

IT'S MORE THAN NUMBERS ON A GLUCOMETER

CURRENT PRIORITIES OF DIABETES MANAGEMENT



Freepic.com

Christine Kessler MN, CNS, ANP-BC, BC-ADM, FAANP
Metabolic Medicine Associates
Journeys Weight Loss Clinic

DISCLOSURES

- **Novo Nordisk:** Advisor/Speaker (obesity, T2DM);
- **Acella:** Speaker: Hypothyroidism, desiccated thyroid extract (DTE)

All financial disclosures have been mitigated

OBJECTIVES

- List the FIVE categories of diabetes and clues to their presentation
- Identify those at risk for diabetes and/or insulin resistance
- Review the pathogenesis of Type 2 diabetes including at least 8 contributing metabolic impairments leading to dysglycemia
- Discuss laboratory findings in diagnosing prediabetes, Type 1 Diabetes and Type 2 diabetes
- Discuss how to obtain useful fingerstick blood glucose data
- Review risks and treatment of hypoglycemia
- Identify underlying neuropathy, retinopathy, and nephropathy using appropriate assessment tools

THE DIABETES EPIDEMIC

THE SWEETEST PEOPLE IN THE WORLD

- **DIABETES**

- **Total:** 37.3 million (11.3%) of the US population have diabetes

- **Diagnosed:** 28.7 million

- **Undiagnosed:** 8.5 million people

- **PREDIABETES**

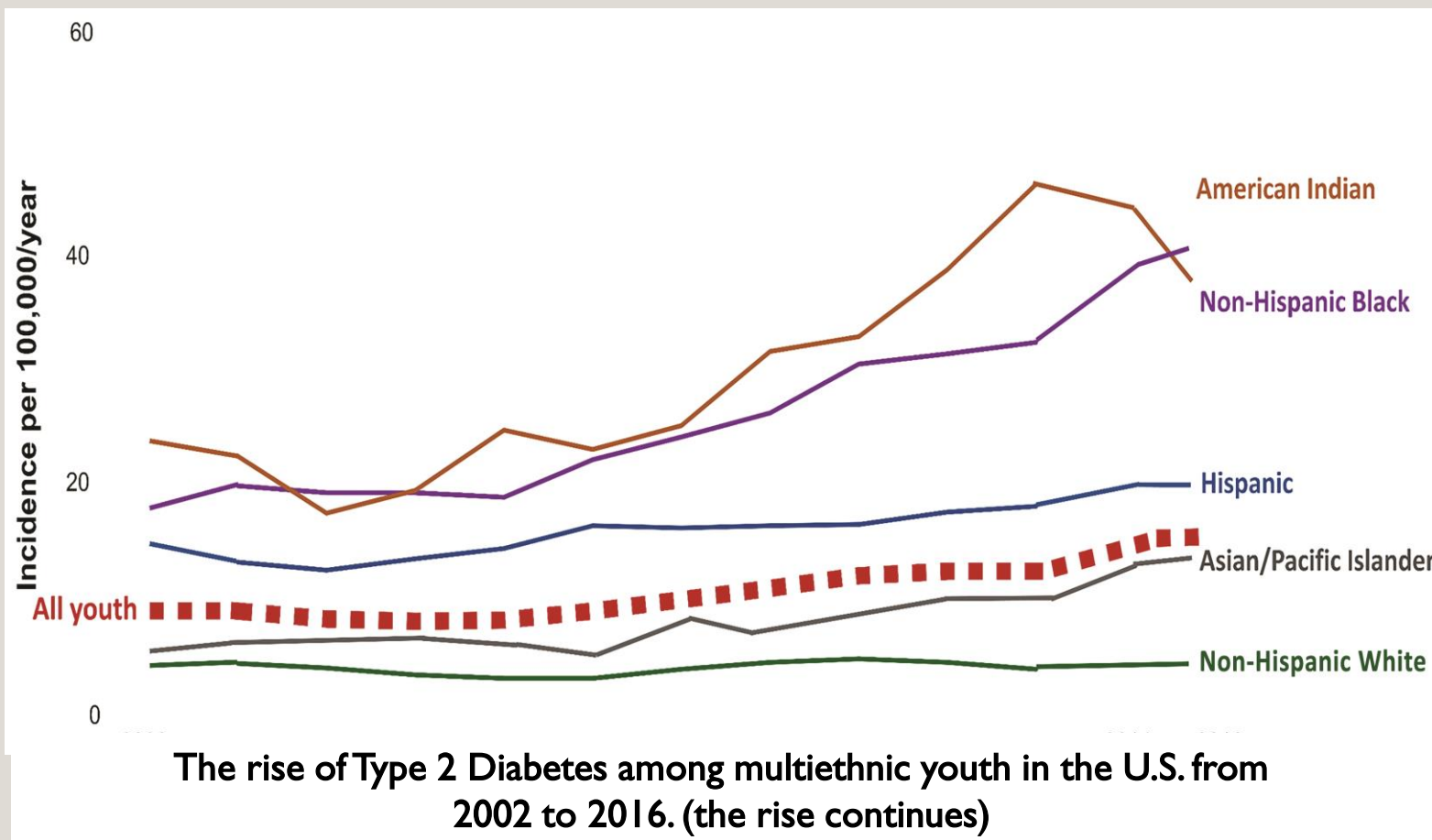
- **Total:** 96 million (38.0%) adults (over 18 yrs) have prediabetes

- **65 years or older:** 26.4 million (48.8%) have prediabetes!

- 1 in 3 people estimated to have diabetes by 2050

- Every 8 seconds someone dies from something related to

Youth-onset T2DM



Expected
400%
increase
within next
25 years

What types of diabetes are there?

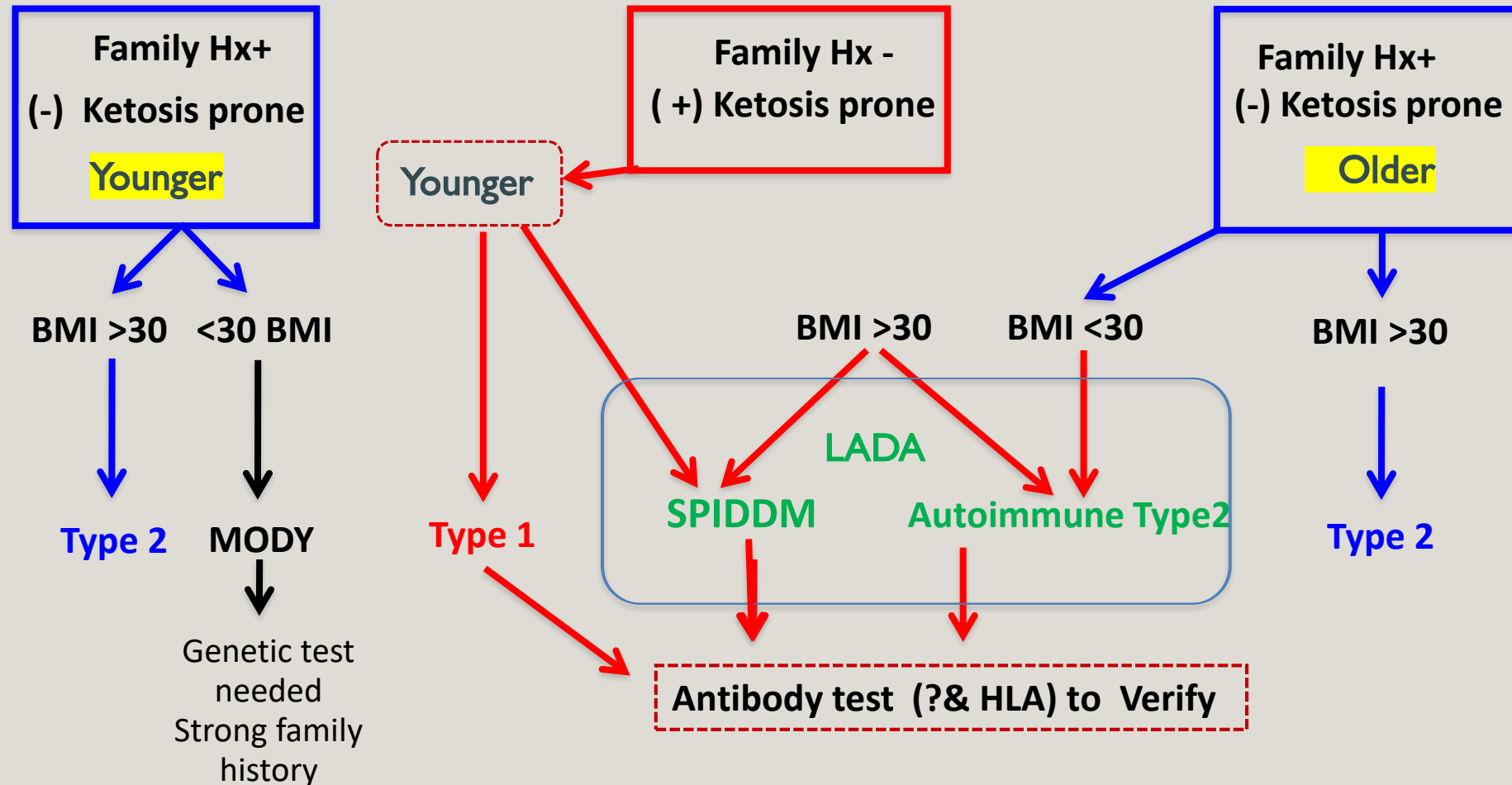
- **Autoimmune Type 1 (leads to absolute insulin deficiency)**
 - Type 1 diabetes (more rapid development)
 - Latent autoimmune diabetes in adults (LADA) (slow development)
 - An “event” will trigger the onset
- **Type 2 diabetes** (most common) (non-autoimmune)
 - progressive loss of β -cell function & relative insulin deficiency
 - Associated with IR and metabolic syndrome (now in younger pts)
- **Gestational diabetes**
 - Found in 2nd or 3rd trimester (unmasks underlying DM presence or risk)
- **MODY**
 - 4 main types (1-2% of those with DM—usually misdiagnosed)
 - HNF1-alpha; HNF1-beta; HNF4-alpha; glucokinase
- **Exocrine pancreas disease/impairment**
 - Pancreatitis, cystic fibrose, adiposity
 - Drug-induced– glucocorticoid use

Suspicious based on:

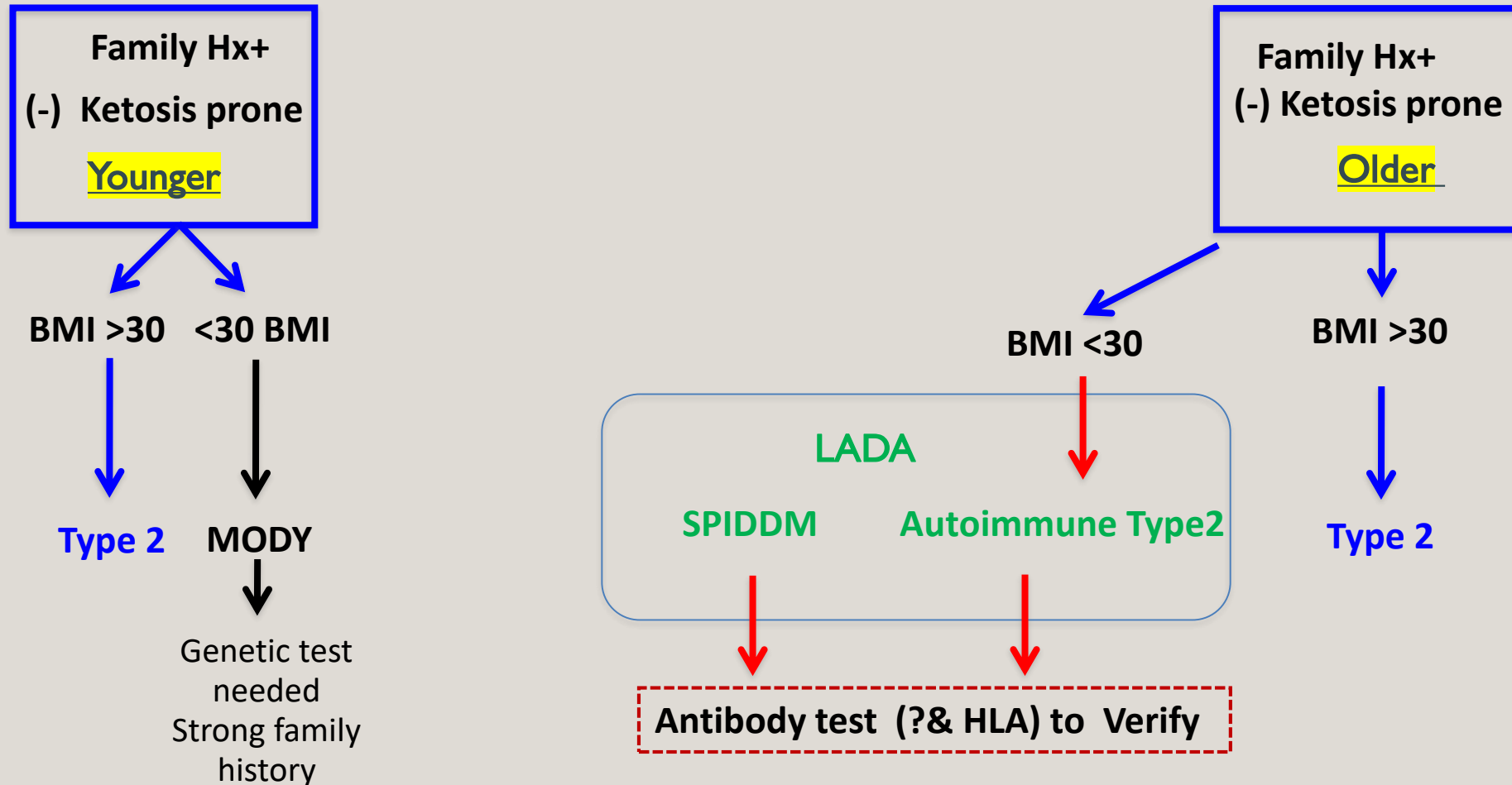
Family History (genes)
Age
Ketosis prone
BMI
Antibodies

**Greater risk in those with
underlying or family history of
autoimmune disease**

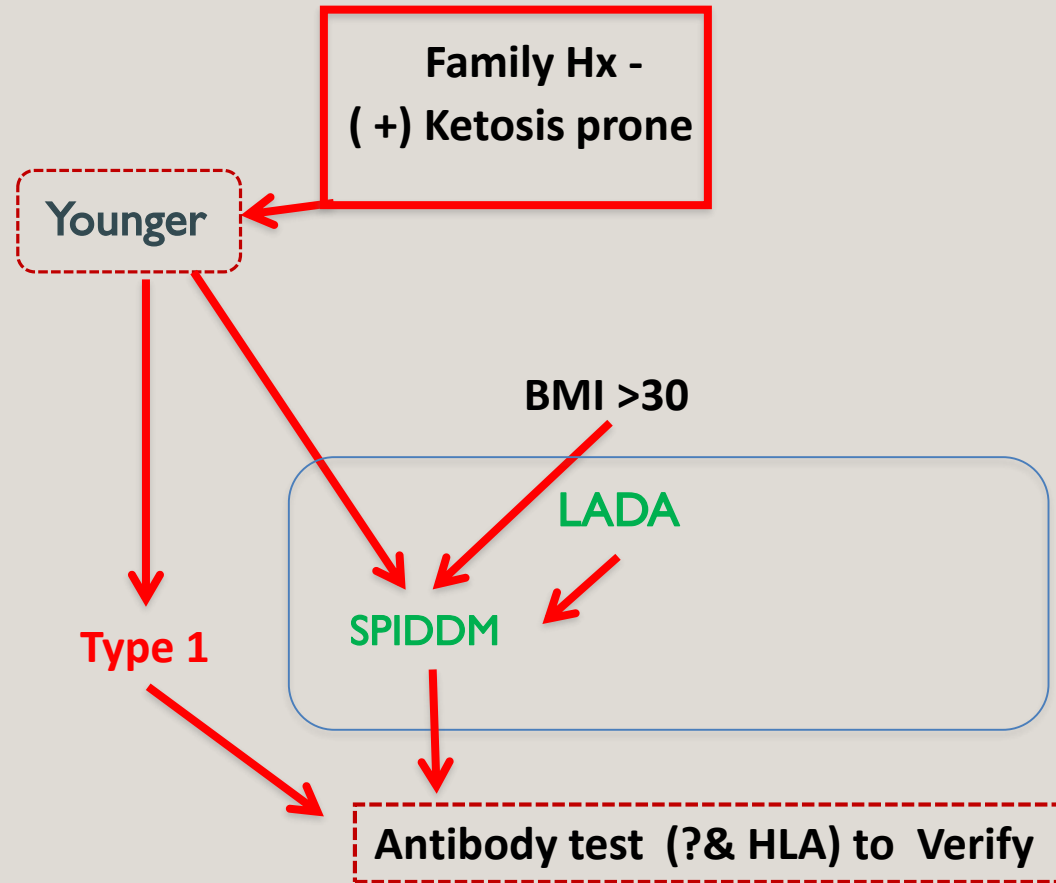
TIPS TO TYPES OF DIABETES



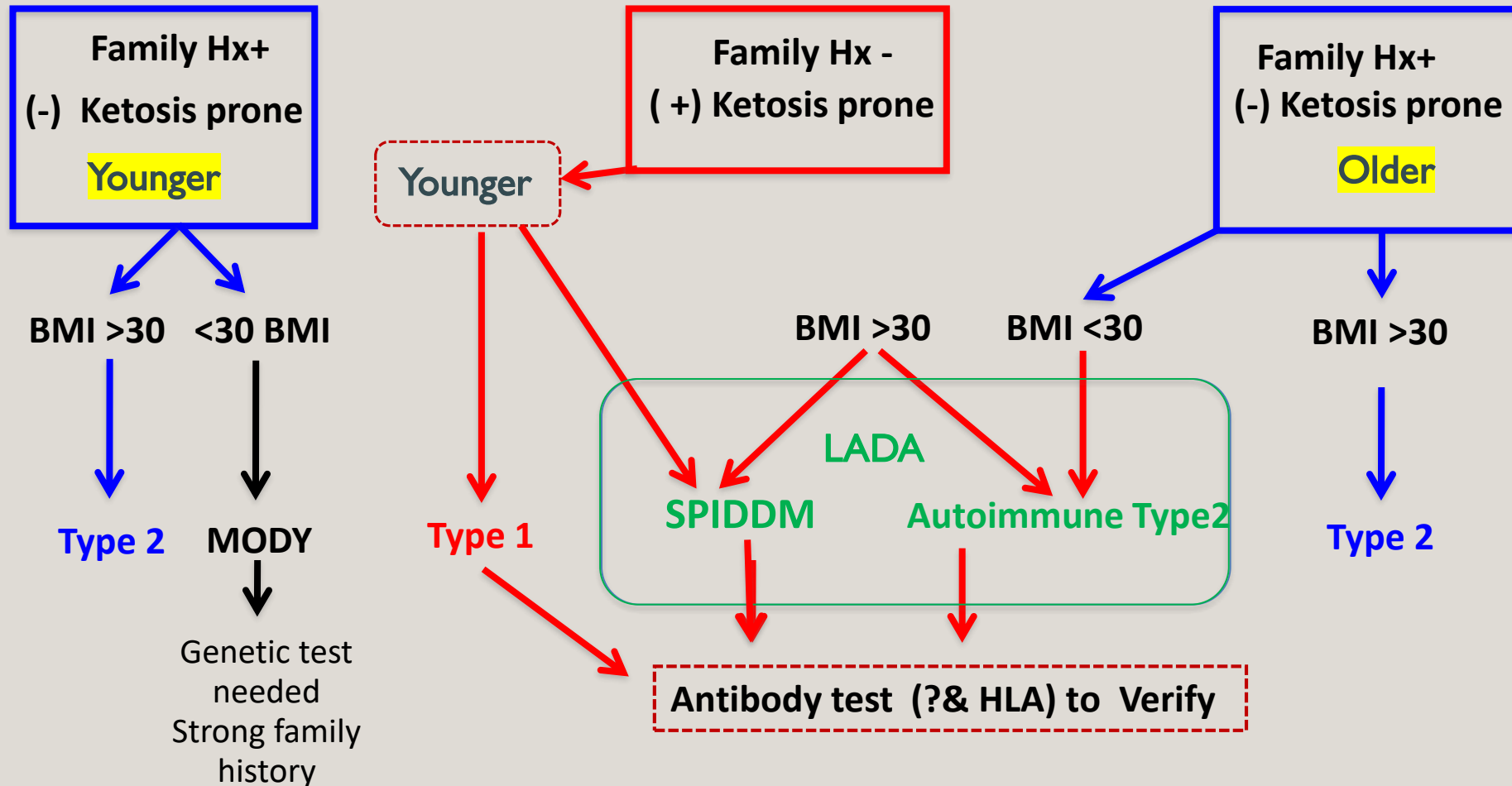
TIPS TO TYPE OF DIABETES



TIPS TO S OF DIABETES

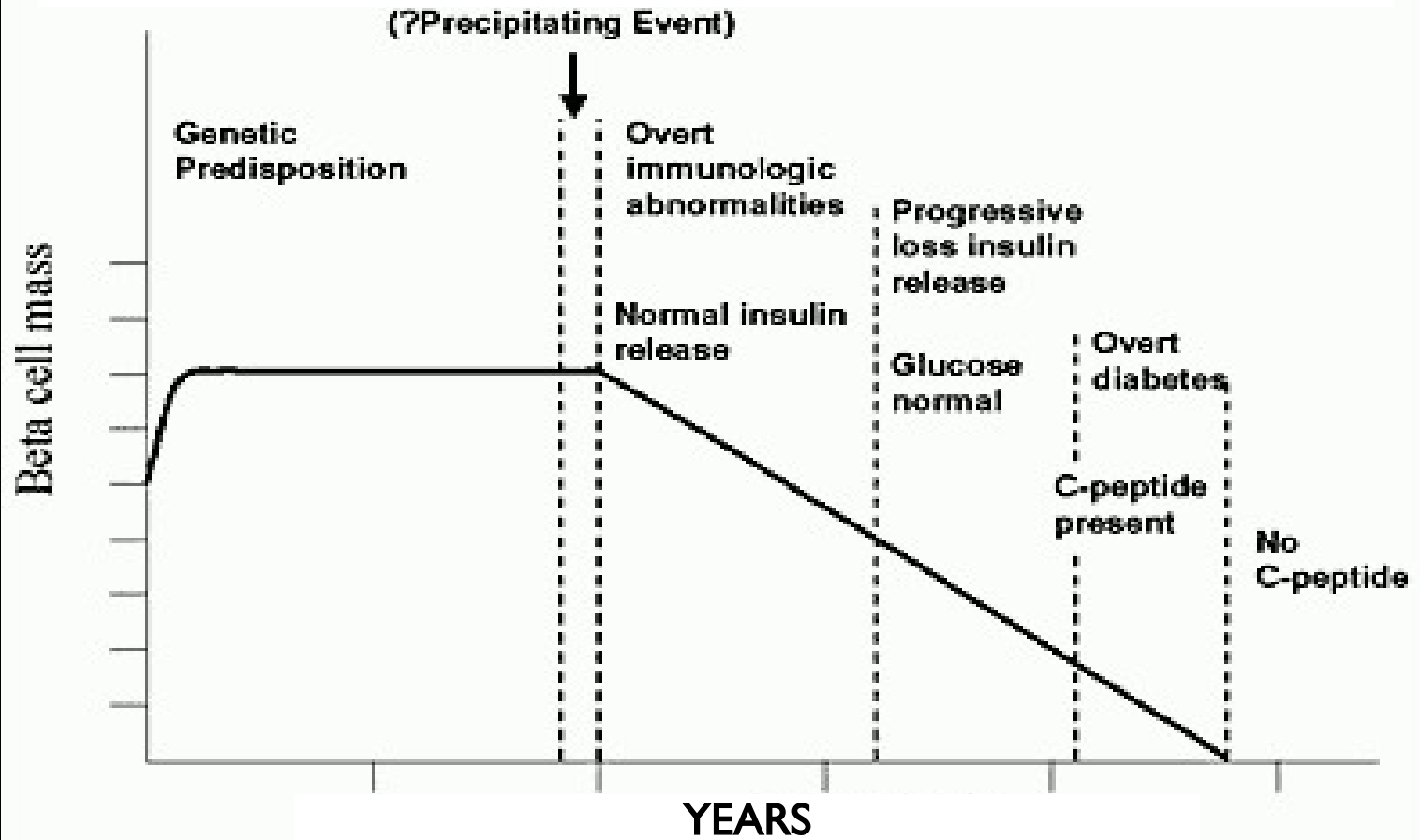


TIPS TO TYPES OF DIABETES



Genetics-Environment-Biology

The progression of events leading to Type I Diabetes



Examples of Triggers:

Endocrine disrupting chemical
Virus (esp norovirus,)
Certain foods (grains, bovine milk, etc
Vax reactions (yep)
Stress
PTSD
more

Image adapted by speaker

Type I Diabetes Stages

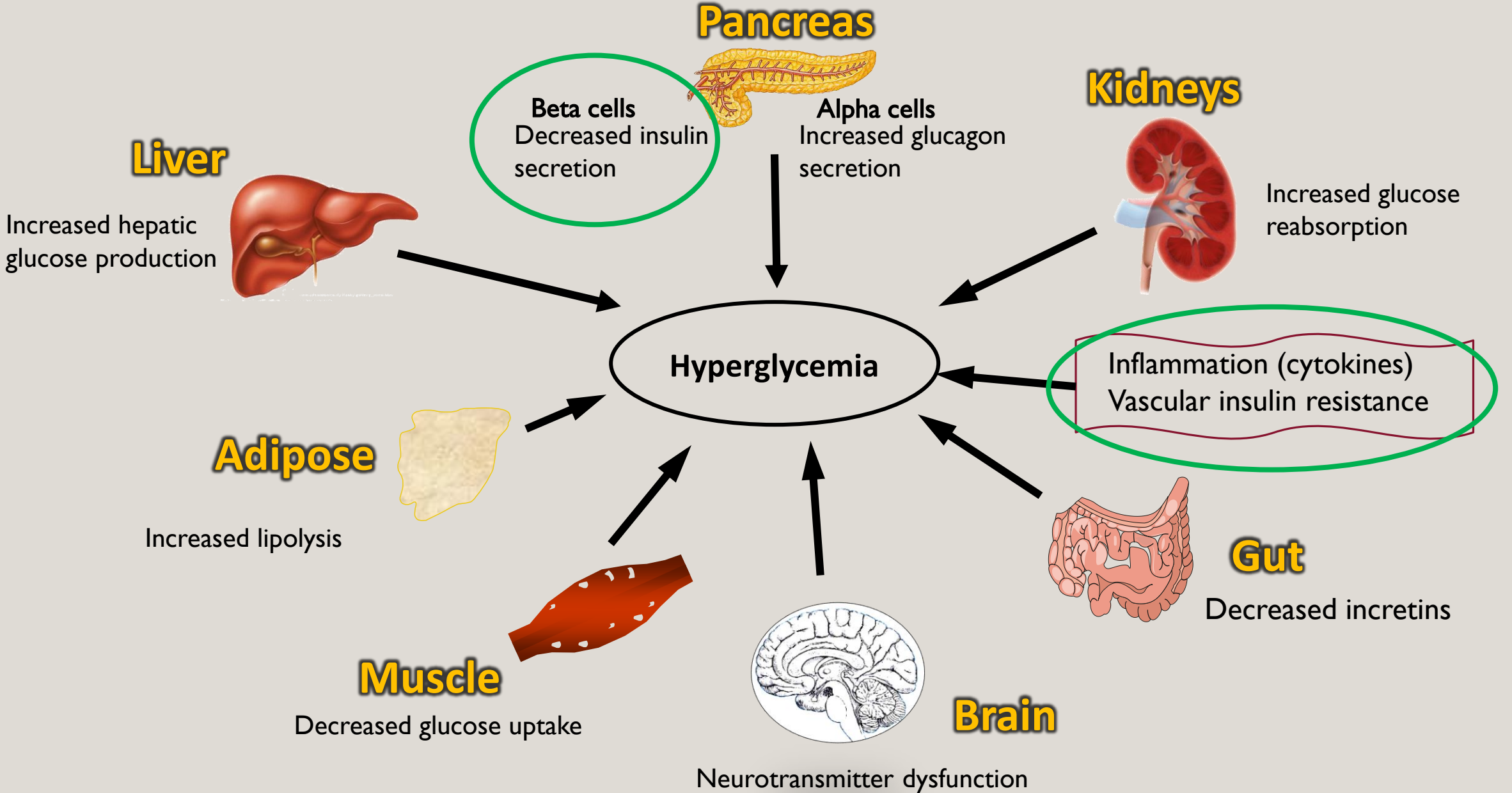
	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity	• Autoimmunity	• Autoimmunity
	• Normoglycemia	• Dysglycemia	• Overt hyperglycemia
	• Presymptomatic	• Presymptomatic	• Symptomatic
Diagnostic criteria	<ul style="list-style-type: none"> • Multiple islet autoantibodies • No IGT or IFG 	<ul style="list-style-type: none"> • <u>Islet autoantibodies</u> (usually multiple) • <u>Dysglycemia</u>: IFG and/or IGT • <u>FPG</u> 100–125 mg/dL • <u>2-h PG</u> 140–199 mg/dL • <u>A1C</u> 5.7–6.4% or ≥10% increase in A1C 	<ul style="list-style-type: none"> • Autoantibodies may become absent • Diabetes by standard criteria

Diabetes Care 2023;46(Supplement_1):S19–S40

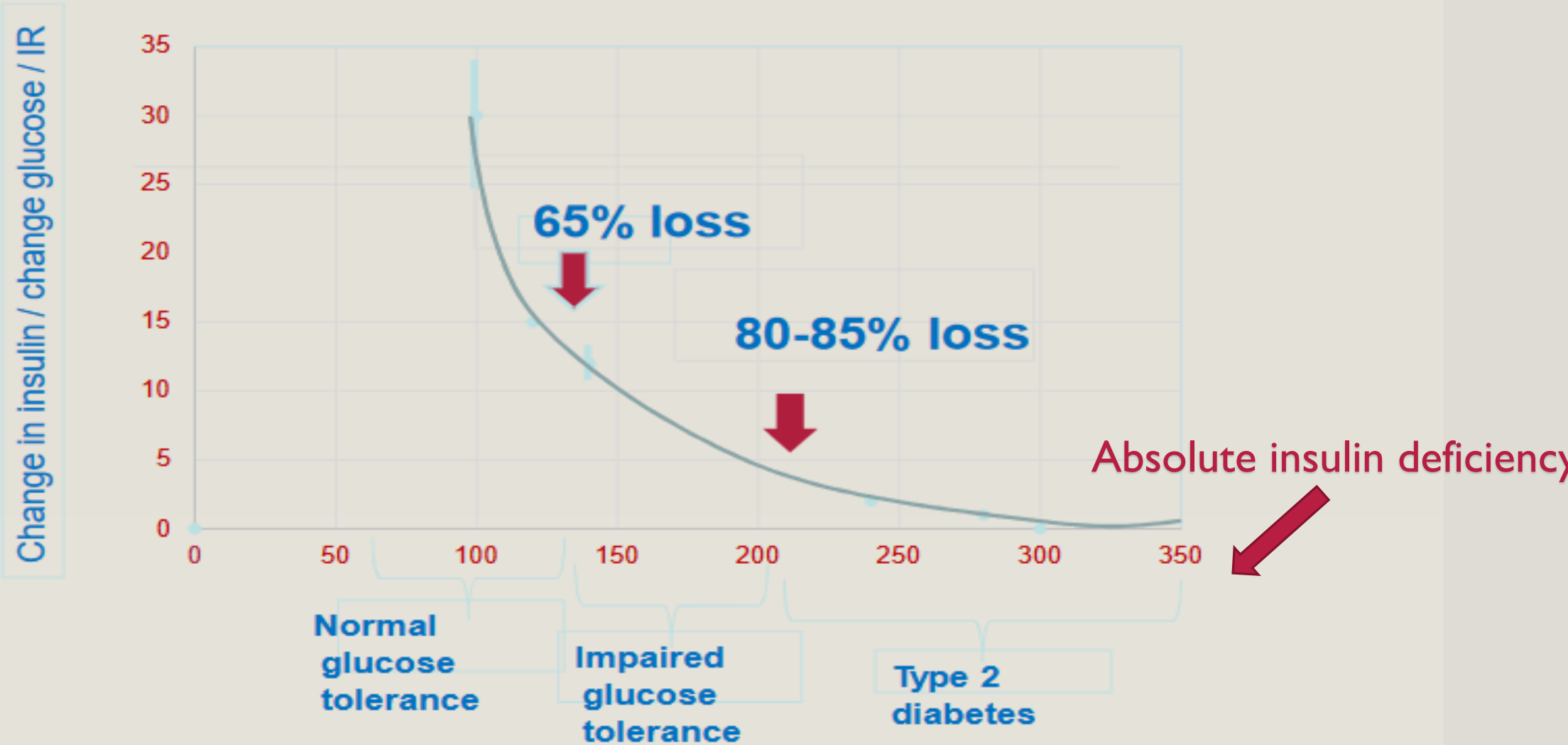
Diabetes 2017;66:241–255

BMJ Open 2019;9:e031586

PATHOGENESIS OF DIABETES (INFLAMMATION & INSULIN RESISTANCE)



BETA CELL FAILURE & INSULIN REDUCTION IN T2DM



WHO'S AT GREATER RISK FOR DIABETES?

- Family history
- Hx of Autoimmune disease (139 of these)
- Age
- Gender or ethnic influences (African American, Latino, Native American, Asian American, Pacific Islander)
- Gestational diabetes
- Hx of carpal tunnel or Duprey's contracture?
- Morbid obesity
- New onset hyperglycemia in acute care setting?

Diagnosing diabetes

	Normal	Pre Diabetes	Diabetes
Fasting	< 100	100-125	126+
Postprandial	<140	140-199	200+
HbA1c	<5.7	5.7-6.4	6.5+

Diagnosing diabetes

	Normal	Pre Diabetes	Diabetes
Fasting			
Post			
HbA1C	<5.7	5.7-6.4	6.5+

For diagnosis of Diabetes, must have **TWO abnormal** findings from the **SAME** sample (i.e, FBG and A1C)

POINTS ABOUT THE A1C

- Reflects AVERAGE blood glucose over a 3 month period
- It does not reflect blood glucose variations
- Its accuracy can be affected by the following:

False Increase:

Anemias (iron/Vit B12 deficiency)

Asplenia

Uremia

High triglycerides (>1750 mg/dl)

Chronic ETOH use

Chronic salicylate use

Chronic opioid use

HGB variants

Blood transfusion (high sugar in storage medium)

Vitamin C ingestion (depends on lab methods)

False Decrease:

Anemia (blood loss)

Splenomegaly

Pregnancy (1st & 2nd trimester)

Ribavirin & interferon-alpha

Vitamin E use

Blood transfusion (dilution effect)

Vitamin C ingestion (depends on lab methods)

**Are there other
options?**

MOST COMMON ANTIBODY TESTS FOR AUTOIMMUNE DIABETES

- **Positive rate in new-onset type 1 diabetes patients (combined analysis with 98% detection rate):**
 - ✓ • GAD-65 antibodies
 - ✓ • ICA 512 antibodies
 - ✓ • Insulin antibodies
 - ✓ • ZnT8 antibodies
- The higher the # of antibodies the higher the certainty of T1DM
- 2% of patients with T2DM have positive antibodies

Self-monitoring blood glucose levels



Pixabay.com

Seeing is believing?

What I used to see all the time

morning	lunch	Snack	Dinner	Before B
266	193	108	104	225
391	215	286	222	232
151	58		22	133
4	95		132	190
142	201		276	120
167	162		159	232
227	339		22	109
193	245		235	99
198	242	112	130	190
112	117		324	247
104	245		219	301
86	271		204	211
94	151		269	104

Tips on how to use SMBG finger-sticks
to get a picture of what is going on.

For the visit

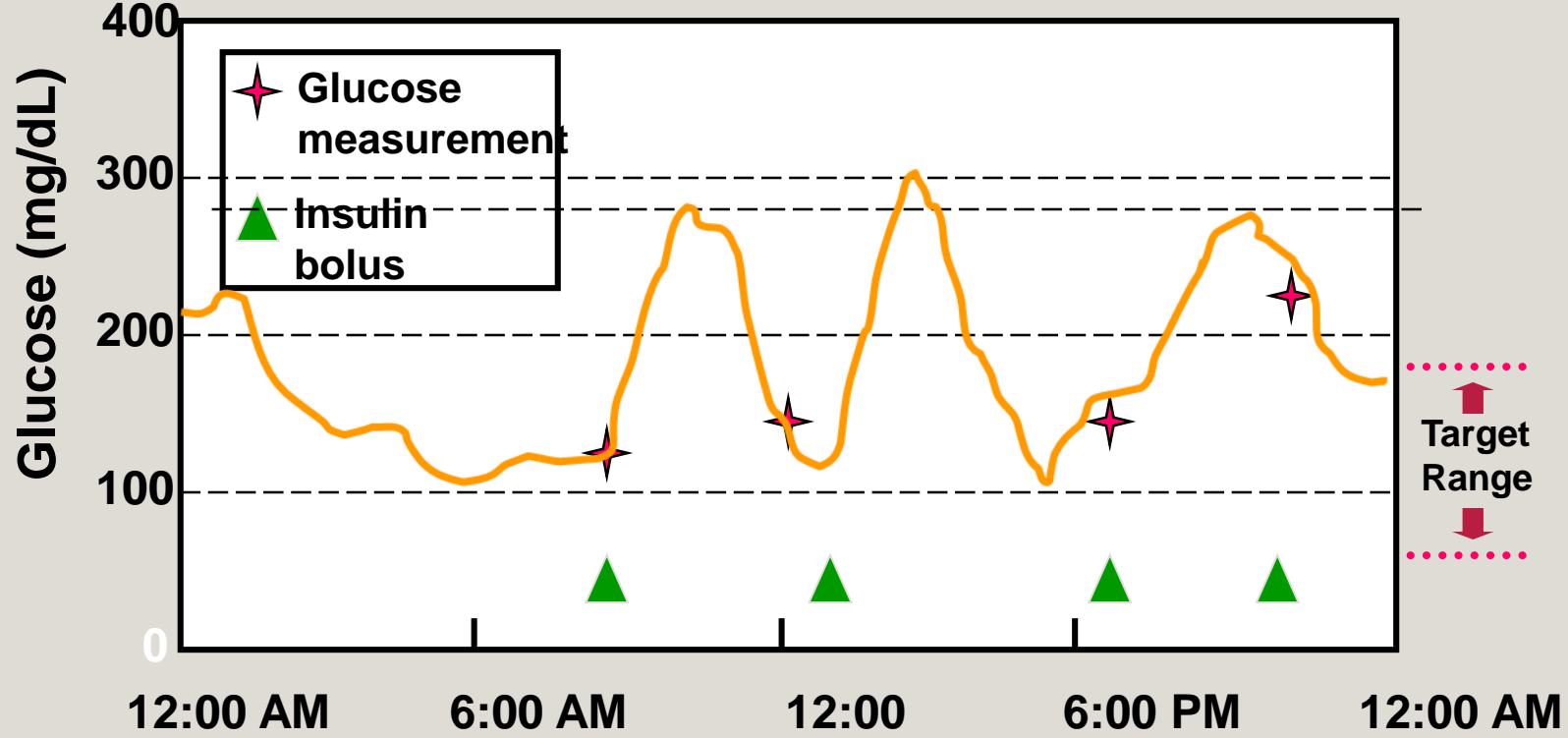
Paired tests—or 7 check in a week

	Fasting	Post Break-fast	Pre Lunch	Post Lunch	Pre Supper	Post Supper	Bed
Monday	X	X					
Tuesday							
Wed.			X	X			
Thurs.							
Friday					X	X	
Sat.							
Sunday							X

Testing 7 checks a week

	Fasting	Post Break-fast	Pre Lunch	Post Lunch	Pre Supper	Post Supper	Bed
Monday	X						
Tuesday		X					
Wed.			X				
Thurs.				X			
Friday					X		
Sat.						X	
Sunday							X

Fingerstick Blood Glucoses



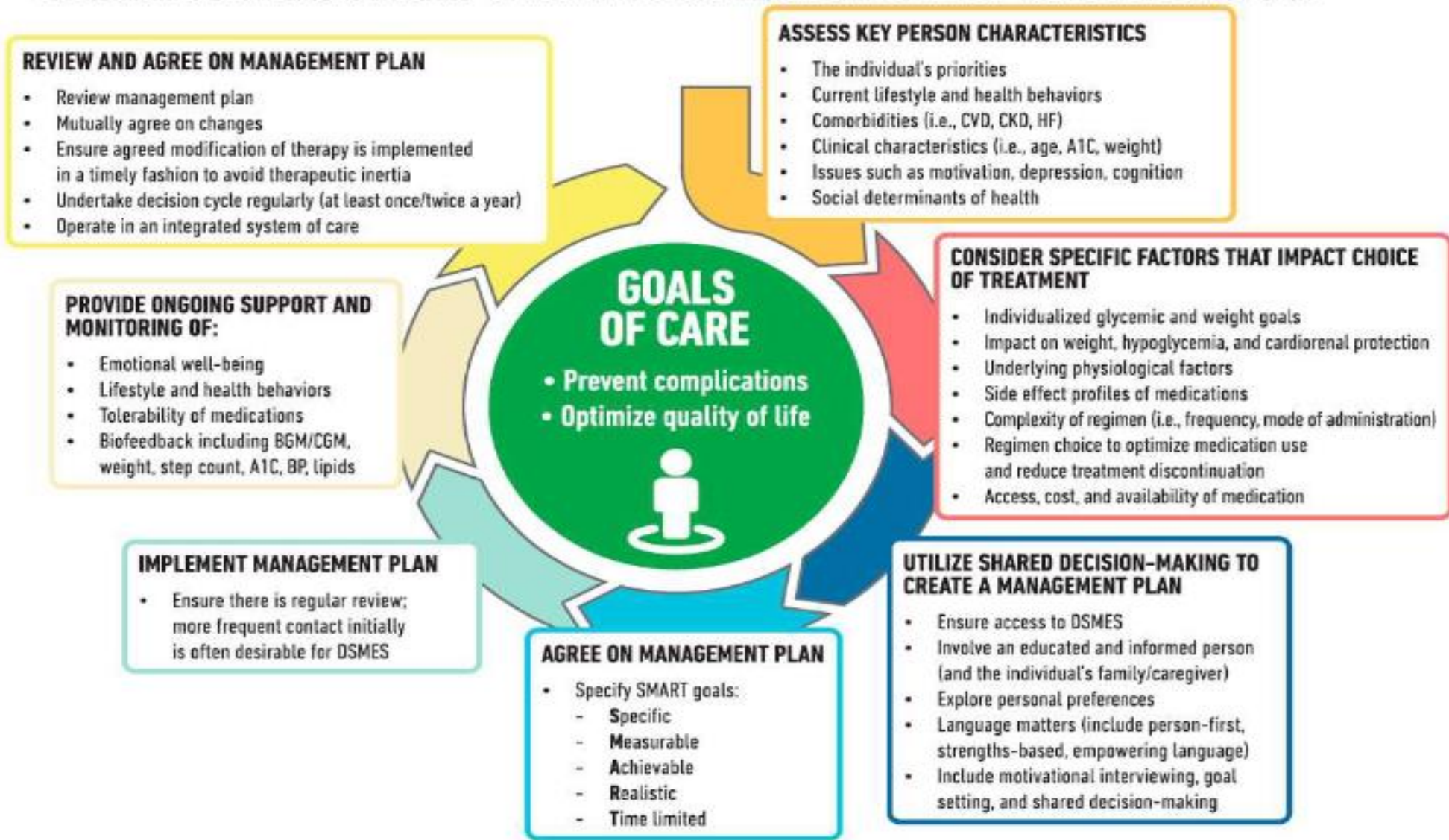
Diabetes Technology is here to STAY



**It's time to medically manage
the patient**

What do the guidelines say?

DECISION CYCLE FOR PERSON-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



WHAT IS THE CURRENT FOCUS FOR DIABETES CARE?

- Improving glycemic control
- Preventing Beta Cell failure
- Cardiometabolic health (*macrovascular*)
 - Weight (adiposity) reduction
 - Reducing NAFLD
 - Lipid & BP stabilization
 - Monitor for PAD
 - Monitor for hypothyroidism & other CMD risk
- Screening for & treatment of the “opathies” (*microvascular*)
 - Retinopathy
 - Nephropathy
 - Neuropathy (peripheral & autonomic)

Real focus on lifestyle:
dietary, activity, behaviors

Will better glycemic control help macro- & microvascular impairment?

GOALS FOR ADULTS WITH DIABETES

<u>Risks</u>	<u>Goals</u>	<u>Less stringent goals</u>
A1C	<7.0%	<8.0%
Blood Pressure	<140/90 mmHg	<140/90 mmHg
Cholesterol, non-HDL	<130 mg/dL	<160 mg/dL
Smoking, current	Nonsmoker	Nonsmoker
Percentage meeting all goals	18.2 (14.6–22.5)	35.8 (31.7–40.2)

GUIDELINES FOR THE “OPATHIES”

- **RETINOPATHY**
- Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes.
- People with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis.
- If there is no evidence of retinopathy for one or more annual eye exams and glycemia is well controlled, then screening every 1–2 years may be considered

GUIDELINES FOR THE “OPATHIES”

- **Nephropathy**
- *DM & DKD doubles the risk of CV mortality*
- *DKD increases the risk of hypoglycemia*
- Annual urinary albumin (spot urinary albumin-to-creatinine ratio UACR) and eGFR assessed in T1DM ≥ 5 years and in all people with T2DM regardless of treatment.
- In patients with established kidney disease do the above 1-4 x annually

What are the obvious & not so obvious problems with impaired renal function in DM?

Monitor nephropathy risk & progression

CKD is classified based on: <ul style="list-style-type: none"> • Cause (C) • GFR (G) • Albuminuria (A) 				Albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m ²) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

GUIDELINES FOR THE “OPATHIES”

- **Neuropathy**
- Everyone with DM should be assessed for peripheral neuropathy starting at diagnosis of T2DM & 5 years post diagnosis of T1DM and annually thereafter
- Assess for distal symmetric polyneuropathy: take careful history & assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function).
- If NO sensation—monitor for foot ulcers and fall risk.
- Monitor for signs of autonomic neuropathy as this will indicated an increased risk CVD and mortality

Tips for assessing peripheral neuropathy

Touch

Vibration

Temperature

Reflexes



COMPARING DISTAL DIABETES NEUROPATHIES

- **Large fiber**

- Deep seated pain
- Wasting & weakness
- Ataxia
- Numbness, tingling, pins & needles
- Impaired vibration sense
- Loss of proprioception
- Impaired nerve conduction, reflexes
- Risks of falls & injury

- **Small fiber**

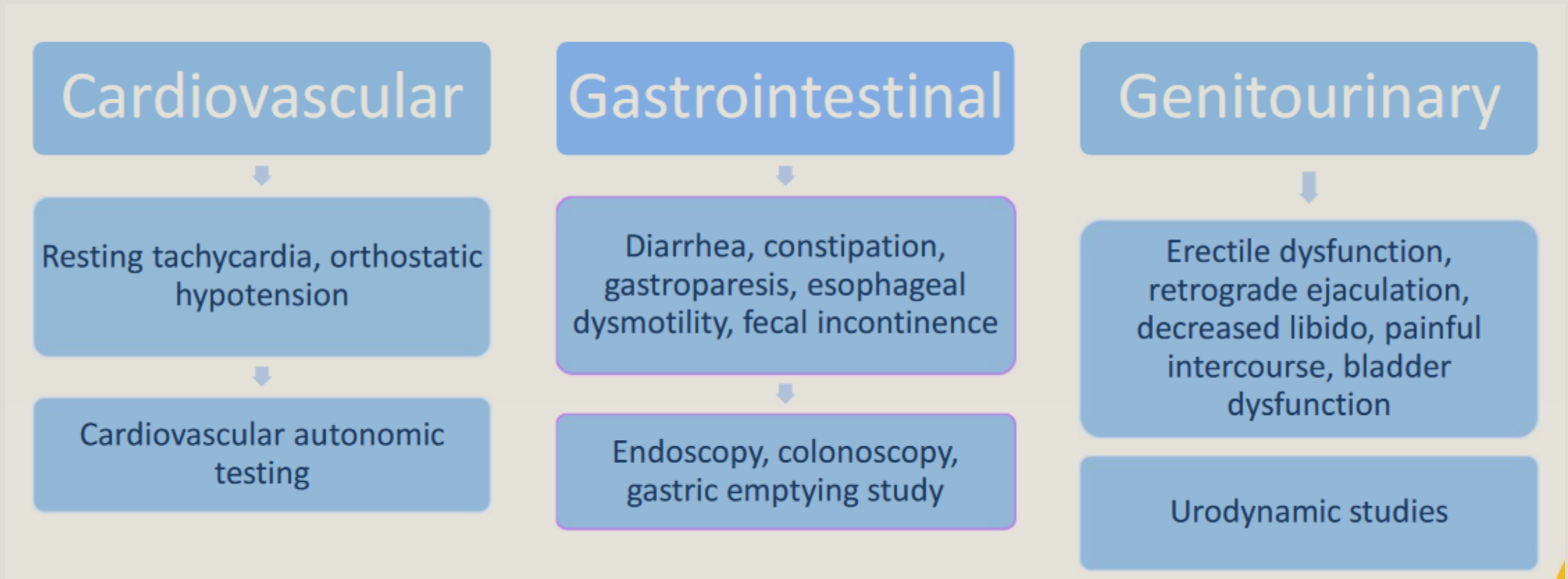
- Superficial (C-type) pain
- Electric shocks, burning sensation
- Autonomic dysfunction
- Thermal imperception
- Normal strength & reflexes
- Highly symptomatic—miserable
- Associated with increased morbidity & mortality

What's the worst finding?

Treatment options for peripheral neuropathy

Therapy Class	Drug Name	Precautions or contraindications
Gabapentinoids	Pregabalin, Gabapentin	Dizziness, somnolence, edema
Serotonin/Norepinephrine Reuptake Inhibitor	Duloxetine, Venlafaxine	Exacerbate restless leg syndrome, sexual dysfunction, dizziness, nausea, avoid with other serotonergic drugs
Central Acting Opioid Analgesics	Tapentadol & Tramadol	Beers Criteria,
Tricyclic Antidepressants	Amitriptyline, nortriptyline	Urinary retention, cardiac disease, avoid with other serotonergic drugs, Beers criteria
Sodium Channel Blockers	Lamotrigine, Lacosamide, Oxcarbazepine, Valproic acid	Blood dyscrasias, CNS effects, liver disease
Topical Analgesic	Capsaicin, Lidocaine patches	Local burning & irritation
Anti-seizure, antimanic	Carbamazepine, Oxcarbazepine	Liver disease, Beers criteria, Hematologic effects, cardiac disease
Nutritional Supplement, Antioxidant	Alpha Lipoic Acid	None listed

Autonomic Neuropathy– LOOK for it

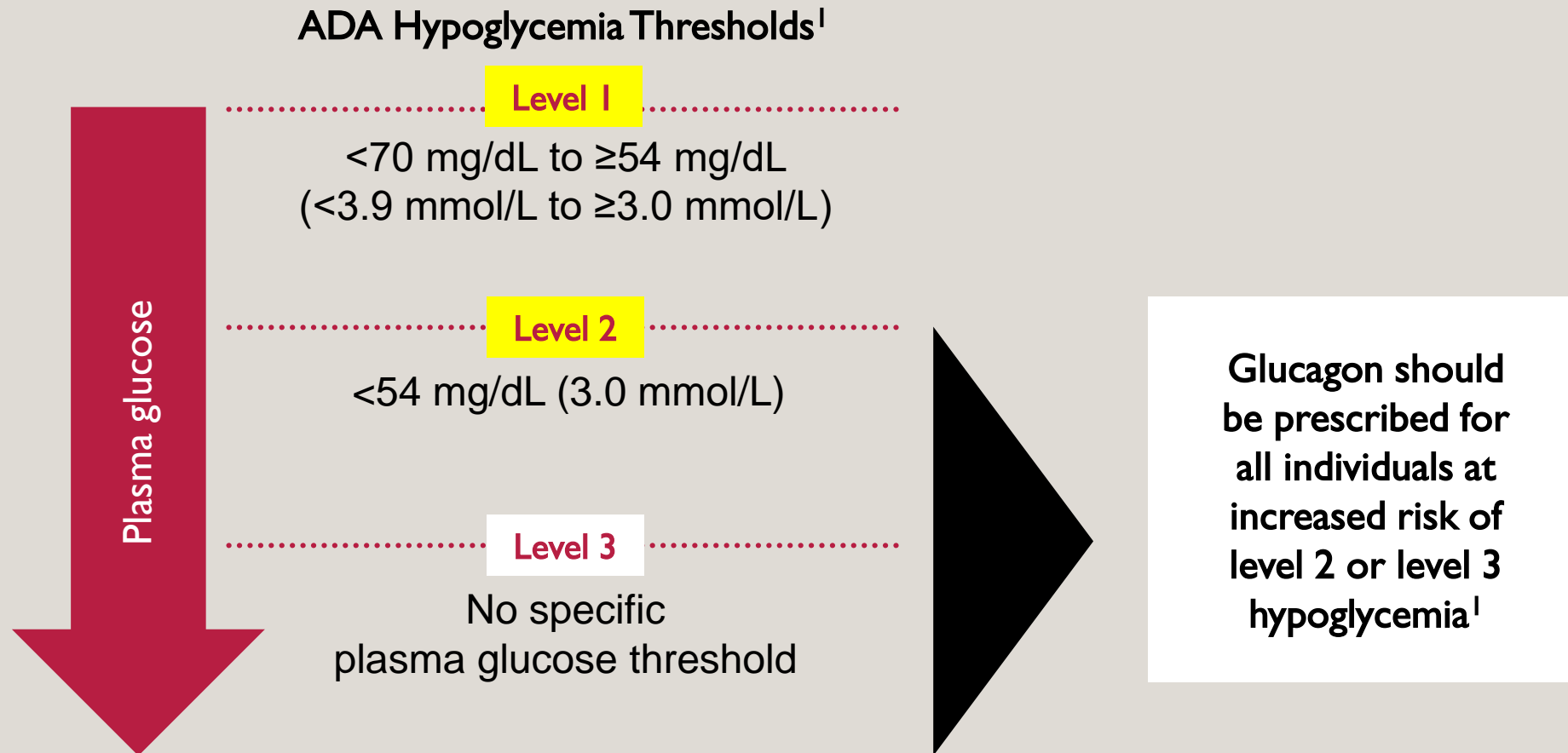


WHAT ABOUT HYPOGLYCEMIA RISK?

When sweet goes sour

Is your patient aware and prepared?

HYPOGLYCEMIA DIAGNOSTIC CRITERIA (PER ADA)



OCCURRENCES OF HYPOGLYCEMIA

T1DM: Pediatric incidence of symptomatic hypoglycemia (SH)

- Pediatric and adult patients receiving intensive insulin therapy have 3-fold higher risk
 - Pediatric pts average of 2 episodes of SH per week
 - 30% to 40% of adults experience SH, at an average of 1-3 episodes/year

T2DM adult patients:

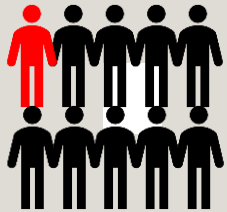
- **21%** of adult patients on insulin experience **SH** once annually
 - 50% have mild/moderate episodes, with 23 events per person-year

WHY IS HYPOGLYCEMIA BAD?!!

- Hypoglycemia is associated with adverse cardiovascular outcomes:
- Increased myocardial contractility, (increased O₂ requirements)
- Prolonged QT interval with dysrhythmias (*due to a rapid drop in serum potassium from increased circulating epinephrine and norepinephrine?*), Ischemic electrocardiogram changes and repolarization abnormalities,
- Angina, arrhythmias, increased inflammation, and sudden death
- Mechanisms for the poor outcome are not completely understood,
 - Likely d/ t increases in *pro-inflammatory cytokines* (TNF α , IL-1 β , IL-6, and IL-8), markers of lipid peroxidation,
 - And *acute endothelial dysfunction* with associated vasoconstriction, increased blood coagulability, cellular adhesion, and oxidative stress

THE SIGNIFICANCE OF SEVERE HYPOGLYCEMIA

Morbidity and mortality of SH are significant and can be barriers to adherence and intensification of diabetes treatments in patients with T1DM and T2DM.



Up to 1 out of every 10 **deaths** of patients with T1DM due to hypoglycemia¹

“Dead-in-bed” syndrome (up to 6% of deaths in patients with T1DM <40 years of age)⁴



Additional clinical consequences

- Increased risk for cardiovascular events
- Loss of consciousness or coma
- Seizures
- Impaired cognitive function
- Increased risk for more SH episodes
- Fear, depression & quality of life impairment

SH=severe hypoglycemia; T1DM=Type 1 diabetes mellitus; T2DM=Type 2 diabetes mellitus.

1. Cryer. *Diabetes Care*. 2012;35:1814-1816; 2. Weston et al. *Diabetes Manage*. 2012;2:233-241; 3. Gagnum et al. *Diabet Med*. 2017;34:56-63; 4. Secrest et al. *Diabet Med*. 2011;28:293-300; 5. Lee et al. *Diabetes Care*. 2020;43:2060-2065; 6. Morales et al. *Am J Med*. 2014;127:S17-S24; 7. Cryer. *N Engl J Med* 2013; 369:362-372; 8. American Diabetes Association. 6-Glycemic Targets: Standards of Medical Care in Diabetes 2020. *Diabetes Care*. 2020;43(Suppl 1):S66-S76; 9. American Diabetes Association. 5-Facilitating behavior change and wellbeing to improve health outcomes: Standards of Medical Care in Diabetes 2020. *Diabetes Care*. 2020;43(Suppl 1):S48-S65; 10. Ross. *Am J Med*. 2013;126(9 Suppl 1):S38-S48.

HYPOGLYCEMIA RISK MEDICATIONS & CONDITIONS

- warfarin
- quinine
- salicylates
- fibrates
- Sulfonamides (including co-trimoxazole)
- monoamine oxidase inhibitors
- NSAIDs
- probenecid
- somatostatin analogues
- selective serotonin reuptake inhibitors.
- loss of counter-regulatory hormone function, (e.g., Addison's disease, growth hormone deficiency, hypothyroidism, or hypopituitarism.)

MANIFESTATIONS OF HYPOGLYCEMIA

- Feeling shaky
- Being nervous or anxious
- Sweating, chills and clamminess
- Irritability or impatience
- Confusion
- Fast heartbeat
- Feeling lightheaded or dizzy
- Hunger
- Nausea
- Color draining from the skin (pallor)
- Feeling sleepy
- Feeling weak or having no energy
- Blurred/impaired vision
- Tingling or numbness in the lips, tongue or cheeks
- Headaches
- Coordination problems, clumsiness
- Nightmares or crying out during sleep
- Seizures

TREATMENT OF OUTPATIENT HYPOGLYCEMIA

- Prevention!
- Quick recognition of symptoms (neuronal starvation)
- Rapid-acting carbohydrate
- Glucagon

CARBOHYDRATE TREATMENT

- **Patient must be conscious and able to swallow!!!**
- The rule of 15: Administer approximately 15 g (or 20 g) of rapid-acting carbohydrate and check BG 10-15 minutes later
 - Repeat dose as needed x 3.
 - If sugars still low---need glucagon

FAST-ACTING CARBOHYDRATE POINTERS

- **Forms of rapid-acting carbs**
 - Sucrose & glucose best (tabs, syrup, drinks)
 - Is orange juice best?
 - What about chocolate or milk?
- **Amount of carbohydrates is best?**
 - Which is the most effective...10g, 15 g, or 20 g?
 - Should it be weight-dosed?
- **Time to resolution of symptoms**
 - If not resolved quickly it will lead to an even slower response with next dose
 - How soon should you really wait to recheck sugars....5 minutes?, 10 minutes? Longer?

GLUCAGON ADMINISTRATION

- Glucagon kits are reconstituted with the provided solution to a 1 mg/mL clear, particulate-free solution. The entire 1 mg (1 mL) is administered SC or IM
- Other formulations of glucagon (premixed injectable solutions and nasal sprays) have recently been developed
- **Reversal of hypoglycemia relies on sufficient hepatic glycogen stores and other factors. Patients normally respond within 15 minutes;**
- *Will Not work in those with alcohol toxicity (blunted glycogen response)*
- **ONLY USE ONCE—do not repeat (won't work)**
- **NEW glucagon pens and nasally-inhaled glucagon (Zegalogue, Gvoke, BAQSIMI)**

**So what pills, pokes and
potions do we have for
diabetes treatment?**

ORAL MEDICATIONS FOR DIABETES

Biguanides

*metformin

Sulfonylureas

*glipizide

*glyburide

*glimepiride

Thiazolidinediones (TZDs)

*pioglitazone (Actos)

rosiglitazone (Avandia)

GLP-1 agonists

semaglutide (Rybelsus)

DPP-4 Inhibitors

sitagliptin (Januvia)

saxagliptin (Onglyza)

linagliptin (Tradjenta)

alogliptin (Nesina)

SGLT 2 Inhibitors

dapagliflozin (Farxiga)

canagliflozin (Invokana)

empagliflozin (Jardiance)

ertugliflozin (Steglatro)

Bexagliflozin (Brenzavvy)

Meglinatides

*nateglinide (Starlix)

*repaglinide (Prandin)

Alpha-glucosidase inhibitors

*acarbose (Precose)

*miglitol (Glyset)

Bile acid sequestrants

*colesevelam (Welchol)

Dopamine agonist

bromocriptine (Cycloset ONLY)

* = generic available

INJECTABLE MEDICATIONS FOR DIABETES

GLP-1 agonist

liraglutide (Victoza)
dulaglutide (Trulicity)
exenatide ER (Bydureon, Bcise)
exenatide (Byetta)
Semaglutide (Ozempic)

GLP-1/GIP agonist

tirzapatide (Mounjaro)

Basal Insulin

insulin glargine u100*
(Lantus, Basaglar)
insulin detemir u100 (Levemir)
insulin glargine u300 (Toujeo)
insulin degludec u100 or u200
(Tresiba)

Rapid Acting Insulin

insulin glulisine (Apidra)
insulin lispro u100 or u200
(Humalog)
insulin lispro-aabc u100 or u200
(Lyumjev)
insulin aspart (Novolog, Fiasp)
insulin human inhaled (Afrezza)

Regular Insulin

insulin regular human u100
(Humulin R, Novolin R, Relion R)
Insulin regular human u500
(Humulin R u500)

Intermediate Insulin

Human insulin isophane, aka NPH
(Humulin N, Novolin N, Relion N)

Split mixes

Humulin 70/30 (70% NPH, 30% regular)
Novolin 70/30 (70% NPH, 30% regular)
Relion 70/30 (70% NPH, 30% regular)
Humalog 50/50 (lispro /lispro protamine)
Humalog 75/25 (75% lispro protamine, 25% lispro)

Mixed injectables – GLP1 and basal insulin

insulin degludec and liraglutide (Xultophy)
insulin glargine and lixisenatide (Soliqua)

Amylin mimetic

Pramlintide (Symlin)

*Indicates units per mL:
u100 = 100 units/mL,
u300 = 300 units/mL, etc.

**MORE ON WHY, HOW AND WHEN TO USE
THESE MEDICATIONS LATER!**

WHAT O-T-C SUPPLEMENTS OR FOOD MIGHT YOUR PATIENTS BE TAKING FOR DIABETES PREVENTION OR CONTROL?

Do they help?

- Cinnamon
- Chromium
- Vitamin B1
- Bitter Melon
- Alpha lipoic acid
- Aloe Vera
- Green tea
- Resveratrol
- Magnesium
- Others.....



Can we cure diabetes?



References

- American Diabetes Association. Standards of Care in Diabetes—2023. [Published: Jan 2023; Accessed: Apr 2023]
- Wei Perng, Rebecca Conway, Elizabeth Mayer-Davis, Dana Dabelea; Youth-Onset Type 2 Diabetes: The Epidemiology of an Awakening Epidemic. *Diabetes Care* 1 March 2023; 46 (3): 490–499.
- Khin PP, Lee JH, Jun H-S. Pancreatic Beta-cell Dysfunction in Type 2 Diabetes. *European Journal of Inflammation*. 2023;21
- Anandhanarayanan A, Teh K, Goonoo M, et al. Diabetic Neuropathies. [Updated 2022 Mar 15]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-.
- Ahmad R, AlLehaibi LH, AlSuwaidan HN, Alghiryafi AF, Almubarak LS, AlKhalifah KN, AlMubarak HJ, Alkhathami MA. Evaluation of clinical trials for natural products used in diabetes: An evidence-based systemic literature review. *Medicine (Baltimore)*. 2021 Apr 23;100(16):e25641
- Deyno S, Eneyew K, Seyfe S, et al. Efficacy and safety of cinnamon in type 2 diabetes mellitus and pre-diabetes patients: A meta-analysis and meta-regression. *Diabetes Res Clin Pract*. 2019 Oct;156:107815
- Sánchez M, González-Burgos E, Iglesias I, et al. Pharmacological Update Properties of Aloe Vera and its Major Active Constituents. *Molecules*. 2020 Mar 13;25(6):1324.
- Abraham et al. *Pediatr Diabetes*. 2018;19(Suppl. 27):178-192; 3. International Hypoglycaemia Study Group; *Diabetes Care*. 2015;38:1583-1591; 4. Edridge et al. *PloS ONE*. 2015;10:e0126427.

Time for a brain break



ckessler@maranatha.net