

The Different Faces of Diabetes – From Type 3 and Beyond



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Pronouns: She, her and hers Founder - www.DiabetesEd.net

Coach Bev has no Conflict of Interest

- ▶ She's not on any speaker's bureau.
- ▶ Does not invest or have any financial relationships with diabetes related companies.
- ▶ Gathers information from reading package inserts, research and articles.
- ▶ The ADA Standards of Medical Care is main resource for course content.

The Different Faces of Diabetes

Objectives:

1. Discuss the diagnosis and symptoms of the different types of diabetes beyond type 1 & 2.
2. Describe clinical manifestations of hypercortisolism, LADA type 3, type 3c, ketosis prone and type 5 diabetes.
3. Consider emotional impact.



Other Types of Diabetes

- ▶ Hypercortisolism
- ▶ LADA
- ▶ Ketosis Prone
- ▶ Type 3c
- ▶ Type 3
- ▶ Type 5



Beta-Cell Mass Loss

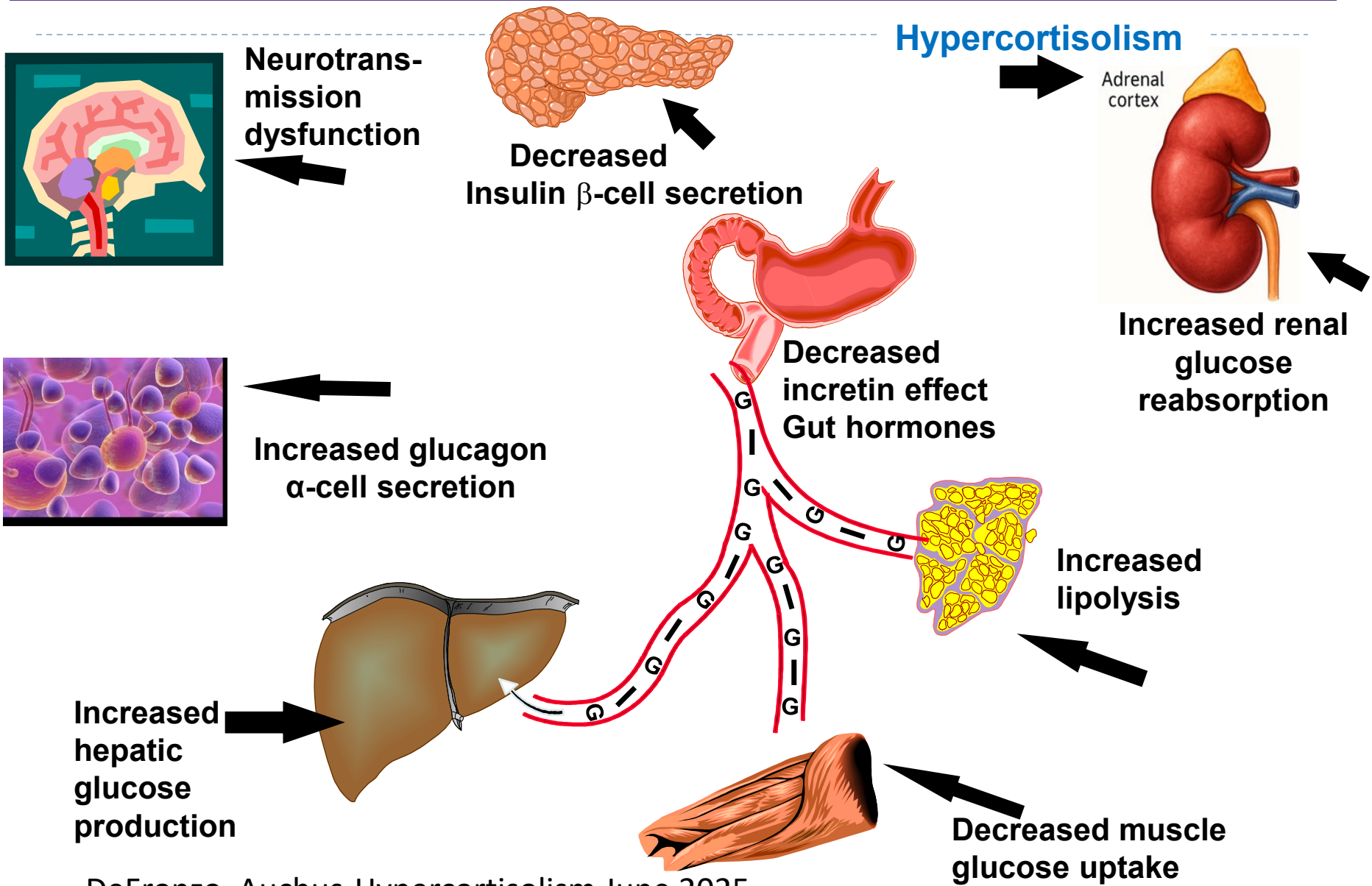
- ▶ In both type 1 and type 2 diabetes,
- ▶ *genetic and environmental factors can result in the progressive loss of β -cell mass and/or function*
- ▶ that manifests clinically as hyperglycemia.
- ▶ Once hyperglycemia occurs, people with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ.



2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025 **FREE**

American Diabetes Association Professional Practice Committee

The Noxious Nine – Pathophysiology T2D



POLL Question #1

- ▶ AJ is a 52-year-old with type 2 diabetes presents with worsening hyperglycemia despite taking three diabetes medications. AJ says, “No matter what I do, I can’t seem to get my blood sugars down”.
- ▶ Which of the following clusters of physical findings would increase your suspicion that AJ is struggling with hypercortisolism?
 - A. Dorsocervical fat pad, wide purple striae and bruising.
 - B. Peripheral muscle hypertrophy, thick hair growth, and flushed skin.
 - C. Weight loss, skin hyperpigmentation, and generalized muscle wasting.
 - D. Pallor, brittle nails, and spoon-shaped fingernails.

Signs of Hypercortisolism



▶ Other signs

- ▶ High blood pressure,
- ▶ Hyperglycemia
- ▶ Visceral adiposity
- ▶ Bone loss, fractures
- ▶ muscle weakness,
- ▶ excessive hair growth,
- ▶ acne,
- ▶ mood changes like irritability and depression.

Hypothalamus → CRH → Pituitary → ACTH → Adrenal → Cortisol

- ▶ Cortisol effects: gluconeogenesis, insulin resistance, fat redistribution

CATALYST Study Findings

- ▶ Findings from the CATALYST study, the largest prospective trial of its kind, suggest that hypercortisolism may be a significant contributing factor in as many as one in four patients with difficult-to-control type 2 diabetes.

CATALYST Study: Hypercortisolism & Difficult-to-Control Type 2 Diabetes

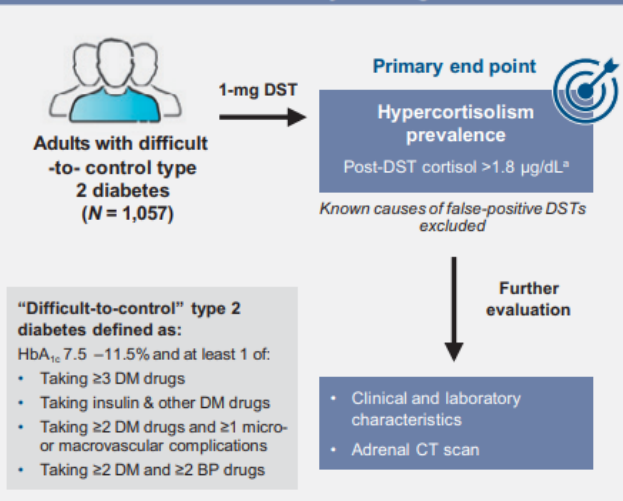
- ▶ **Study Design Overview** Prospective observational screening of ~1,000 adults with HbA1c 7.5–11.5%, on multiple antihyperglycemic agents.
- ▶ Screening tool: Overnight 1 mg dexamethasone suppression test (DST).
- ▶ Hypercortisolism defined as post-DST cortisol >1.8 $\mu\text{g}/\text{dL}$ with adequate dexamethasone levels.

Study Design & Prevalence

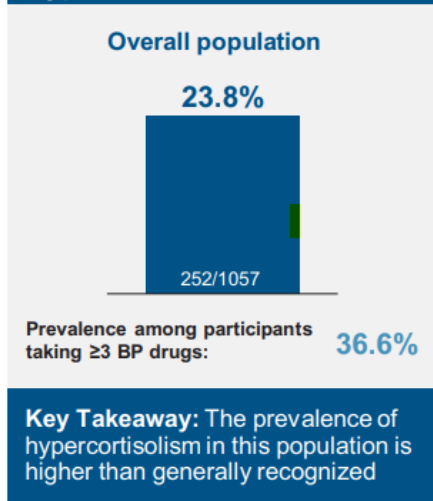


Prevalence of hypercortisolism in patients with difficult-to-control type 2 diabetes

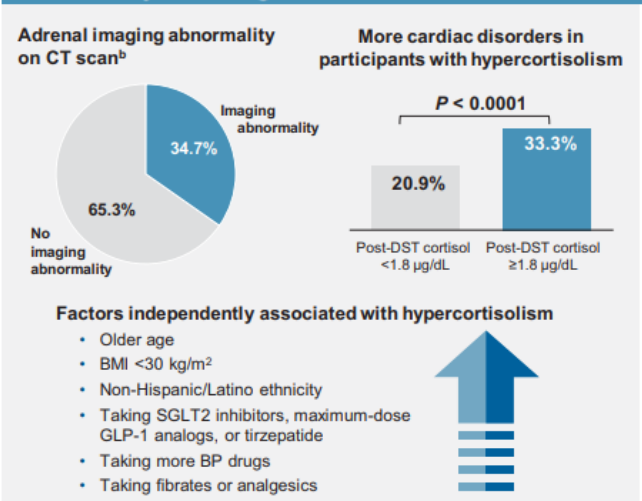
CATALYST Part 1 Study Design (NCT05772169)



Hypercortisolism Prevalence



Other Key Findings



^aWith dexamethasone ≥140 ng/dL. ^bIn patients with hypercortisolism. BP, blood pressure; CT, computed tomography; DM drug, glucose-lowering drug; DST, dexamethasone suppression test; GLP-1, glucagon-like peptide 1.

Findings

- ▶ 23.8% of study participants had hypercortisolism
- ▶ Prevalence 36.6% in those on ≥3 antihypertensives
- ▶ 34.7% adrenal abnormalities on CT

ORIGINAL ARTICLE | APRIL 18 2025

Prevalence of Hypercortisolism in Difficult-to-Control Type 2 Diabetes **FREE**

John B. Buse ; Steven E. Kahn ; Vanita R. Aroda ; Richard J. Auchus; Timothy Bailey; Irina Bancos; Robert S. Busch; Elena A. Christofides ; Ralph A. DeFronzo ; Bradley Eilerman ; James W. Findling; Vivian Fonseca ; Oksana Hamidi; Yehuda Handelsman ; Harold J. Miller; Jonathan G. Ownby; John C. Parker; Athena Phills-Tsimikas; Richard Pratley; Julio Rosenstock ; Michael H. Shanik; Lance L. Sloan; Guillermo Umperrez ; Iulia Cristina Tudor; Tina K. Schlatky ; Daniel Einhorn; CATALYST Investigators

Study Design – Part 2 (Intervention)

Randomized,
double-blind,
placebo-controlled
intervention

N = 136 participants
with confirmed
hypercortisolism

Mifepristone: 300
mg daily escalating
up to 900 mg over
24 weeks

Primary endpoint:
HbA1c reduction;
Secondary: weight,
meds, safety.

Mifepristone is a
glucocorticoid
(cortisol) receptor
Antagonist.

10% experience
adverse side effects
from glucocorticoid
withdraw.

SE's include:
fatigue, N/V,
hypokalemia,
edema, HTN

CATALYST Treatment Outcomes



Inadequately Controlled Type 2 Diabetes and Hypercortisolism: Improved Glycemia With Mifepristone Treatment

CATALYST Treatment Phase: A Randomized, Placebo-Controlled Study

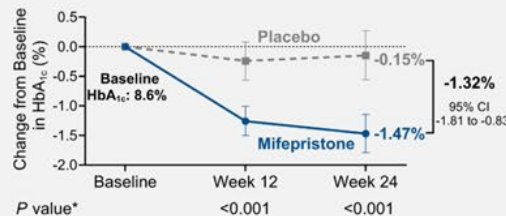
Adults with inadequately controlled T2D & hypercortisolism (based on a DST)



Primary End point:
Change in HbA_{1c} from baseline to week 24

NCT05772169; randomized 2:1, stratified by adrenal imaging abnormality (yes/no)

Primary End Point Met: Mifepristone Improved HbA_{1c}



- Similar effect on HbA_{1c} seen in participants with and without adrenal imaging abnormality

Key Takeaway: In individuals with inadequately controlled T2D and hypercortisolism, treatment with mifepristone may reduce HbA_{1c}.

Other Key Findings

Improvements in glycemic control with mifepristone were accompanied by reductions in:



glucose-lowering medications

(e.g., insulin, sulfonylureas)



Body weight

(-4.4 kg; 95% CI -6.28 to -2.53)



BMI and waist circumference

(-1.5 kg/m² and -5.2 cm; 95% CIs -2.10 to -0.84 and 7.25 to -3.21, respectively)

Safety:

- Adverse events were manageable and consistent with mifepristone's known safety profile
- Adverse events occurring in >10% of participants treated with mifepristone: hypokalemia, fatigue, nausea, vomiting, headache, peripheral edema, diarrhea, and dizziness
- Increases in blood pressure also occurred



Mifepristone significantly improves glycemic control and weight
Next steps: broader screening, novel cortisol-targeted therapies, long-term outcomes.

ORIGINAL ARTICLE | JUNE 23 2025

Inadequately Controlled Type 2 Diabetes and Hypercortisolism: Improved Glycemia With Mifepristone Treatment **FREE**

Ralph A. DeFronzo, Vivian Fonseca, Vanita R. Aroda, Richard J. Auchus, Timothy Bailey, Irina Bancos, Robert S. Busch, John B. Buse, Elena A. Christofides, Bradley Eilerman, James W. Findling, Yehuda Handelsman, Steven E. Kahn, Harold J. Miller, Jonathan G. Owenby, John C. Parker, Athena Phillis-Tsimikas, Richard Pratley, Julio Rosenstock, Michael H. Shank, Lance A. Sloan, Guillermo Umperrez, Samir Shambharkar, Iulia Cristina Tudor, Tina K. Schlaify, Daniel Einhorn; CATALYST Investigators



A1c ↓ ~1.5% vs. 0.2% in placebo group



Weight ↓ ~10 pounds;
waist circumference ↓ ~2 inches



Many reduced or stopped other diabetes meds, including insulin.

Intervention Outcomes

Adverse events mostly mild to moderate (glucocorticoid withdrawal symptoms).

Hypokalemia observed; manageable clinically.

Discontinuation ~40%, mostly due to tolerability issues.

Question: How realistic is this to implement in primary care / Endo settings?

Hypercortisolism in Type 2

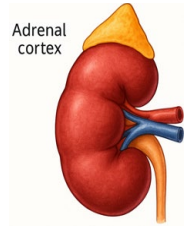
Cortisol increases gluconeogenesis in the liver

Reduces peripheral glucose uptake → insulin resistance

Stimulates protein catabolism and lipolysis

Chronic cortisol elevation → persistent hyperglycemia

- ▶ Can lead to “Difficult to Control Type 2 Diabetes”
- ▶ CATALYST study revealed about 24% of people with elevated BG despite meds, may be due to hypercortisolism.
- ▶ Treatment with mifepristone decreased weight, waistline, BG.



What type of Diabetes?

- ▶ 72 Years old
- ▶ A1c 3 months prior 6.2%
- ▶ A1c now 13.9%
- ▶ BMI 24.5
- ▶ Lost about 10 pounds over last month



What about Latent Autoimmunity Diabetes in Adults (LADA)

- ▶ Slowly progressive autoimmune diabetes with an adult onset should be termed:
 - ▶ LADA or type 1 diabetes.
 - ▶ Slow autoimmune β -cell destruction can lead to a long duration of marginal insulin secretory capacity.
 - ▶ For this classification, all forms of diabetes mediated by autoimmune β -cell destruction independent of age of onset are included under the rubric of type 1 diabetes.



2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025 FREE
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Latent Autoimmunity Diabetes in Adults (LADA)

- ▶ Antibody positive to 1-2 of below
 - ▶ GAD-65 autoantibodies
 - ▶ Insulin Autoantibodies
 - ▶ Islet Cell antigen-2
 - ▶ ZnT8
- ▶ Adult Age at onset
- ▶ Usually benefit from insulin w/in first 6 months of diagnosis
- ▶ Early insulin therapy may preserve beta cell function



Latent Autoimmune Diabetes

Venkatraman Rajkumar; Steven N. Levine.

▶ [Author Information and Affiliations](#)

Last Update: June 21, 2022.

Diabetes Care 26:536-538, 2003

Jerry P. Palmer, MD and Irl B. Hirsch, MD

LADA Clinical Features Compared to Type 2

<u>Feature</u>	<u>LADA</u>	<u>Type 2</u>
▶ Age <50	63%	19%
▶ Acute hyperglycemia	66	24
▶ BMI < 25	33	13
▶ Hx of autoimmune dx	27	12
▶ Family hx autoimmune	46	35

Latent Autoimmune Diabetes

Venkatraman Rajkumar; Steven N. Levine.

Practical Diabetology March 08, Unger MD

▶ [Author Information and Affiliations](#)

Last Update: June 21, 2022.

What kind of Diabetes?

- ▶ 58 yr old, states she has had type 1 diabetes for 18 years. Quit smoking a year ago and gained about 20 lbs. BMI 25.
- ▶ Meds
 - ▶ Humalog 18-23 units before each meal
 - ▶ Glargine 28 units at bedtime
 - ▶ Metformin 500mg TID
- ▶ What tests would you recommend?



**25% of ind's
with Type 1
also have
type 2
diabetes.**

ADA Post Grad, 2010

Type 1 & Type 2 - Double Diabetes?

- ▶ May be appropriate to recognize a person with type 1 diabetes *and* features classically associated with type 2 diabetes (e.g., insulin resistance, obesity, and other metabolic abnormalities).
- ▶ Can help facilitate access to appropriate treatment:
 - ▶ (e.g., GLP-1 RA or SGLT-2 inhibitor therapies for potential weight and other cardiometabolic benefits) and monitoring systems.



2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025 CREB

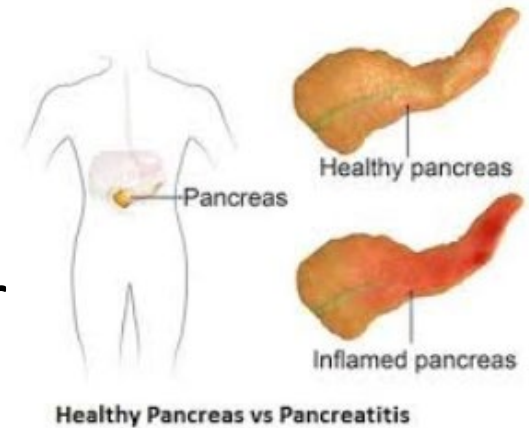
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Type 3c Diabetes (Pancreatogenic)

- ▶ Includes both structural and functional loss of insulin secretion in the context of exocrine pancreatic dysfunction.
- ▶ About 5-10% of diabetes, often misdiagnosed as type 2 diabetes.
- ▶ The diverse set of etiologies includes:
 - ▶ pancreatitis (acute and chronic) ~70%
 - ▶ trauma or pancreatectomy
 - ▶ neoplasia
 - ▶ cystic fibrosis
 - ▶ hemochromatosis
 - ▶ fibrocalculous pancreatopathy
 - ▶ rare genetic disorders, and idiopathic

Pancreatitis

- ▶ People with diabetes 2xs risk of acute pancreatitis
- ▶ After episode of pancreatitis, one third of people will get prediabetes or diabetes
 - ▶ About 25% to 80% of people with chronic pancreatitis develop Type 3c diabetes.
- ▶ Pancreatitis is an exocrine dysfunction:
 - ▶ Disrupts global architecture or physiology of pancreas
 - ▶ Results in both exocrine and endocrine dysfunction.

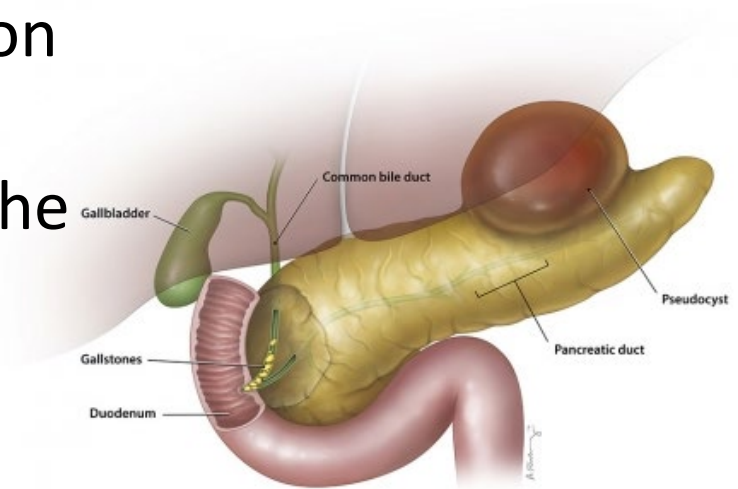


2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025 [PDF](#)

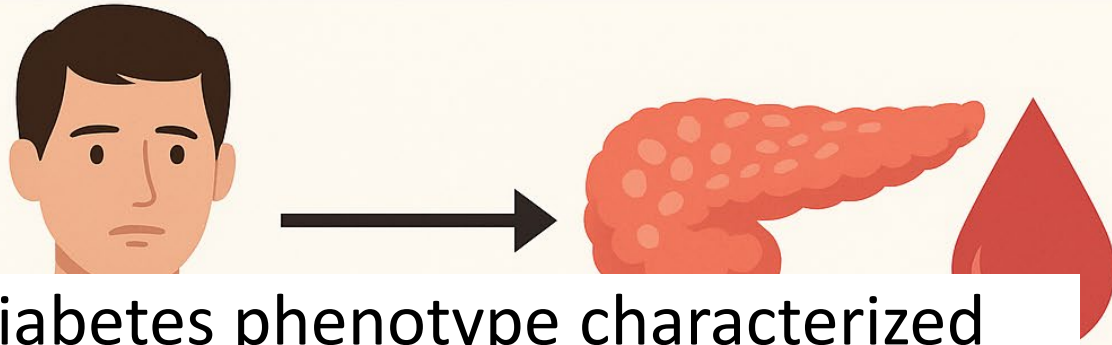
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Pancreatitis

- ▶ Pancreatitis caused by digestion of the organ from pancreatic enzymes normally carried to the SI through pancreatic duct.
- ▶ Detected through elevated Amylase levels & pain
- ▶ Causes:
 - ▶ HIV meds and other meds
 - ▶ Alcohol ingestion
 - ▶ Gallstones blocking pancreatic enzyme flow to small intestine
 - ▶ Elevated triglycerides
 - ▶ Cancer, injury and other



KETOSIS-PRONE DIABETES



- ▶ A unique diabetes phenotype characterized by diabetic ketoacidosis (DKA) at onset, without autoimmune markers or obesity.
- ▶ Transient insulin deficiency with preserved or recoverable beta-cell function
- ▶ Can resemble type 1 or type 2 diabetes
- ▶ Often in non-obese individuals
- ▶ More common in Black, Hispanic, and Asian populations

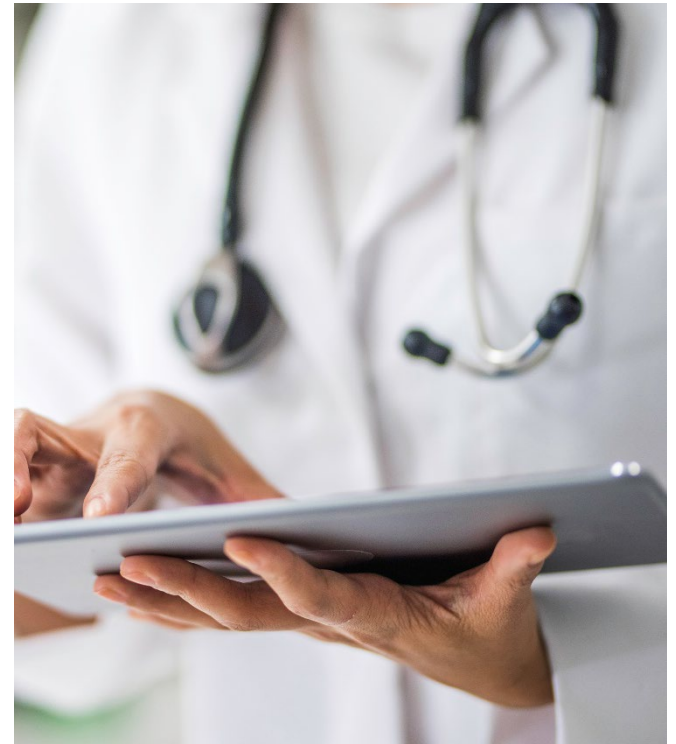
NE

odes

Ketosis-Prone Diabetes (KPD)

Presentation & Future

- ▶ Present with DKA
- ▶ Negative for islet cell autoantibodies (GAD, IA-2)
- ▶ C-peptide testing post-recovery to assess insulin production
- ▶ Insulin often tapered or discontinued
- ▶ Transition to oral agents in some cases
- ▶ Requires ongoing monitoring for recurrence of ketosis

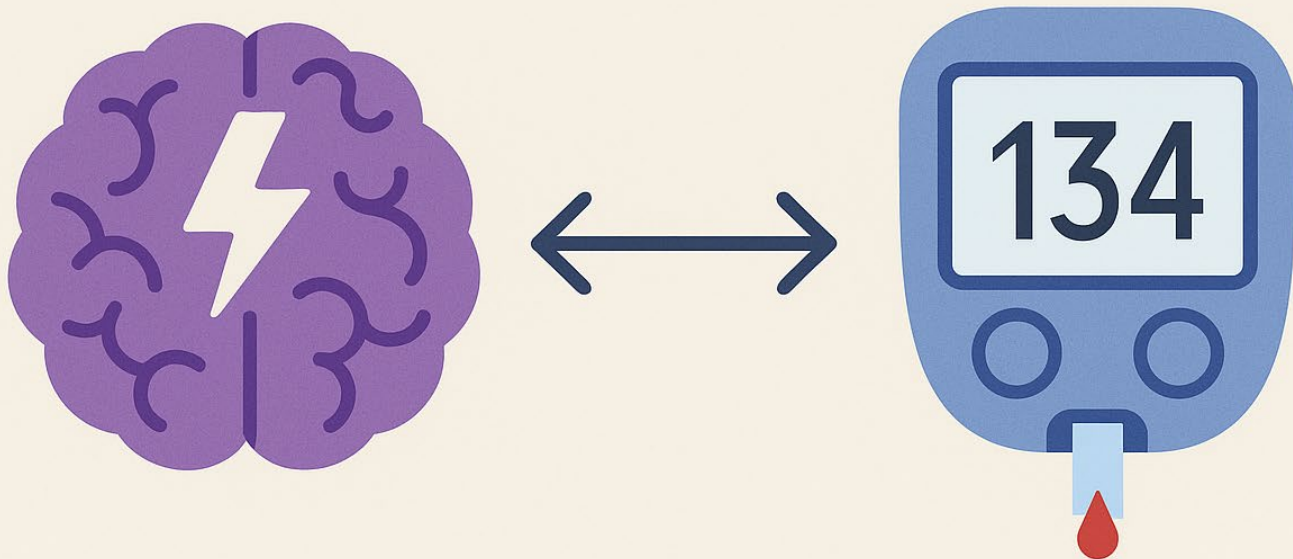


Regardless of the cause, hyperglycemia needs to be treated.



Diabetes Type 3

TYPE 3 DIABETES



The link between insulin resistance
and neurodegeneration

What is 'Type 3 Diabetes'?

- ▶ A term linking Alzheimer's disease to insulin resistance in the brain.
- ▶ Not an official diagnostic category.
- ▶ Still an emerging field with ongoing studies
- ▶ Suggests that Alzheimer's may be a form of brain-specific diabetes.

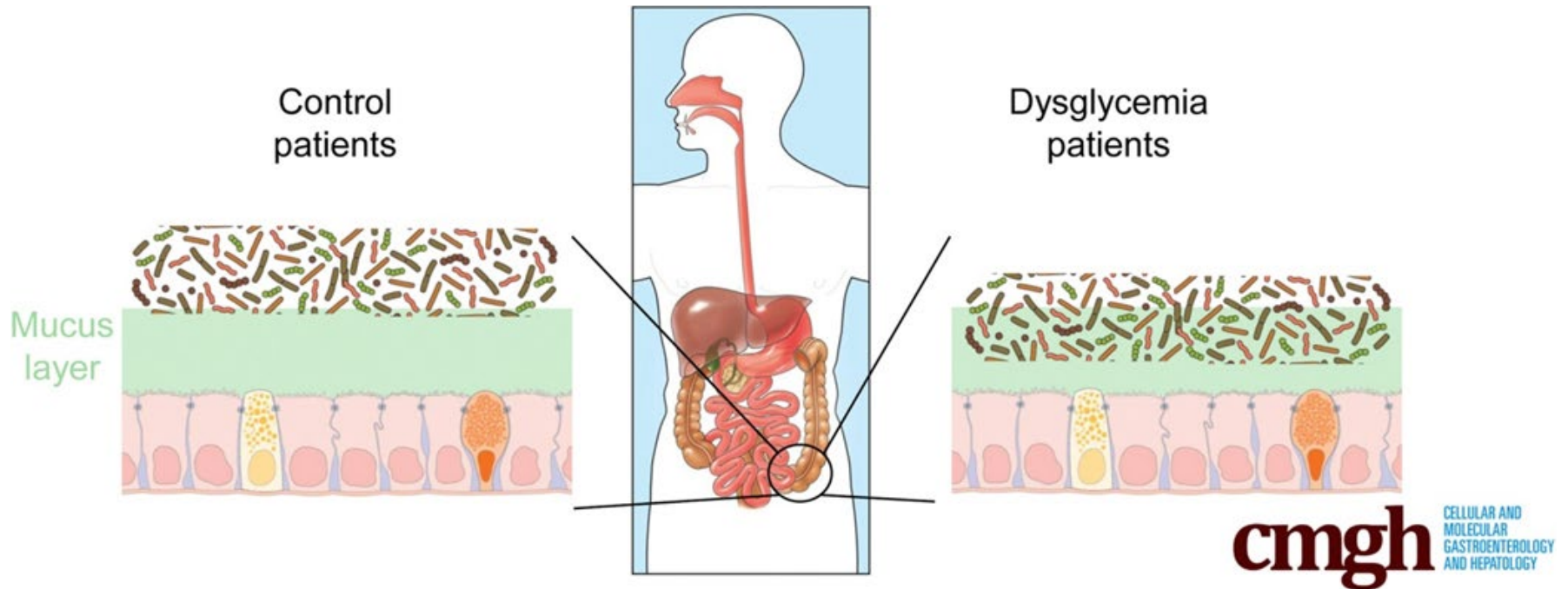


▶ [Int J Mol Sci. 2020 Apr 30;21\(9\):3165. doi: 10.3390/ijms21093165](https://doi.org/10.3390/ijms21093165)

Alzheimer's & Diabetes Link

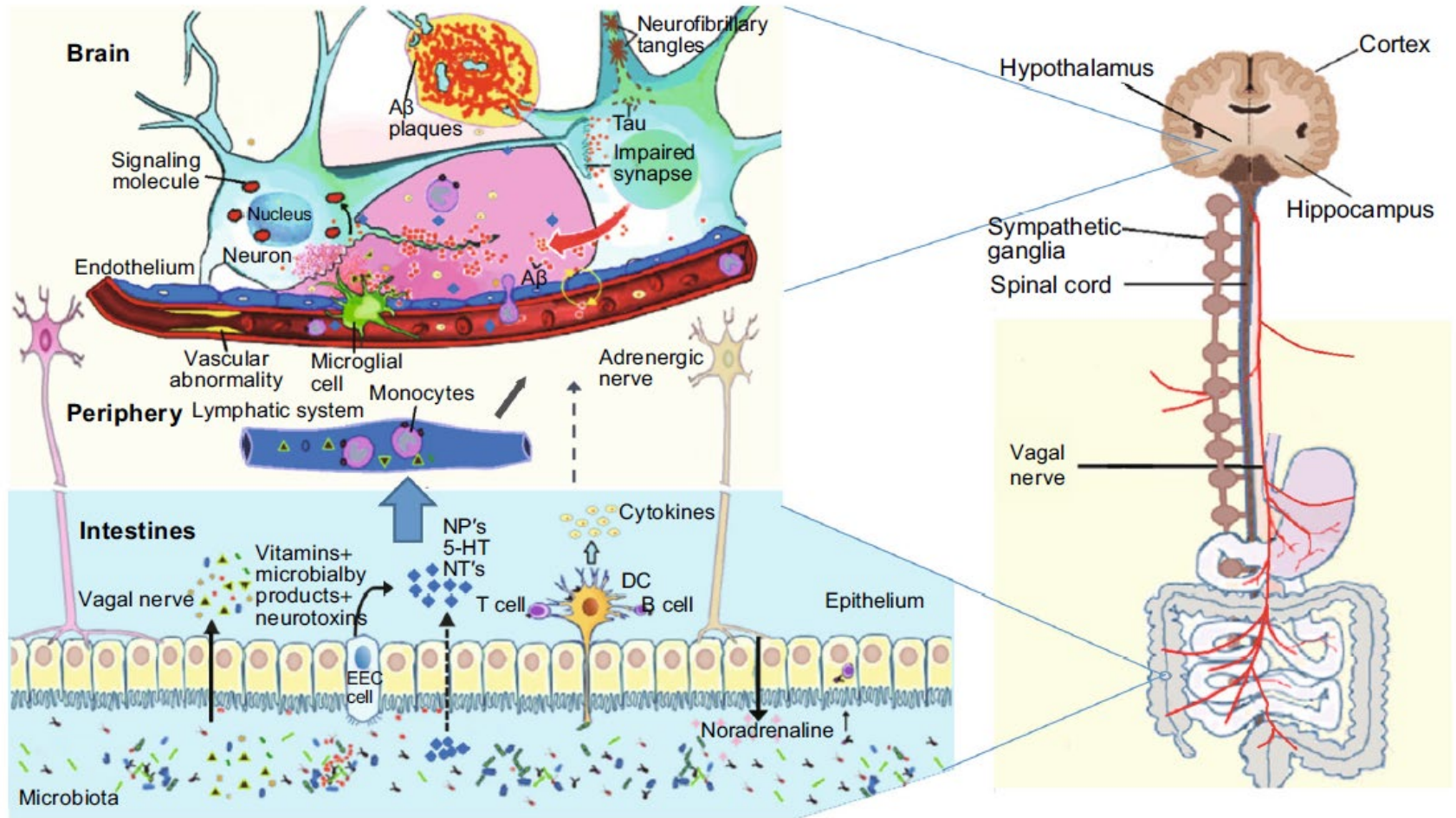
- ▶ Type 2 Diabetes increases Alzheimer's risk by 60–80%
- ▶ Reduced insulin receptors in brains of people with Alzheimer's
- ▶ Insulin signaling is crucial for clearing amyloid beta plaques from brain.
- ▶ The brain uses insulin for memory and learning-neuromodulator.
- ▶ Insulin resistance contributes to cognitive decline.
- ▶ Amyloid beta plaques and tau tangles are influenced by insulin signaling and availability.
- ▶ Lead to neurodegeneration.

Colonic Microbiota Encroachment Correlates With Dysglycemia in Humans



*Benoit Chassaing, Shreya M. Raja, James D. Lewis, Shanthi Srinivasan, Andrew T. Gewirtz
Cellular and Molecular Gastroenterology and Hepatology (September 2017)*

Link Between Gut and Brain



*Benoit Chassaing, Shreya M. Raja, James D. Lewis, Shanthi Srinivasan, Andrew T. Gewirtz
Cellular and Molecular Gastroenterology and Hepatology (September 2017)*

Potential Interventions

- ▶ Lifestyle: Mediterranean diet, physical activity.
- ▶ Optimize glucose and blood pressure.
- ▶ Investigational: Intranasal insulin, GLP-1 agonists
- ▶ Reduce systemic inflammation.
- ▶ Improved nutrition and gut health.





'Type 3 Diabetes' reflects the link between metabolic and brain health

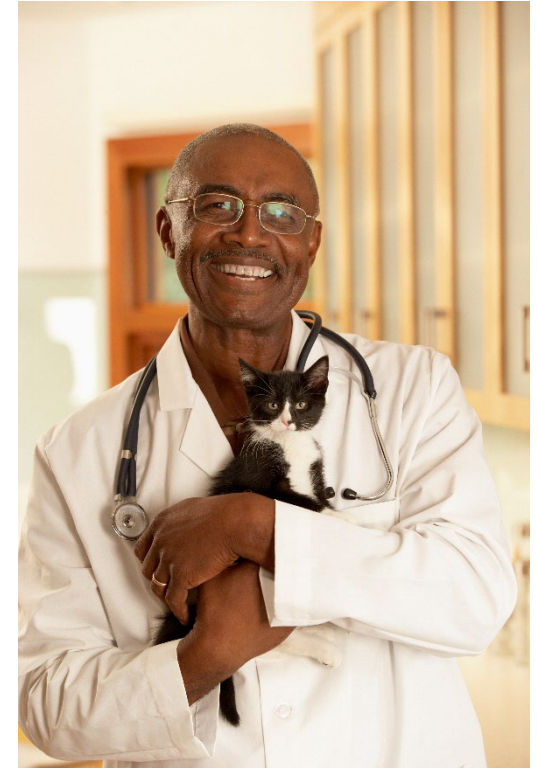


Early intervention can support cognitive function



Encourages whole-person, compassionate care

Summary



Type 5 Diabetes

- ▶ Form of diabetes linked to chronic malnutrition or prolonged starvation
- ▶ This condition primarily affects young, undernourished individuals in low- and middle-income countries, particularly in regions like Asia and Africa.
- ▶ Estimates suggest that up to 25 million people worldwide may be affected with type 5 diabetes.

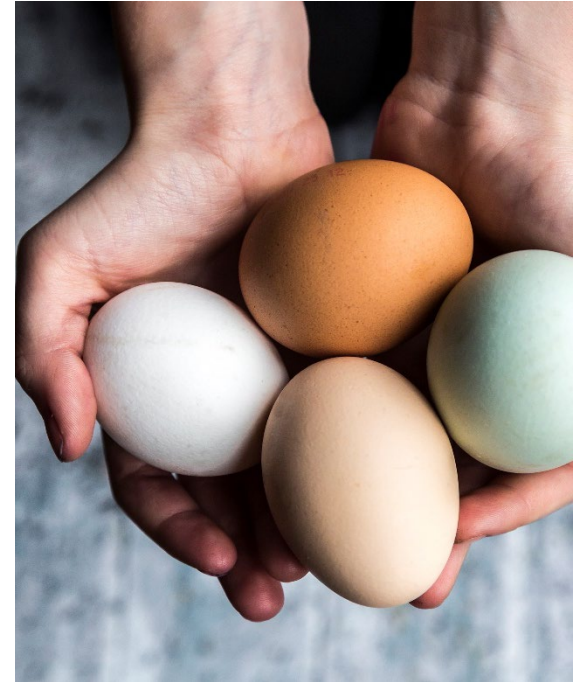
- ▶ Mechanism:
 - ▶ Severe beta-cell dysfunction from malnutrition
 - ▶ Impaired insulin secretion (not autoimmune)
 - ▶ May present with hyperglycemia & ketosis
 - ▶ Genetic component



<https://idf.org/news/new-type-5-diabetes-working-group/>

Features and Management

- ▶ Typical features:
 - ▶ Onset in adolescents/young adults
 - ▶ History of prolonged malnutrition
 - ▶ Thin body habitus with muscle wasting
 - ▶ Hyperglycemia + recurrent ketosis, but not autoimmune
- ▶ Management:
 - ▶ High-protein, low-carbohydrate diet
 - ▶ Micronutrient supplementation
 - ▶ Careful monitoring of insulin therapy, as inappropriate insulin administration can be harmful.
- ▶ Improving nutrition and addressing poverty/food insecurity are central to treatment.



Diabetes Admit for Hyperglycemia

- ▶ John is admitted for hyperglycemia because he stopped taking his diabetes meds.
- ▶ HCP says, “Don’t you realize you are going to get complications, like kidney disease or amputation if you don’t take your medications?”
- ▶ Door Closed – No Connection made

How Does John Feel?

- ▶ Embarrassed
- ▶ Ashamed
- ▶ Defeated
- ▶ Angry
- ▶ Unheard



How does HCP feel?

- ▶ Frustrated
- ▶ Defeated
- ▶ Worried

Diabetes Visit – Let's Go *through*

A small adjustment can make a **BIG** Difference

- ▶ HCP says, “John, I am worried about you and your elevated blood glucose. Can you share what is going on in your life?”
- ▶ Door Open – Connection made

How Does John Feel?

- ▶ Heard & Seen
- ▶ Recognized
- ▶ Connected
- ▶ Engaged

How does the HCP feel?

- ▶ Connected
- ▶ Concerned
- ▶ Collaborative





Missed Appointments due to Stigma and Shame

A recent survey of over 2,600 people with diabetes across eight countries revealed that nearly 40% of missed doctor's appointments are due to stigma or shame.

Create a Judgement Free Zone – Roll out the Carpet of Acceptance

There are no bad or good blood glucose numbers.

There is no such thing as cheating.
You are not failing at your diabetes.
It is not your fault you have diabetes.
Thank you for showing up today.



Embark Trial – Emotions as Priority

I have finally given myself permission to make addressing the emotional aspects of diabetes a priority.

~Coach Beverly



Commit to Listening at least Half of the Time



Diabetes is Complex

- ▶ Goal – achieve well being and negotiated outcomes
- ▶ Social Drivers of Health:
 - ▶ Environmental
 - ▶ Social
 - ▶ Behavioral
 - ▶ Emotional
- ▶ Keep it person centered while integrating care into daily life
 - ▶ Consider the individual



Thank You



- ▶ Questions?
- ▶ Email:
info@diabetesed.net
- ▶ Web: www.diabetesed.net
- ▶ Phone 530-893-8635

