intensification ***after appropriate basal insulin titration*** (40% did not require prandial insulin)

Note from CG – with GLP1 RA med, even lower need for prandial insulin

- Albiglutide + glargine study*: 54% did not require bolus insulin
  - Anticipate greater response with more potent GLP1 RA meds

# Adding prandial (rapid-acting) insulin – usually need both meal coverage & correction – not just correction

**Bolus (mealtime, prandial) Insulin** –as rapid-acting insulin - limits hyperglycemia after meals – should ***hold if NPO or not eating***

**Correction Insulin** – ***extra rapid-acting insulin given for high blood glucose*** to decrease BG levels to target range – based on patient's "sensitivity or correction factor" - can be used to:

- add more insulin to a mealtime bolus to correct for a high premeal blood glucose (e.g., 5u if BG 80-140, 6u (5u+1u) if 141-170, 7u(5+2u) if 171-200, etc.)
- Used alone to correct a high blood glucose outside of mealtime or if NPO

No need to do carb counting but can get an estimate of what a "small", "medium" or "large" meal is for her (e.g., 30 grams CHO, 60 grams CHO, 90 grams CHO)

- Utilize an ICR to estimate dose for each (e.g., 1:10)
  - Give 3 units for a small meal, 6 for a medium meal and 9 for a large meal
  - Can add correction insulin if pre-meal BG is above target

# Estimating an Insulin to Carb Ratio

**Based on Total Daily Dose**

- 8—11 units 1:50
- 12—14 units 1:40
- 15—18 units 1:30
- 19—21 units 1:25
- 22—27 units 1:20
- 28—35 units 1:15
- 36—45 units 1:12
- 46—55 units 1:10
- 56—65 units 1:8
- 66—80 units 1:6
- 81—120 units 1:5
- >120 units 1:4

Based on the 500 Rule

**Based on Body Weight**

- <60 lb. 1:30
- 60—80 lb. 1:25
- 81—100 lb. 1:20
- 101—120 lb. 1:18
- 121—140 lb. 1:15
- 141—170 lb. 1:12
- 171—200 lb. 1:10
- 201—230 lb. 1:8
- 231—270 lb. 1:6
- >270 lb. 1:5

Fails to consider body composition & insulin resistance

With patient taking GLP1 RA would go with a lower ICR and titrate as needed –
e.g., 1:10 instead of 1:6

# Quick “cheat sheet” for *starting point* for Correction Factor(CF)/Sensitivity Factor(SF)

**CF based on patient weight**

- <60 lb. = 100
- 60—80 lb. = 75
- 81—100 lb. = 60
- 101—120 lb. = 50
- 121—140 lb. = 45
- 141—170 lb. = 40
- 171—200 lb. = 30
- 201—230 lb. = 25
- 231—270 lb. = 20
- >270 lb. = 15

Or – if patient already treated with insulin
Can use:

- 1700/TDD* - or
- 3x their Insulin to Carb ratio Factor

*Based on 3x ICR weight formula*

# After titrating Trulicity….

- After Trulicity dose is titrated up and basal insulin titrated for control of basal glycemia – if still need to address postprandial hyperglycemia
  - Would start with her largest meal of the day
  - Maybe use an ICR of 1:10 to calculate meal coverage for “small, medium or large” meals (e.g., 3-6-9)
  - Maybe use a correction dose of 1/20 (for every 20 points above target add 1 unit) – but with the GLP1 RA 1/30 might be effective (use CGM data to guide)
    - You can have her do the math herself or you can generate a scale for her – e.g., for medium meal:
      - 70-140 take 6 units;
      - 141-160 take 7 units; (141-170)
      - 161-180 take 8 units; (171-200)
      - 181-200 take 9 units, (201-230)
      - 201-220 take 10 units,(231-260) etc.

She can use correction insulin at other times if needed – allow at least 4 hours between doses

- 150-170 (150-180) take 1u
- 171-190 (181-210) take 2u
- 191-210 (211-240) take 3u, etc.

# Extra Slides

# Association Between Time in Range and the Postprandial Glucose Contribution Rate in Noninsulin-Treated Patients With Type 2 Diabetes

## Diabetes Technology & Therapeutics

- Published in Diabetes:  TAKE-HOME MESSAGE
- This study assessed the association between time in range (TIR) and postprandial glucose in patients with type 2 diabetes (N = 729) not treated with insulin. Based on an analysis of continuous glucose monitoring data, the postprandial glucose contribution rate was correlated with TIR and was higher than the basal glucose contribution rate in patients with a TIR of ≥66.3%.
- Effective glycemic control should include targeting postprandial glucose in patients with high TIR and basal glucose in those with low TIR.
- – Jacqueline A. Seiglie, MD, MSc
- Abstract: BACKGROUND
- Whether time in range (TIR), a parameter derived from continuous glucose monitoring (CGM), is a marker of postprandial hyperglycemia remains to be determined. In this study, we examined the association between TIR and postprandial glucose in non-insulin-treated type 2 diabetic patients.
- METHODS
- Our cross-sectional study included 729 non-insulin-treated patients with type 2 diabetes who underwent CGM without any changes in drug therapy on admission. The 24-h CGM record was analyzed for average glucose, standard deviation, percentage coefficient of variation, time above range, TIR, time below range, area under the curve (AUC) of basal glucose, AUC of postprandial glucose, and postprandial glucose contribution rate (%). The primary endpoint was the association between TIR and the postprandial glucose contribution rate.
- RESULTS
- We made TIR groups divided into 10% increments for a 7-group and compared with <40% to >90%. The basal and postprandial glucose AUCs correlated negatively with TIR. The postprandial glucose contribution rate correlated with TIR. The cutoff value for TIR, where postprandial glucose contribution rate was lower than the basal glucose contribution rate, was 66.3%.
- CONCLUSIONS
- In non-insulin-treated type 2 diabetic patients, postprandial glucose AUC was higher in the high TIR group, whereas the basal glucose AUC was higher in the low TIR group. Good glycemic control can be achieved with therapeutic interventions that target postprandial glucose and basal glucose in patients with TIR ≥66.3% and <66.3%, respectively. University Medical Information Network [UMIN] ID: UMIN0000254333.

# Glucose toxicity

International Textbook of Diabetes Mellitus, Fourth Edition, Chapter 27, Hannele Yki-Järvinen MD, FRCP, Donald A. McClain
First published: 06 March 2015 https://doi.org/10.1002/9781118387658.ch27

## Summary

- **The ability of the blood glucose concentration itself to induce insulin resistance and impair insulin secretion has been referred to as "glucose toxicity."** Although acute hyperglycemia increases glucose uptake, chronic hyperglycemia induces peripheral insulin resistance, that is, a decrease in skeletal muscle glucose uptake. In type 1 diabetes, this phenomenon appears to be the main cause of peripheral insulin resistance. If insulin sensitivity is compared between type 2 diabetic patients and equally obese nondiabetic subjects, insulin resistance is directly proportional to average glycemia, and can be ameliorated with any intervention that lowers glucose concentrations. As in muscle, while acute hyperglycemia stimulates, chronic hyperglycemia decreases insulin secretion. Improvement in glucose control by any therapy therefore improves insulin secretion. Regarding the molecular mechanisms of glucose toxicity, the hexosamine pathway has been convincingly linked to glucose-induced insulin resistance and β-cell failure. This pathway metabolizes a small fraction of glucose to UDP-N-acetylglucosamine, which responds to increased cellular glucose flux in insulin-dependent tissues by downregulating insulin-stimulated glucose uptake.

# Basal (fasting) Hyperglycemia

- Predominate source of excess glucose in
  - Poorly controlled Type 2 diabetes or if A1c >8%
  - Most new onset Type 2 diabetes
    - Impaired fasting glycemia (IFG)
    - Impaired glucose tolerance (IGT)

- Excess glucose from hepatic glucose output
  - Inadequate insulin
  - Excessive glucagon
  - Excessive free fatty acid (from adipose tissue & inadequate insulin)

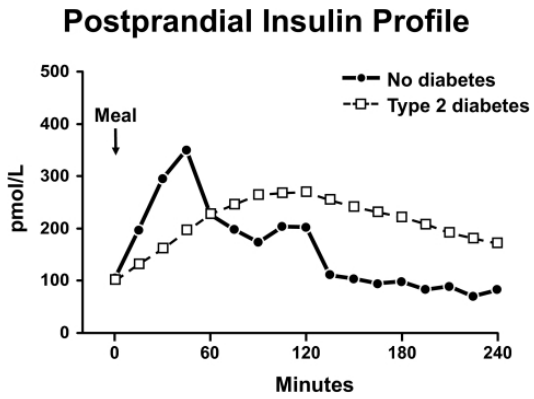
# Basal (fasting) Hyperglycemia

- Most medications impact
  - **Metformin**
  - **Longer acting insulins** (Insulin direct effect on liver & on adipose tissue to reduce FFA = reduce hepatic glucose output)
  - **Sulfonyl-urea medications**
  - **TZDs**
  - **Long-acting GLP-1 Receptor agonists** (increase insulin (direct effect on liver/ reduce FFA from adipocytes) & reduce glucagon = reduced hepatic glucose output)
  - **DPP4-inhibitors**
  - **SGLT-2 inhibitors**

# Postprandial Hyperglycemia

- Predominate source of excess glucose in
  - Better controlled Type 2 diabetes as A1c nears 7%
  - Longer duration of Type 2 diabetes (>10 years)
- More complex
  - Normal:
    - rapid rise in Insulin & Amylin + gut hormones (GLP-1);
      - reduction in glucagon,
      - slowing of gastric emptying;
      - increase in satiety to reduce eating

# Postprandial Hyperglycemia




- More complex
  - Type 2 Diabetes:
    - Reduced & delayed rise and peak in insulin
    - Reduced & delayed rise and peak in amylin & gut hormones (GLP-1)
      - Gastric emptying not delayed (rapid absorption-spike)
      - Glucagon not reduced (high output of glucose from liver)
      - Satiety not enhanced (eating more)
  - Basal-Bolus Insulin
    - High BG after meal, low BG later, weight gain

# Postprandial Hyperglycemia

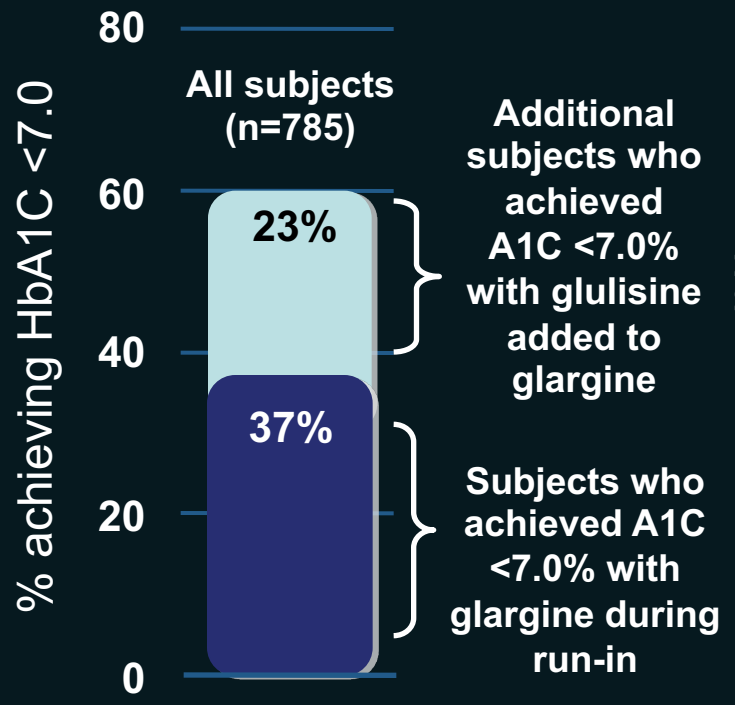
- Fewer medications or treatment options impact
  - Metabolic surgery
  - Alpha- Glucosidase Inhibitors (Precose, Glyset)
  - Stepwise addition of prandial insulin
    - More rapidly absorbed prandial insulin
  - Insulin delivery systems & closed-loop systems (CSII)
    - V-Go system
  - Shorter acting GLP-1 receptor agonists (Byetta, Adlixin)
  - Amylin receptor agonist (Symlin (pramlintide))

# Basal-Plus studies

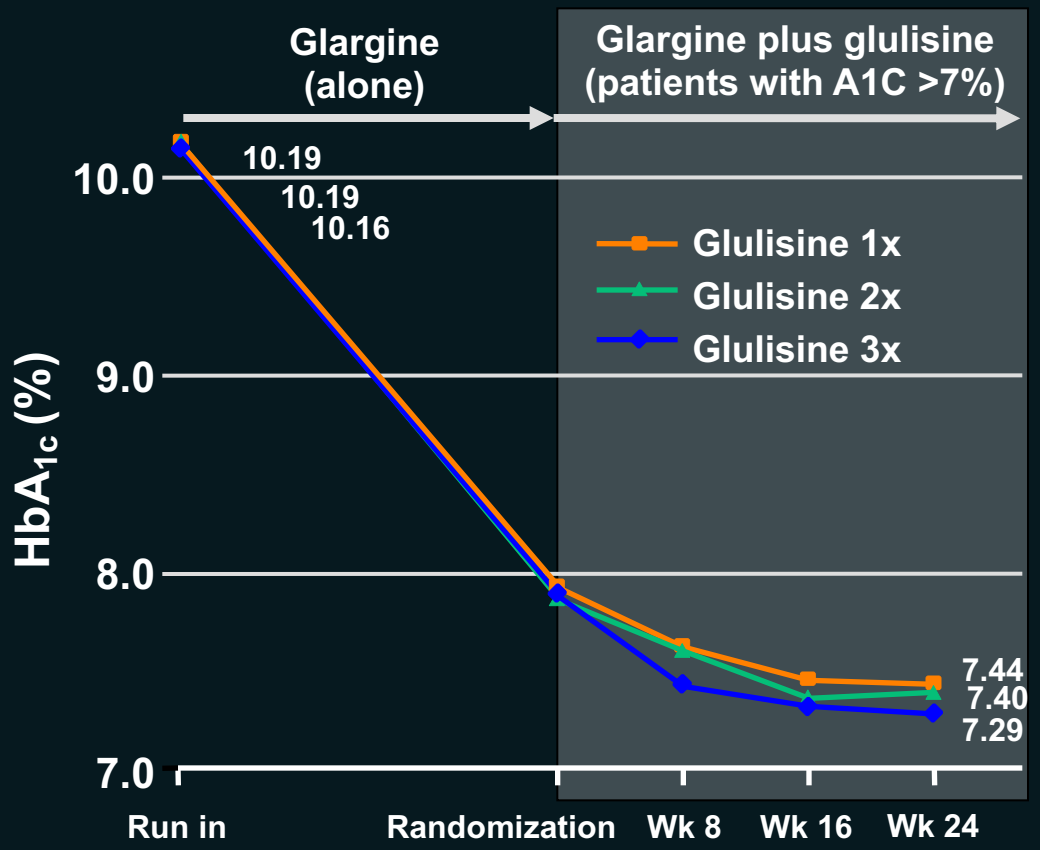
- Five proof-of-concept studies have shown that **adding one injection of prandial insulin to a basal insulin** regimen can improve glycemic control.
  - In the OPAL study 38, patients receiving insulin glargine and OADs were randomized to receive a single injection of **rapid acting insulin before breakfast or the largest meal of the day**. The two regimens were *similarly effective* in reducing HbA1c from baseline levels of 7.3–7.4% to 6.9–7.0%.
  - Owens et al.  also determined that adding a single injection of rapid acting insulin to insulin glargine, **before the main meal**, improved HbA1c 0.3–0.4%, without an increase in hypoglycemia.
  - In the ELEONOR study 40, addition and titration of insulin glargine followed by a single dose of rapid-acting insulin at the **meal with the highest postprandial excursion** was associated with improvements in HbA1c and a low incidence of hypoglycemia, and with marked improvements in treatment satisfaction.
  - In the START study, also, a single bolus of **rapid acting insulin added at breakfast in** patients receiving insulin glargine was *as effective in improving HbA1c when implemented using either patient-managed or physician-managed titration algorithms .*
  - Davidson et al. showed that, in terms of HbA1c reduction, ***rapid acting insulin once or twice daily was non-inferior to three times daily***, but that more patients reached their HbA1c target with three injections.

# 1.2.3 Study: Glargine Plus 1, 2 or 3 Doses of Glulisine

Responders in the whole population (n=785)




Evolution of A1C in the randomized population (n=343)




Adapted from Raccah D. http://www.fesemi.org/grupos/obesidad/noticias/ponencias_iv_reunion/Prof.%20Denis%20Raccah.pdf. Accessed April 9, 2010.

# A Dose–Response Relationship Between Insulin Glargine 100 Units/mL and Glycemic Control

Diabetes, Obesity and Metabolism February 21, 2019

- TAKE-HOME MESSAGE
- In this meta-analysis of three trials (458 patients), the authors developed a basal insulin clinical response curve in order to assess the efficacy of increasing insulin doses on glycemic measures, body weight and hypoglycemia.
  - Specifically, they evaluated HbA1c values, fasting plasma glucose, body weight, and incidence of hypoglycemia.
  - They determined that basal insulin is associated with many small improvements in fasting plasma glucose and HbA1c levels at doses >0.3 IU/kg/day, and, at doses >0.5 IU/kg/day, is associated with weight gain.
- The authors concluded that, after a threshold of 0.5 IU/kg/day of basal insulin, clinicians should consider other antihyperglycemic treatment adjuncts to reduce glycemic measures.

**A Dose–Response Relationship Between Insulin Glargine 100 Units/mL and Glycemic Control**
Diabetes, Obesity and Metabolism February 21, 2019

- The analysis confirms the proposed cut-off of **0.5 U/kg** as the one where further up-titration of insulin glargine is not only futile for improving glucose control, but also the dose where only further weight gain can be observed.
  - using the well-known titration regimens works very nicely on lowering HbA1c in a *linear* way until a dose of 0.3 U/kg.
    - Using doses higher than 0.3 U/kg already gives less improvements in HbA1c per unit than for the same increment at lower doses.
  - At 0.5 U/kg, the effect on **HbA1c plateaus and only weight gai**n is seen.
    - These observations should be interpreted with some caution when extrapolating to other insulins, where the relationship with dose may be different.

The study is important for clinicians, and it confirms what is suggested in the ADA/EASD consensus paper:

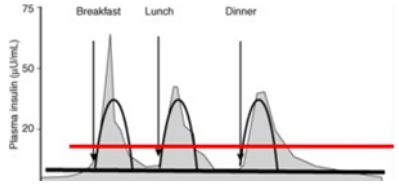
- 1) consider ***combining*** different glucose-lowering agents at lower doses; and
- 2) when ***basal insulin exceeds 0.5 U/kg, combining insulin with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin*** *rather than further up-titration of the basal insulin* should be considered.

# Insulin Management of Type 2 Diabetes Mellitus

ALLISON PETZNICK, DO, Northern Ohio Medical Specialists, Sandusky, Ohio

Am Fam Physician. 2011 Jul 15;84(2):183-190.

- Metformin combined with insulin is associated with decreased weight gain, a lower insulin dose, and less hypoglycemia compared with insulin alone
  - Metformin should be continued if possible because it is proven to reduce all-cause mortality and cardiovascular events in overweight patients with diabetes.
- Insulin therapy may be initiated as
  - augmentation, starting at 0.3 unit per kg,
  - replacement, starting at 0.6 to 1.0 unit per kg.
    - When using replacement therapy, 50 percent of the total daily insulin dose is given as basal (0.3-0.5 u/kg), and 50 percent as bolus, divided up before breakfast, lunch, and dinner.




- The goal of basal insulin is to suppress hepatic glucose production and improve fasting hyperglycemia .
  - If basal insulin is titrated too high, it will also partially cover meals and lead to hypoglycemia during the night or if a meal is missed.
  - Long-acting analogue insulin may be administered once or twice daily, depending on the dose. Lower doses may not last 24 hours, whereas higher doses may impede insulin absorption.

# Covering Meal Carbs

- The **insulin-to-carb ratio (ICR)** is a way to get the right amount of insulin for the carbohydrates in a meal (or snack) –
  - it means the patient will take ***1 unit of insulin for a certain amount of carbohydrate***
  - Even if eating **fixed amounts of carb** at a meal – need to have appropriate ICR for the **fixed meal insulin dose**
- E.g. - If the insulin-to-carb ratio (ICR) is 1 unit of insulin for every 10 grams of carbohydrate (written 1:10) - will take 1 unit of insulin for every 10 grams of carbohydrate eaten – if eat 60 grams will take 6 units
  - If ICR is 1:15 – will take 1 unit for every 15 grams of carb eaten
    - If eat 60 grams of Carb will take 4 units
  - For fixed meal doses – e.g. patient eats ~45 grams of carb each meal and weighs ~120# with estimated ICR of 1:15 - will take 3 units with each meal
  - Or if patient eats 30g Carb with Breakfast, 45 grams with Lunch & 60 grams with Dinner – would take 2u with B, 3u with L and 4 units with D

# Calculating the Correction Dose

**Correction dose of Insulin =** $\frac{\text{Current BG- Target BG}}{\text{CF}}$

**Correction Factor (CF) or Sensitivity Factor (SF)**

The CF = the mg/dl drop in BG caused by 1 unit of insulin (depends on sensitivity to insulin - weight, age, renal function)

The right correction dose will return the BG to within 30 mg/dl of the target blood glucose about 3-4 hours after the dose is injected

# 1700 Rule* to Calculate the Sensitivity Factor

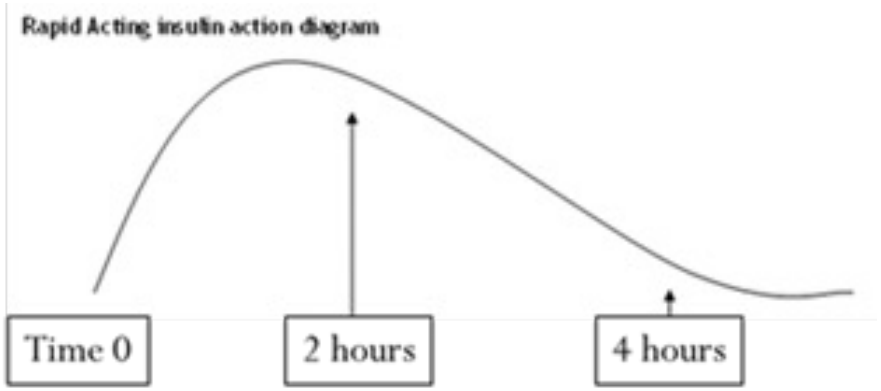
- Divide: 1700 by Total Daily Insulin to estimate the Sensitivity Factor (SF) /Correction Factor (CF)
  - Example: 14 units basal insulin + 16 units bolus insulin = 30 units total daily insulin
  - 1700/30 = 50.
- This Correction Factor means that 1 unit of insulin will lower blood glucose by approximately 50mg/dl.

- HOW TO USE THE CORRECTION FACTOR TO CALCULATE A CORRECTION DOSE:
- **Correction Dose Formula**:
  - (Current BG) - (Target BG)/CF = Correction dose
  - Example: Current BG = 200 mg/dl, Target BG = 100 mg/dl, Correction Factor or Sensitivity Factor = 50
  - So, 200-100/50 = 100/50 = 2.0 units of insulin for a Correction dose
- If numeracy / math challenged: provide **range**
  - e.g. 151-200 - 1unit; 201-250 - 2units, 251-300 – 3units, 301-350- 4u, etc

# Guide for Using Correction Insulin

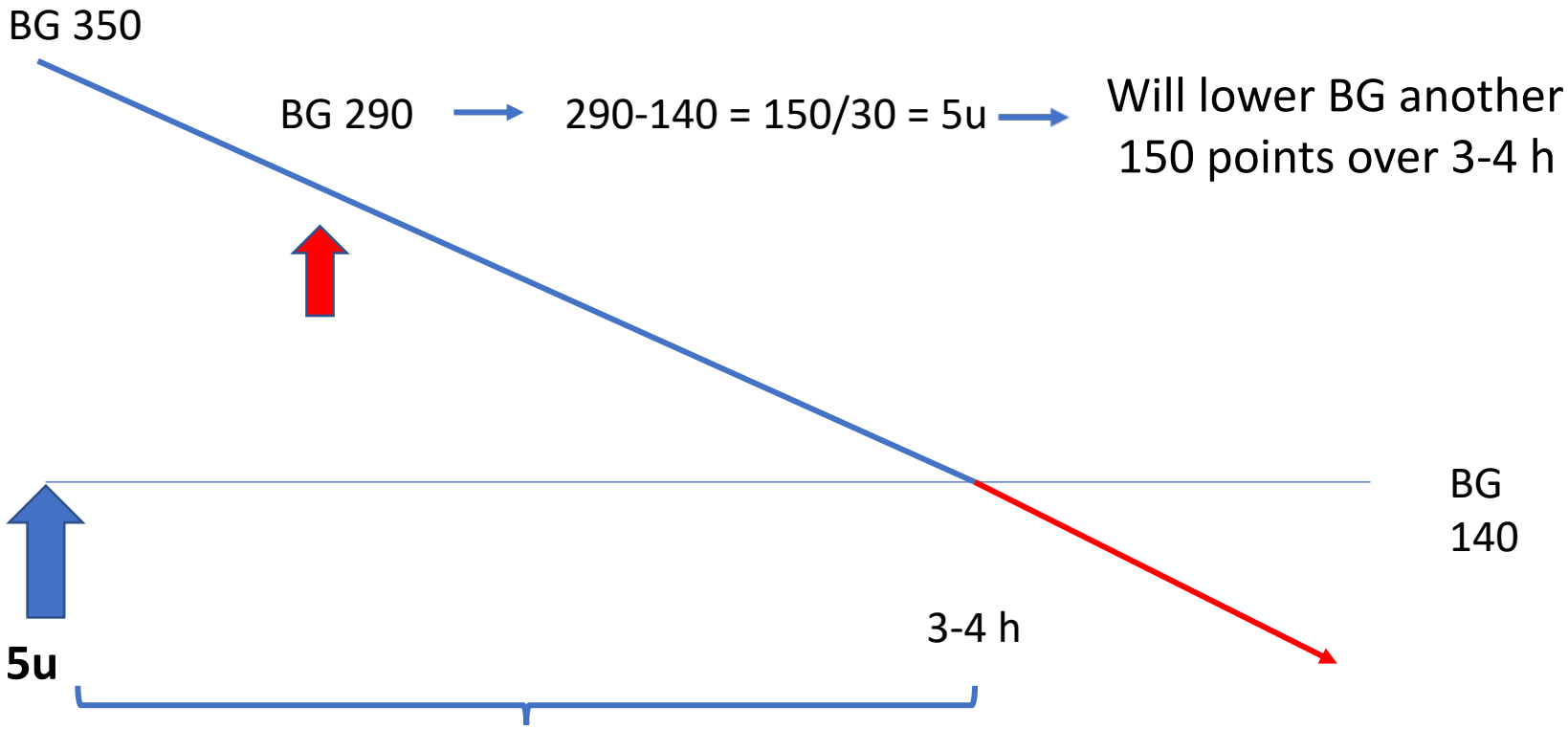
Only give (dose) **Correction Insulin**

- every ***3-4 hours for analog insulin*** –
- every ***4-6 hours for Regular insulin*** –
- otherwise end up **"stacking" insulin** and risk of low BG
  - Explain it takes Fast Insulin 3-4 hours to **finish working**



# “Stacking” Correction Doses

**Correction dose: 350-140 =210/30 = 7 units**




**7u will lower BG 210 points over 3-4 hours**

# Meta-Analysis Diabetes Metab Res Rev. 2019 Jan;35(1):e3082. GLP-1 receptor agonist added to insulin versus basal-plus or basal-bolus insulin therapy in type 2 diabetes: A systematic review and meta-analysis

Marco Castellana 1, Angelo Cignarelli 1, Francesco Brescia 1, Luigi Laviola 1, Francesco Giorgino 1

PMID: 30270567 DOI: 10.1002/dmrr.3082


- Abstract
- Background: Current guidelines recommend that antihyperglycaemic treatment in patients with type 2 diabetes not achieving the HbA1c target on basal insulin should be intensified with a glucagon-like peptide-1 receptor agonist (GLP-1RA) or basal-plus/basal-bolus (BP/BB) insulin regimen. We conducted a systematic review and meta-analysis to compare the effects of GLP-1RA/insulin combinations versus BP/BB.

- Methods: The review was registered on PROSPERO (CRD42017079547). PubMed, Scopus, CENTRAL, and ClinicalTrials.gov were searched until July 2018. All randomized controlled trials (RCTs) reporting HbA1c , body weight, daily insulin dose, hypoglycaemic events, and discontinuation due to lack of efficacy were included. A subgroup analysis on different combinations of GLP-1RA and insulin was performed.

- Results: Out of 1885 retrieved papers, 13 RCTs were included in the review. Compared with BP/BB, GLP-1RA/insulin combinations were associated with a similar HbA1c reduction (Δ = -0.06%; 95% confidence interval [CI], -0.14 to 0.02; P = 0.13; I2 = 52%), greater weight loss (Δ = -3.72 kg; 95% CI, -4.49 to -2.95; P < 0.001; I2 = 89%), and lower incidence of hypoglycaemic events (relative risk [RR] = 0.46; 95% CI, 0.38-0.55; P < 0.001; I2 = 99%). The daily insulin dosage among GLP-1RA/insulin users was 30.3 IU/day (95% CI, -41.2 to -19.3; P < 0.001; I2 = 94%), lower than with BP/BB. No difference was found for discontinuation due to lack of efficacy.

- Conclusions: The present review supports treatment intensification with GLP-1RA added to insulin versus BP/BB in uncontrolled type 2 diabetes. This could provide similar antihyperglycaemic efficacy while leading to weight loss and sparing of hypoglycaemia and insulin dose. As a consequence, a considerable number of patients with type 2 diabetes could be potentially shifted from BP/BB to GLP-1RA/insulin combinations.