HYPERTENSION AND HYPERGLYCEMIA: TWIN SISTERS MASQUERADING AS CUSHING SYNDROME

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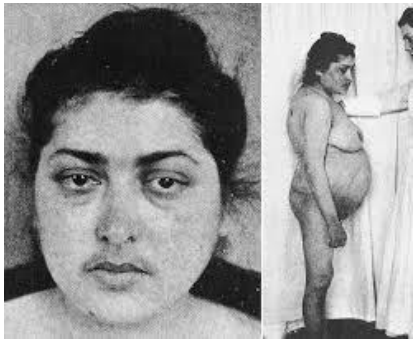
SOME PATIENTS WITH HYPERCORTISOLISM PRESENT WITH CLASSIC PHENOTYPIC FEATURES OF CUSHING SYNDROME[1,2]

- Easy bruising
- Facial plethora
- Proximal myopathy (or proximal muscle weakness)
- Striae (especially of reddish purple and >1 cm wide)
- Dorsocervical fat pad (“buffalo hump”)
- Facial fullness
- Obesity
- Supraclavicular fullness
- Acne
- Hirsutism



Original publication: Bulletin of the Johns Hopkins Hospital, 1932. Reprint: *Obes Res*, 1994. Accessed November 21, 2022. doi:10.1002/j.1550-8528.1994.tb00097.x

MOST PATIENTS WITH HYPERCORTISOLISM PRESENT WITHOUT CLASSIC PHENOTYPIC FEATURES[1,2]: BIG FOUR

Symptoms	Signs	Overlapping Conditions
Features that best discriminate Cushing syndrome; most do not have a high sensitivity		
	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially of reddish purple and >1 cm wide)	
Cushing syndrome features that are common in the general population and/or less discriminatory		
Depression	**Dorsocervical fat pad ("buffalo hump")**	**Hypertension[c]**
Fatigue	**Facial fullness**	**Incidental adrenal mass**
Weight gain	**Obesity**	**Vertebral osteoporosis[c]**
Back pain	**Supraclavicular fullness**	**Polycystic ovary syndrome**
Changes in appetite	**Thin skin[c]**	**T2DM[c]**
Decreased concentration	**Peripheral edema**	**Hypokalemia**
Decreased libido	**Acne**	**Kidney stones**
Impaired memory (especially short-term)	**Hirsutism or female balding**	**Unusual infections**
Insomnia	**Poor skin healing**	
Irritability		
Menstrual abnormalities		

[a]Features listed in random order.[2] [b]Highlighted features may be present without classically described phenotypic features. [c]Cushing syndrome is more likely if onset of the feature is at a younger age.[2]

1. Aresta C, et al. *Endocr Pract*. 2021;27(12):1216-1224. 2. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540.a

PREVALENCE OF HYPERGLYCEMIA SECONDARY TO HYPERCORTISOLISM

40 million Americans have T2DM

↓ ~25% have A1c > 8.0%

10 million Americans

↓ ~50% are on > 2-3 OHAs ± insulin

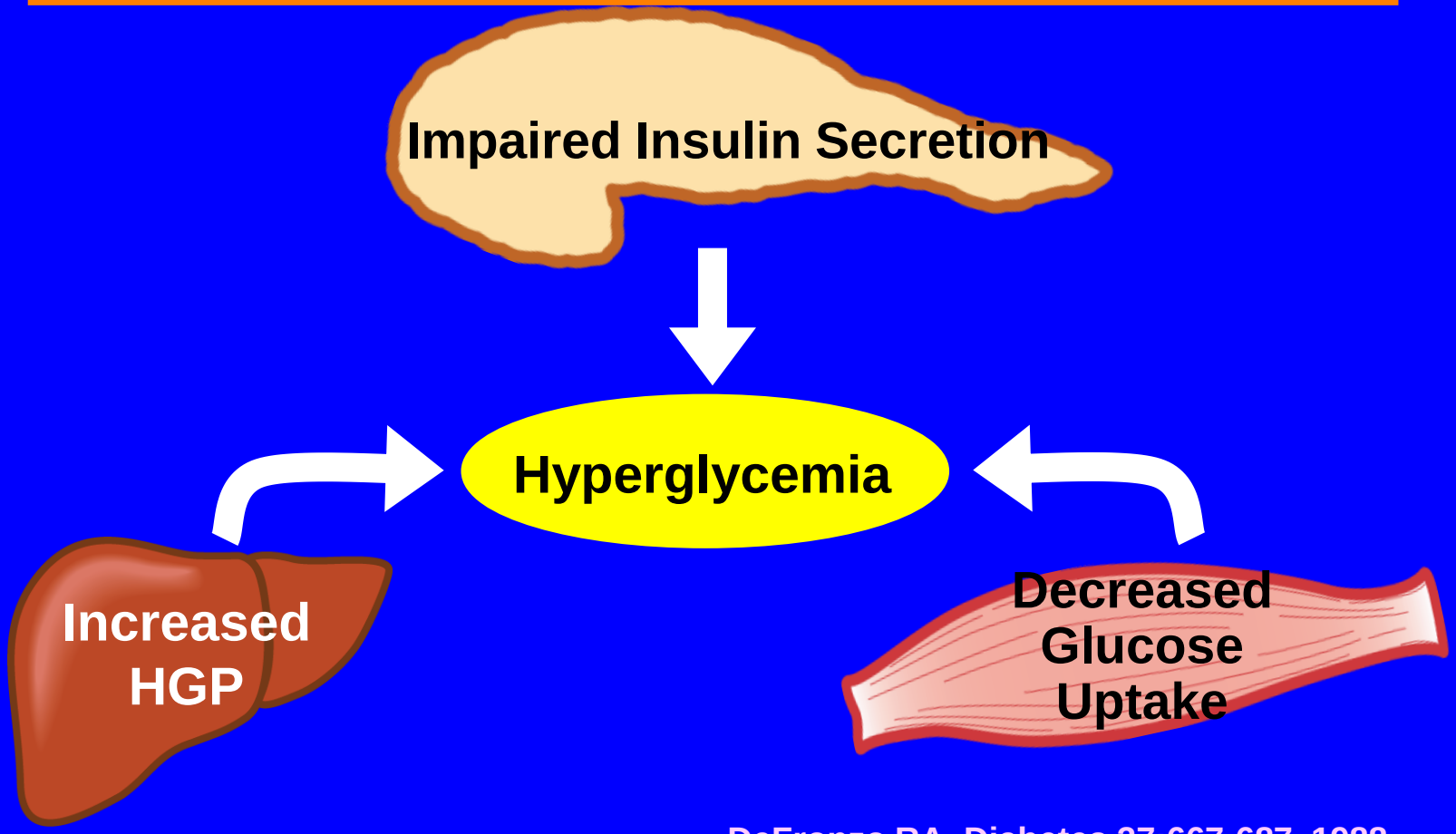
5 million Americans

↓ ~25% have hypercortisolism

1,250,000 Americans

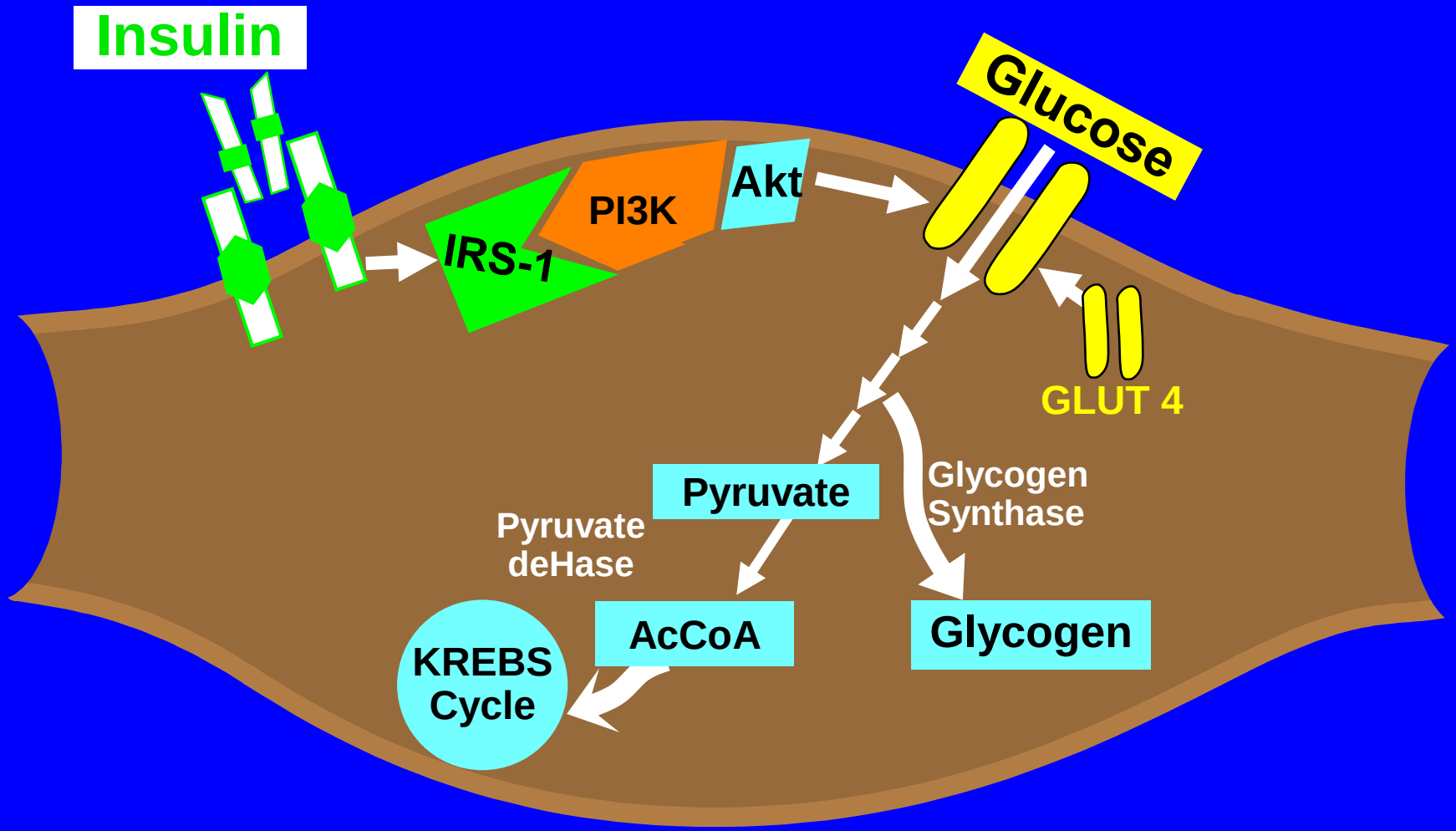
HOW DOES HYPERCORTISOLISM CAUSE HYPERGLYCEMIA?

THE TRIUMVIRATE

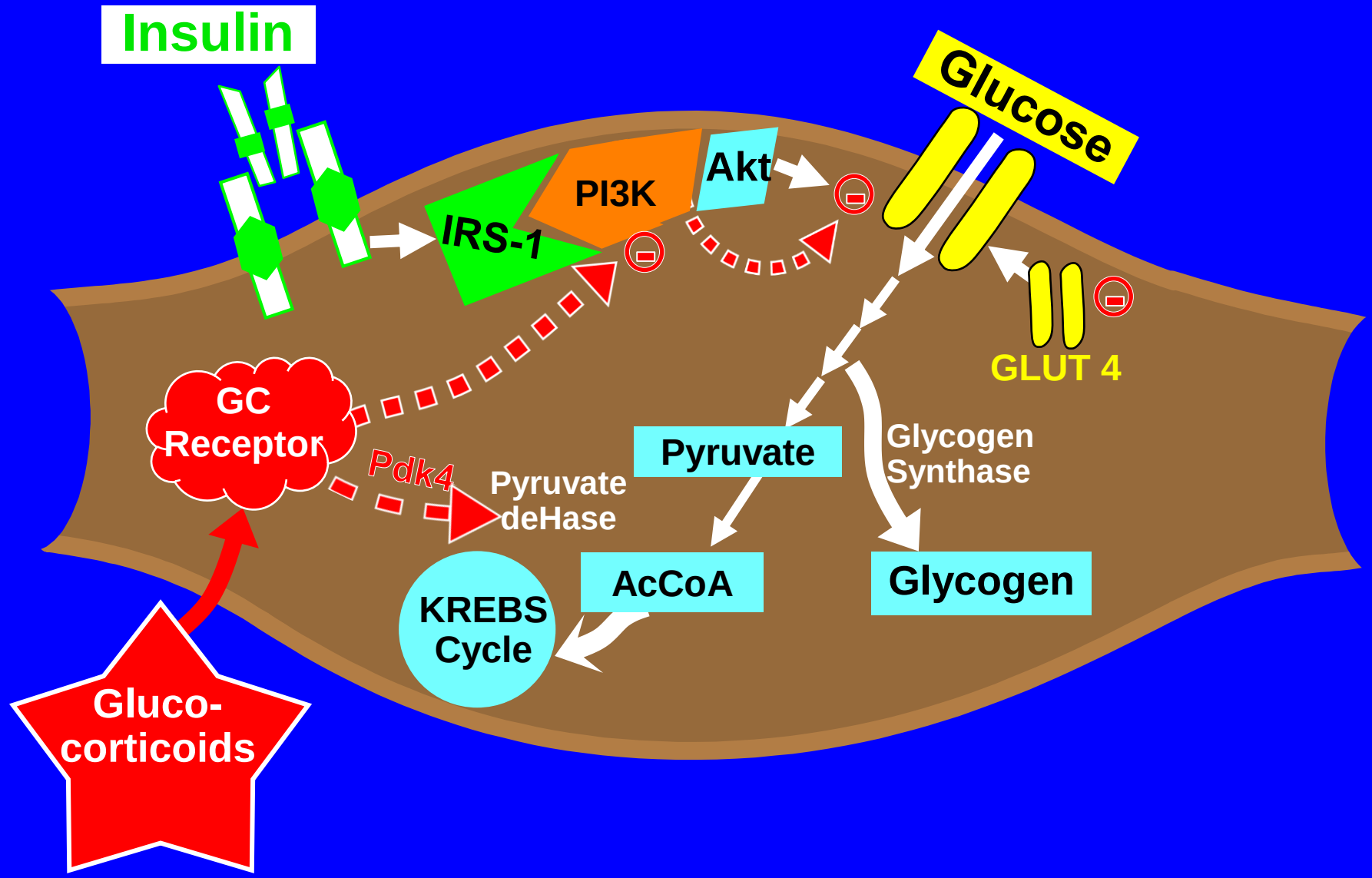


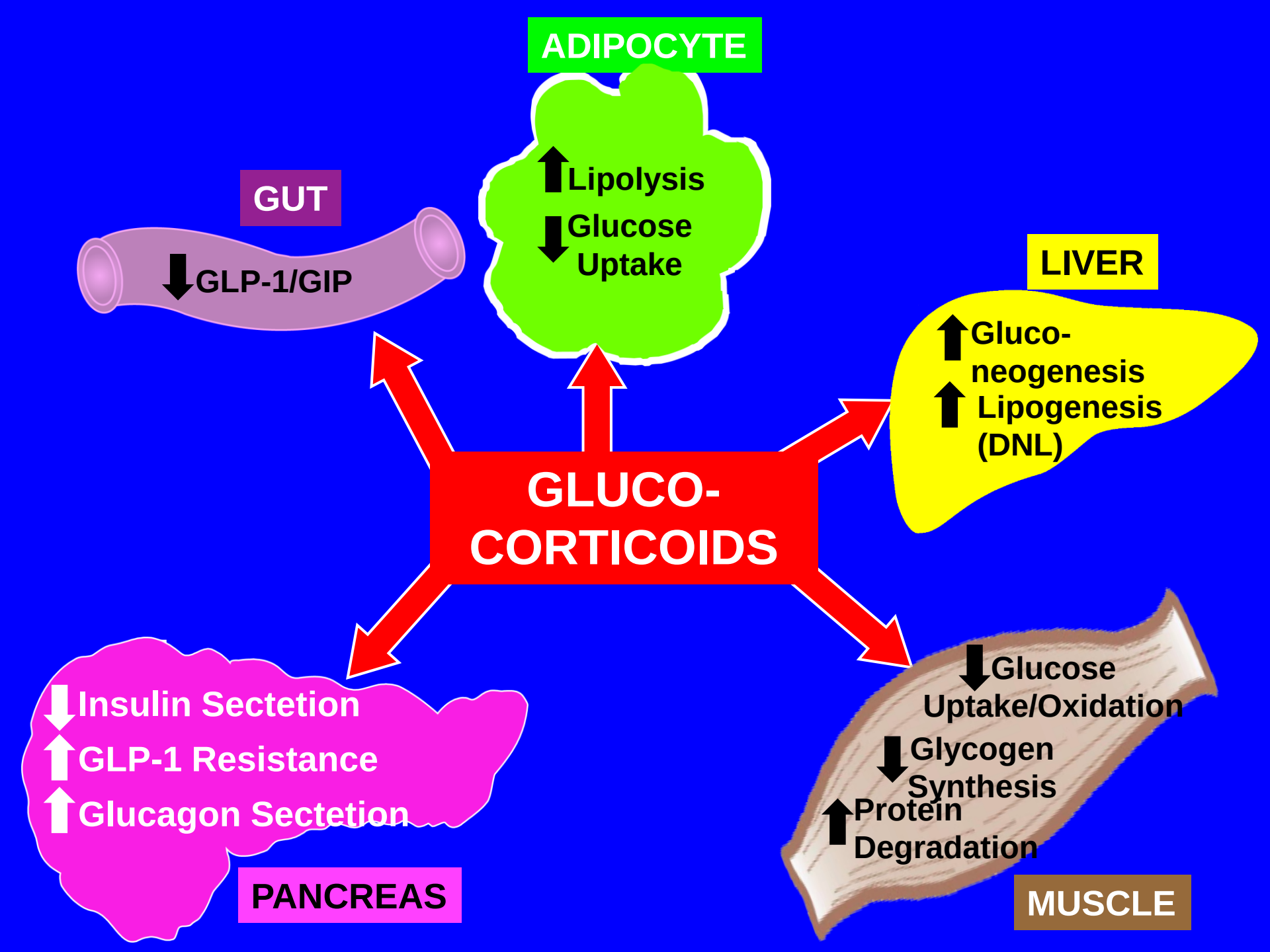
DeFronzo RA, Diabetes 37:667-687, 1988

INSULIN-STIMULATED MUSCLE GLUCOSE UPTAKE



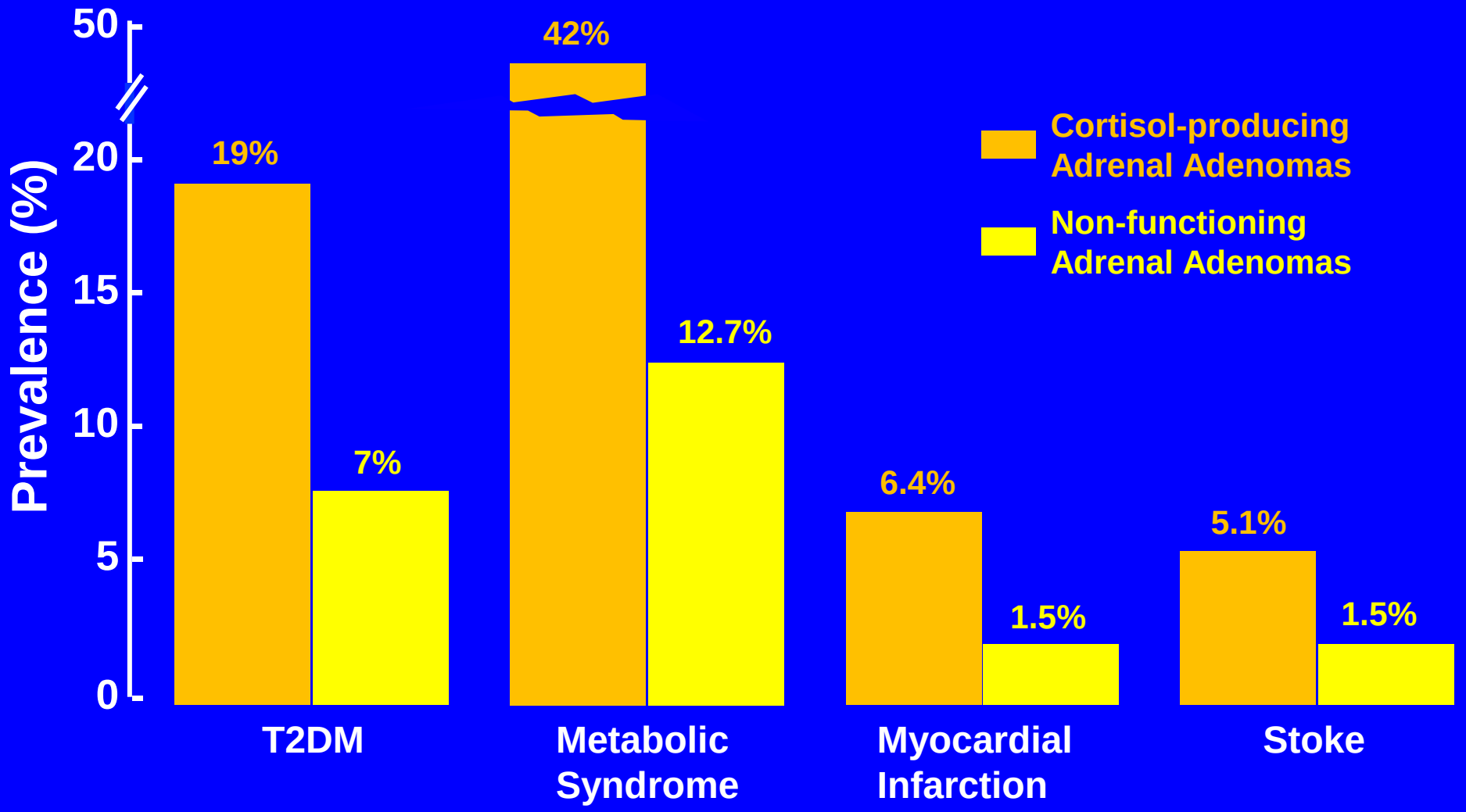
GLUCOCORTICOID-INDUCED MUSCLE INSULIN RESISTANCE



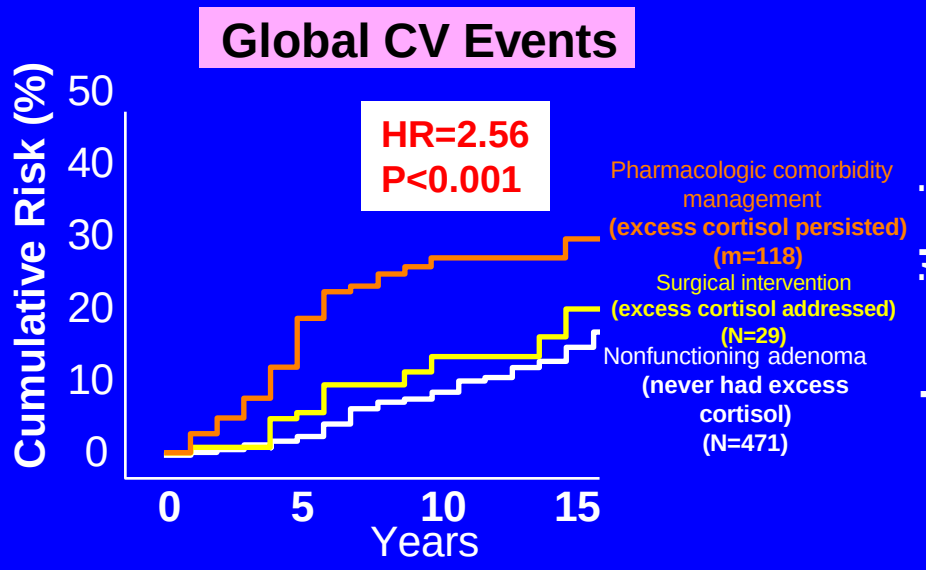

ADIPOCYTE
Lipolysis
Glucose Uptake
GUT
GLP-1/GIP
LIVER
Gluco-neogenesis
Lipogenesis (DNL)
GLUCO-CORTICOIDS
Insulin Sectetion
GLP-1 Resistance
Glucagon Sectetion
PANCREAS
Glucose Uptake/Oxidation
Glycogen Synthesis
Protein Degradation
MUSCLE

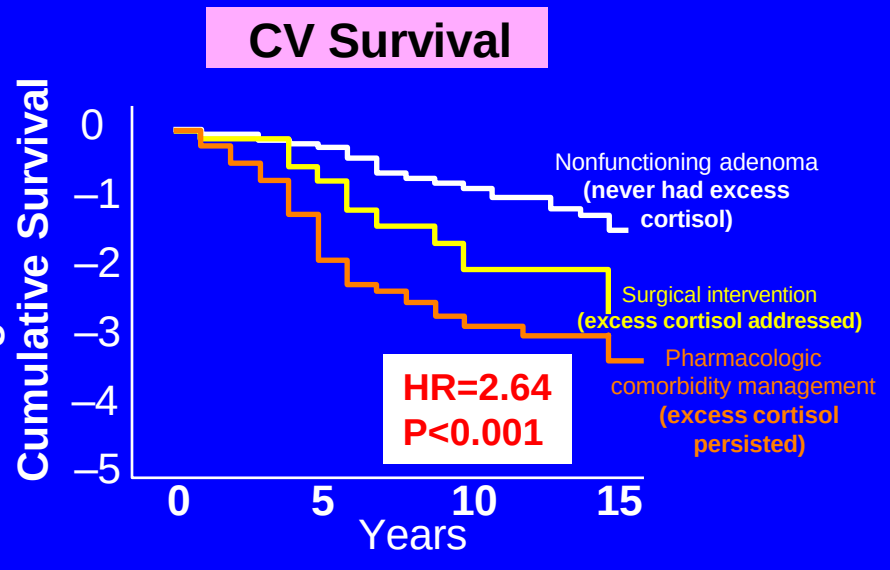
PATIENTS (N=628) WITH HYPERCORTISOLISM DUE TO ADRENAL SOURCE HAVE HIGHER RATES OF CARDIOMETABOLIC COMORBIDITIES

Functioning versus Nonfunctioning Adrenal Adenomas



PHARMACOLOGIC TREATMENT OF COMORBIDITIES WITHOUT TREATING HYPERCORTISOLISM IS INEFFECTIVE AT REDUCING LONG-TERM CARDIOVASCULAR EVENTS





Patients with adrenal autonomous cortisol secretion who do not receive treatment targeting their hypercortisolism are at increased risk for future CV events and CV mortality

Petramala L, et al. *Endocrine*. 2020;70(1):150-163.

EPIDEMIOLOGY OF HYPERTENSION IN CUSHING'S SYNDROME (CS)

- **Hypertension occurs in 80-85% of individuals with Cushing's Syndrome and, as a clinical feature, is second only to weight gain/obesity**
- **Systolic and diastolic blood pressure are increased in parallel; males and females are equally affected**
- **LVH and diastolic dysfunction are common in CS**

Barbot et al, Front Endo 10:1-9, 2019; Li et al, Gland Surg 9:43-58, 2019; Isidori et al, J Hyperten 33:44-60, 2015; Fallo et al, J Hyperten 40:2085-2101, 2022

MECHANISM OF HYPERTENSION IN CUSHING'S SYNDROME

(1) Activation of mineralocorticoid and glucocorticoid receptors

(2) Renin-angiotensin system

(3) Sympathetic nervous system

(4) Imbalance between vasodilators and vasoconstrictors

(5) Obstructive sleep apnea syndrome (OSAS)

(6) Direct effect of cortisol on the arterial vasculature

HYPERCORTISOLISM AND HYPERTENSION

- Cortisol and aldosterone have similar binding affinity to the mineralocorticoid receptor
- Cortisol binding to mineralocorticoid receptor ⟶ salt and water retention
- Cortisol binding to glucorticoid receptor ⟶ activates renal epithelial sodium channel (ENaC)

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THANK YOU!