Diabetic Complications

MED341

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Objectives

- Acute Diabetic Complications
  - Diabetic Ketoacidosis
  - Hyperglycemic Hyperosmolar State
  - Hypoglycemia
- Chronic Diabetic Complications
  - Diabetic Retinopathy
  - Diabetic Nephropathy
  - Diabetic Neuropathy
  - Cardiovascular Disease
- How to Screen and Prevent Diabetes Complications

Acute Diabetic Complications

Diabetic KetoAcidosis (DKA)

- Status of ***metabolic acidosis*** due to absolute (or relative) insulin deficiency in association with increased levels of glucagon and other counter-regulatory hormones resulting in ***increased ketone*** production

- ⬆ hepatic glucose production

- ⬆ activity of the *hormone-sensitive lipase* in AT

  Triglycerides → → glycerol and free fatty acid

- In the liver: Free fatty acids → → ketones

Precipitating Causes of DKA

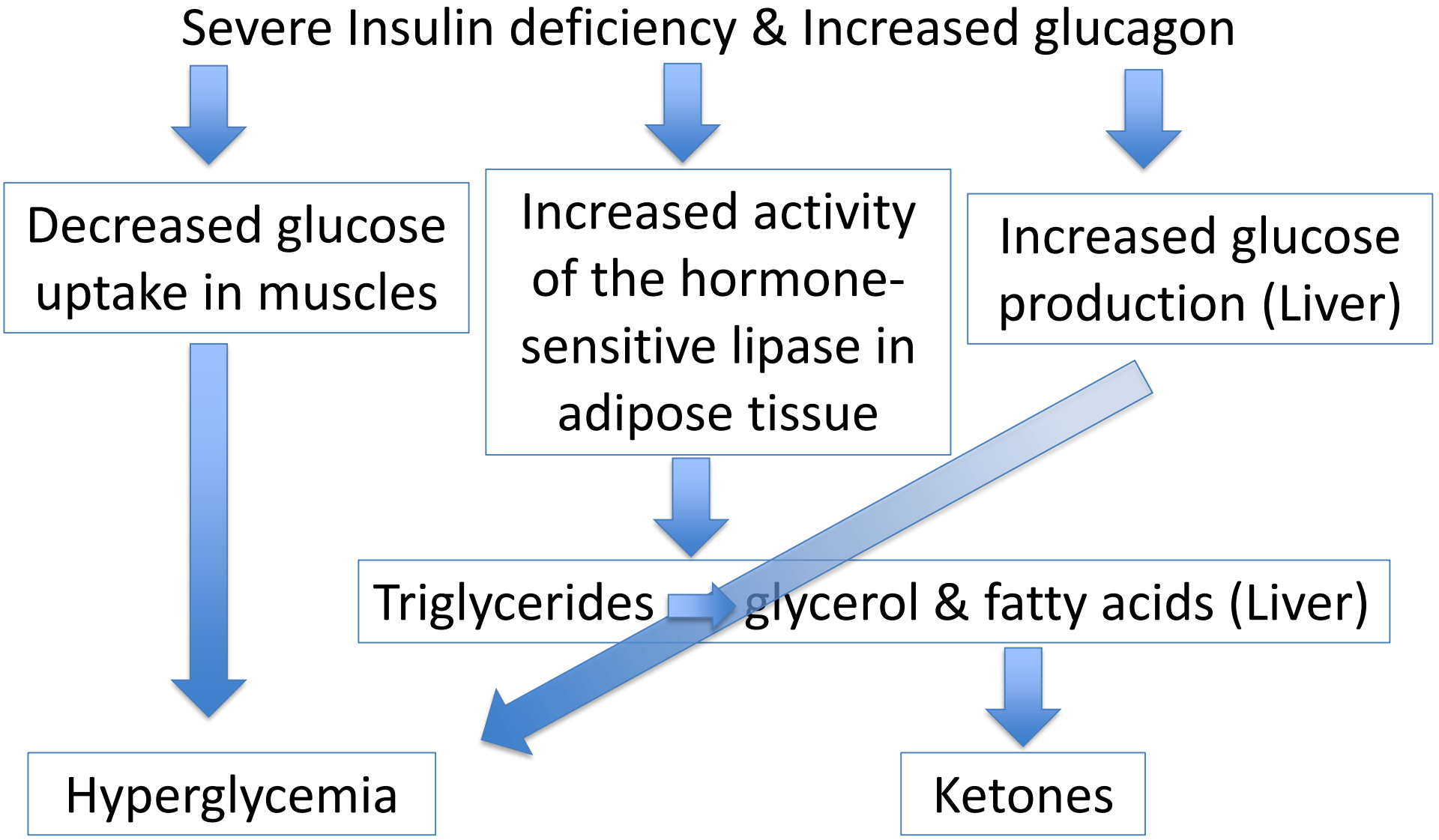
Table 1 | **Precipitating causes of diabetic ketoacidosis**

Precipitating cause	Australia[115]	Brazil[116]	China[117]	Indonesia[118]	Korea[119]	Nigeria[120]	Spain[121]	Syria[122]	Taiwan[123]	USA[15,23]
New diagnosis of diabetes mellitus, %	5.7	12.2	NR	3.3	NR	NR	12.8	NR	18.2	17.2–23.8
Infection, %	28.6	25.0	39.2	58.3	25.3	32.5	33.2	47.8	31.7	14.0–16.0
Poor adherence to treatment, %	40.0	39.0	24.0	13.3	32.7	27.5	30.7	23.5	27.7	41.0–59.6
Other, %	25.7	15.0	10.9	17.1	11.2	4.8	23.3	7.8	6.2	9.7–18.0
Unknown, %	NA	8.8	25.9	8.0	30.8	34.6	NA	20.9	16.2	3.0–4.2

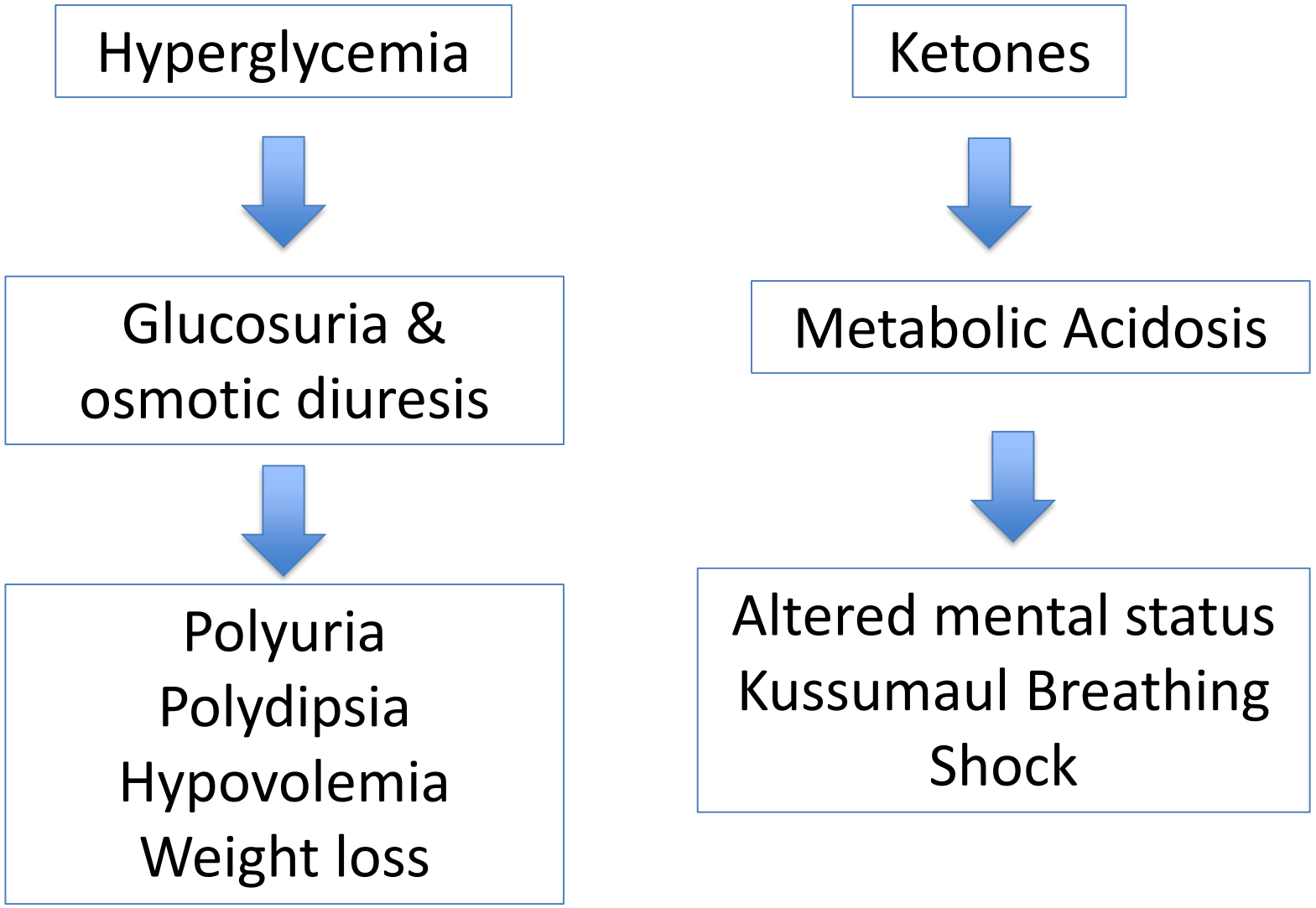
NA, not applicable; NR, not reported.

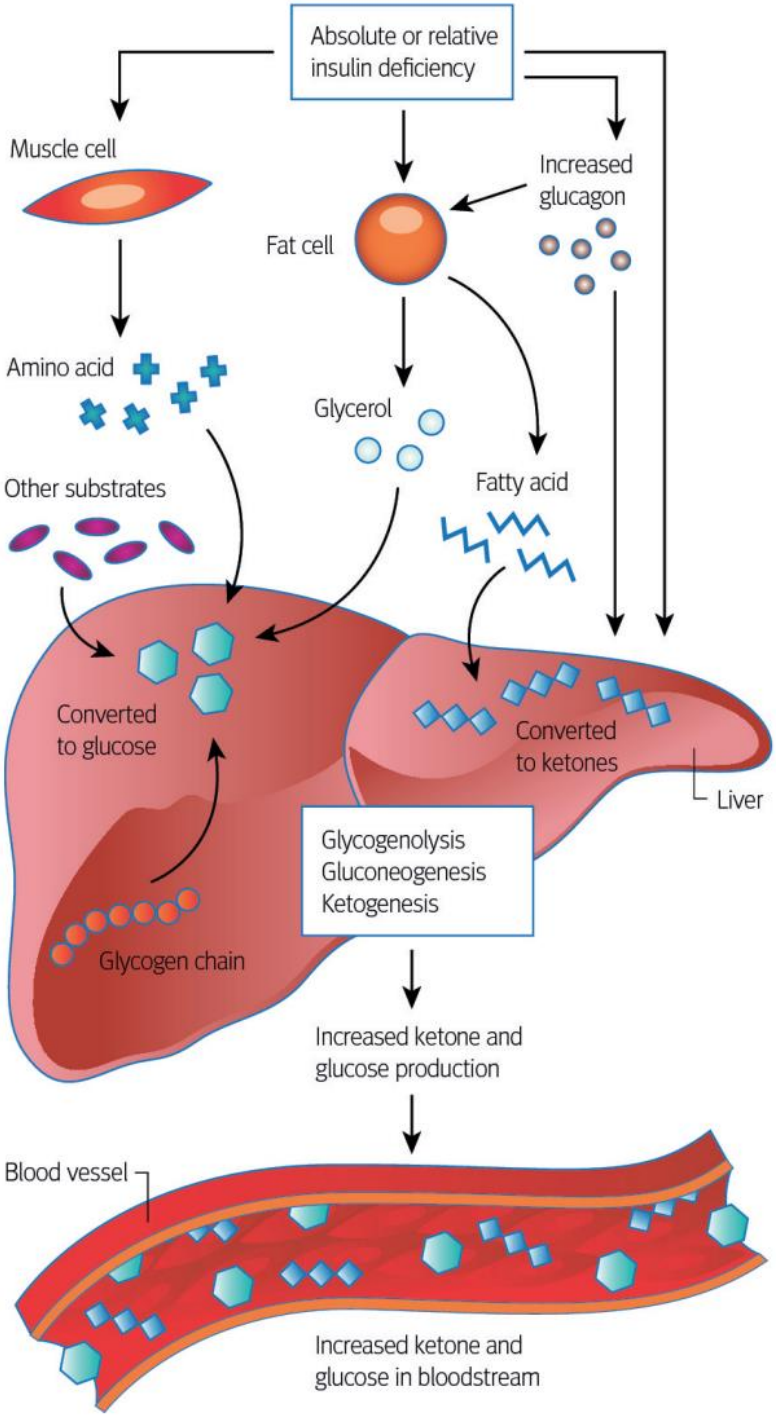
- Drugs: Corticosteroids, sympathomimetics, atypical anti-psychotics, SGLT-2 inhibitors

Pathophysiology of DKA



Pathophysiology of DKA





Misra et al., BMJ. 2015

Clinical Features of DKA

- Polyuria, polydipsia, & weight loss
- Nausea & vomiting
- Abdominal pain
- Change in mental status
- Dehydration
- Hypothermia
- Deep labored breathing (Kussmaul respiration)

Laboratory Findings in DKA

Hyperglycemia + Hyperketonemia + metabolic acidosis

Measure	DKA		
	Mild	Moderate	Severe
Plasma glucose level, mmol/l	13.9	13.9	13.9
Arterial or venous pH	7.25–7.30	7.00–7.24	<7.00
Bicarbonate level, mmol/l	15–18	10–14	<10
Urine or blood acetoacetate (nitroprusside reaction)	Positive	Positive	Positive
Urine or blood β-hydroxybutyrate, mmol/l	>3	>3	>3
Effective serum osmolality, mmol/kg*	Variable	Variable	Variable
Anion gap, mmol/l	>10	>12	>12
Alteration in sensorium	Alert	Alert or drowsy	Stupor or coma

Management of DKA

Aggressive rehydration + Lowering glucose + Cessation of ketogenesis + Correcting electrolyte imbalances

Most patients with DKA are treated in ICU

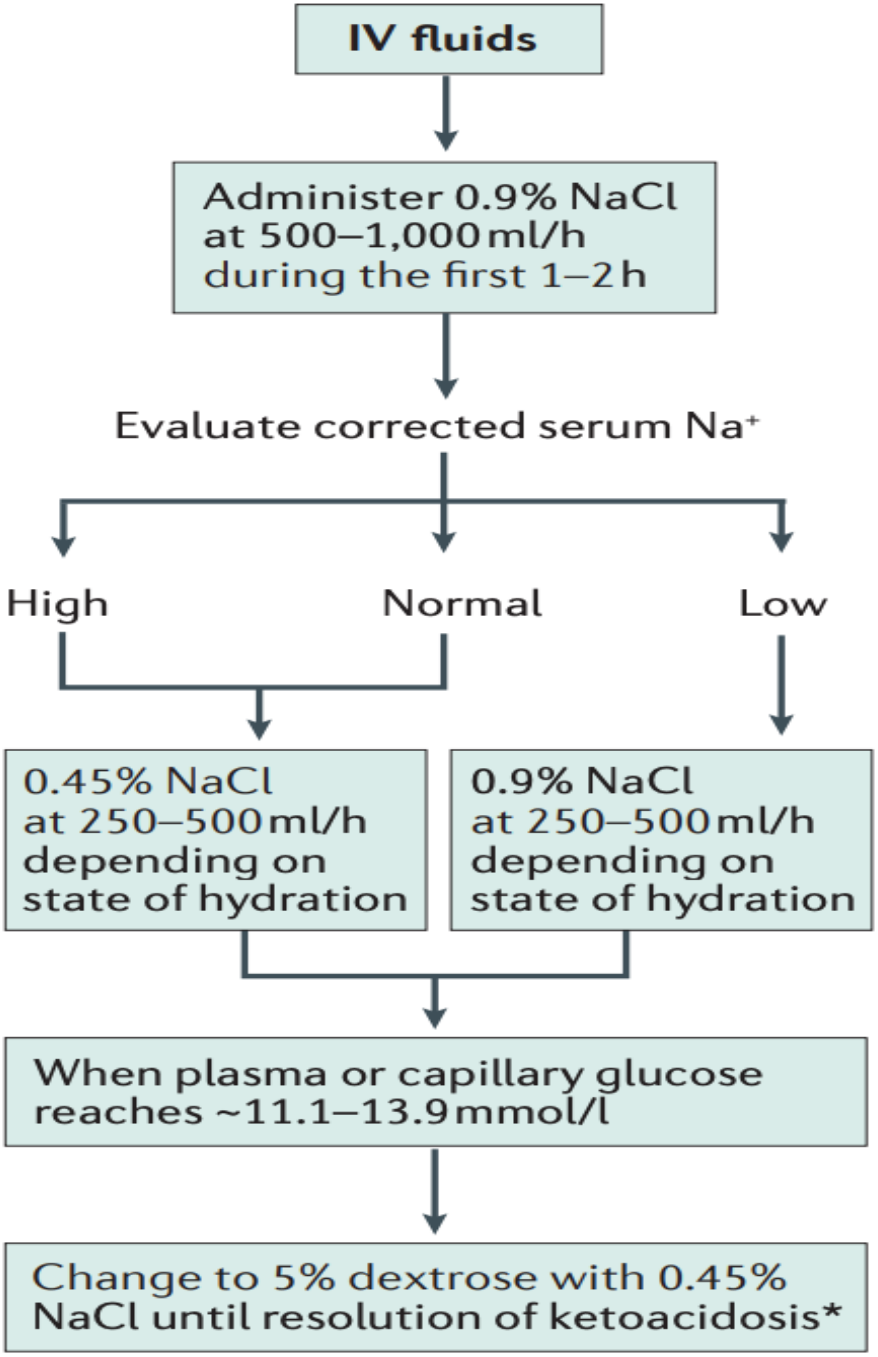
DKA is associated with increased mortality

Management of DKA

Rehydration

- IVF is the most critical step
- Water deficit is ~ 100ml/kg of body weight
- Isotonic saline @ 500-1000 ml/hr during the 1st 2-4 h
- Followed by: isotonic saline 250—500 ml/h

- Once the plasma glucose is ~250 mg/dl, switch IVF to D5% IVF


IV fluids
Administer 0.9% NaCl at 500–1,000 ml/h during the first 1–2 h
Evaluate corrected serum Na+
High
Normal
Low
0.45% NaCl at 250–500 ml/h depending on state of hydration
0.9% NaCl at 250–500 ml/h depending on state of hydration
When plasma or capillary glucose reaches ~11.1–13.9 mmol/l
Change to 5% dextrose with 0.45% NaCl until resolution of ketoacidosis*

Management of DKA

Insulin

- Insulin is the next step after IVF
- Reduces serum glucose and suppresses ketogenesis

- Most of the time: we use IV insulin infusion but mild DKA can be treated with subcutaneous insulin

- Most protocols: IV insulin bolus → 0.1 unit/kg

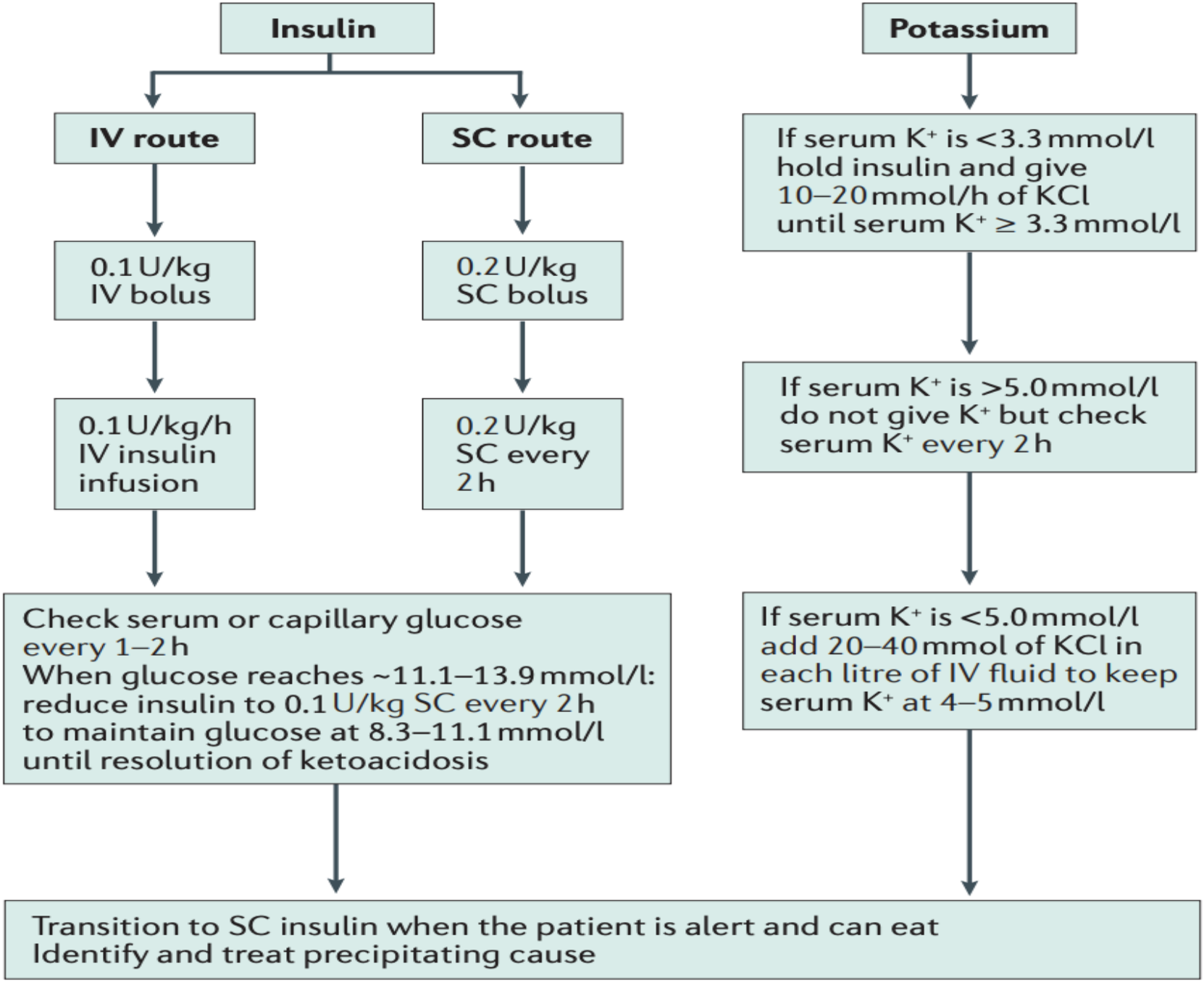
- Followed by: IV insulin infusion → 0.1 unit/kg/h

Management of DKA

Electrolytes

- DKA is associated with total-body K+ deficit
- Serum K^+ is often normal or high (do not get fooled!)
- K^+ Shift from intracellular to extracellular compartment with acidosis
- Insulin therapy moves K^+ back into the cells (watch for a drop in K^+)
- K^+ replacement starts early (when K^+ is normal)
- Rate of K infusion depends on K^+ level and eGFR

- Consider bicarbonate infusion if pH <7
- Phosphate replacement is almost never required


Insulin
IV route
SC route
0.1 U/kg IV bolus
0.2 U/kg SC bolus
0.1 U/kg/h IV insulin infusion
0.2 U/kg SC every 2 h
Check serum or capillary glucose every 1–2 h
When glucose reaches ~11.1–13.9 mmol/l: reduce insulin to 0.1 U/kg SC every 2 h to maintain glucose at 8.3–11.1 mmol/l until resolution of ketoacidosis
Potassium
If serum K+ is <3.3 mmol/l hold insulin and give 10–20 mmol/h of KCl until serum K+ ≥ 3.3 mmol/l
If serum K+ is >5.0 mmol/l do not give K+ but check serum K+ every 2 h
If serum K+ is <5.0 mmol/l add 20–40 mmol of KCl in each litre of IV fluid to keep serum K+ at 4–5 mmol/l
Transition to SC insulin when the patient is alert and can eat
Identify and treat precipitating cause

Hyperglycemic Hyperosmolar State (HHS)

- Status of ***severe hyperglycemia*** due to insulin resistance & relative insulin deficiency resulting in ***increased serum osmolality***
- ~ 10 times higher mortality than DKA
- Develops slower than DKA (over several days)

- No ketosis
- Serum glucose level is higher than seen in DKA
- More sever dehydration & higher plasma osmolality than DKA

- Gradual worsening of polydipsia, polyuria, & weight loss
- Impaired consciousness is more common than DKA

Pathophysiology of HHS

- Results from relative insulin deficiency (there is some detectable insulin)
- Less activation of the hormone-sensitive lipase in adipose tissues & less free fatty acid production compared to DKA

- No ketones production but higher serum glucose than in those with DKA

- Sever dehydration and plasma hyperosmolality → impaired consciousness

Laboratory Findings in HHS

Measure	DKA			HSS
	Mild	Moderate	Severe	
Plasma glucose level, mmol/l	13.9	13.9	13.9	33.3
Arterial or venous pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Bicarbonate level, mmol/l	15–18	10–14	<10	>15
Urine or blood acetoacetate (nitroprusside reaction)	Positive	Positive	Positive	Negative or low positive
Urine or blood β-hydroxybutyrate, mmol/l	>3	>3	>3	<3
Effective serum osmolality, mmol/kg*	Variable	Variable	Variable	>320
Anion gap, mmol/l	>10	>12	>12	<12
Alteration in sensorium	Alert	Alert or drowsy	Stupor or coma	Stupor or coma

Management of HHS is similar to that of DKA

Hypoglycemia

- Plasma glucose <3.9 mmol/L (<70 mg/dl)
- Severe hypoglycemia: need for assistance from another person to correct glucose

- Most frequent & serious adverse effect of glucose-lowering therapies
- Hypoglycemia in a patient with diabetes is almost always due to glucose-lowering therapies
- Major barrier to achieving desirable glucose control

- Occurs in 30-40% of patients with T1DM
- Occurs in 10-30% of patients with insulin-treated T2D

- Insulin & sulfonylureas are the most frequent causes

Box 2 | **Factors contributing to hypoglycaemia**

- Insufficient patient education
- Medications (insulin, sulfonylureas, glinides, quinolones)
- Aggressive treatment protocols targeting normoglycaemia
- Poor coordination of insulin administration and food delivery
- Abrupt changes in nutritional intake
- Abrupt discontinuation of parenteral or enteral nutrition among insulin-treated patients
- Decline in renal or hepatic function
- Severe illness
- Tapering of steroid doses without appropriate reductions in insulin
- Inappropriate insulin dosing
- Counter-regulatory hormone deficiencies
- Impaired awareness of hypoglycaemia
- Dementia
- Age >65 years
- Sepsis

Hypoglycemia

- **Treatment:** (Rule of 15)
  - **Give 15 grams of carbohydrates**
    - 4 glucose tablets
    - ½ cup of fruit juice or regular soda
    - 1 tablespoon of sugar or honey
  - **Wait 15 minutes and re-check glucose**
  - **Repeat the same if glucose is still less than 70 mg/dl**
    - If glucose is above 70 mg/dl, have the patient eat a regular meal or a snack that contains protein (e.g. nuts, cheese, chicken, meat, etc)
  - Remember, the patient should not be driving with hypoglycemia or (within 1 hour after treating hypoglycemia)

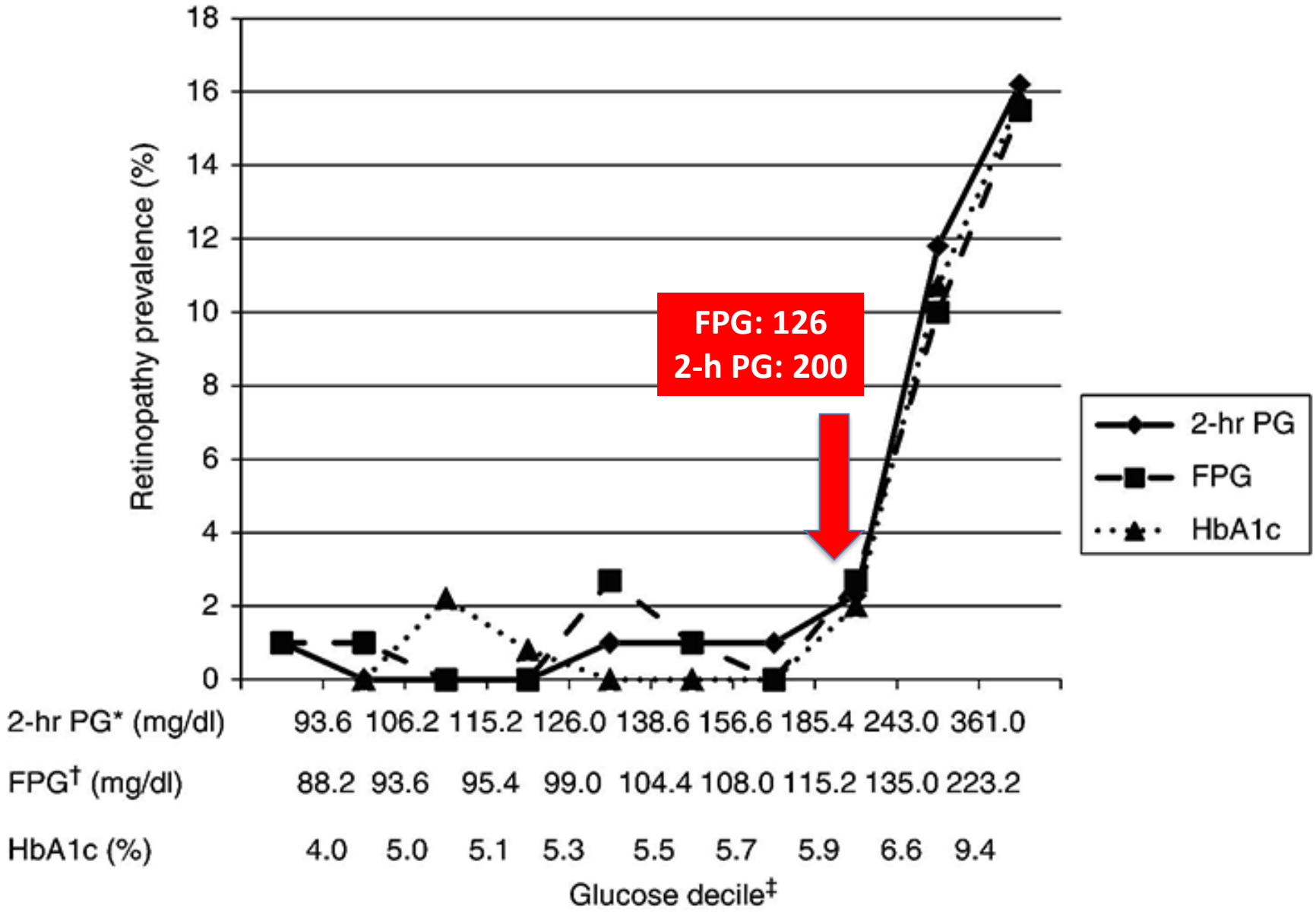
Objectives

- Acute Diabetic Complications
  - Diabetic Ketoacidosis
  - Hyperglycemic Hyperosmolar State
  - Hypoglycemia
- Chronic Diabetic Complications
  - Diabetic Retinopathy
  - Diabetic Nephropathy
  - Diabetic Neuropathy
  - Cardiovascular Disease

Micro- and Macrovascular Complications

- ✓ Micro-: Retinopathy, Neuropathy, and Nephropathy
- ✓ Macro-: Ischemic Heart Disease, Cerebrovascular events, PAD
- ✓ Mortality

The definition of Diabetes is based on risk of Retinopathy



Complications of Type 2 Diabetes

- Diabetes is the leading cause of:
  - Blindness
  - Renal failure
  - Non-traumatic lower extremity amputation

- The presence of DM complication tremendously increases medical care cost

- Usually present after long period of hyperglycemia

- Fortunately, they can be delayed/prevented by early DM detection and better glucose control

Diabetic Retinopathy

- **Non-proliferative**: usually appears in the 1st decade of the disease or early 2nd decade.
  - Characterized by retinal vascular microaneurysms, blot hemorrhage, and cotton-wool spots
- **Proliferative**: hypoxemia & neovascularization leading to virtuous hemorrhage, fibrosis, and retinal detachment
- **Macular edema**: can occur in non proliferative or proliferative stage

Treatment of Retinopathy

- Prevention (most effective treatment)
- Glycemic & BP control will slow the progression
- Laser Photocoagulation
- Ocular injection (Anti-VEGF therapy for macular edema)

- Yearly Screening (Dilated Eye Exam)

Diabetic Nephropathy

- Albuminuria (Albumin: Cr >30 mg/g)
- Always think about the other risk factors e.g HTN

- Patients with diabetic nephropathy, almost always, have evidence of diabetic retinopathy

- If your patient with diabetes has nephropathy but no retinopathy; it is very likely that the nephropathy is ***NOT*** due to diabetes

Treatment of Diabetic Nephropathy

- Prevention is the most effective therapy
- Aim is to slow the disease progression (or reverse it)
- Glucose & BP control is key
- ACE I (or ARBs) are recommended to treat nephropathy
- SGLT-2 inhibitors can be used
- Remember to change doses (or stop) medications that are renally cleared if eGFR is low

- Screen with Urinary Albumin: Creatinine & eGFR

Diabetic Neuropathy

Polyneuropathy

- Most common form is distal symmetric polyneuropathy
- Tingling, numbness, loss of sensation
- Loss of fine touch, proprioception, and vibration. Loss of ankle deep reflex

Mononeuropathy

- Dysfunction of cranial or peripheral nerves
- less common

How To Prevent These Complications?

UKPDS: Type 2 diabetes complications

- ✓ A study done in multiple centers in UK from 1977 – 1997

Does intensive glucose control reduce risk of vascular complications?

(Is there going to be a difference in the ***incidence of diabetes complications*** if we lower A1C down to 7% ***versus*** if we keep it at 8%?)

What did we learn from this study?

Intensive glucose therapy (lowering A1C to 7%) lowered risk of:

- microvascualr complications by 25% (after 15 years)
- Microalbuminuria by 33% after 12 years
- Any diabetes-related endpoint by 12%

- There was a direct relationship between the glucose level and risk of vascular complications
- Intensive glucose control is essential in lowering the risk of diabetes complications

What did we learn from this study?

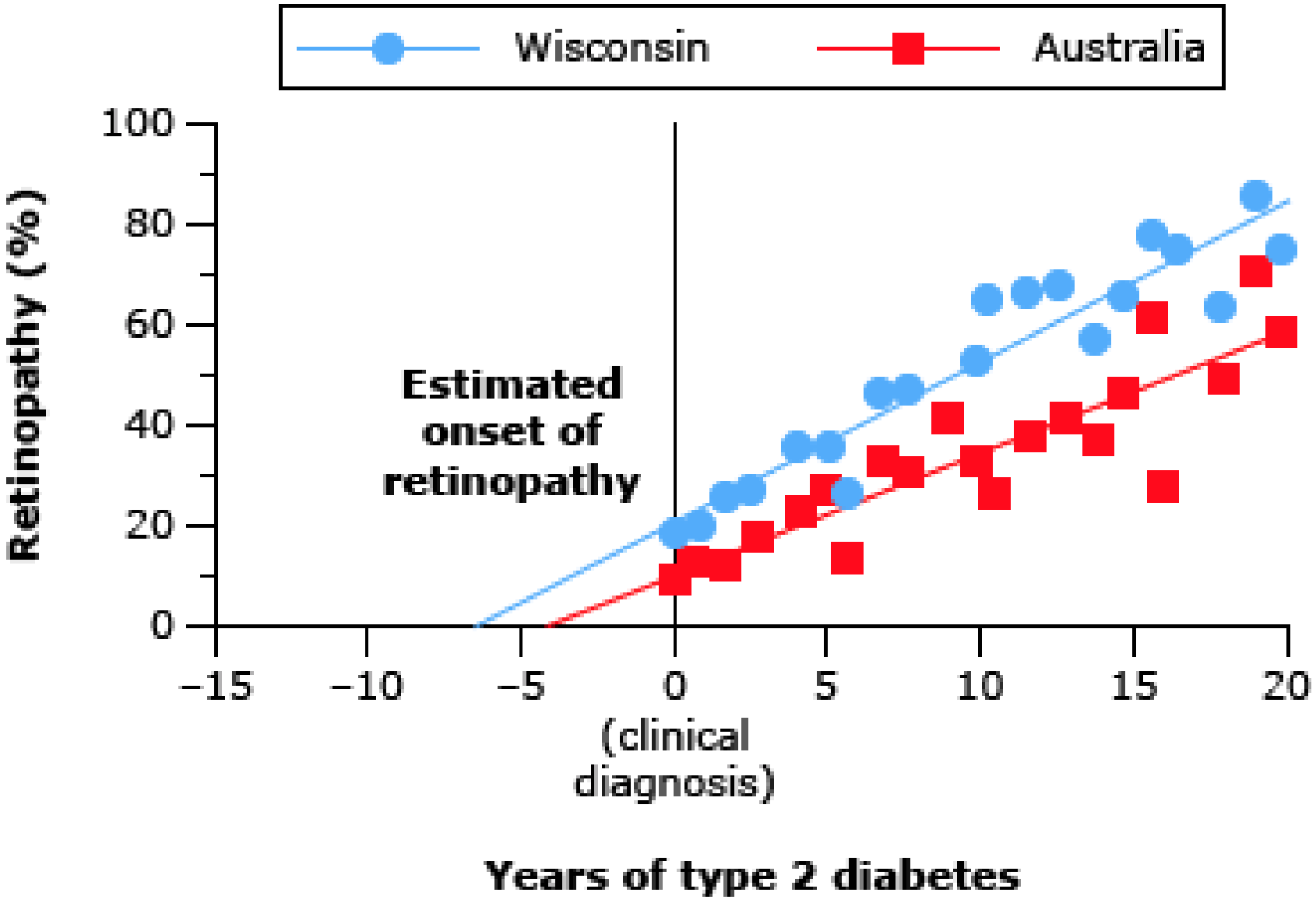
- Tight Blood Pressure control (144/82 mmHg) in patients with type 2 diabetes lowered the risk of:

  - Death by 32%
  - Stroke by 44%
  - microvascualr complications by 37%
  - Heart Failure by 56%
  - Retinopathy progression by 34%
  - Any diabetes-related endpoint by 24%

When & how to screen for the diabetes complications?

- T2D: Start screening for complications at time of diagnosis:
  - Yearly Dilated Eye Exam
  - Yearly Albumin:Cr ratio & Serum Creatinine
  - Yearly foot exam (ask the patient to examine feet, routinely)
  - Other screening tests if clinically indicated

- T1D: The same but start screening 5 years after the time of diagnosis

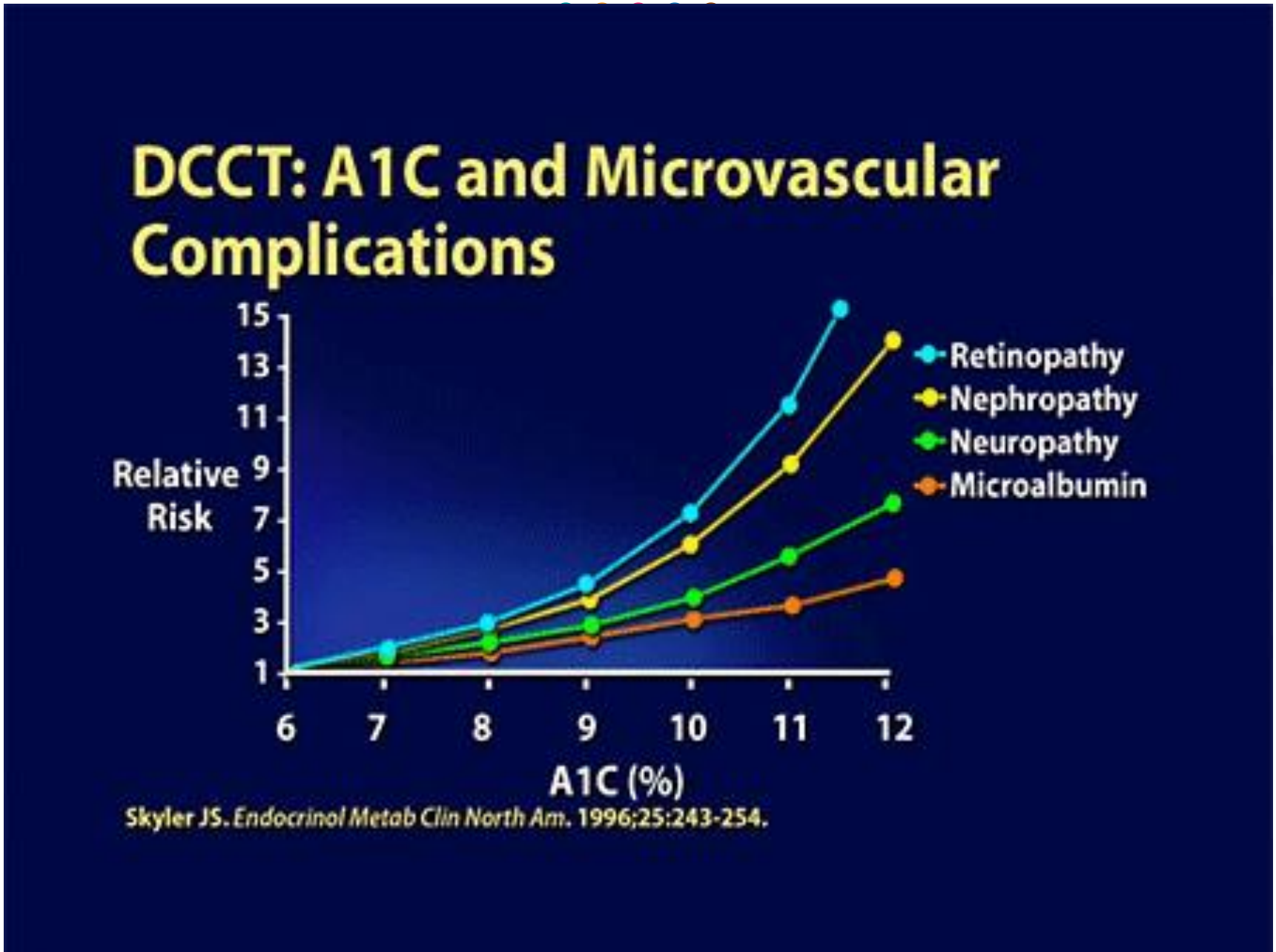

Wisconsin
Australia
Retinopathy (%)
100
80
60
40
20
0
Estimated onset of retinopathy
−15
−10
−5
0
5
10
15
20
(clinical diagnosis)
Years of type 2 diabetes

DCCT: Type 1 Diabetes & Complications

- Similar to UKPDS but in patients with T1D

“Would glucose control ameliorate the long-term complications of diabetes?

Chronic Complications of Diabetes (T1D)



Other Complications of Diabetes

- Gastroparesis
- Recurrent Infections
- Dental diseases
- Hearing loss
- Fatty Liver Disease
- Osteoporosis
- Psychological disorders

How to Reduce the Risk of Diabetes Complications

- ❑ Early Diagnosis & Routine Screening Tests
- ❑ Maintain a good glucose control (A1C around 7%)
- ❑ Maintain a good BP control (ACE or ARB) (< 140/90)
- ❑ Maintain a good control of lipid (statin)
- ❑ Smoking cessation
- ❑ Aspirin (only in patient with high CVD risk)
- ❑ Physical activity

Thank you

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