

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

Severe Insulin deficiency & Increased glucagon



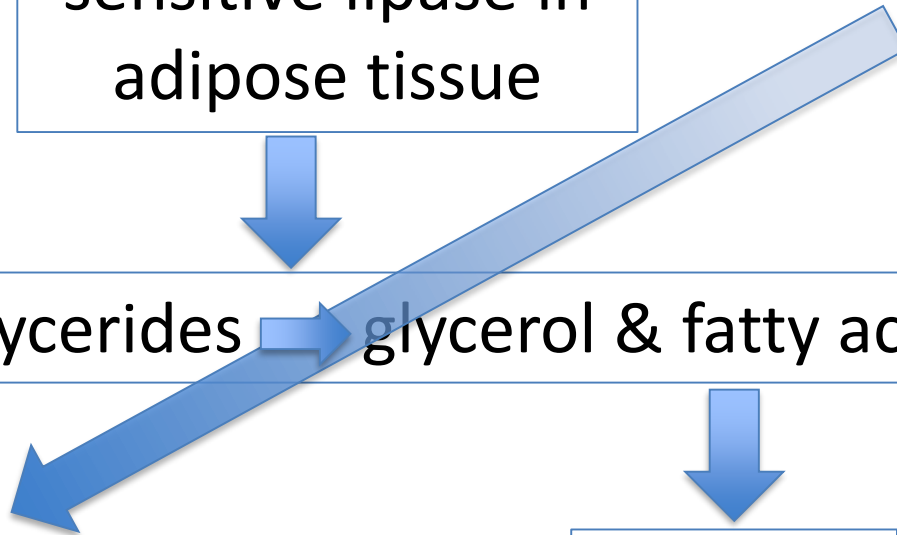
Decreased glucose uptake in muscles

Increased activity of the hormone-sensitive lipase in adipose tissue

Increased glucose production (Liver)



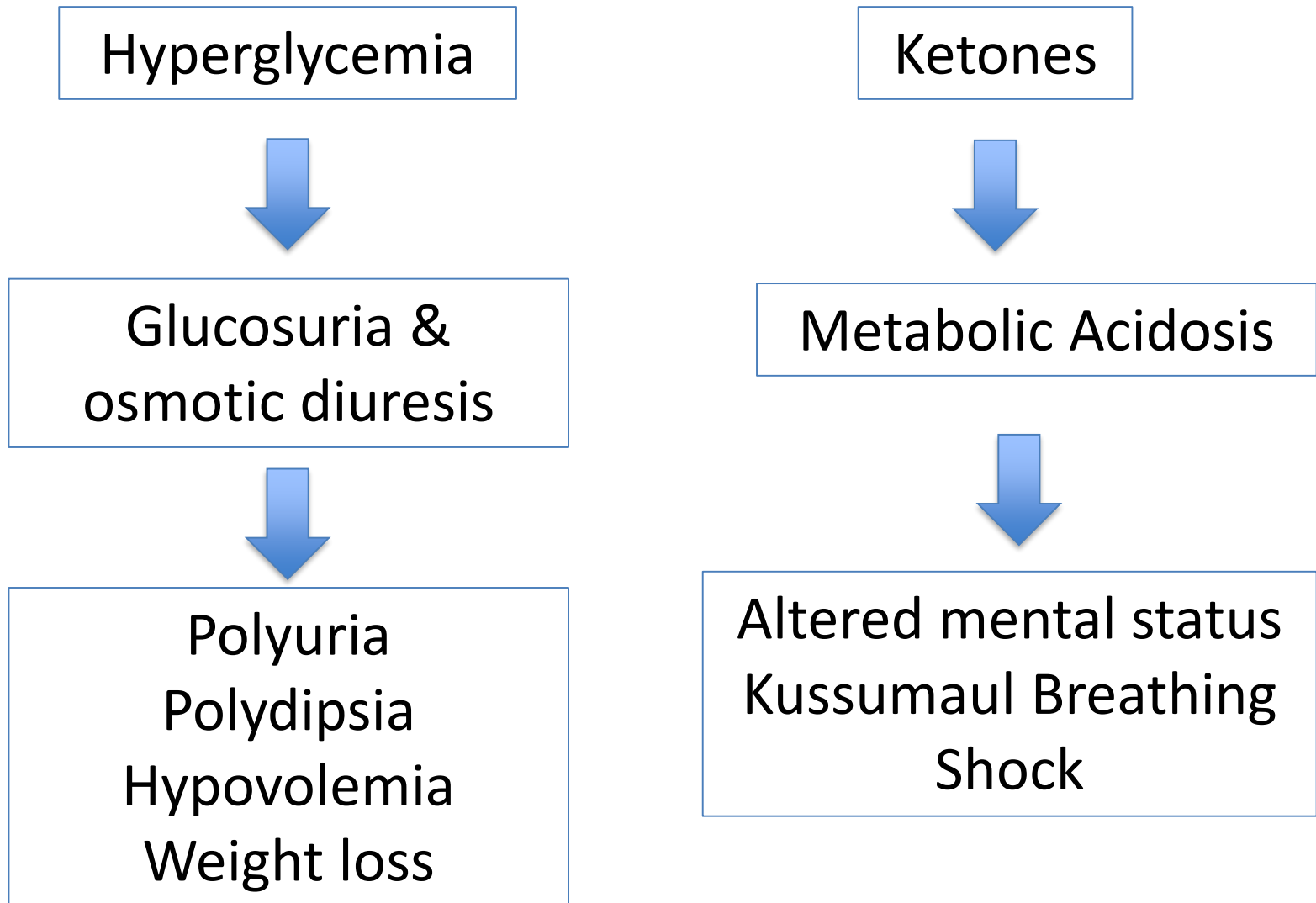
Triglycerides → glycerol & fatty acids (Liver)

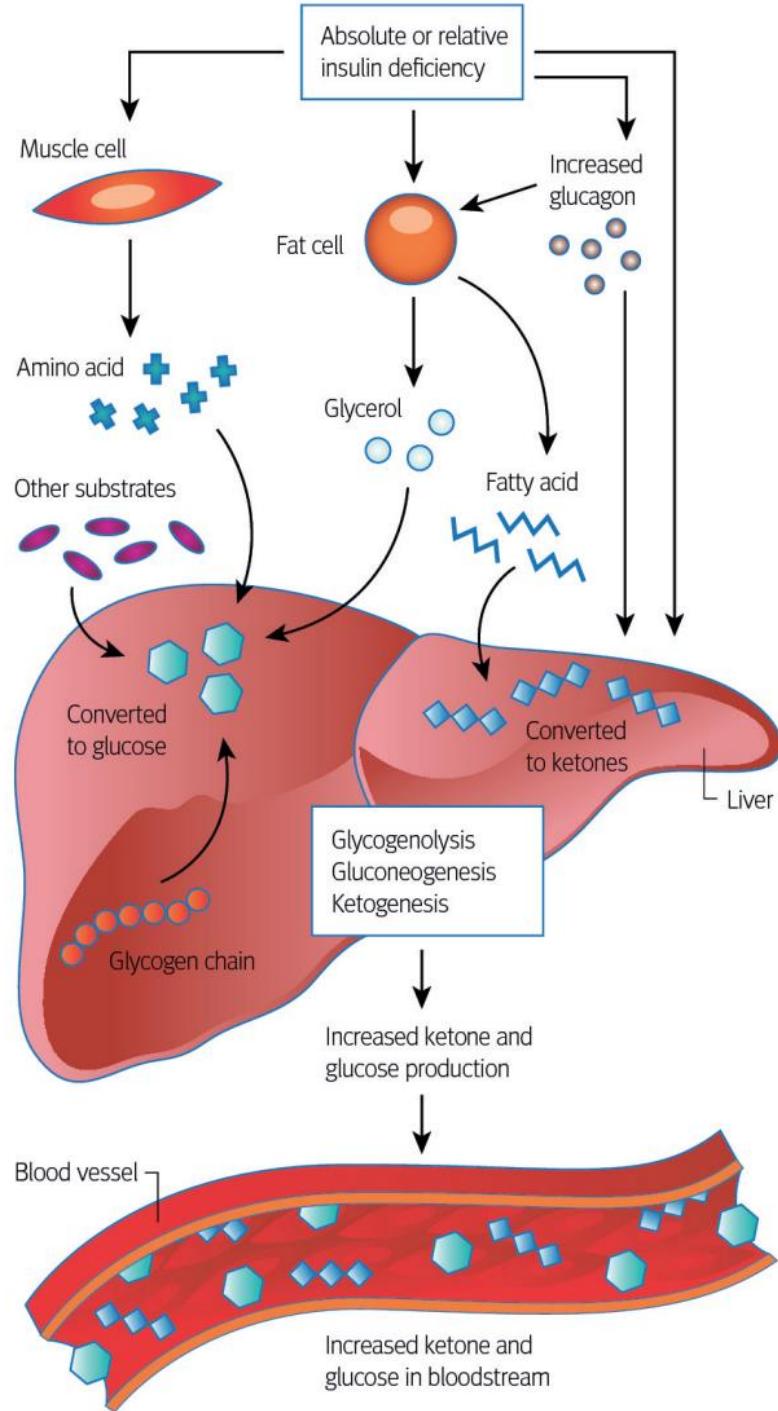


Hyperglycemia

Ketones

Pathophysiology of DKA





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

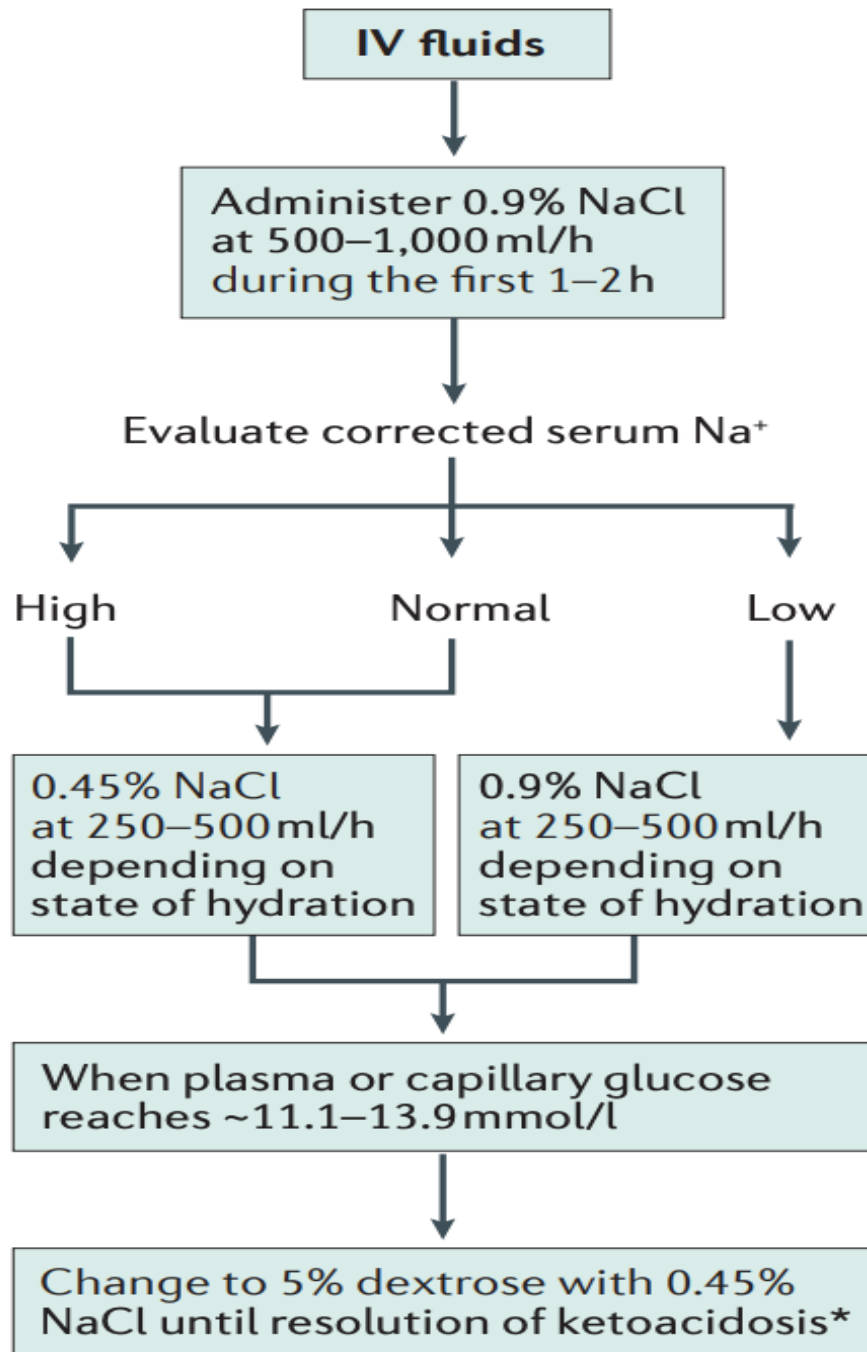
DKA is associated with increased mortality

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



Management of DKA

Insulin

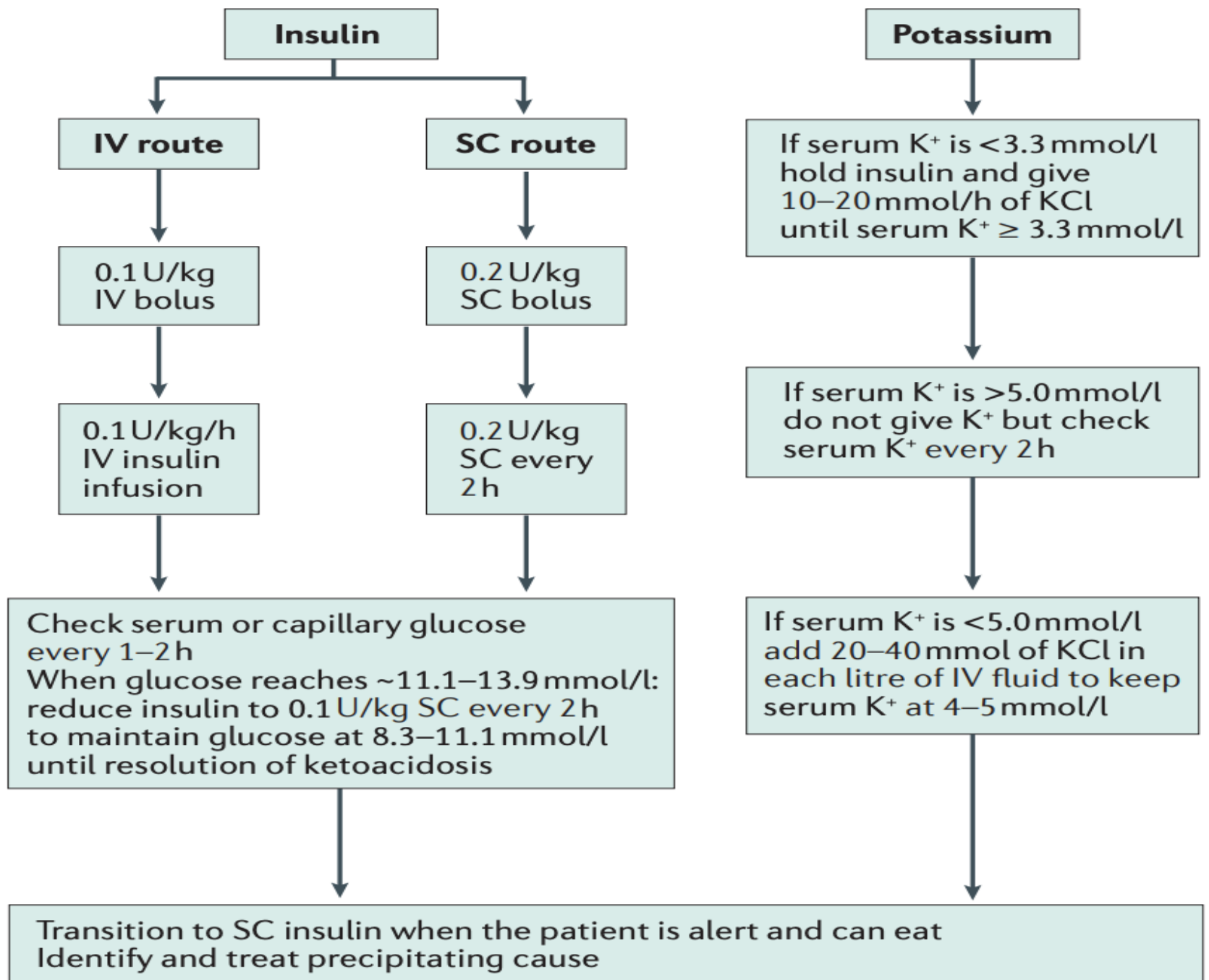
- Insulin is the next step after IVF
- Reduces serum glucose and suppresses ketogenesis
- Most of the time: we use IV insulin infusion but mild DKA can be treated with subcutaneous insulin
- Most protocols: IV insulin bolus → 0.1 unit/kg
- Followed by: IV insulin infusion → 0.1 unit/kg/h

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



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 severe 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			HHS
	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



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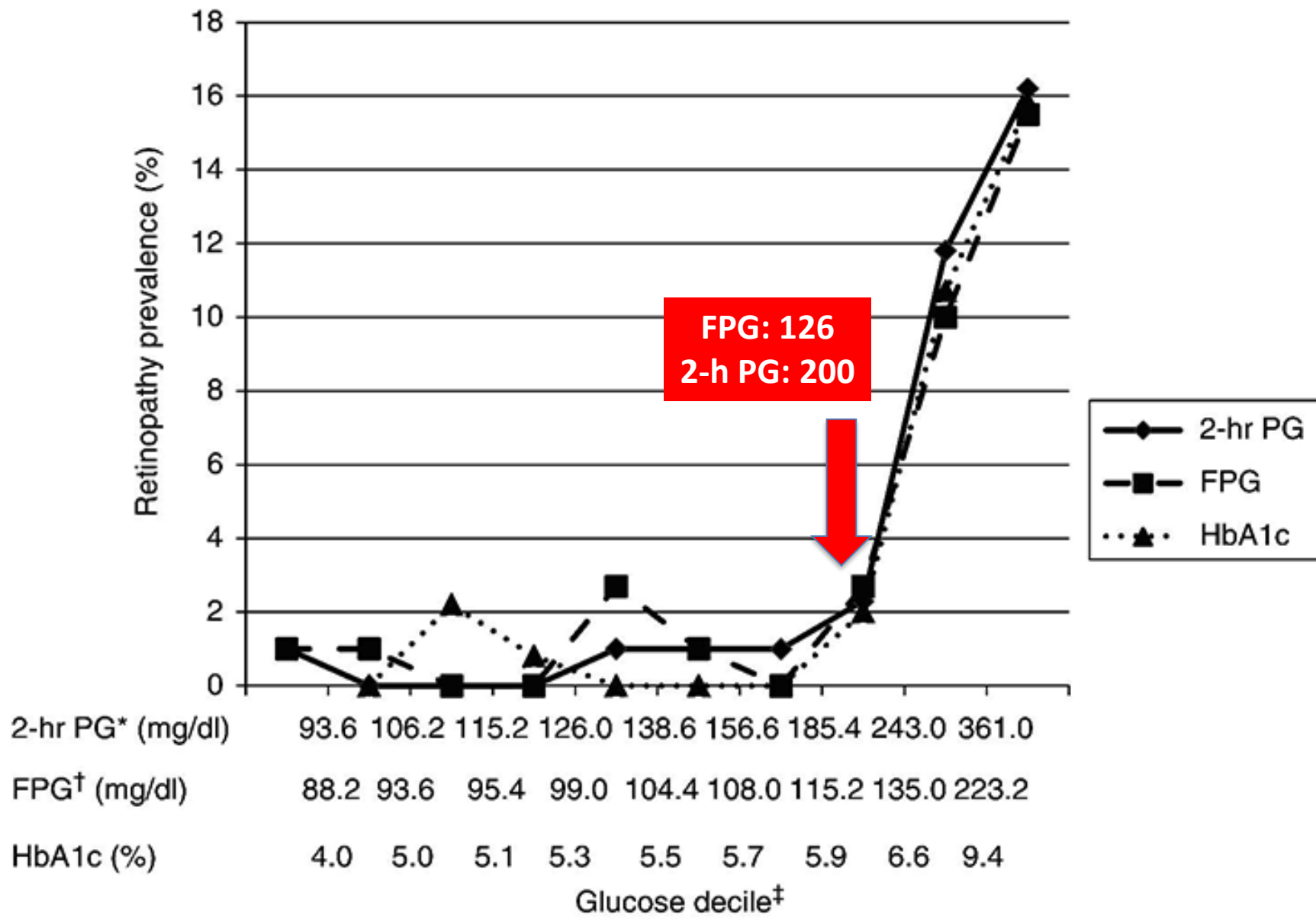
Chronic Diabetic Complications

- 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 vitreous 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:

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

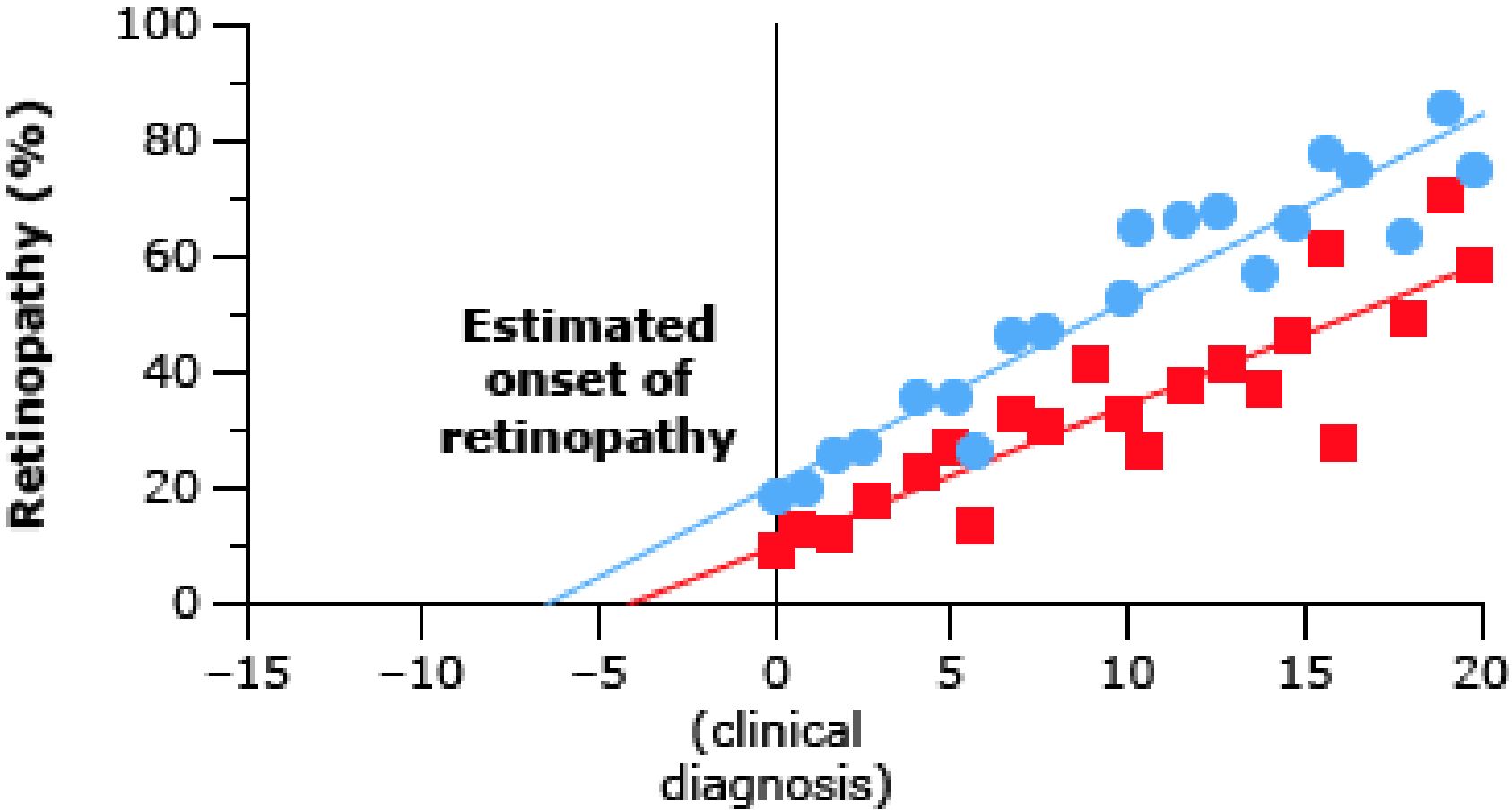
- There was a direct relationship between the glucose level and risk of vascular complications
- Intensive glucose control is essential in lowering the risk of diabetes complications

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%
 - microvascular 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



Years of type 2 diabetes

DCCT: Type 1 Diabetes & Complications

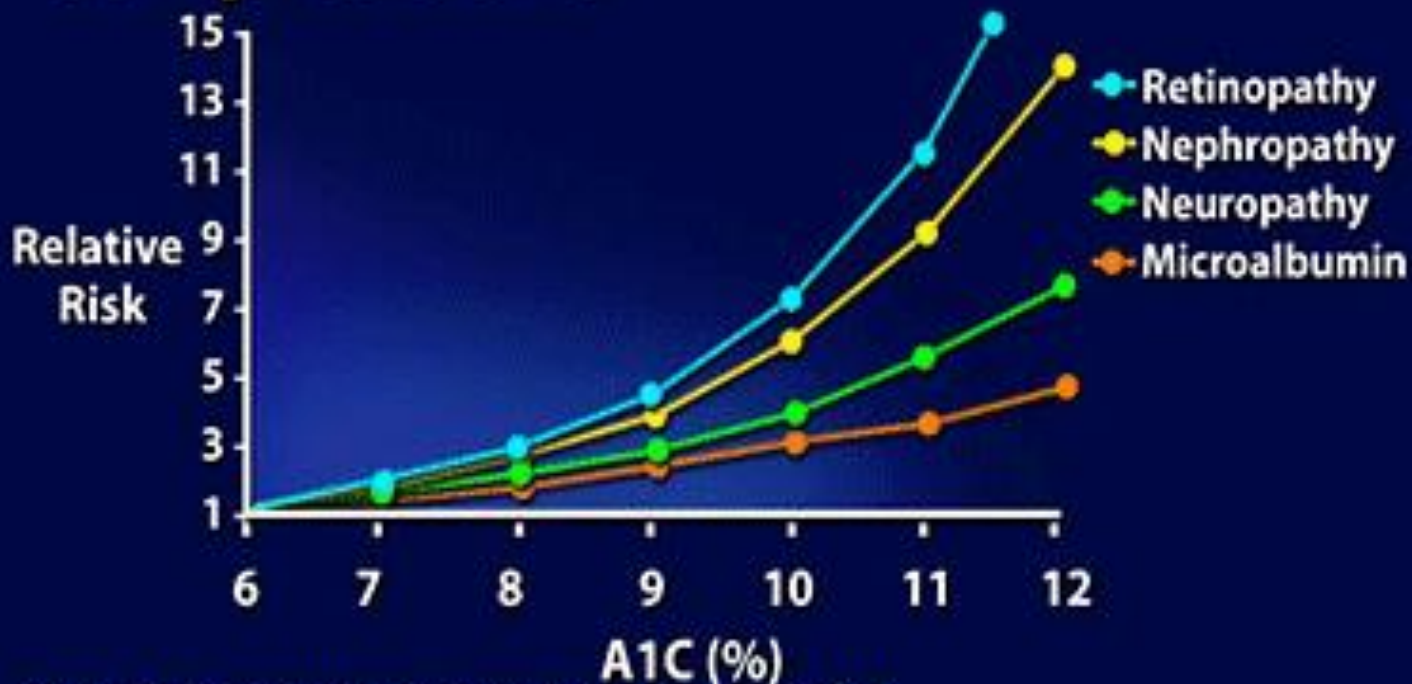


□ Similar to UKPDS but in patients with T1D

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

Chronic Complications of Diabetes (T1D)

DCCT: A1C and Microvascular Complications



Skyler JS. *Endocrinol Metab Clin North Am.* 1996;25:243-254.

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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