MANAGEMENT OF HYPOGLYCEMIA IN PATIENTS WITH DIABETES

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No financial interests or conflicts to declare

OBJECTIVES

- Develop an approach to manage and prevent hypoglycemia in Type 1 (T1D) and Type 2 (T2D) diabetes
- Develop an understanding of factors contributing to hypoglycemia
- Understand the physiology of normal and abnormal responses to low glucose
- Provide information that will help improve diabetes care in your patients

CASE #1 PRESENTATION

A 45 year old Caucasian female new to your practice has a 15 year history of T1D. She was brought to the ED after being treated in the field for hypoglycemia (30mg/dl) which responded to D50 treatment. She reports a history of multiple ED visits over the last 2 years as well as the need for family members to administer glucagon for near LOC. She does not report any Sx of low glucose before she experienced LOC. She has been on an insulin pump using Humalog and does not regularly check glucose levels on her meter. She "feels" she knows what dose she needs and boluses frequently for the small meals she eats throughout the day. She also has a Hx of hypothyroidism and takes T4 regularly. Physical shows normal BP with a resting pulse of 100, BDR, bilateral lower extremity PN, no Sx or findings of vascular disease, bowel sounds are hypoactive with positive sucusion splash 5 hours post prandially. Labs show normal TSH, LFTs. CMP shows creatinine 1.8, elevated microalbumin, normal LFTs and electrolytes, glucose 75mg/dl elevated total cholesterol and TG, trace ketones, normal ABG.

CASE #2 PRESENTATION

Patient is a 69 year old black male with HTN, hyperlipidemia, obesity and a Hx of T2D for 5 years who is new to your clinic. He has a Hx of poor glucose control and no known diabetes complications. He comes to clinic complaining of Sx of low blood glucose during the day, hunger, headache, feeling anxious. His physical exam shows normal vital signs, no DR, no PN, and is otherwise normal except for extensor surface hyperkeratosis and acanthosis with multiple skin tags found on his neck and axilla. He is retired, sedentary, eats three meals a day and snacks often at night. He checks glucoses infrequently. He is on Metformin 2500mg daily, an SGLT-2 inhibitor, 5mg BID glyburide and 20 units of Lantus in the AM which was recently added to his regime by his PMD. He has checked his glucose when symptomatic for hypoglycemia on occasion and reports glucoses in the mid 100s.

His HbA1c is in the clinic lab currently. Other labs are normal.

DEFINITION OF HYPOGLYCEMIA

- General definition; 70mg/dl or less
- Accompanying *Sx* and relief with glucose administration
- Special considerations;
  - chronic *hyperglycemia* shifts hypoglycemic threshold upward, e.g., patient feels low at glucose of >100mg/dl
  - whereas tight control can lower threshold for Sx of hypoglycemia, e,g, from 70mg/dl to 40mg/dl.

SYMPTOMS OF HYPOGLYCEMIA

- Symptoms are characterized as neurogenic/autonomic or neuroglycopenia
- General Sx
  - hunger
  - fatigue
  - headache
  - nausea
- Autonomic/neurogenic Sx
  - increased HR
  - sweating,
  - tremor
- CNS/neuroglycopenic Sx
  - confusion
  - blurry vision
  - personality change, e.g. irritability

- !! Symptoms are relieved by glucose ingestion or glucagon injection

INCIDENCE OF HYPOGLYCEMIA IN DIABETIC PATIENTS

- Intensive glucose control increases hypoglycemic risk; (5.5% standard insulin Tx vs. 16.2% intensive insulin Tx)
- Studies using CGM monitoring showed higher rates of hypoglycemia; 63% of T1D and 47% of T2D with unrecognized asymptomatic hypoglycemia
- 74% of hypoglycemia events occurred overnight
- Hypoglycemia incidence increases several fold with longer duration of both T1D and T2D, e.g., >5 years

MEDICAL CONSEQUENCES OF HYPOGLYCEMIA; WHY HYPOGLYCEMIA CAN BE DANGEROUS

- Acute
  - Confusion
  - Loss of consciousness
  - Seizure
  - Trauma, falls, car accident, injury operating machinery
  - Precipitation of cardiac ischemia, arrythmias
  - Death
- Chronic
  - Cognitive loss
  - ? Cause of lower IQ/cognitive function when hypoglycemia occurs in the developing brain of children
  - Loss of symptoms of low glucose; lowering of autonomic threshold for sensing low glucose

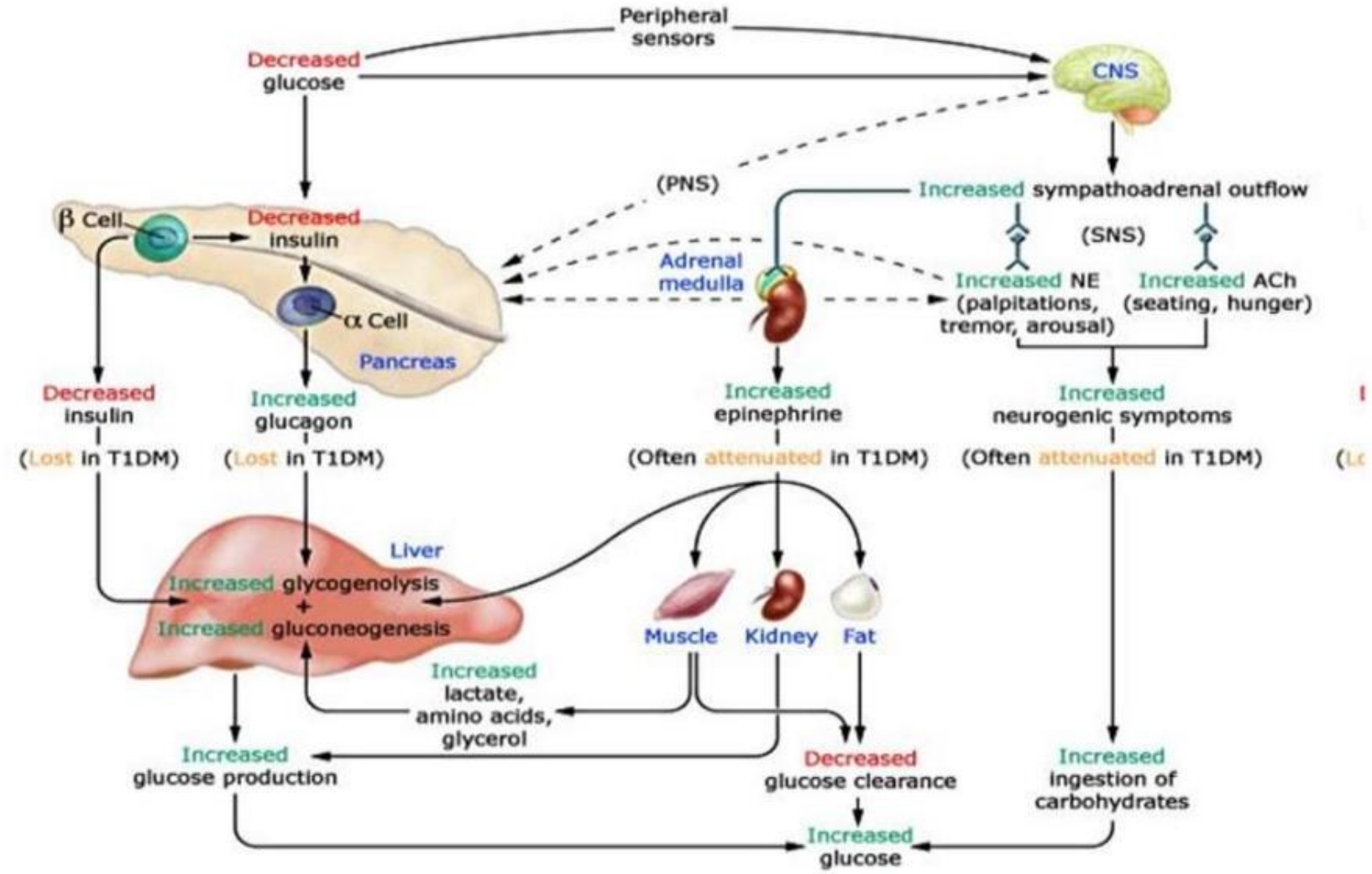
COMMON CAUSES OF HYPOGLYCEMIA IN DIABETIC PATIENTS

- Insulin use; long and short-acting insulins
- Sulfonylureas, meglitinides
- Incidental over dosing, miscalculation with insulin/carb ratio-based dosing, correction factor, basal insulin, incorrect carbohydrate counting
- Missing meals, prolonged fasting
- Post-Exercise
- Medications; quinolones, pentamidine, quinine, beta blockers, ACE-I ARB, iGF-1
- Heavy alcohol use

PHYSIOLOGIC RESPONSE TO HYPOGLYCEMIA

- Autonomic; epinephrine, norepinephrine, ACh
- Pituitary; ACTH, GH
- Adrenal cortex; cortisol
- Adrenal medulla and AN nervous system; NE, EPI, ACh
- Pancreas; glucagon* (abnormal low response in Type 1 diabetes)
- Liver; gluconeogenesis, glycogenolysis
- Tissue production of glucose substrates, lactate, amino acids

Physiological and behavioral defenses against hypoglycemia



Decrements in insulin and increments in glucagon are lost and increments in epinephrine and neurogenic symptoms are often attenuated in insulin-deficient - T1DM and advanced T2DM.

SNS: sympathetic nervous system; PNS: parasympathetic nervous system; NE: norepinephrine; ACh: acetylcholine; α-cell: pancreatic islet α-cells; β -cell: pancreatic islet β -cells.

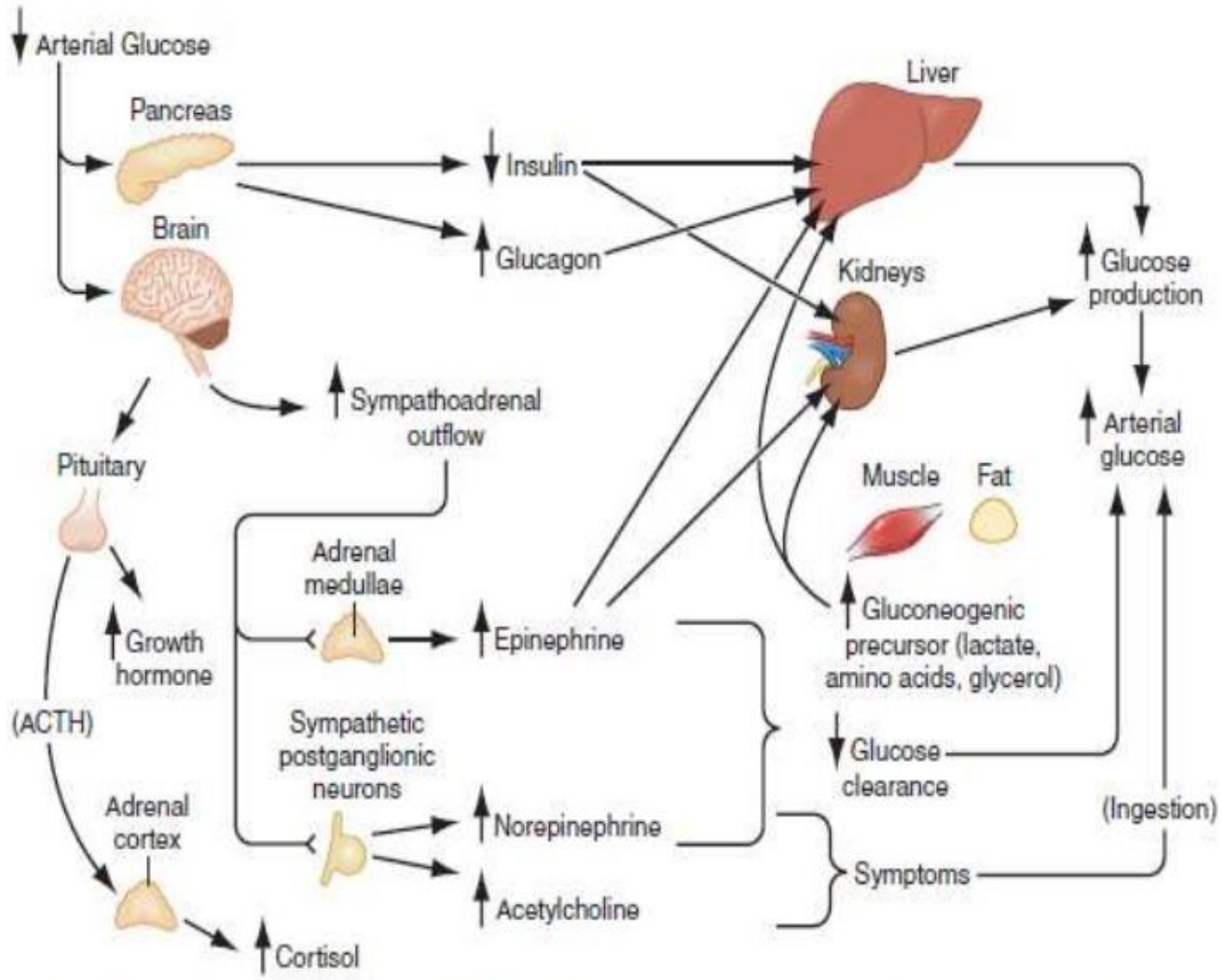


Figure 345-1 Physiology of glucose counterregulation—the mechanisms that normally prevent or rapidly correct hypoglycemia. In insulin-deficient diabetes, the key counterregulatory responses—suppression of insulin and increase of glucagon—are lost, and the stimulation of sympathoadrenal outflow is attenuated.

PREDISPOSING FACTORS/DISEASES CONTRIBUTING TO HYPOGLYCEMIA RISK

- Glucagon (deficient response in Type 1 Diabetes)
- Autoimmune endocrine disease associated with T1D
  - Pituitary Deficiency; e.g., GH, ACTH
  - Addison's Disease
- Liver disease; NASH in Type 2 Diabetes
- Renal disease
- CHF
- Sepsis
- Chronic caloric insufficiency
- Gastroparesis; slow gastric emptying and delayed glucose absorption in conjunction with mismatch of insulin pharmacokinetics
- Gastric bypass surgery for obesity
- Heavy alcohol use

TREATMENT OF HYPOGLYCEMIA

- Conscious patient
  - Confirm low glucose with meter or CGM
  - Oral glucose, 2-4 glucose tabs, ½ cup of sweetened soda or OJ, 6 pieces of hard candy
  - Repeat glucose testing 5-15 minutes post initial test
  - If symptoms are worsening in this time frame repeat glucose ingestion and continue to monitor glucose levels
  - Consider mixed CHO meal or IV Glucose Tx if long acting insulin is the cause

TREATMENT OF HYPOGLYCEMIA

- Semi-conscious patient
  - Check gag reflex
  - Administer oral glucose carefully
- Unconscious patient
  - Glucagon injection (1mg SC or IM) by bystander
  - Nasal glucagon
  - IV glucose, or clysis if no IV site

GENERAL APPROACH TO LONG-TERM MANAGEMENT OF DIABETES AND AVOIDANCE OF HYPOGLYCEMIA

- T1D
  - Education, education, education
  - Consider combination of long-acting and short-acting insulins
  - Glucose monitoring/CGM
  - Insulin pump with CGM, variable basal rates, auto suspend, sine and square wave, duration of action
- T2D
  - Education
  - Modulation of oral agents doses, other non-insulin injectable drugs, long-acting insulins with our without short acting insulin

GENERAL APPROACH TO LONG-TERM MANAGEMENT OF DIABETES AND AVOIDANCE OF HYPOGLYCEMIA

- Determine if patient has Sx with low glucose and at what glucose threshold
- Relaxation of diabetes control, e.g, modulation of insulin, OHGA, other T2D meds, review insulin dosing regime
- Review of dietary habits and types of food ingested and when
- Timing of insulin doses and meals
- Review glucose logs/meter
- Review exercise programs
- Assess home situation, e.g., living alone, cognitive abilities, ability to respond to low glucose
- Review medications and supplements

ALTERED GLUCOSE THRESHOLDS FOR HYPOGLYCEMIA

Case. #1

Autonomic neuropathy vs. desensitized autonomic response

Contributing factor; gastroparesis, recommend GE study

Case #2

Relative Hypoglycemia

MANAGEMENT OF ASYMPTOMATIC HYPOGLYCEMIA (DEFICIENT NEUROGENIC HYPOGLYCEMIC RESPONSE)

- Occurs in patients with frequent hypoglycemic episodes and “tight” glucose control. e.g., HbA1c
- Patients often have severe low glucose with impaired recognition and difficulty responding with appropriate action
- Blunted autonomic and counterregulatory hormone responses due to chronic low glucose and desensitization
- Management; eliminate hypoglycemia by relaxing diabetes treatment
- **Acquired autonomic neuropathy as a diabetes complication; not effected by loosening control

MANAGEMENT OF RELATIVE HYPOGLYCEMIA

- Occurs in patients with chronic hyperglycemia, e.g., >200mg/dl
- More intensive diabetes management and “normalization” of glucose leads to symptoms of hypoglycemia at ”non” hypoglycemic levels
- Management;
  - Lower glucoses slowly over a few weeks
  - Have patient monitor closely when symptoms occur and educate patient on actual glucose levels, encourage testing with Sx
  - Abnormal response will abate over time

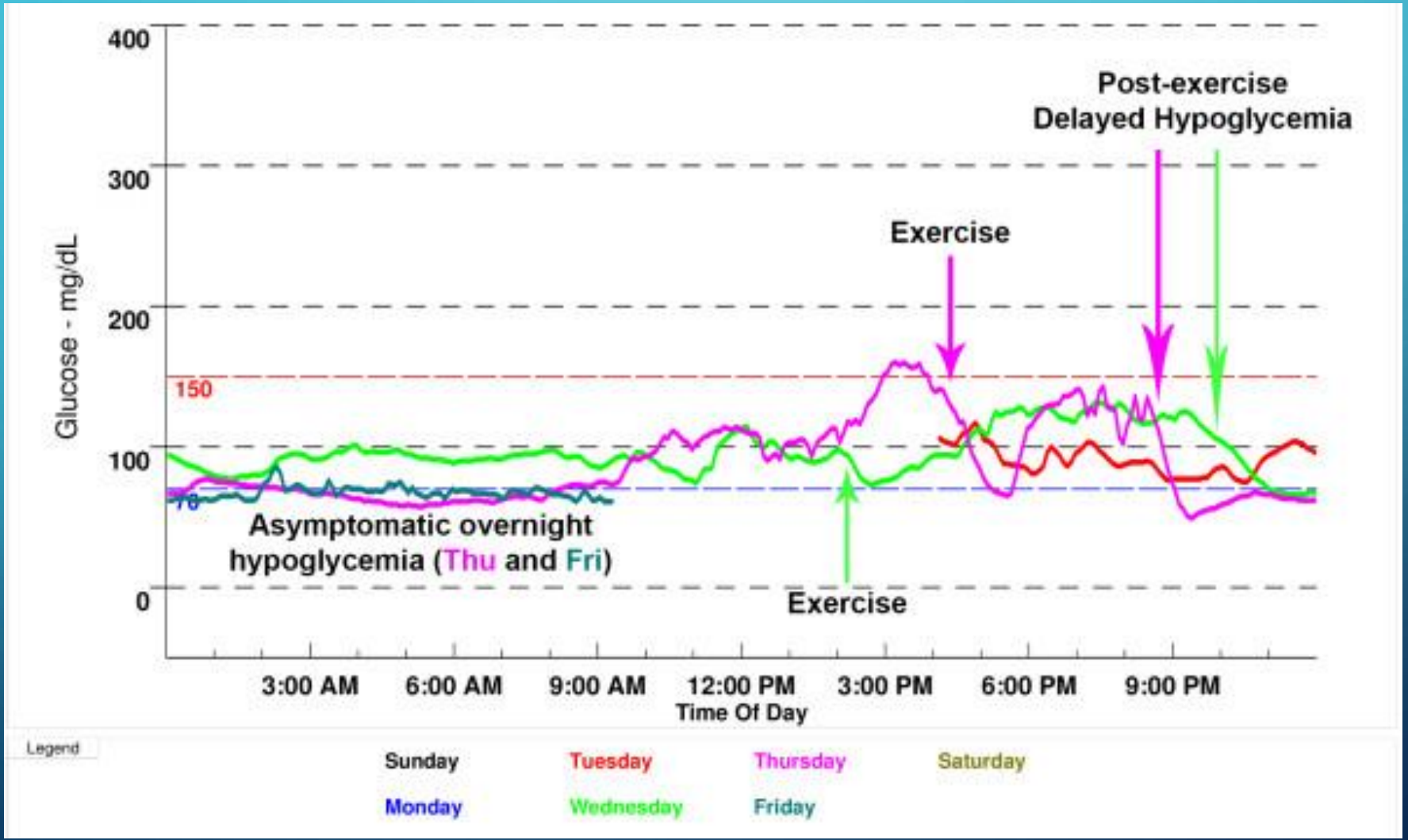
	Time for onset of action	Time until peak action	Duration of action
Rapid-acting insulins			
Regular human insulin	30–60 min	2–4 h	5–8 h
Aspart	12–18 min	30–90 min	3–5 h
Glulisine	12–30 min	30–90 min	3–5 h
Lispro	15–30 min	30–90 min	3–5 h
Intermediate-acting analogues			
NPH	1–2 h	4–12 h	12–16 h
Lispro protamine	30–60 min	4–12 h	12–16 h
Long-acting analogues			
Detemir	1–2 h	6–8 h	up to 24 h
Glargine	1–2 h	None	20–26 h
Glargine U300	1–2 h	None	up to 36 h
Degludec	30–90 min	None	>42 h
Pre-mixed			
70% NPH, 30% regular	30–60 min	2–4 h	10–16 h
50% NPH, 50% regular	30–60 min	2–5 h	10–16 h
30% aspart protamine, 70% aspart	5–15 min	1–4 h	10–16 h
50% aspart protamine, 50% aspart	15–30 min	1–4 h	10–16 h
70% aspart protamine, 30% aspart	15–30 min	1–12 h	10–16 h
50% lispro protamine, 50% lispro	10–15 min	1–4 h	10–16 h
75% lispro protamine, 25% lispro	10–15 min	1–12 h	10–16 h

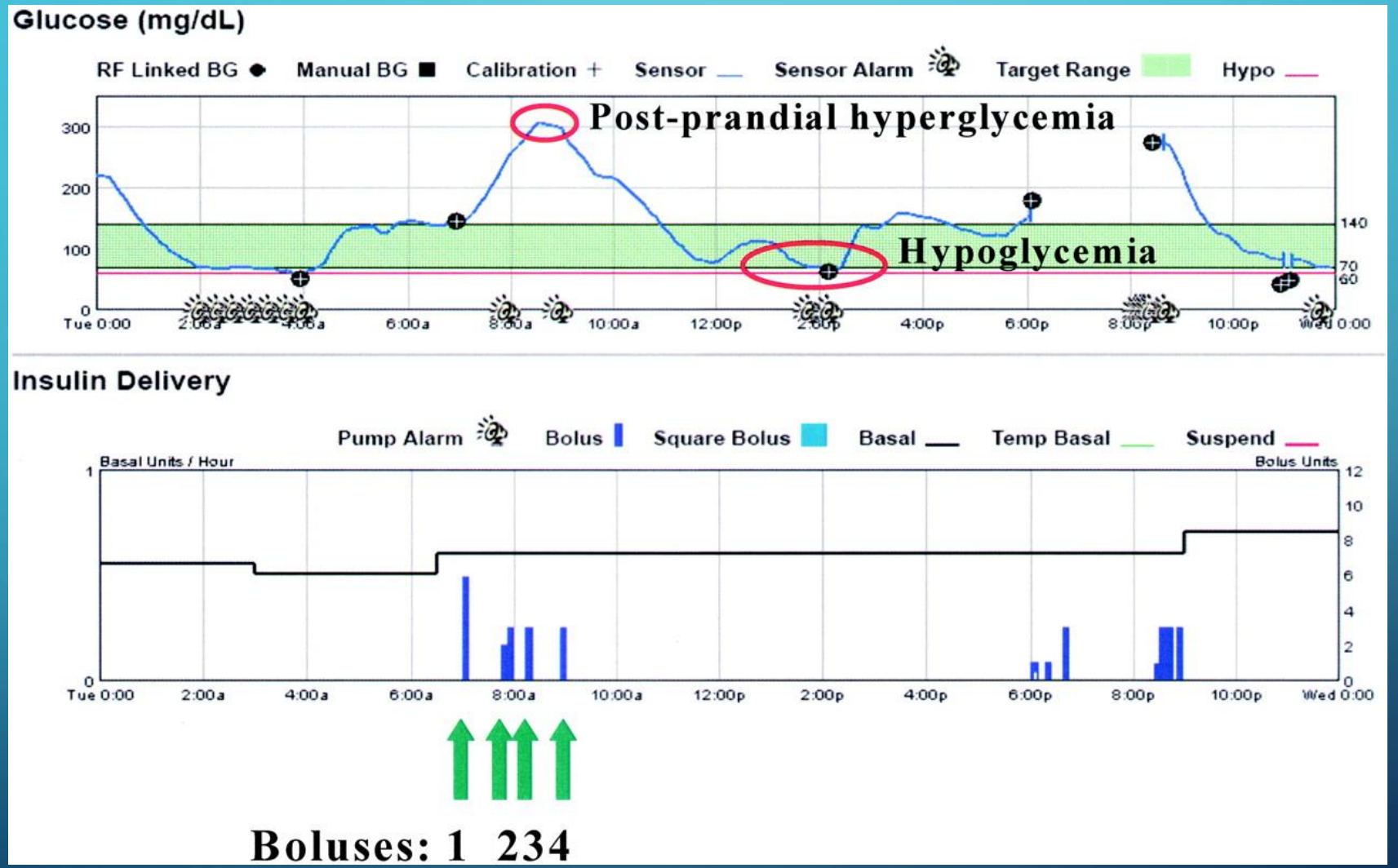
NPH=neutral protamine hagedorn.

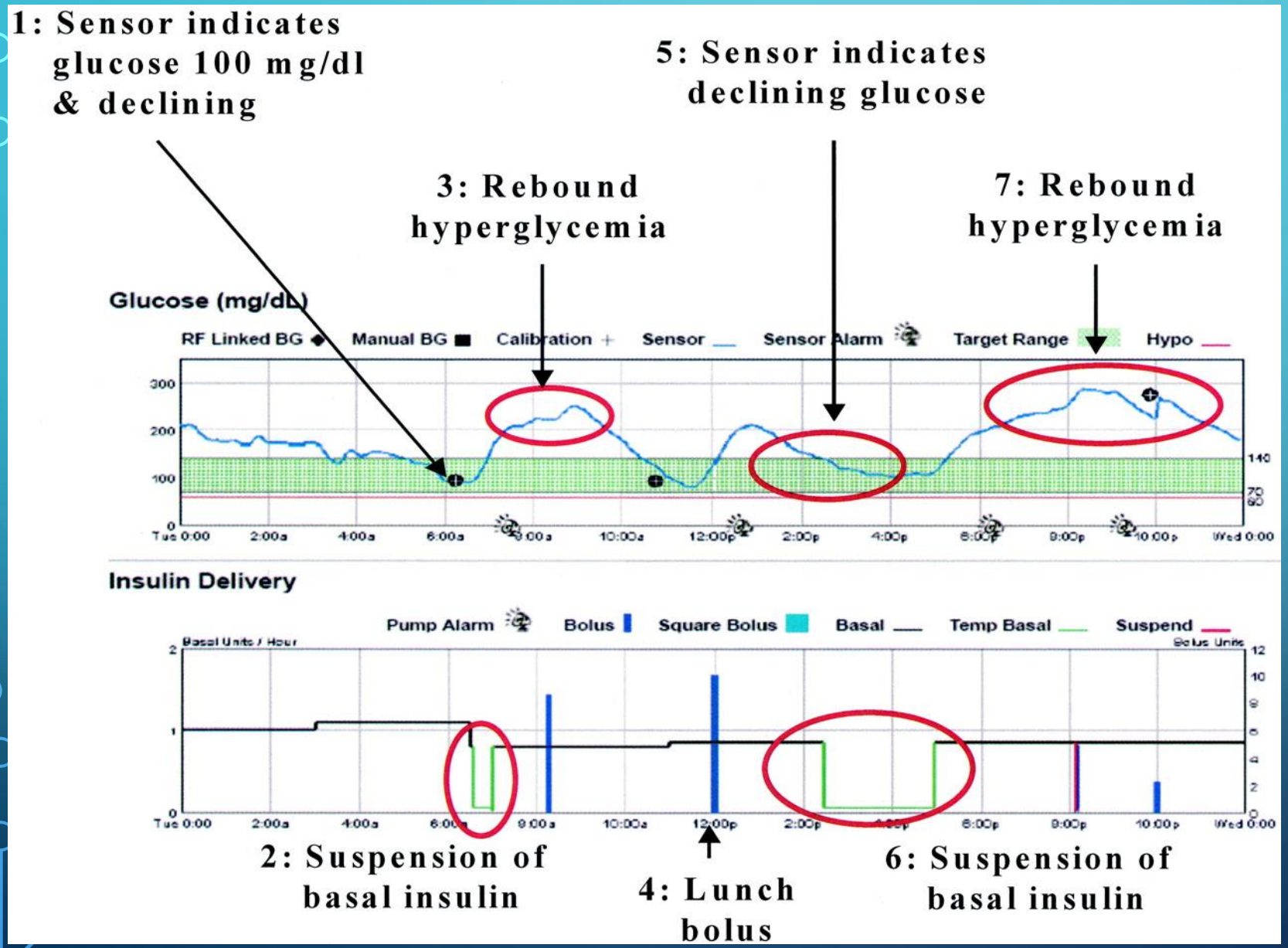
Table 1: **Pharmacokinetics of available insulin formulations**

KNOW YOUR INSULIN PK TO MODIFY INSULIN REGIMES TO REDUCE HYPOGLYCEMIA

Consider CGM detection of hypoglycemia and potential causes




Glucose (mg/dL)
RF Linked BG
Manual BG
Calibration
Sensor
Sensor Alarm
Target Range
Hypo
Post-prandial hyperglycemia
Hypoglycemia
300
200
100
0
140
70
60
Tue 0:00
2:00a
4:00a
6:00a
8:00a
10:00a
12:00p
2:00p
4:00p
6:00p
8:00p
10:00p
Wed 0:00
Insulin Delivery
Pump Alarm
Bolus
Square Bolus
Basal
Temp Basal
Suspend
Basal Units / Hour
Bolus Units
1
0
12
10
8
6
4
2
0
Tue 0:00
2:00a
4:00a
6:00a
8:00a
10:00a
12:00p
2:00p
4:00p
6:00p
8:00p
10:00p
Wed 0:00
Boluses: 1 234


1: Sensor indicates glucose 100 mg/dl & declining
5: Sensor indicates declining glucose
3: Rebound hyperglycemia
7: Rebound hyperglycemia
Glucose (mg/dL)
RF Linked BG
Manual BG
Calibration
Sensor
Sensor Alarm
Target Range
Hypo
300
200
100
0
140
70
60
Tue 0:00
2:00a
4:00a
6:00a
8:00a
10:00a
12:00p
2:00p
4:00p
6:00p
8:00p
10:00p
Wed 0:00
Insulin Delivery
Pump Alarm
Bolus
Square Bolus
Basal
Temp Basal
Suspend
Basal Units / Hour
Bolus Units
2
1
0
12
10
8
6
4
2
0
Tue 0:00
2:00a
4:00a
6:00a
8:00a
10:00a
12:00p
2:00p
6:00p
8:00p
10:00p
Wed 0:00
2: Suspension of basal insulin
4: Lunch bolus
6: Suspension of basal insulin

TAKE AWAYS

- Patient education on Sx, Tx, predisposing factors, diet, effects of illness, insulin PK, glucagon use training for friends, significant others and family
- Patients with tight control and a long Hx of diabetes are at increased risk for hypoglycemia
- Question patients for aSx lows (autonomic insensitivity) and if in tight control loosen Tx so that glucose is in the mid to upper 100s and monitor for return of hypoglycemic Sx over the ensuing weeks
- Look for predisposing factors, e.g., Addison's, pituitary insufficiency, autonomic neuropathy, diet, exercise, liver disease, renal disease gastroparesis and etc.
- For Relative Hypoglycemia gradually increase Tx, increase glucose monitoring and advise patient that Sx will abate as they physiologically adapt to lower , more normal glucose levels.
- Strongly consider CGM to help define episodes and understand potential causes.

THANK YOU

Questions and Comments

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