MANAGING POSTPRANDIAL GLUCOSE IN PATIENT WITH DIABETES MELLITUS

Sheila S. Mercado Mendez

Adult Endocrinologist

Diplomate of the American Board of Endocrinologist

Thyroid Postgraduate Post-Graduate Course, Diabetes & Romulo Ayuso's Memorial Lecture in Thyroid Cancer

August 29,2020

DISCLOSURE

- No conflict of interest

INTRODUCTION

- In the management of diabetes, health care providers usually assess glycemic control with:
  - Fasting plasma glucose (FPG)
  - Premeal glucose measurements
  - HbA1c
- Elevated postprandial glucose (PPG) concentrations may contribute to suboptimal glycemic control

INTRODUCTION

- Strategies for the management of hyperglycemia associated with type 2 diabetes is challenging
- Current consensus guidelines:
  - American Diabetes Association (ADA), American Association of Clinical Endocrinologist (AACE) and the European Association for the Study of Diabetes (EASD)
  - Recognize that many different drug combinations can be used to **achieve A1C goals**
    - Reflects both basal and postprandial glucose levels

American Diabetes Association®

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AACE
The Voice of Clinical Endocrinology

The Loss of Postprandial Glycemic Control Precedes Stepwise Deterioration of Fasting With Worsening Diabetes

Louis Monnier, md[1]
Claude Colette, phd[2]
Gareth J. Dunseath, mphil[3]
David R. Owens, md[3]

OBJECTIVE — The aim of the study was to determine whether the loss of fasting and postprandial glycemic control occurs in parallel or sequentially in the evolution of type 2 diabetes.

RESEARCH DESIGN AND METHODS — In 130 type 2 diabetic patients, 24-h glucose profiles were obtained using a continuous glucose monitoring system. The individuals with type 2 diabetes were divided into five groups according to A1C levels: 1 (<6.5%, $n = 30$), 2 (6.5–6.9%, $n = 17$), 3 (7–7.9%, $n = 32$), 4 (8–8.9%, $n = 25$), and 5 (≥9%, $n = 26$). The glucose profiles between the groups were compared. The overall glucose concentrations for the diurnal, nocturnal, and morning periods, which represent the postprandial, fasting, and the dawn phenomenon states, respectively, were also compared.

RESULTS — Glucose concentrations increased steadily from group 1 to 5 in a stepwise manner. The initial differences in mean glucose concentrations reaching statistical significance occurred *1*) between groups 1 and 2 (6.4 vs. 7.7 mmol/l, $P = 0.0004$) for daytime postprandial periods, followed by differences; *2*) between groups 2 and 3 (7.5 vs. 9.3 mmol/l, $P = 0.0003$) for the morning periods (dawn phenomenon); and finally *3*) between groups 3 and 4 (6.3 vs. 8.4 mmol/l, $P < 0.0001$) for nocturnal fasting periods.

CONCLUSIONS — The deterioration of glucose homeostasis in individuals with type 2 diabetes progressed from postprandial to fasting hyperglycemia following a three-step process. The first step related to the three diurnal postmeal periods considered as a whole, the second step occurred during the morning period, and the third and final step corresponded to sustained hyperglycemia over the nocturnal fasting periods. Such a description of the key stages in the evolution of type 2 diabetes may be of interest for implementing antidiabetes treatment.

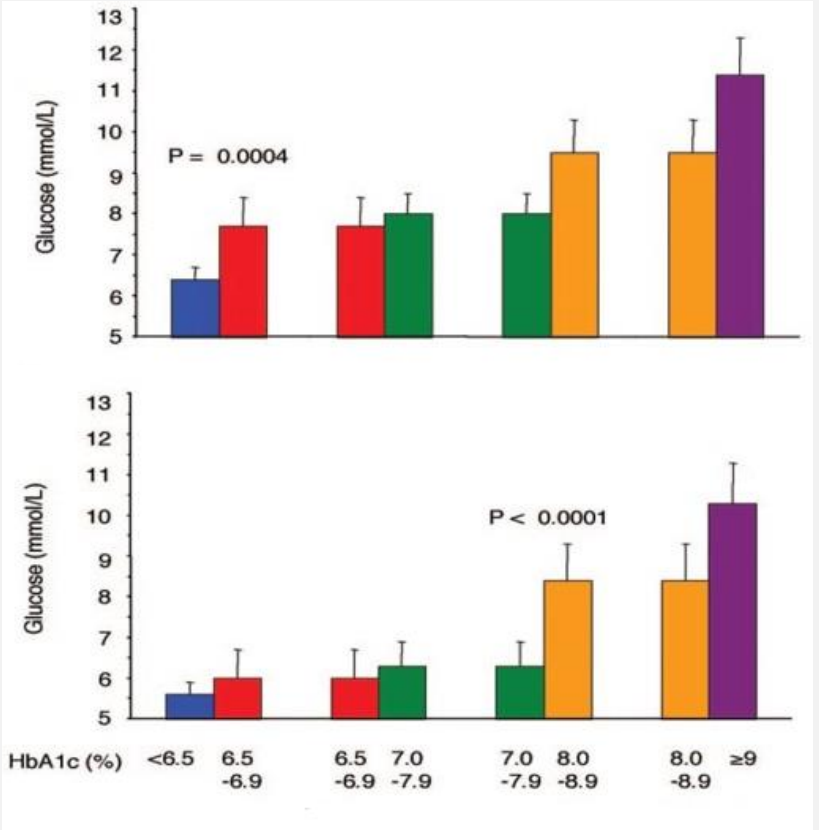
Diabetes Care 30:263–269, 2007

contributors to the overall hyperglycemia in patients with an A1C <7.3%, while fasting increments represent the major contributor to worsening diabetic control. These results, along with the findings of others (9), indicate that postprandial glucose deteriorates before fasting glucose. However, the exact sequence of events in the deterioration of glycemic status is not completely understood. It remains unclear whether the loss in glucose control during fasting or postprandial periods occurs in parallel or sequentially. Furthermore, it is known that postmeal glucose excursions after breakfast, lunch, and dinner are not equally affected and may deteriorate at different rates over the time course of the disease, which may also differ across different population groups. To gain further insight into these questions, which are of practical importance for tailoring the introduction of available antidiabetes treatments, we used the CGMS data (10) in 130 patients with type 2 diabetes. The glucose profiles obtained during this investigation were further analyzed after the patients had been stratified into 5 groups according to A1C levels.

PROGRESSIVE DETERIORATION OF THE GLYCEMIC PROFILES ACCORDING TO A1C LEVELS

As A1C levels approach normal range

PPG contributes more than FPG to overall hyperglycemia



Daytime postprandial periods

Nocturnal glucose periods

PATHOGENESIS OF POSTPRANDIAL HYPERGLYCEMIA

- In nondiabetic individuals
- Basal glucose levels are maintained within a narrow range by continuous low-level of insulin secretion into the portal circulation
  - Regulates the rate of hepatic glucose production during the periods between meals.
- **In the postprandial state:**
  - As soon as the blood glucose concentration starts to rise, there is an increase in rapid pulsatile insulin secretion.
  - Increases uptake of glucose by the liver, muscle, kidney, adipose tissue, and other insulin-dependent tissues.
  - Suppresses hepatic and renal gluconeogenesis

PATHOGENESIS OF POSTPRANDIAL HYPERGLYCEMIA

- The physiologic response of the beta cell to an increase in plasma glucose concentration is biphasic:
  - First-phase insulin release (0-10 minutes) followed by a steady and longer-lasting second phase.
- Rapid early-phase insulin secretion is the chief determinant of PPG levels
  - The loss of early-phase insulin response characterizes type 2 diabetes mellitus and IGT

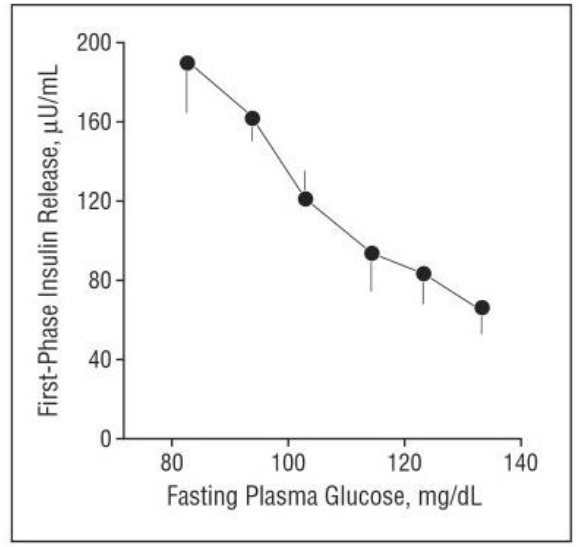


Figure 6. Relationship between early (first-phase insulin release during hyperglycemic clamp studies) and fasting plasma glucose levels. Data from Van Haeften et al.[68] To convert glucose to millimoles per liter, multiply by 0.05551.

PATHOGENESIS OF POSTPRANDIAL HYPERGLYCEMIA

- Absorption of glucose form gastrointestinal tract:
  - Insulin secretion is stimulated by oral glucose is ingested than it is when glucose is infused intravenously

- Incretin effect
  - Responsible for 50% to 70% of the insulin response to glucose
  - Caused mainly by glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP)
  - GLP-1 and GIP secretion are stimulated primarily by glucose ingestion

- The GLP-1 response to a meal is decreased in type 2 diabetes mellitus

PATHOGENESIS OF POSTPRANDIAL HYPERGLYCEMIA

- The first step in the deterioration of glucose homeostasis is the loss of postprandial glycemic control due to the loss of first-phase insulin secretion
- Decreased insulin sensitivity in peripheral tissues
- Consequent decreased suppression of hepatic glucose output after meals due to insulin deficiency

IMPORTANCE

- Postprandial hyperglycemia can be the rate-limiting factor for achieving optimal glycemic control
- There is also evidence suggesting that postprandial hyperglycemia may be an independent risk factor for:
  - cardiovascular disease
  - stroke
  - retinopathy
  - renal failure

IS POSTMEAL HYPERGLYCEMIA HARMFUL?

IS POSTMEAL HYPERGLYCEMIA HARMFUL?

- High postprandial glucose levels may lead to increased oxidative stress on the beta cell
- Inadequate insulin production during chronic hyperglycemia results from decreased insulin gene transcription due to hyperglycemia
- Hyperglycemia may induce apoptosis of beta cells

Reviews/Commentaries/Position Statements

CONSENSUS STATEMENT

Postprandial Blood Glucose

AMERICAN DIABETES ASSOCIATION

- The panel concluded:
  - No clinical trials have assessed whether postprandial hyperglycemia plays a unique role in the pathogenesis of diabetic specific complication
  - No prospective clinical trial have examined whether treatments that primarily lowers post prandial decrease cardiovascular events
  - Further studies are needed in order to determined whether postprandial hyperglycemia is an independent risk factor for CVD

American Diabetes Association®

EPIDEMIOLOGICAL EVIDENCE

- The DECODE Study -Diabetes Epidemiology
  - Data form 25,000 subjects in different areas of Europe
  - No previously diagnose with DM
  - All cause mortality during a mean follow up period of 7.3 years were assessed after stratification according to fasting and post-challenge plasma glucose
  - Subject with with 2 hr OGTT plasma >140 mg/dL has a relative risk if mortality twofold higher than subjects with NGT

EPIDEMIOLOGICAL EVIDENCE

- The Hoorn Study
  - 2,363 participant aged 50-70 without know diabetes
  - 8 year follow up
  - 2 hr glucose better predictor of mortality than HBA1c
  - An elevated 2 hour postprandial plasma glucose 2 SD's above the population mean increase the risk for death
    - CVD increased 62% even after excluding individuals with preexisting CVD and correcting for other risk factor

Epidemiological studies showing an association between postprandial hyperglycemia with risk of CVD and mortality	
Honolulu Heart Program	One-hr post prandial glucose predicts coronary heart disease
Chicago Heart Study	2-h postchallenge glucose predicts all-cause mortality and increase risk of cardiovascular mortality
Whitehall Study, (Paris)	2-h postchallenge glucose predicts all-cause and CHD mortality
Diabetes Intervention Study	Postmeal but not fasting glucose is associated with CHD

IS THE TREATMENT OF POSTMEAL HYPERGLYCAEMIA BENEFICIAL IN IMPROVING CLINICAL OUTCOMES AND GLYCEMIC CONTROL (HBA1C)

INTERVENTION STUDIES

- Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM)
  - 1,418 subjects diagnosed with IGT were randomized in a double-blind fashion
  - Acarbose (100 mg t.i.d.) vs placebo
  - Follow-up period of 3.9 years.
- Primary outcome
  - The development of type 2 diabetes diagnosed using a 75-g oral glucose tolerance test
- Secondary outcomes:
  - Changes in blood pressure, lipid profile, insulin sensitivity and cardiovascular events

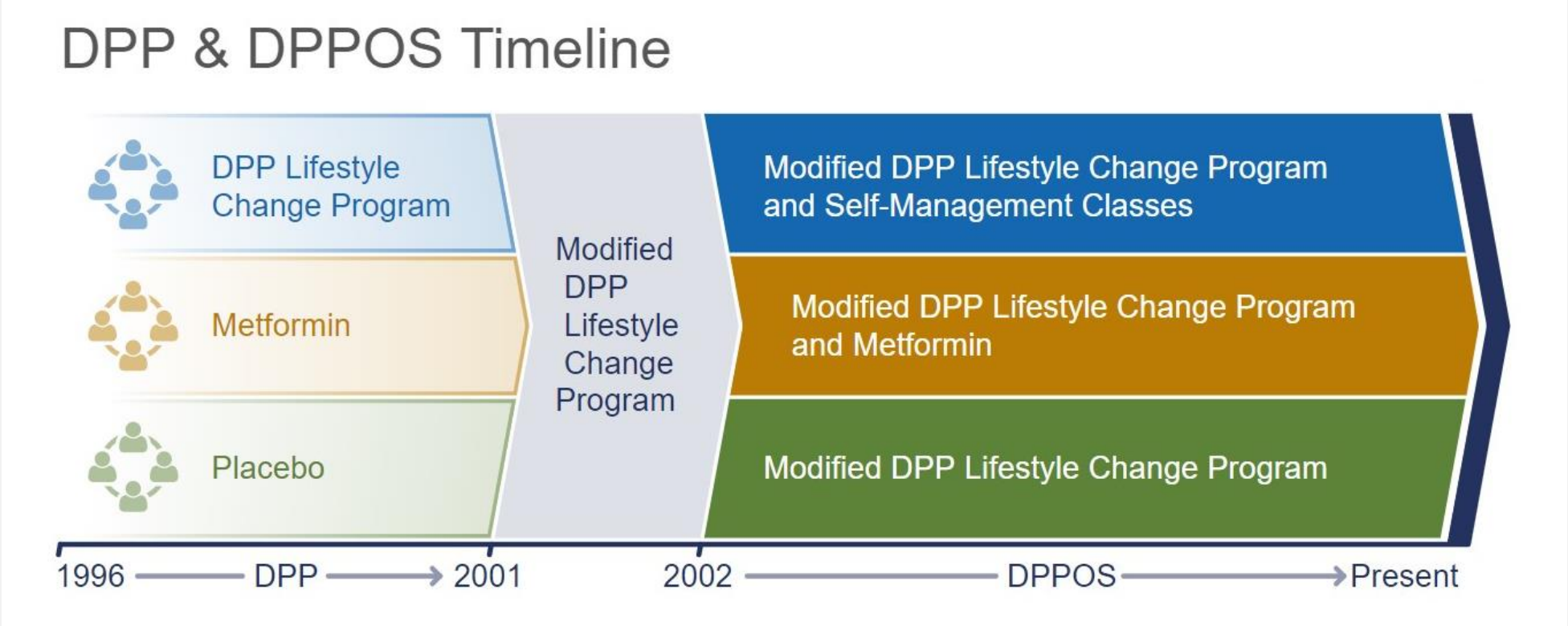
INTERVENTION STUDIES

- STOP-NIDDM
  - 36% reduction in the risk of progression to diabetes
  - 34% risk reduction in the development of new cases of hypertension
  - 49% risk reduction in cardiovascular events
    - Significant reduction in cardiovascular events even after adjusting for other risk factor
  - Acarbose treatment was associated with a significant decrease in the progression of intima-media thickness.

TREATMENT APPROACHES TO POSTPRANDIAL GLUCOSE

DIET AND PHYSICAL ACTIVITY

- Diabetes Prevention Program (DPP) and ongoing DPP Outcomes Study (DPPOS)

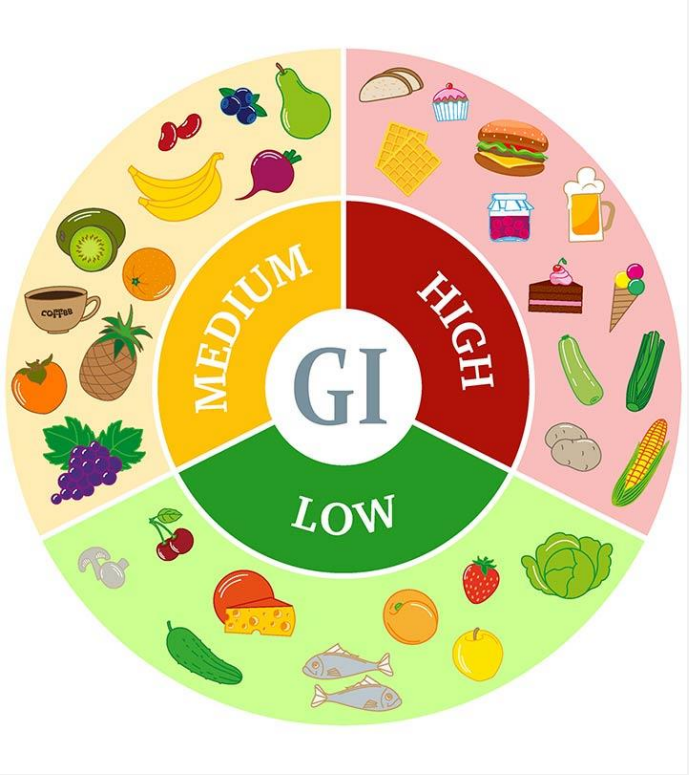


DIET AND PHYSICAL ACTIVITY

- After an average follow-up of 2.8 years in the DPP
  - 58% relative reduction in the progression to diabetes was observed in the lifestyle group
  - 31% relative reduction in the group who took Metformin when compared with participants who took a placebo
- At the 15-year follow-up
  - Participants from the DPP Lifestyle Change Program continued to have a delay in the development of diabetes by 27 %
  - participants who continued to take metformin had a delay in the development of diabetes by 18 %

DIET AND PHYSICAL ACTIVITY

- Glycemic index
  - Compares the plasma glucose levels attained after eating a certain food to the levels after ingesting pure glucose
- Consumption of foods with a low glycemic index results in lower PPG levels
- The appreciation that PPG values are primarily dependent on carbohydrate intake has led to the technique of carbohydrate counting
  - Premeal insulin flexibly - adjust their dose of insulin in accordance with the number of grams of carbohydrate



GLYCEMIC INDEX CHART

Low Glycemic (55 or Below) High Glycemic (70 or Higher)





SNACKS	G.I.	STARCH	G.I.	VEGETABLES	G.I.	FRUITS	G.I.	DAIRY	G.I.
Pizza	33	Bagel, Plain	33	Broccoli	10	Cherries	22	Yogurt, Plain	14
Chocolate Bar	49	White Rice	38	Pepper	10	Apple	38	Yogurt, Low Fat	14
Pound Cake	54	White Spaghetti	38	Lettuce	10	Orange	43	Whole Milk	30
Popcorn	55	Sweet Potato	44	Mushrooms	10	Grapes	46	Soy Milk	31
Energy Bar	58	White Bread	49	Onions	10	Kiwi	52	Skim Milk	32
Soda	72	Brown Rice	55	Green Peas	48	Banana	56	Chocolate Milk	35
Doughnut	76	Pancakes	67	Carrots	49	Pineapple	66	Yogurt, Fruit	36
Jelly Beans	80	Wheat Bread	80	Beets	64	Watermelon	72	Custard	43
Pretzel	83	Baked Potato	85	Onions	75	Dates	103	Ice Cream	60

PHARMACOLOGIC INTERVENTIONS

- Pharmacologic therapy have reported a significant lowering of the incidence of diabetes
  - Diabetes Prevention Program - metformin reduced the risk of IGT progression to diabetes by 31%
  - STOP NIDDM trial - a-glucosidase inhibitor acarbose reduced the risk by 32%
- All oral hypoglycemics have a favorable effect on postprandial hyperglycemia

METFORMIN

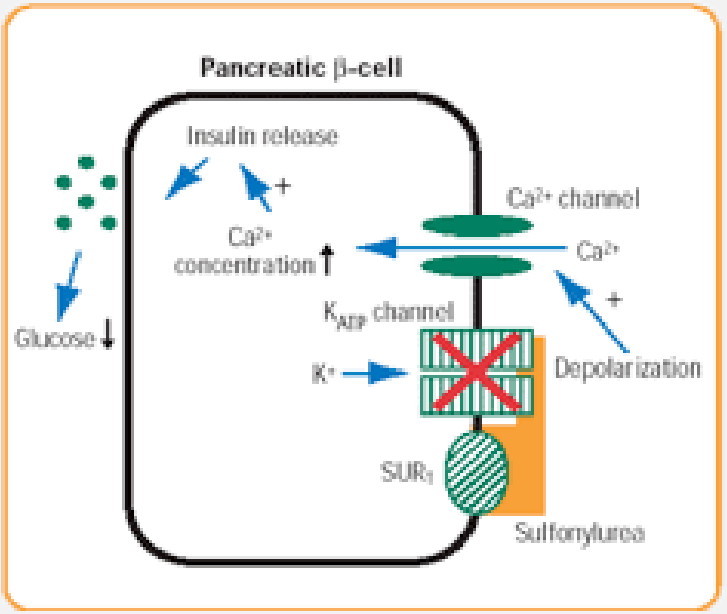
- Decrease hepatic glucose output by inhibiting gluconeogenesis after meal
  - Antilipolytic effect that lowers serum free fatty acid concentration reducing substrate availability for gluconeogenesis after meals
- Increases insulin-mediated glucose utilization in peripheral tissues

THIAZOLIDINEDIONES

- Pioglitazone
- Improve postprandial peripheral glucose utilization in adipose tissues and muscle
- Decrease glucose production by liver - lesser degree
- Most of the antihyperglycemic effects associated with TZDs are the result of lowered FPG these agents have only mild effects on PPG
- Not be an appropriate treatment option
  - Can lead to fluid retention, increased risks of congestive heart failure, and increased fracture risk for postmenopausal women

SULFONYLUREAS

- Reduce postprandial glucose through stimulation of insulin secretion and perhaps additional extrapancreatic effects
- The sulfonylurea receptor is a component of the adenosine triphosphate (ATP)-sensitive potassium channel (K-ATP channel) in the pancreatic beta cells
- Sulfonylurea binding leads to inhibition of these channels
  - Alters the resting potential of the cell to stimulation of insulin secretion
- **Glipizide** is short-acting and is occasionally used specifically for post meal hyperglycemia
  - They stimulate a rapid but short lived (for 1-2 hours) release of insulin from pancreatic ß-cells.



MEGLITINIDES

- Two agents are commercially available: nateglinide and repaglinide
- Mechanism of action similar to sulfonylureas
  - act by closing ATP channels on β-cell membranes increasing insulin secretion
- Meglitinides have a rapid onset and short duration of action
  - Administered with meals to reduce postprandial hyperglycemia
  - Attractive for some patients with irregular meal schedules, because of their rapid onset and short duration of action

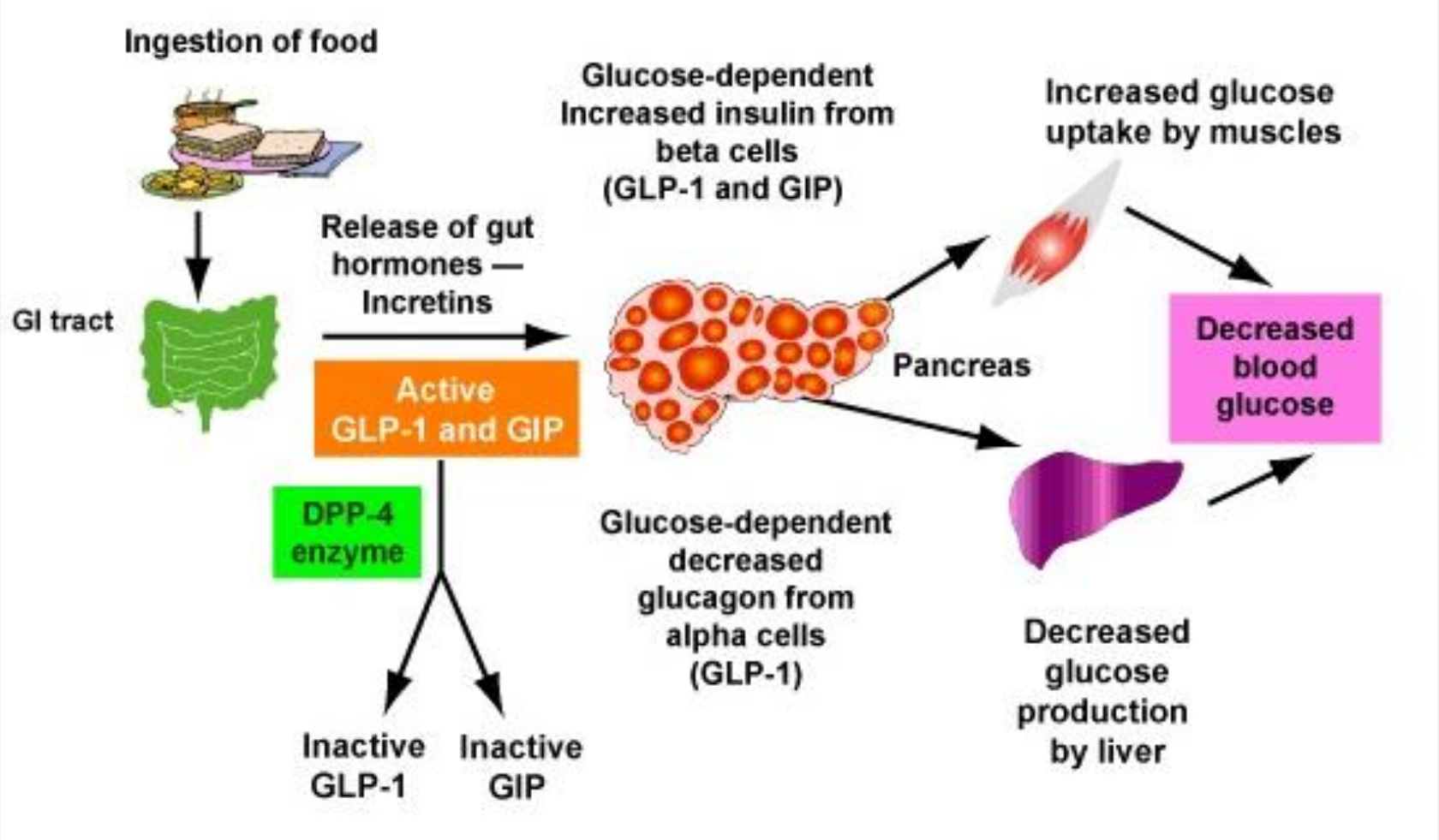
SULFONYLUREAS/ MEGLITINIDES

- Disadvantage:
  - Risk of hypoglycemia
  - Weight
  - More frequent dosing – meglitinides
  - Modest decrease in A1C with meglitinides than with most other antidiabetic drug classes
    - More expensive than sulfonylureas

ALPHA-GLUCOSIDASE INHIBITORS

- Acarbose and Miglitol
- a-Glucosidase inhibitors have a direct effect on postprandial hyperglycemia
- Block the breakdown of disaccharides to monosaccharides in the brush border of the small intestine
  - Essential for absorption of carbohydrates
- Effectively compensate for defective early-phase insulin by:
  - Delays intestinal carbohydrate absorption
  - Attenuate post-meal plasma glucose excursions
- The overall glucose lowering effect of these agents is somewhat inferior to that of the sulfonylureas
- The effect on postprandial hyperglycemia is much greater than on fasting glucose levels

ROLE OF INCRETINS IN GLUCOSE HOMEOSTASIS



ROLE OF INCRETINS IN GLUCOSE HOMEOSTASIS

- It is estimated that GLP-1 and GIP are responsible for 50%–70% of postprandial insulin release
- GLP-1 suppresses inappropriate glucagon secretion by pancreatic α-cells
  - At pharmacologic doses, delays gastric emptying by inhibiting gastroduodenal motility
  - Associated with an increase in satiety and reduced food intake

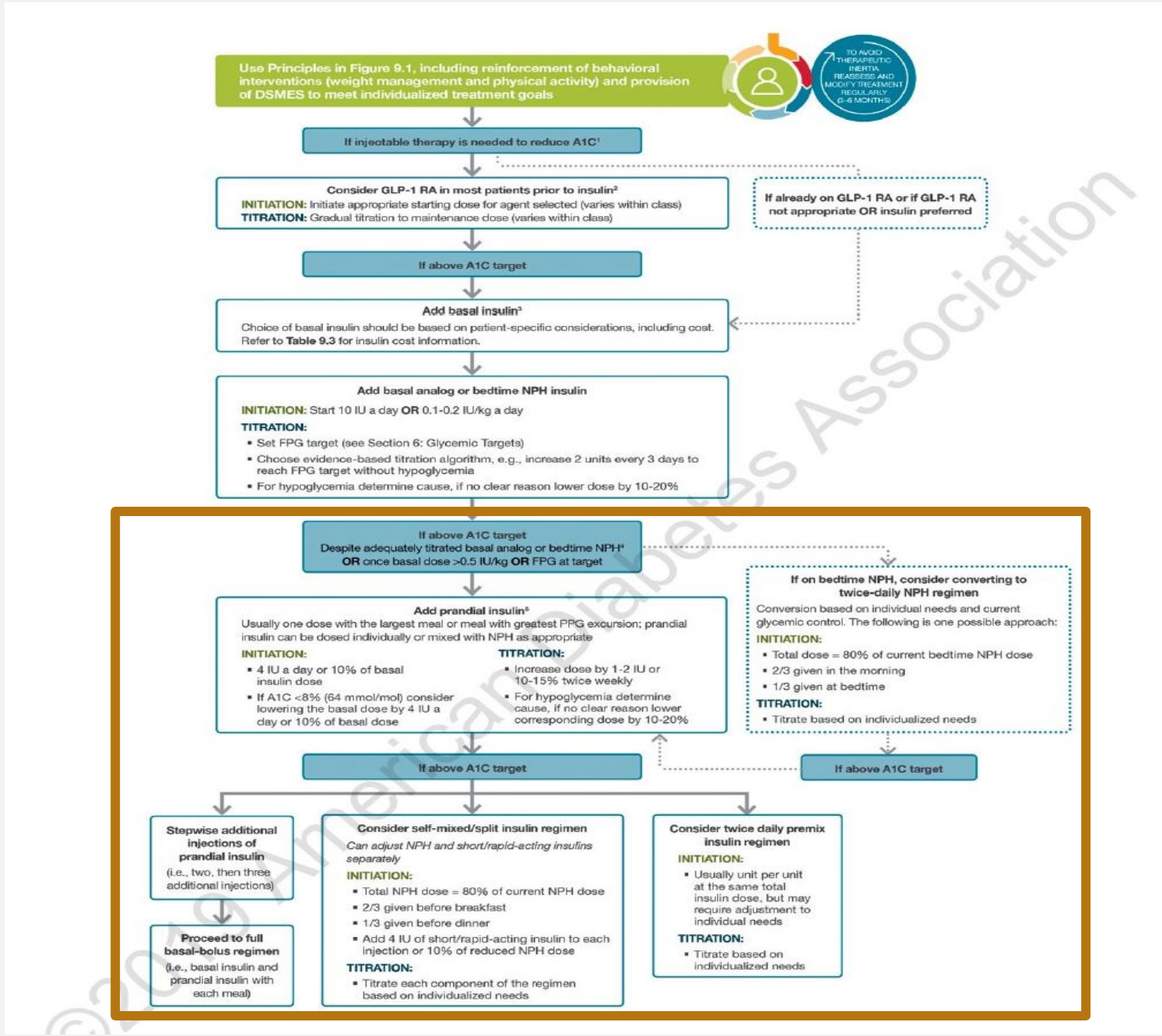
DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

- Linagliptin, saxagliptin, sitagliptin, alogliptin and vildagliptin
- DPP-4 inhibitors act by inhibiting the DPP-4 enzyme
  - Degrades GLP-1 thereby increasing the active form of the hormone
  - Stimulates glucose-dependent insulin secretion and suppresses glucagon release
- Decrease post meal glucose and improve HbA1c without causing hypoglycemia

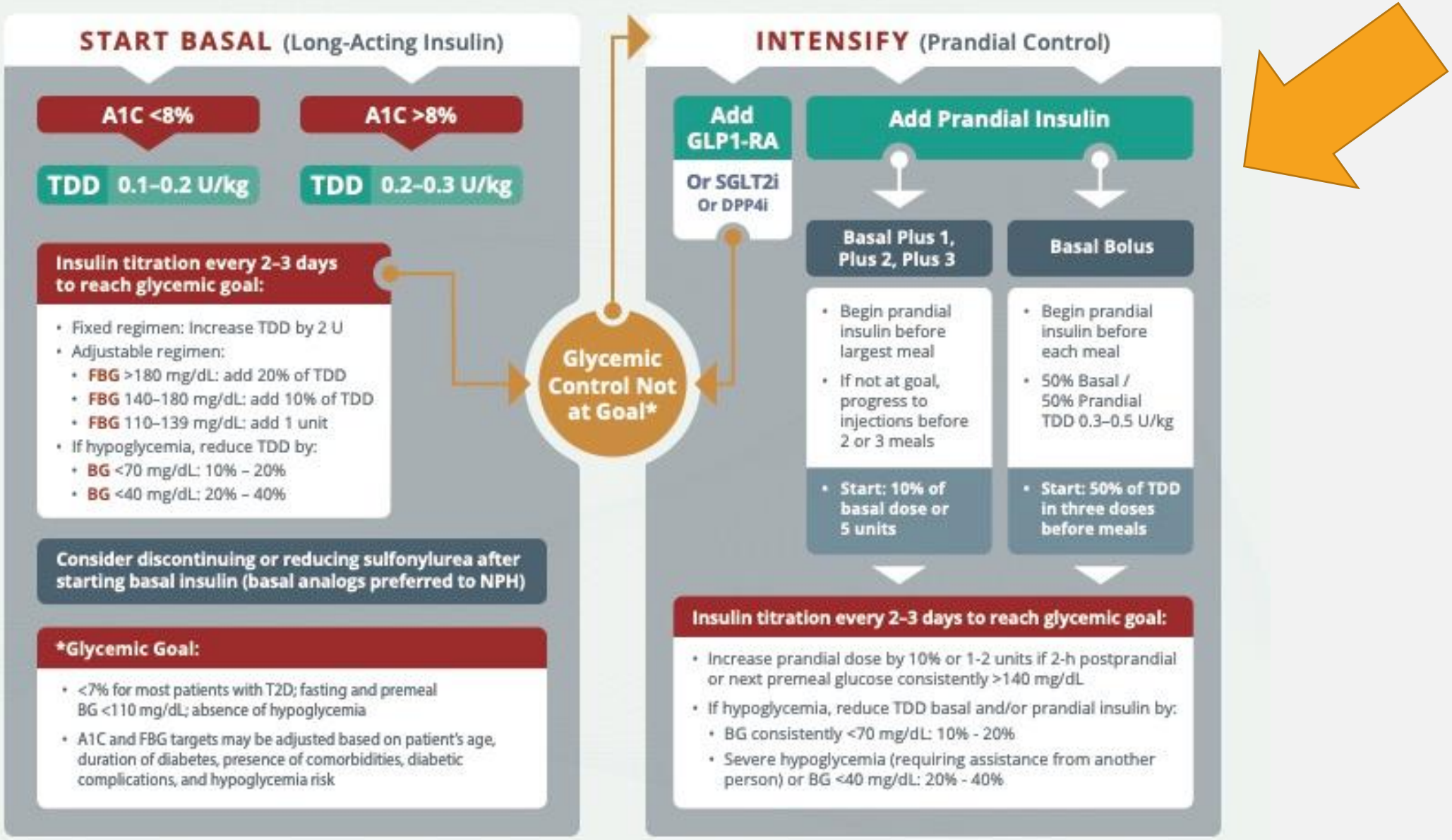
GLP-1 RECEPTOR AGONIST

- The incretin effects which are triggered by orally ingested glucose
  - Potentially useful role in combating postprandial hyperglycemia with a low risk of hypoglycaemic
- Exenatide, liraglutide, dulaglutide, semaglutide (IM and PO)
- Glucagon-like peptide 1 infusions
  - Compared with long-acting GLP-1 receptor agonists, short-acting GLP-1 receptor agonists (exenatide twice daily and lixisenatide)
    - Tend to have a more pronounced effect on postprandial hyperglycemia and gastric emptying and less effect on fasting glucose


THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION
VOLUME 43 | SUPPLEMENT 1
JANUARY 2020
Diabetes Care
WWW.DIABETES.ORG/DIABETESCARE
JANUARY 2020
SUPPLEMENT
1
AMERICAN DIABETES ASSOCIATION
STANDARDS OF MEDICAL CARE IN DIABETES—2020
Diabetes Care


Use Principles in Figure 9.1, 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: Gradual titration 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 9.3 for insulin cost information.
Add basal analog or bedtime NPH insulin
INITIATION: Start 10 IU a day OR 0.1-0.2 IU/kg a 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%
If above A1C target
Despite adequately titrated basal analog or bedtime NPH[4] OR once basal dose >0.5 IU/kg OR FPG at target
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 IU a day or 10% of basal insulin dose
If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose
TITRATION:
Increase dose by 1-2 IU 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
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 IU 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 premix 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

ALGORITHM FOR ADDING/INTENSIFYING INSULIN



PRANDIAL INSULIN

- **Regular insulin**
- After regular insulin is injected subcutaneously, the hexamers that have formed dissociate into dimers and monomers that are absorbed
  - This causes a delay in rise of insulin concentrations in the bloodstream
  - Resulting in a need to inject at least 30 minutes before the meal to best cover post-meal glycemic excursions
- The duration of action can exceed the duration of the postprandial rise in glucose observed after most meals, particularly meals that are not high in carbohydrate and fat.
  - This can cause hypoglycemia several hours after eating

PRANDIAL INSULIN

- **Analog insulins**
- Insulin lispro, aspart and glulisine
- New ones: faster aspart and lispro-aabc
- Use recombinant DNA technology
- Have faster onset and shorter duration of action than regular insulin for pre-meal coverage
- Produce more physiologic insulin profiles
  - Especially for type 1 diabetes and reduce the risk of hypoglycemia.

Pharmacokinetics of the most commonly used insulin preparations

Insulin type	Approximate onset of action	Peak effect	Approximate duration of action*
Lispro, lispro-aabc, aspart, faster aspart, glulisine	3 to 15 minutes	45 to 75 minutes	2 to 4 hours
Regular	30 minutes	2 to 4 hours	5 to 8 hours

PRANDIAL INSULIN

- **Inhaled insulin**
- The inhalation of insulin premeals improves postprandial glycemia in both type 1 and type 2 diabetic patients
- Inhaled insulin is rapidly absorbed from the alveoli.
- Despite the rapid absorption of inhaled insulin, the duration of action is longer than that of the rapid-acting subcutaneous insulin analogues
- Inhaled insulin dosing can only be adjusted in 4-unit increments
- Contraindicated in the presence of chronic lung disease.
  - Requires initial pulmonary function testing

PRAMLINTIDE

- Pramlintide is a synthetic analogue of the beta-cell hormone amylin
- Inhibits glucagon secretion, delays gastric emptying and acts as a satiety agent
- Co-administration of pramlintide with lispro or regular human insulin reduced PPG excursions by 81% compared with lispro insulin alone
- Adjunctive therapy with pramlintide lowers HbA1c without weight gain and with less hypoglycemia in type 1 diabetes mellitus

PRAMLINTIDE

- Indications:
  - Only approved for diabetic patients taking prandial insulin
- Requires injections with each meal in the setting of type 1 diabetes and at least twice daily in type 2 diabetes.
  - Before meals that contain at least 250 calories or 30 grams of carbohydrates
- It cannot be mixed in a syringe with insulin.

CURRENT AND EMERGING MANAGEMENT TECHNOLOGIES

- CMG
  - Provides a dynamic, real-time measuring interstitial glucose concentration
  - Contributed greatly to understanding PPG excursions along with overall patterns of glycemia
- Continuous Subcutaneous Insulin Infusion (CSII, or insulin pump)
  - Aims to mimic normal insulin secretion by continuously infusing rapid-acting insulin at preselected rates, with patient-activated bolus doses at mealtimes or as corrections for hyperglycemia

CONCLUSION

- Most guidelines for Type 2 Diabetes, recommend a general HbA1c target of <7.0%
  - Emphasizing the need to take into account patient factors in determining the appropriate target for an individual
- The data reviewed in this presentation support the concept that postmeal glucose makes a significant contribution to overall glycaemia reflected in the HbA1c level
  - Especially when HbA1c is below 8.0%
- In people with HbA1c levels between 7.0 and 8.0%
  - Assessing postmeal glucose is warranted
  - If found to be elevated, blood glucose lowering therapy should preferentially choose an agent which specifically lowers postmeal glucose.

REFERENCES

- Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, Kollman C, Kruger D, McGill JB, Polonsky W, Toschi E, Wolpert H, Price D; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA. 2017;317(4):371–378.
- Ceriello, A., & Colagiuri, S. (2008). International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations. *Diabetic Medicine, 25*(10), 1151-1156. Retrieved 8 22, 2020, from https://ncbi.nlm.nih.gov/pmc/articles/pmc2701558
- Gerich, J. E., & Woerle, H. J. (2006). Clinical significance of postprandial hyperglycemia. *Drug Development Research, 67*(7), 587-590. Retrieved 8 22, 2020, from https://onlinelibrary.wiley.com/doi/abs/10.1002/ddr.20128
- Kieffer TJ, Habener JF. Endocr Rev. 1999; 20:876-913. Ahren B Curr Diab Rep. 2003;2: 365-372. Diabetes Care. 2003
- Maffettone, A., Rinaldi, M., & Fontanella, A. (2018). Postprandial hyperglycemia: a new frontier in diabetes management? *Italian Journal of Medicine, 12*(2), 108-115. Retrieved 8 22, 2020, from https://italjmed.org/index.php/ijm/article/view/itjm.2018.961
- Monnier, L., Colette, C., Dunseath, G., & Owens, D. R. (2007). The Loss of Postprandial Glycemic Control Precedes Stepwise Deterioration of Fasting With Worsening Diabetes. *Diabetes Care, 30*(2), 263-269. Retrieved 8 22, 2020, from https://care.diabetesjournals.org/content/30/2/263
- Rendell, M. S., & Jovanovic, L. (2006). Targeting postprandial hyperglycemia. *Metabolism-clinical and Experimental, 55*(9), 1263-1281. Retrieved 8 22, 2020, from https://ncbi.nlm.nih.gov/pubmed/16919548

QUESTION