

# Diabetes

SWEET SIPHON VS SIPHON LACKING FLAVOUR

# Diabetes – two completely different problems

Normal blood sugar level is 3.6-6.2

- Common symptom of diabetes is peeing a lot

Insulin Dependant Diabetes Mellitus vs Non-IDDM

- Diabetes Mellitus (“sweet siphon”) – glucose in urine
  - Type 1 / IDDM / Juvenile onset
    - Autoimmune destruction of beta cells
  - Type 2 / NIDDM / Adult onset
    - Inability to produce enough insulin / respond to insulin to regulate blood glucose
- Diabetes insipidus (“siphon lacking flavor”) – dilute, colourless urine
  - Inability to produce or respond to ADH

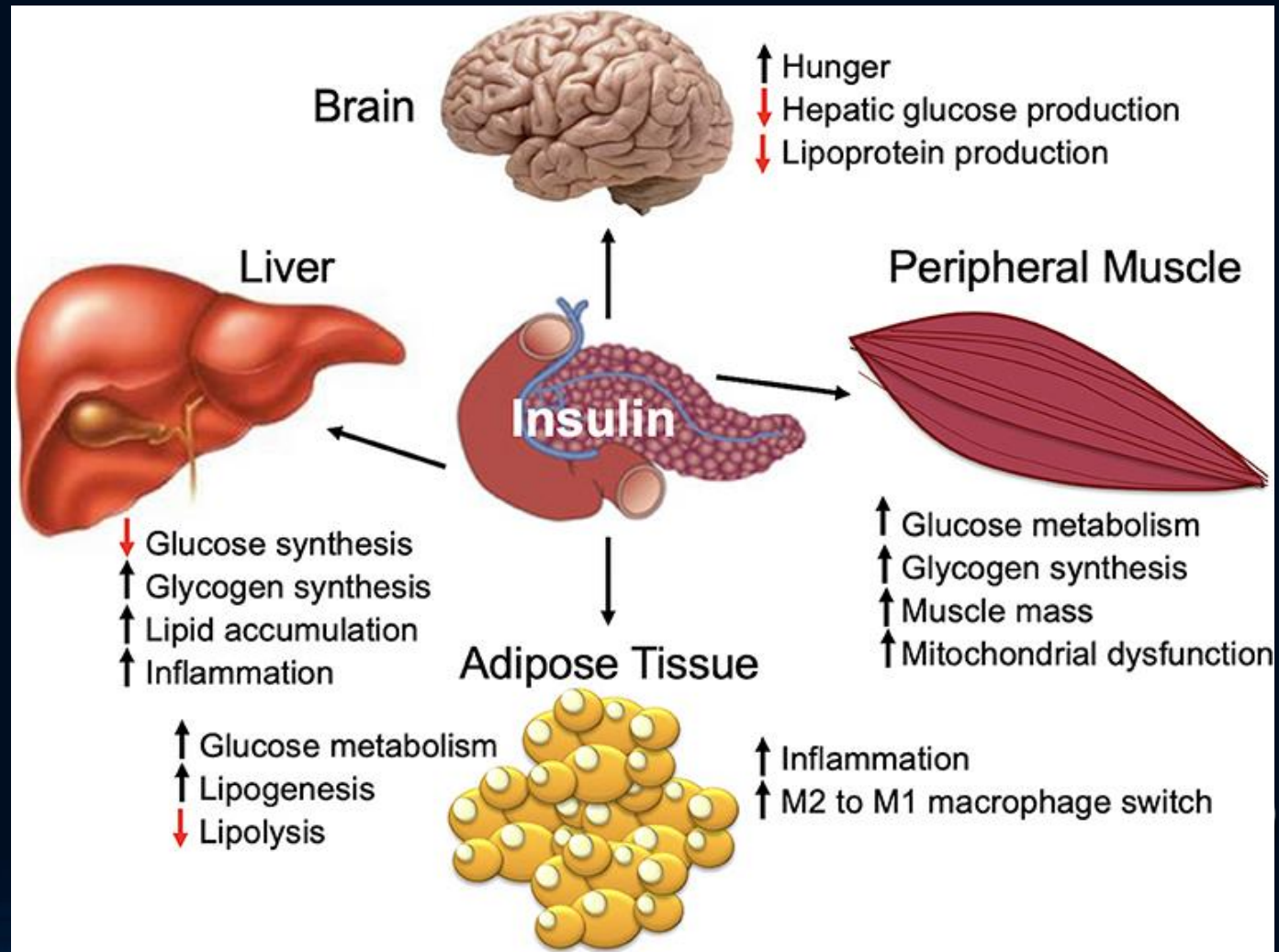
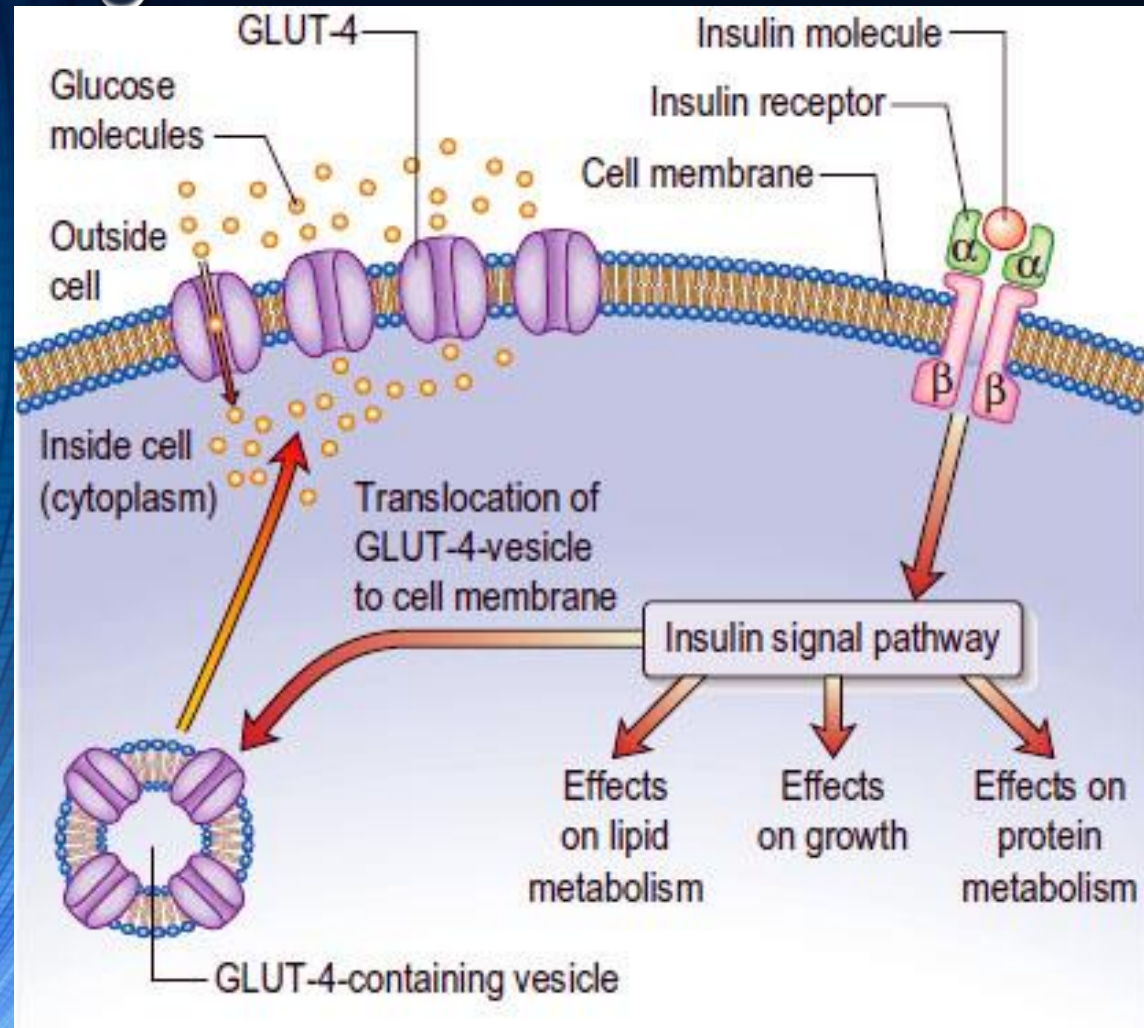
# Diabetes

INSULIN DEPENDENT DIABETES MELLITUS (TYPE I)



Lowers sugar by  
allowing it to enter  
cells from blood

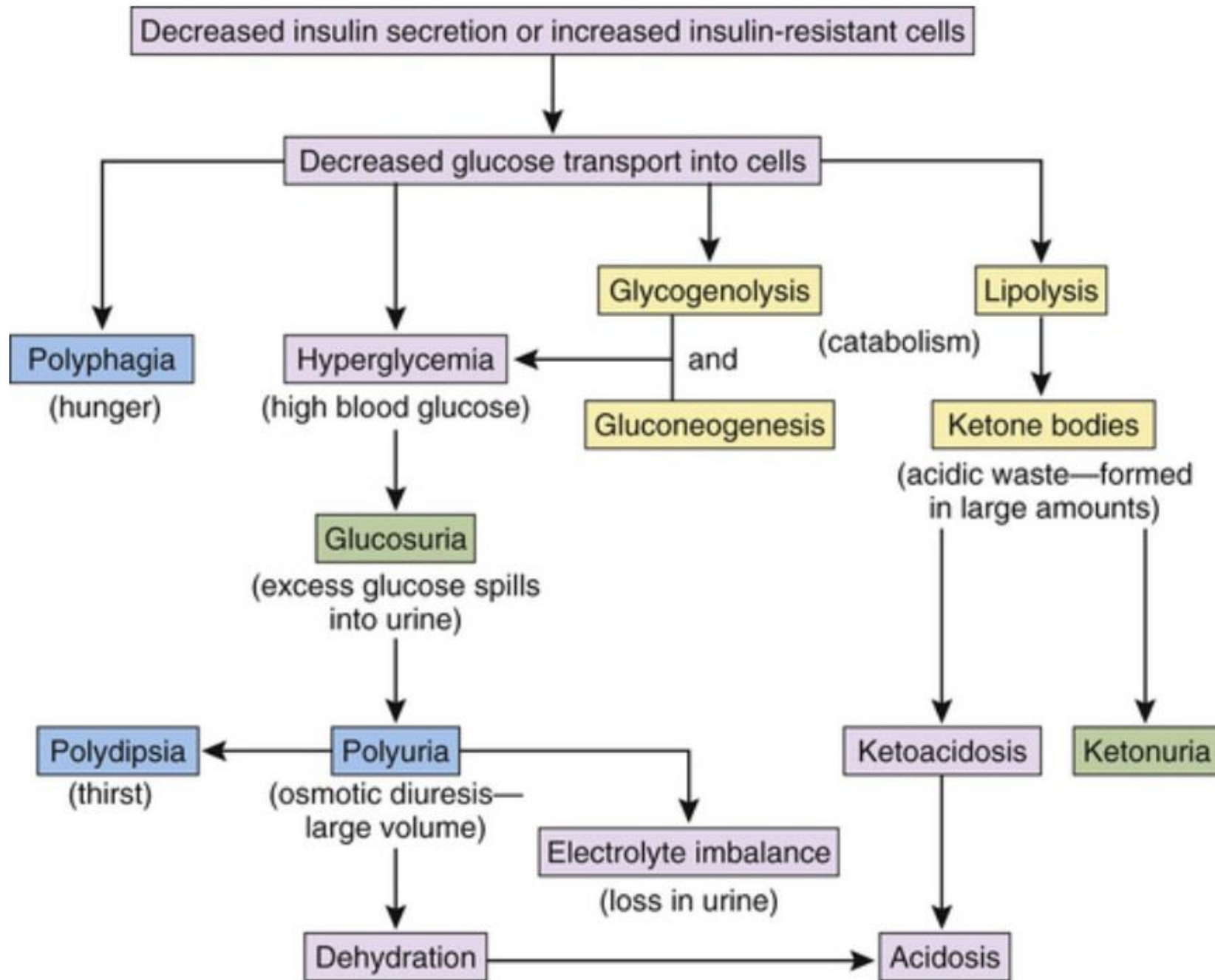
# Insulin Effects



# Diabetes Mellitus – IDDM

- Etiology
  - Autoimmune destruction of pancreatic beta islet cells, most common in Caucasian pops
- Pathophysiology
  - As blood glucose increases, insulin is not secreted in response to this signal
  - Thus blood glucose remains higher than normal → hyperglycemia
  - Consequences
    - Glucose is freely filtered by kidneys but reabsorption is limited by tubular maximum thus more glucose in urine → glycosuria
    - Glucose has osmotic effect and limits reabsorption of water → polyuria
    - Excessive H<sub>2</sub>O loss causes dehydration → increased ADH secretion → polydipsia
    - Nutrients are not stored by cells in same way without insulin → polyphagia





# Diabetes Mellitus – IDDM

- Clinical Manifestations

- Hyperglycemia ( $>11$  mmol/L; normal is  $<6.2$  mmol/L)
- Polydipsia, polyphagia, polyuria (glucosuria)
- Patients tend to be thin despite eating lots
- Usually diagnosed around age 14 though signs can be present much earlier
- Patients may be fatigued, weak, irritable
- Blurred vision

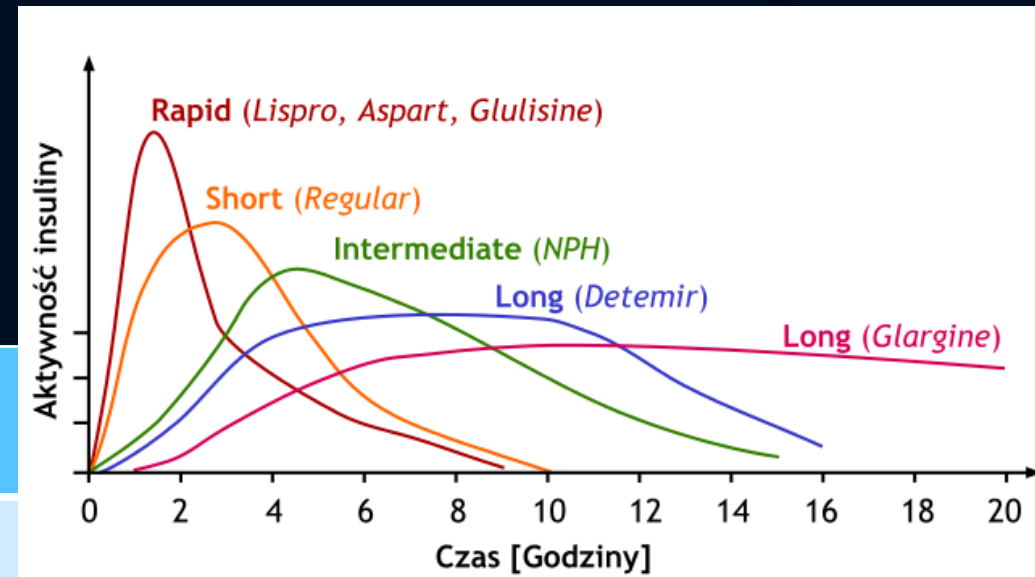
- Treatment

- Insulin replacement therapy



# Insulin Formulations

| Type                          | onset       | Peak          | Duration     |
|-------------------------------|-------------|---------------|--------------|
| Rapid – lispro                | 15 min      | 30 – 60 mins  | < 5 hours    |
| Short – regular (clear)       | 60 min      | 2 – 3 hours   | 5 – 7 hours  |
| Intermediate – isophane / NPH | 1 – 4 hours | 8 – 12 hours  | 18 -24 hours |
| Long – zinc                   | 4 – 8 hours | 18 – 24 hours | 36 hours     |





# Diabetes

NON INSULIN DEPENDENT DIABETES MELLITUS (TYPE II)

# Diabetes Mellitus – NIDDM

- Etiology
  - Skeletal muscle cells, adipocytes and liver cells become less responsive to insulin
  - Pancreas does not secrete enough insulin to adequately reduce blood sugar
  - Cause is unknown but many risk factors
    - Aging (adult onset), sedentary lifestyle, obesity, CHO / lipid rich diets, genetic components
- Pathophysiology
  - As blood glucose increases, insulin is secreted but cannot adequately reduce blood glucose  
→ hyperglycemia (does take longer to reach this level than in IDDM)
  - reduced insulin sometimes causes increased glucagon secretion (lack of inhibition)
  - Consequences
    - Hyperglycemia, glycosuria, polyuria develop for same reasons as IDDM but may be more insidious
    - Polydipsia takes time to manifest

# • Diabetes Mellitus – NIDDM

- Clinical Manifestations

- Similar to IDDM but may take longer to develop than in IDDM
- As obesity is a risk factor, patients tend to be heavier
- Adult onset used to mean later adulthood but condition is becoming more common in younger individuals

- Treatment – three layers

- Regular exercise and healthy diet
- Oral hypoglycemic meds
  - Drugs that increase insulin secretion (incretins, sulfonylureas, meglitinides)
  - Drugs that increase receptor sensitivity (biguanides, glitazones)
  - Drugs that reduce CHO absorption (alpha glucosidase inhibitors)
  - Drugs that promote satiety (amylin, pramlintide, sibutramine)
- Insulin



# Common Oral Hypoglycemic Medication

|  |  |   |   |
|--|--|---|---|
| <b>Biguanides</b>                      | <ul style="list-style-type: none"><li>• Metformin</li></ul>  | <b>Meglitinides</b>                               | <ul style="list-style-type: none"><li>• Repaglinide</li><li>• Nateglinide</li></ul>                     |
| <b>Sulfonylureas</b><br>2nd generation | <ul style="list-style-type: none"><li>• Glimepiride</li><li>• Gliclazide</li><li>• glyburide</li></ul>                           | <b>GLP-1 agonists</b>                             | <ul style="list-style-type: none"><li>• Exenatide</li><li>• Dulaglutide</li><li>• Liraglutide</li></ul> |
| <b>TZDs</b>                            | <ul style="list-style-type: none"><li>• Pioglitazone</li><li>• Rosiglitazone</li></ul>   | <b><math>\alpha</math>-Glucosidase inhibitors</b> | <ul style="list-style-type: none"><li>• Acarbose</li></ul>  |
| <b>DPP-4 inhibitors</b>                | <ul style="list-style-type: none"><li>• Sitagliptin</li><li>• Vildagliptin</li><li>• Saxagliptin</li><li>• Linagliptin</li></ul> | <b>Amylin mimetic</b>                             | <ul style="list-style-type: none"><li>• Pramlintide</li></ul>   |
| <b>SGLT-2 inhibitors</b>               | <ul style="list-style-type: none"><li>• Dapagliflozin</li><li>• Canagliflozin</li><li>• Empagliflozin</li></ul>                  | <b>Bile acid sequestrant</b>                      | <ul style="list-style-type: none"><li>• Colesevelam</li></ul>   |

# Diabetes

COMPLICATIONS HYPOGLYCEMIA

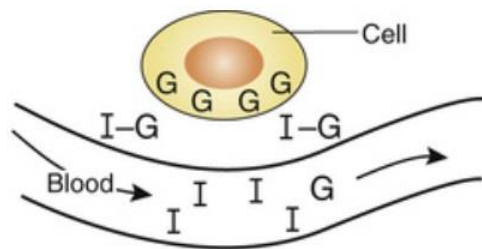
figure out reasons  
why diabetics can  
become  
hypoglycemic

neonates suck at storing  
sugar, so without constant  
sugar intake, they become  
hypoglycemic

# Hypoglycemia

- What if the patient takes too much insulin (or oral hypoglycemic medication)?
- Hypoglycemia
  - Tachycardia, diaphoresis, headache, shakiness, irritability, anxiety, drowsiness
- Treatment
  - Source of glucose – OJ, chocolate bar etc
  - Exogenous – Glucagon, Dextrose solution (iv)





1. Excess insulin in blood

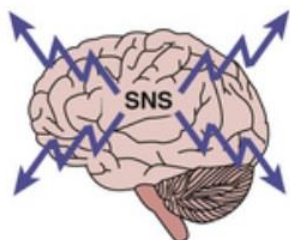
2. Increased transport of glucose into cells

3. Hypoglycemia  
Decreased CNS function

4. Stimulates SNS

**Clinical signs**

- weakness, confusion
- pallor
- diaphoresis
- tremors
- tachycardia



5. Increased gluconeogenesis

6. Excess insulin transports glucose into cells

# Insulin-induced Hypoglycemia

6. Excess insulin transports glucose into cells

Glucose intake

Return to normal state

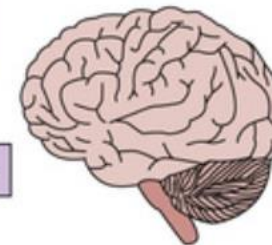
7. No glucose intake

8. Blood glucose levels decrease further

9. Neurons cannot function

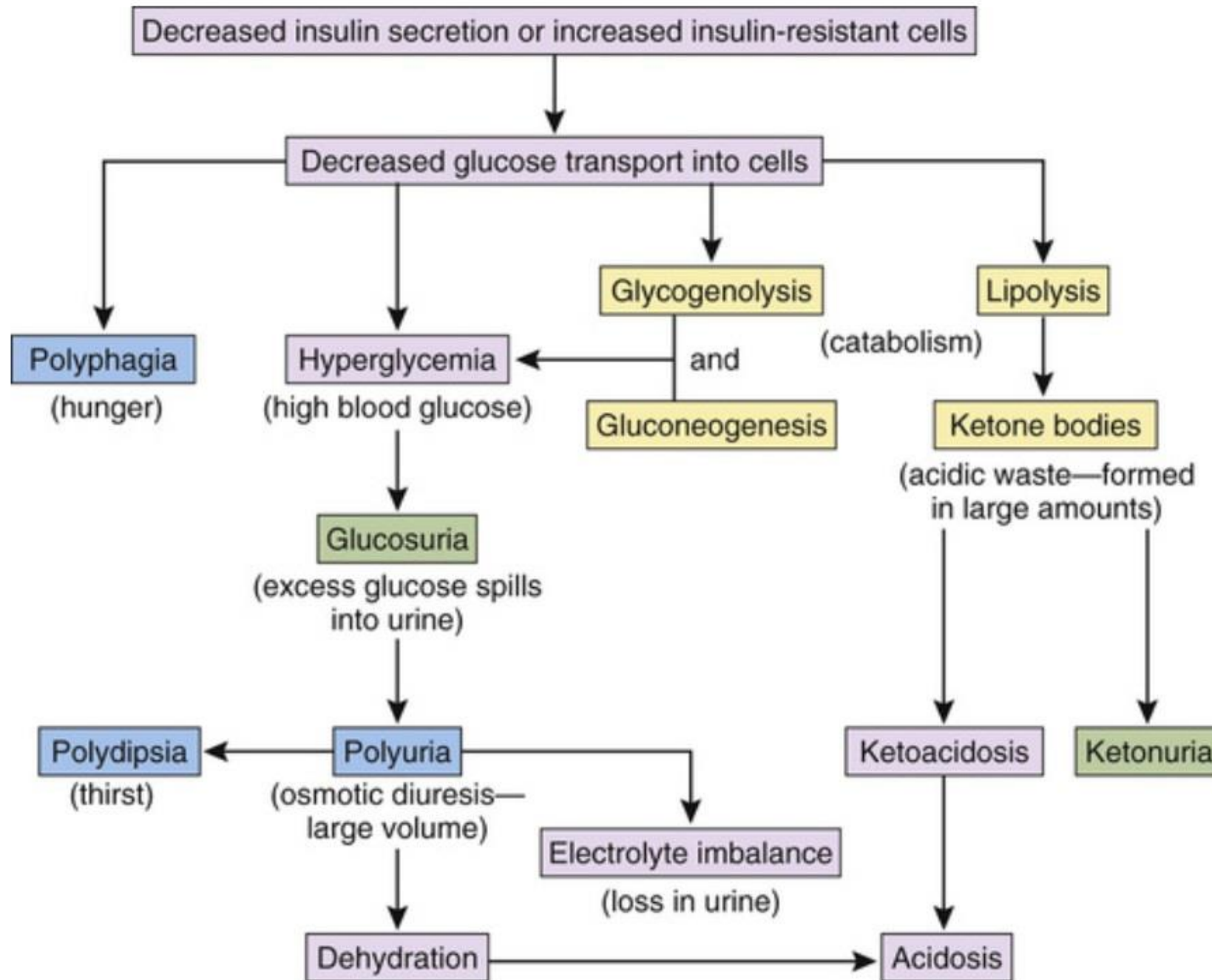
10. Coma and death

I = Insulin  
G = Glucose



# Diabetes

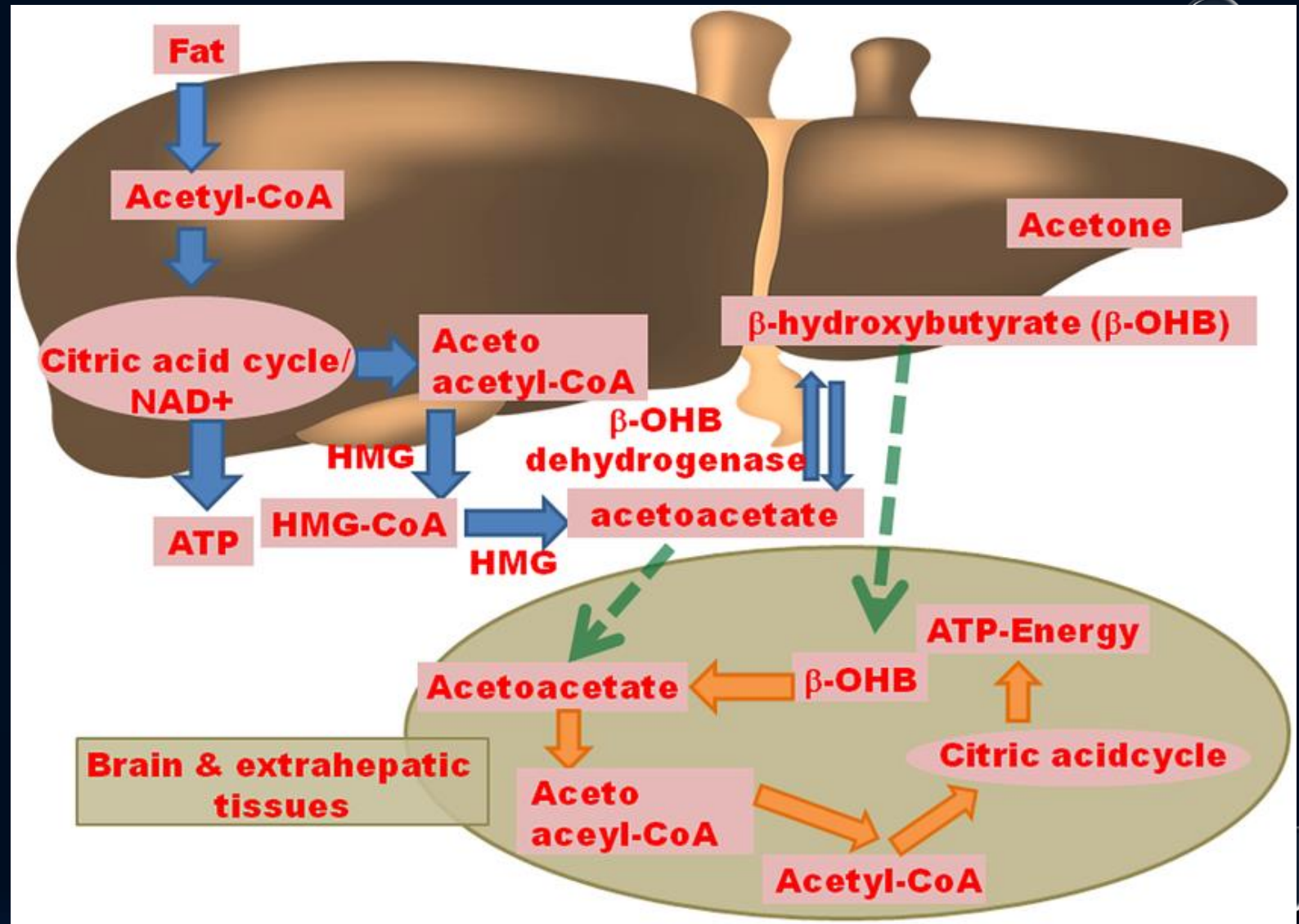
COMPLICATIONS: HYPERGLYCEMIA





# Ketoacid Production

1. Lipolysis (triglycerides broken into free fatty acids)
2. Beta-oxidation: fatty acids to Acetyl-CoA in liver mitochondria
3. HMG-CoA Pathway: Acetyl-CoA cannot enter Citric Acid Cycle (limited oxaloacetate) goes into ketogenic pathway. 2 x Acetyl-CoA combine to HMG-CoA
4. Ketone Formation: HMG-CoA cleaved (HMG-CoA lyase) into acetoacetate (ketoacid)
5. Acetoacetate converted to other two:  $\beta$ -hydroxybutyrate, acetone (excreted breath and urine)



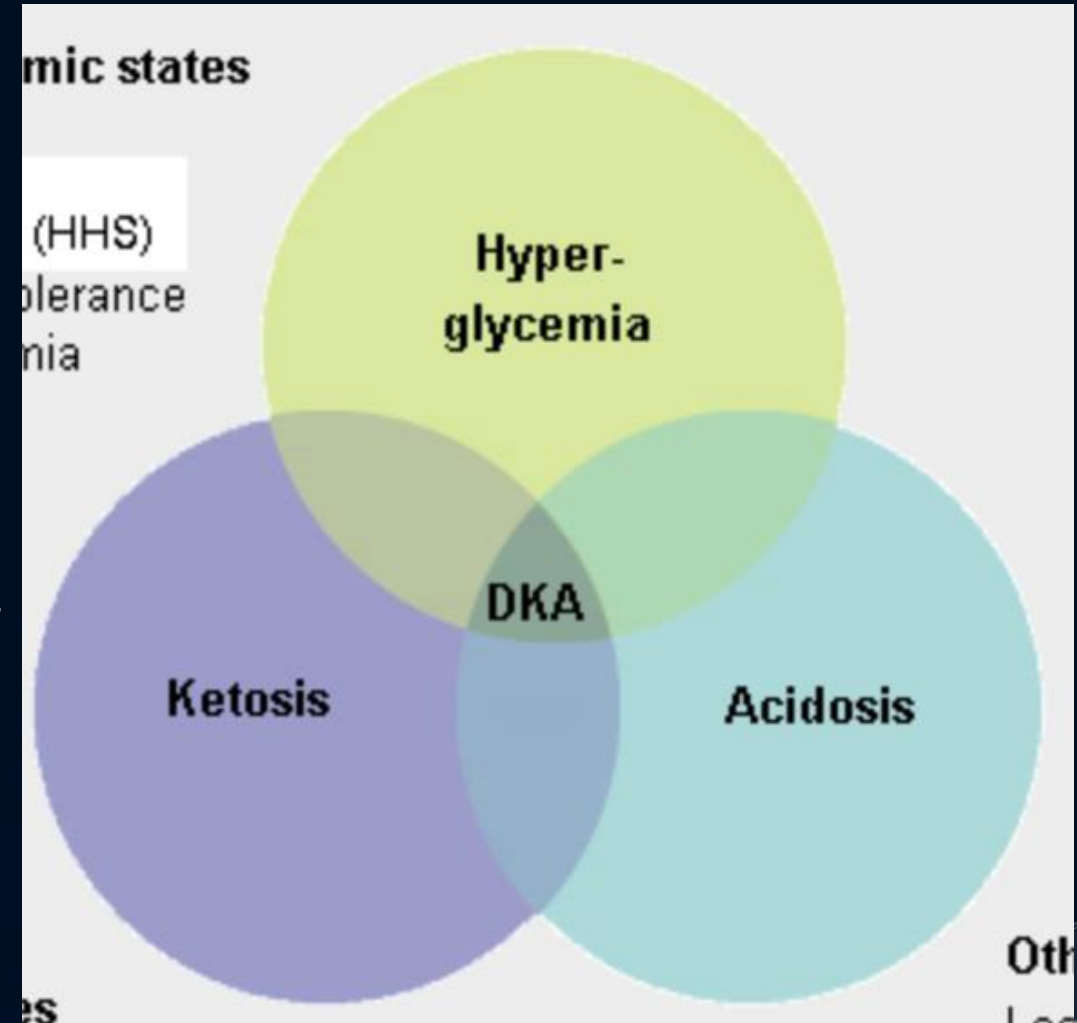
# Diabetic Ketoacidosis (DKA)

Acidosis causes potassium to leak out of cells. So blood potassium levels stay normal, but cells become hypokalemic

Acidosis causes hyperventilation, resulting in Kussmaul Respiration

ketacids also cause GI upsets

- Life-threatening condition
  - Without insulin, cells mobilize glycogen stores and then lipid stores
  - FFA circulate in blood then converted to KETO-ACIDS in liver then into blood
  - Limit to cellular absorption of keto-acids so they begin to accumulate in blood
  - Keto-acids cause excess of  $H^+$  in blood → metabolic acidosis
    - Transient hyperkalemia (why?)
    - Increased rate and depth of breathing (why?)
    - Hypovolemia
    - Keto-acids (ketone bodies) have fruity smell → fruity smelling breath



# Hyperosmolar Hyperglycemic Syndrome (HHS)

- Old Name - Non-ketotic hyperosmolar hyperglycemic syndrome (NKHHS)
  - Poor control of glucose and poor hydration leads to increased concentration of glucose in blood
    - Meds like diuretics and glucocorticoids can contribute
    - Infections also increase risk
  - Because some insulin is present, lipolysis and metabolism of lipids for use as an energy source is suppressed → no ketosis
  - Lack of glucose uptake into skeletal muscle cells and adipocytes promotes gluconeogenesis and glycogenolysis → further increased blood glucose
  - Blood glucose can reach as high as 600 mg/dL (normal is < 140 mg/dL)
  - Excessive fluid loss can increase ECF osmolarity to > 320 mosm/L
  - Much higher mortality rate (up to 20%) than DKA (<1%)
    - Without acidosis, it is more difficult to identify compared to DKA
    - Excessive fluid loss decreases BP, causes EL imbalances (why might hypokalemia occur?)



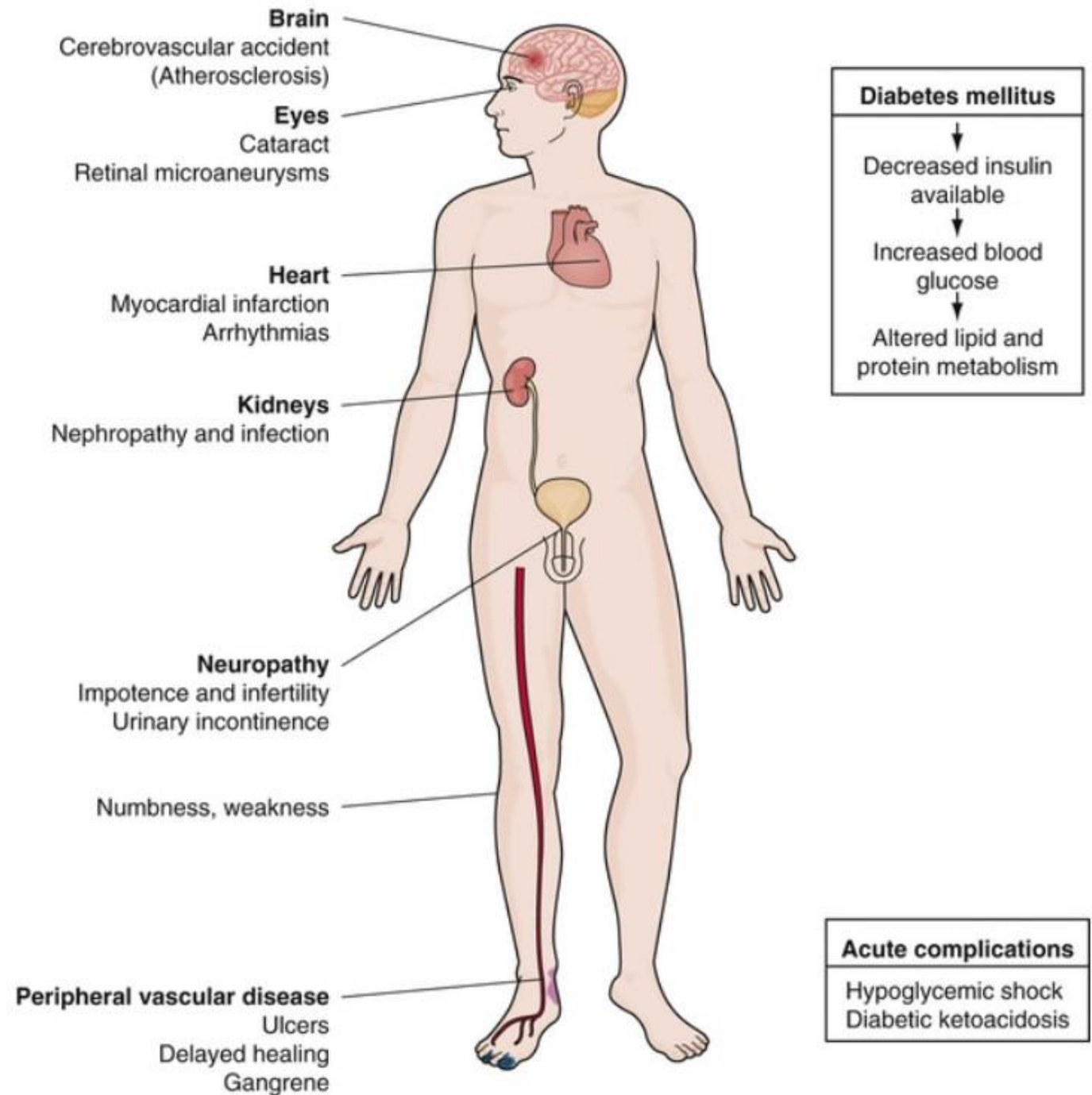
# Diabetes Mellitus – General Chronic Complications

- Vascular complications
  - Macrovascular / macroangiopathy – increased risk of atherosclerosis, stroke
  - Microvascular / microangiopathy
    - Retinopathy – increased risk with aging; progresses to neovascularization which eventually causes fibrosis, retinal detachment and blindness
    - Nephropathy – leads to chronic renal failure (irreversible loss of nephrons) due to glomerulosclerosis (initial increased filtering leading to damage to glomeruli through I / N / F process); hypertension
- Increased risk of infection
  - Poor circulation, increased glucose supports bacteria, poor healing due to reduced insulin
- Neuropathies
  - Autonomic – GI, bladder, tachycardia, postural hypotension
  - Sensory – loss of sensation in feet and lower legs → ulcerations, infections, tissue necrosis

# HHS vs DKA

| DKA  | HHS  |
|--|--|
| Hyperglycemia                                      | Severe hyperglycemia<br>(elevated osmolality)            |
| Metabolic acidosis                                 | pH > 7.3   |
| Ketonemia (elevated beta-hydroxybutyrate)          | Minimal or negative ketonemia                            |
| Volume depletion                                   | Profound volume depletion                                |
| Young > Elderly, T1DM > T2DM<br>Acute presentation | Elderly > Young; T2DM, 20%<br>without hx of T2DM illness |
| Acute presentation                                 | Longer, protracted course of<br>illness                  |

# Diabetes Mellitus – Chronic Complications





# Diabetes

DIABETES INSIPIDUS

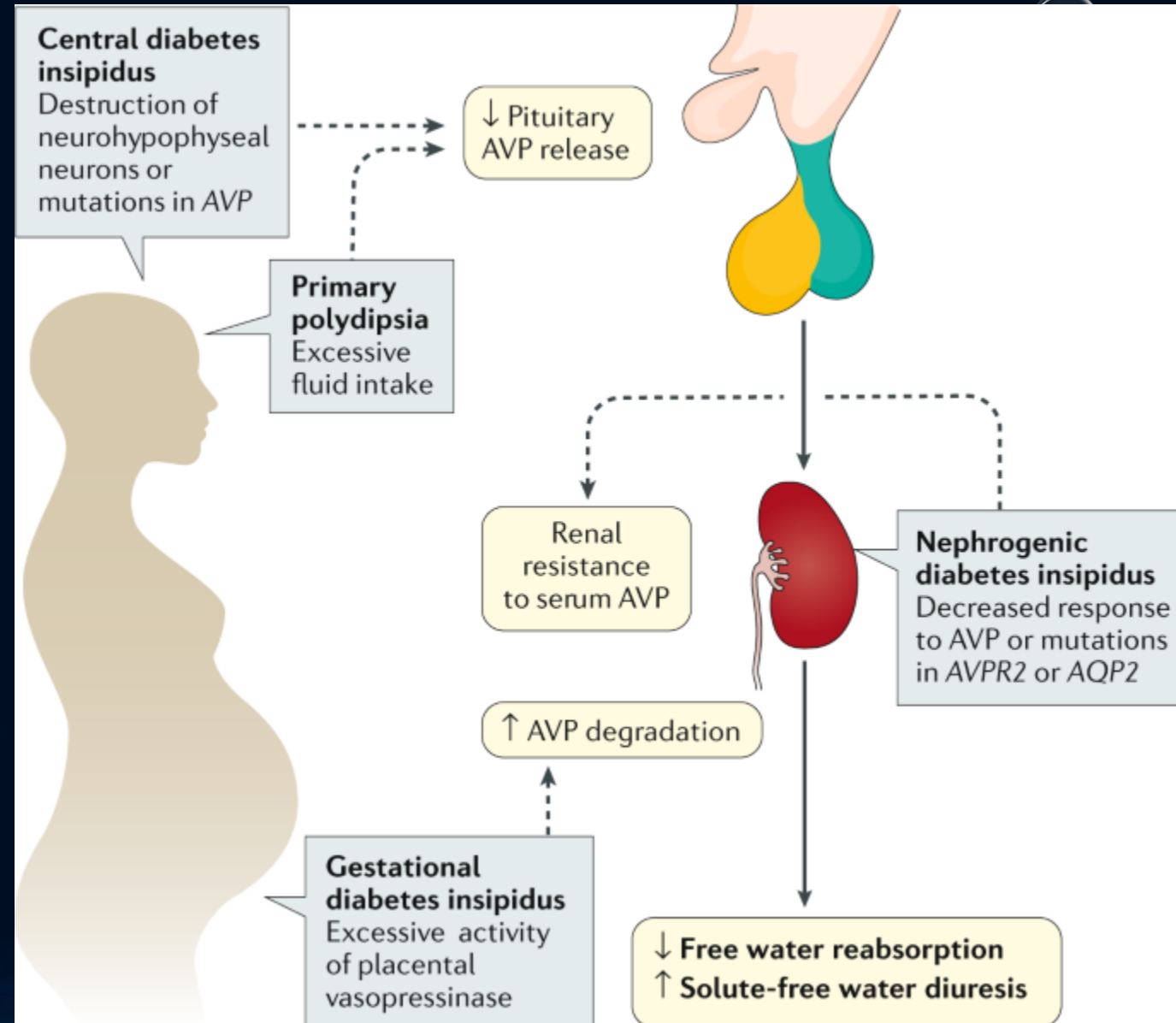
# Diabetes Insipidus

## • Etiology

- Central – inability to produce and secrete ADH – idiopathic, tumour, surgery, trauma
- Nephrogenic – inability to respond to ADH; lack of reabsorption of water
- Dipsogenic – constant thirst → big water load = lots of pee
- Gestational – with pregnancy, placenta produces enzyme that metabolizes ADH

## • Pathophysiology

- ADH is responsible for creation of aquaporin channels to facilitate reabsorption of water; without proper ADH function, much fewer aquaporins = decreased water reabsorption



# Diabetes Insipidus

- Clinical Manifestations
  - Excessive thirst
  - Excessive peeing (dilute urine)  $> 3\text{L} / \text{day}$ 
    - risk of dehydration and EL imbalances, especially hypokalemia (why?)
- Treatment – it depends
  - Central – exogenous ADH / desmopressin
  - Nephrogenic – deal with primary problem, thiazide diuretics can alter  $\text{Na}^+$  intake which can support more water reabsorption
  - Dipsogenic – not sure
  - Gestational – desmopressin