Acid-base disorders in diabetes

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ACID –BASE DISORDERS IN DIABETES

- **High anion-gap metabolic acidosis**

1. **Fully established ketoacidosis: (volume depletion, often with reduced glomerular filtration rate)**
2. **Lactic acidosis: Levels of l-lactate and d-lactate are increased in diabetic ketoacidosis**
3. **MALA**

- **Hyperchloremic normal-gap metabolic acidosis**

1. **In the early phase or in the recovery phase of diabetic ketoacidosis**
2. **Renal tubular acidosis of renal insufficiency, type 4 renal tubular acidosis**

- **Mtabolic alkalosis**

1. **Vomiting, which often occurs in patients with diabetic ketoacidosis and diabetic gastroparesis**
2. **Administration of loop or thiazide diuretics**
3. **Acidosis induced hypochloremic alkalosis**

- **Adult respiratory distress syndrome**

Diabetic ketoacidosis (DKA) and the hyperosmolar state (HHS) appear as 2 extremes in hyperglycemic the spectrum of diabetic decompensation.

The incidence of DKA is between 4.6 and 8.0 per 1000 person-years among patients with diabetes, whereas that of HHS is less than 1 per 1000 person-years.

The estimated mortality rate for DKA is between 4% and 10%, whereas the rate for HHS varies from 10% to 50%, the range most likely owing to underlying illnesses.

Risk factors

- Infection remains the most important precipitating factor in the development of DKA and HHS. In 20%–25% of cases, infections are the first manifestations of previously undiagnosed diabetes mellitus.
- Omissions or inadequate insulin doses are frequent precipitating factors, particularly for DKA.
- silent myocardial infarction
- cerebrovascular accident
- mesenteric ischemia
- acute pancreatitis
- use of medications such as steroids, thiazide diuretics
- In 2%–10% of cases of DKA, no obvious precipitating factor can be identified

DKA

Definition

DKA occurs when the metabolic
acidosis presents an arterial pH lower than 7.3 or serum bicarbonate lower than 15 mEq/dl, and, moreover, in the presence of a worsening increase in the concentration of ketones in blood and, consequently, in urine.

In DKA, the glycemia is usually high (above 240 mg/dl) but it may also present normal.

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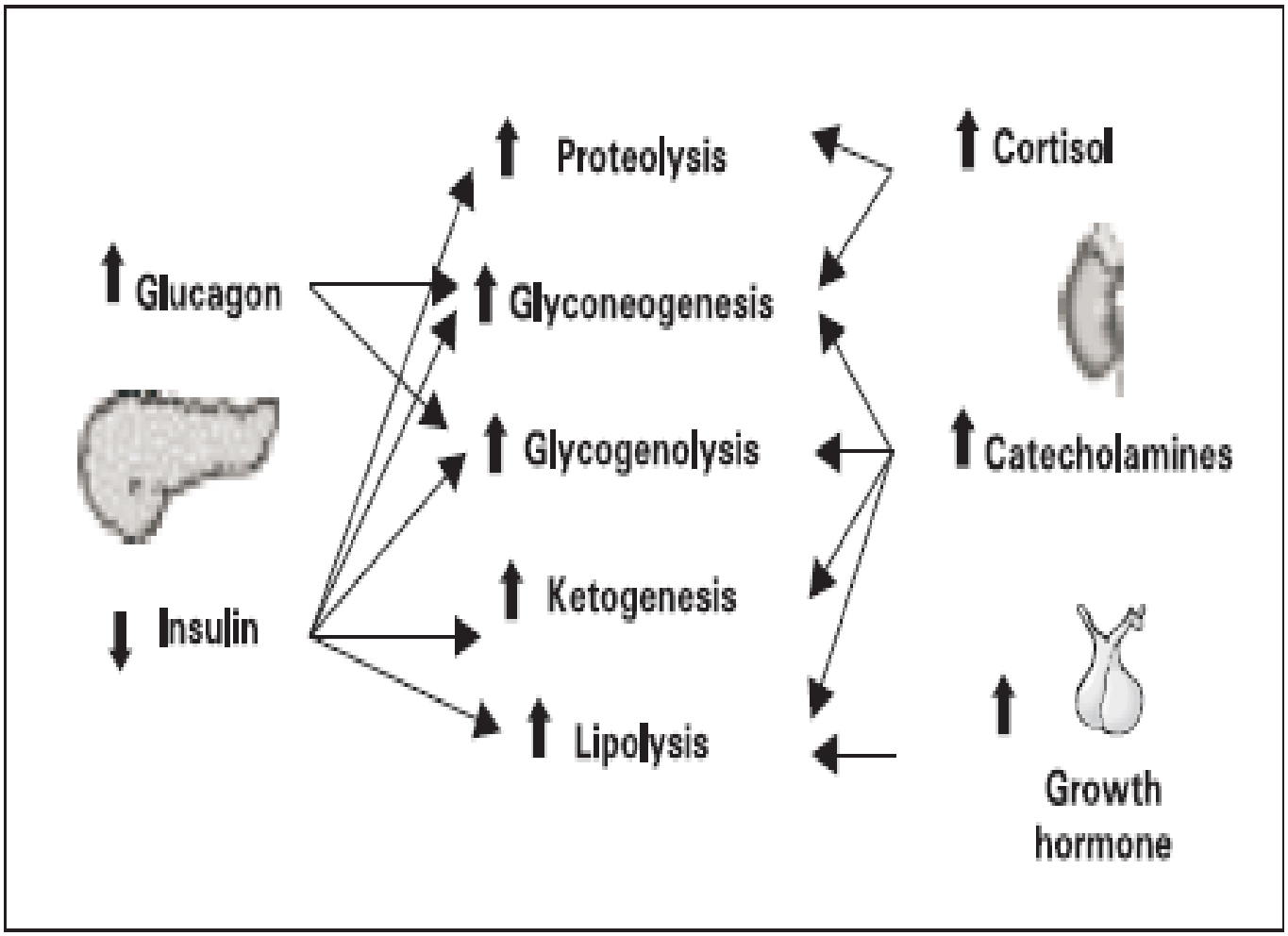
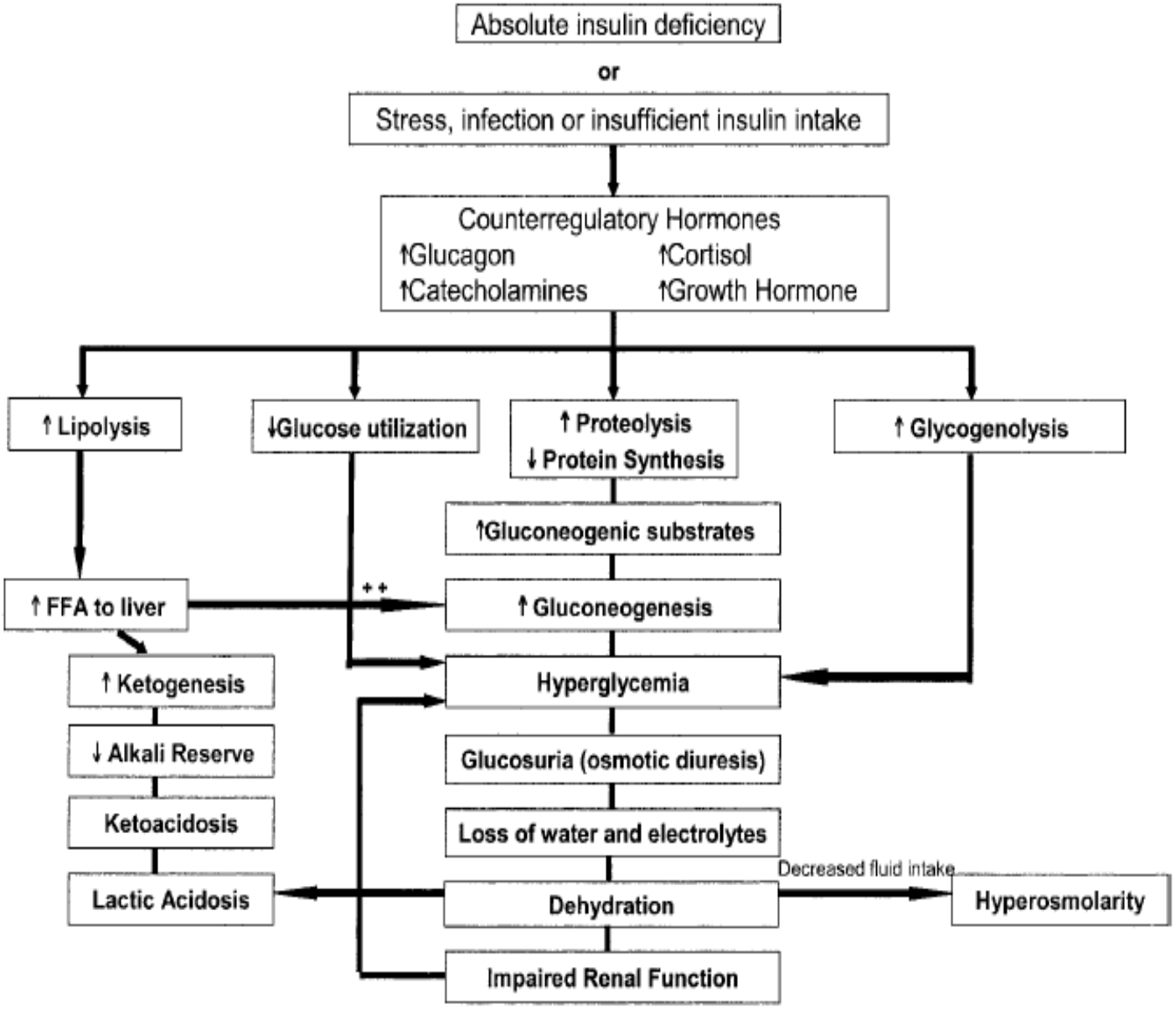
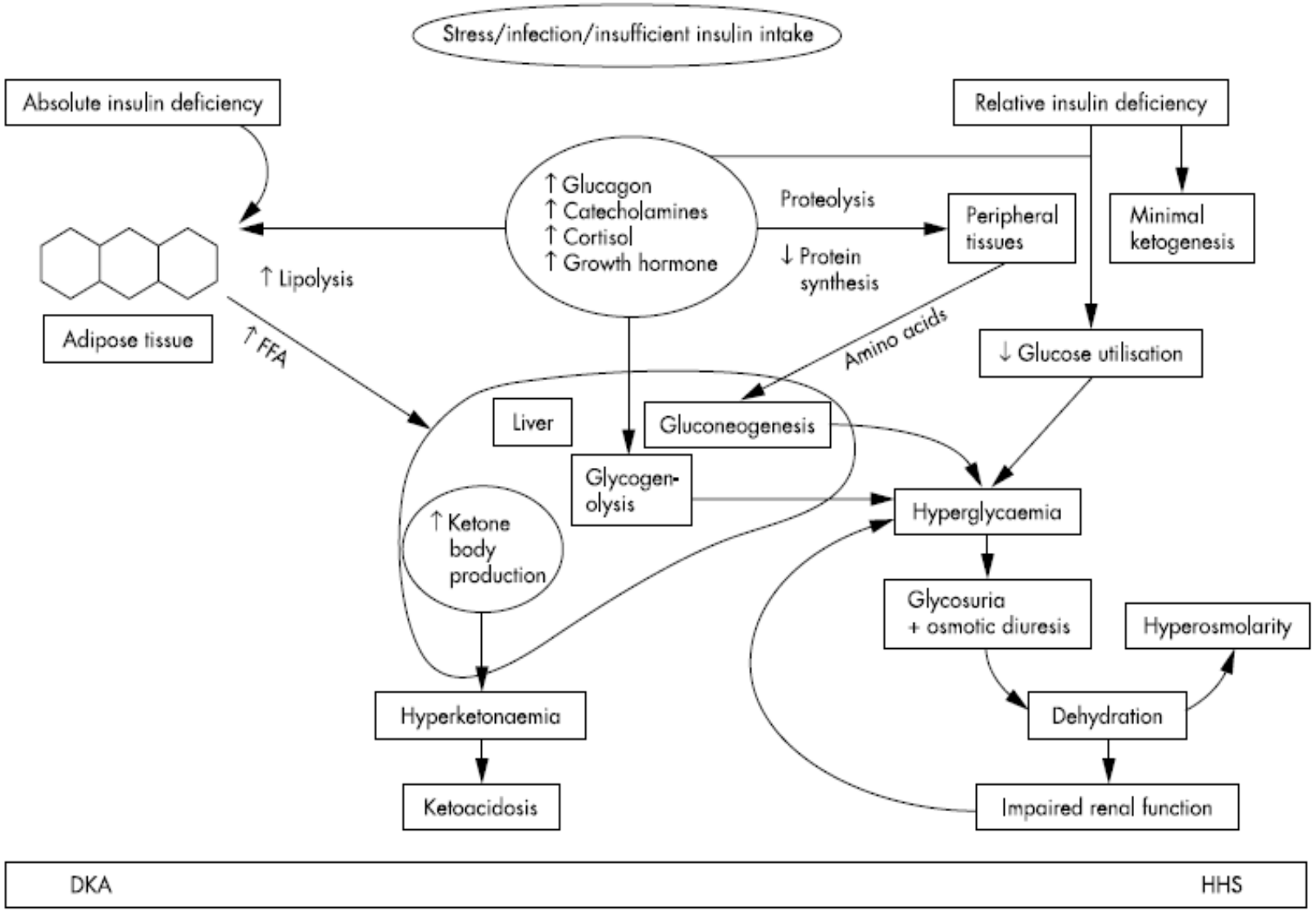
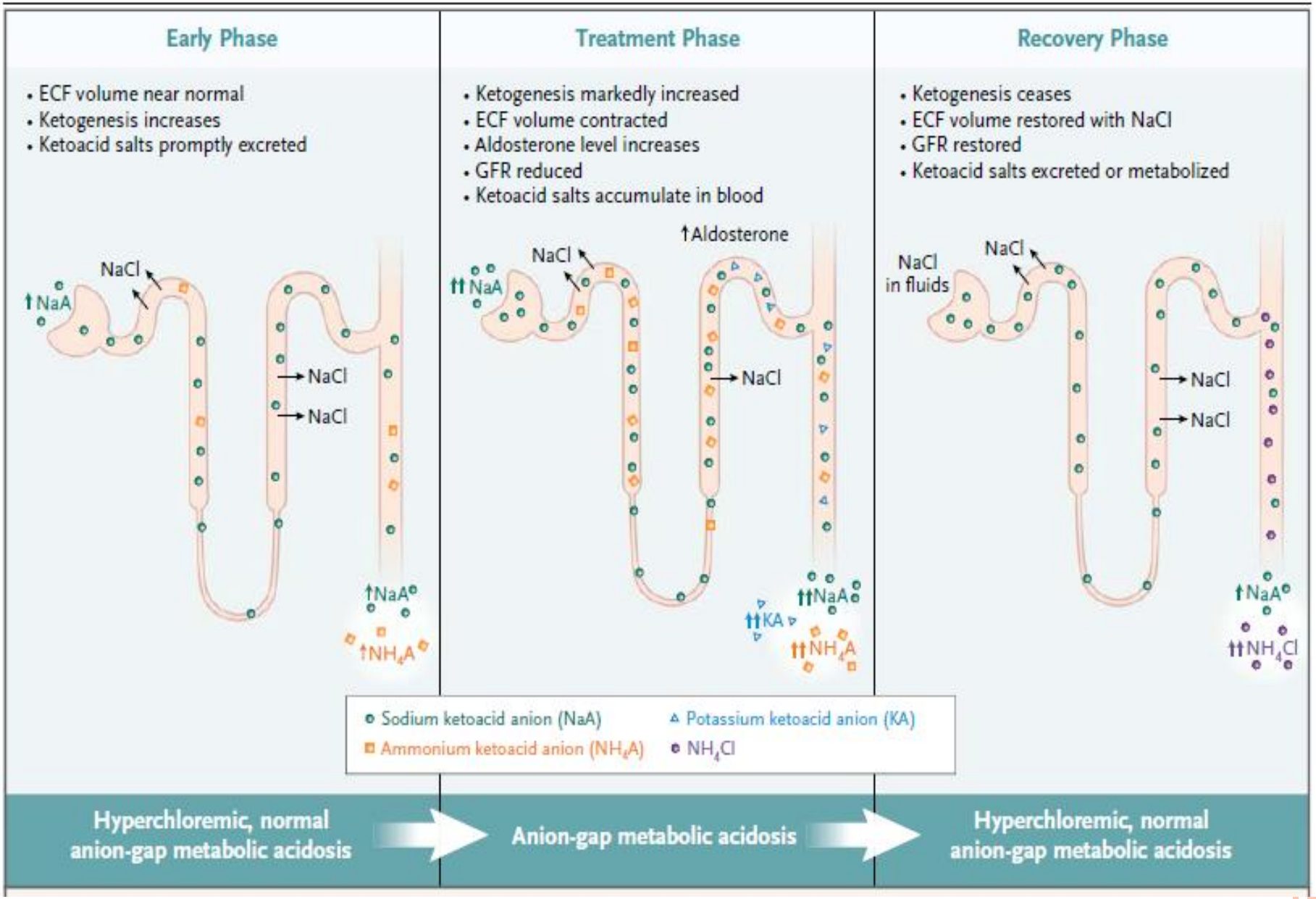


J Pediatr (Rio J) 2001; 77(1): 9-16: Diabetes mellitus, cerebral edema ,diabetic ketoacidosis, fluid therapy.

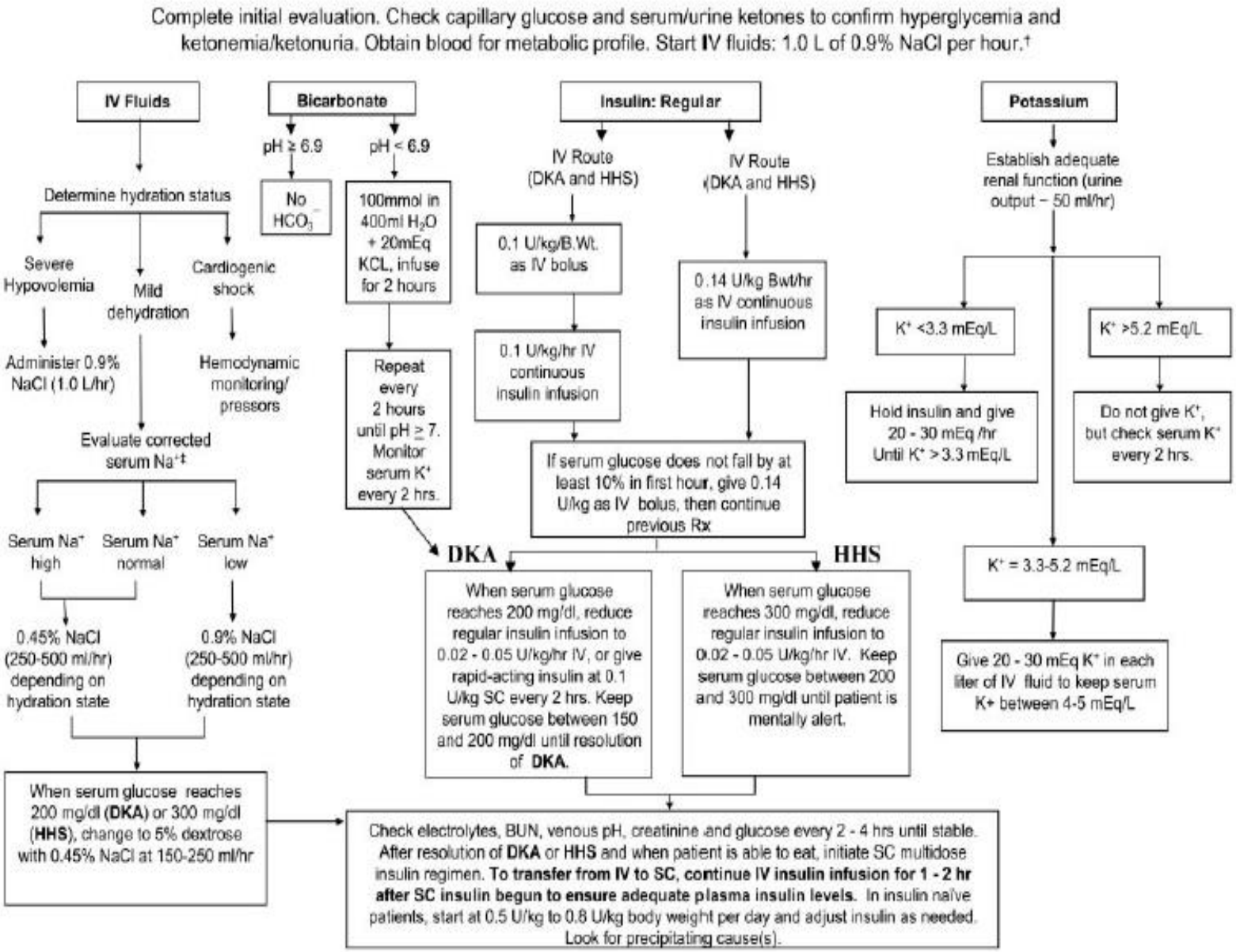

Absolute insulin deficiency
or
Stress, infection or insufficient insulin intake
Counterregulatory Hormones
↑Glucagon
↑Cortisol
↑Catecholamines
↑Growth Hormone
↑ Lipolysis
↓Glucose utilization
↑ Proteolysis
↓ Protein Synthesis
↑ Glycogenolysis
↑Gluconeogenic substrates
↑ FFA to liver
++
↑ Gluconeogenesis
↑ Ketogenesis
Hyperglycemia
↓ Alkali Reserve
Glucosuria (osmotic diuresis)
Ketoacidosis
Loss of water and electrolytes
Decreased fluid intake
Lactic Acidosis
Dehydration
Hyperosmolarity
Impaired Renal Function



Postgrad Med J 2004;80:253–261.



N Engl J Med 373;6 ;August 6, 2015


Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain blood for metabolic profile. Start IV fluids: 1.0 L of 0.9% NaCl per hour.†
IV Fluids
Determine hydration status
Severe Hypovolemia
Mild dehydration
Cardiogenic shock
Administer 0.9% NaCl (1.0 L/hr)
Hemodynamic monitoring/ pressors
Evaluate corrected serum Na+‡
Serum Na+ high
Serum Na+ normal
Serum Na+ low
0.45% NaCl (250-500 ml/hr) depending on hydration state
0.9% NaCl (250-500 ml/hr) depending on hydration state
When serum glucose reaches 200 mg/dl (DKA) or 300 mg/dl (HHS), change to 5% dextrose with 0.45% NaCl at 150-250 ml/hr
Bicarbonate
pH ≥ 6.9
pH < 6.9
No HCO3−
100mmol in 400ml H2O + 20mEq KCL, infuse for 2 hours
Repeat every 2 hours until pH ≥ 7. Monitor serum K+ every 2 hrs.
Insulin: Regular
IV Route (DKA and HHS)
IV Route (DKA and HHS)
0.1 U/kg/B.Wt. as IV bolus
0.1 U/kg/hr IV continuous insulin infusion
0.14 U/kg Bwt/hr as IV continuous insulin infusion
If serum glucose does not fall by at least 10% in first hour, give 0.14 U/kg as IV bolus, then continue previous Rx
DKA
When serum glucose reaches 200 mg/dl, reduce regular insulin infusion to 0.02 - 0.05 U/kg/hr IV, or give rapid-acting insulin at 0.1 U/kg SC every 2 hrs. Keep serum glucose between 150 and 200 mg/dl until resolution of DKA.
HHS
When serum glucose reaches 300 mg/dl, reduce regular insulin infusion to 0.02 - 0.05 U/kg/hr IV. Keep serum glucose between 200 and 300 mg/dl until patient is mentally alert.
Potassium
Establish adequate renal function (urine output ~ 50 ml/hr)
K+ <3.3 mEq/L
Hold insulin and give 20 - 30 mEq /hr Until K+ > 3.3 mEq/L
K+ >5.2 mEq/L
Do not give K+, but check serum K+ every 2 hrs.
K+ = 3.3-5.2 mEq/L
Give 20 - 30 mEq K+ in each liter of IV fluid to keep serum K+ between 4-5 mEq/L
Check electrolytes, BUN, venous pH, creatinine and glucose every 2 - 4 hrs until stable. After resolution of DKA or HHS and when patient is able to eat, initiate SC multidose insulin regimen. To transfer from IV to SC, continue IV insulin infusion for 1 - 2 hr after SC insulin begun to ensure adequate plasma insulin levels. In insulin naïve patients, start at 0.5 U/kg to 0.8 U/kg body weight per day and adjust insulin as needed. Look for precipitating cause(s).

Once the ketoacidosis in DKA has been corrected :

(plasma glucose level < 11.0 mmol/L, serum bicarbonate level ≥ 18 mmol/L, venous pH > 7.3 and anion gap < 12 mmol/L).

LACTIC ACIDOSIS

Severe lactic acidosis is defined as a high anion gap metabolic acidosis with a blood lactate concentration >5.0 mmol/l (normal 0.4–1.2 mmol/l).

Both types 1 and 2 diabetes mellitus seem to predispose to the development of lactic acidosis. One large population-based study has shown an incidence of lactic acidosis of 3% among all patients with diabetes mellitus compared with 0.1% in the nondiabetic population.

Clin J Am Soc Nephrol 10: 1476–1483, August, 2015

Table 4 Causes of lactic acidosis

Type A (anaerobic/hypoxic)	Type B (aerobic)
Shock:	Systemic disease:
Cardiogenic	Diabetes
Endotoxic	Neoplasia
Hypovolaemic	Liver disease
Cardiac failure	Drugs/toxins:
	Biguanides
Asphyxia	Ethanol
	Methanol
Carbon monoxide poisoning	Salicylates
	Inborn errors of metabolism:
	Type 1 glycogen storage disease
	Fructose 1,6-diphosphatase deficiency

Adapted from Stacpoole *et al.*[80]

LACTIC ACIDOSIS IN DIABETIC KETOACIDOSIS

Originally, elevated lactate values in patients with DKA were thought to be the result of inadequate tissue perfusion and oxygenation ,the resulting relative hypoxaemia stimulates the process of anaerobic glycolysis, where pyruvic acid is converted to l-lactate, yielding two ATP molecules.

More recently, however, it was demonstrated that the metabolic derangements itself present in DKA might contribute as well to the elevated lactate levels. **This could be explained by various intracellular and extracellular mechanisms.** First, an increased amount of d-lactate is formed in erythrocytes. Since erythrocytes do not require insulin for glucose uptake, intracellular glucose concentrations approach ambient extracellular levels during ketoacidosis. A substantial portion of the glucose in the erythrocyte is converted to pyruvate and finally l-lactate by aerobic glycolysis to produce ATP. The remainder is metabolised by the sorbitol pathway and the pentose-phosphate shunt to produce methylglyoxal, which is a toxic endogenous glucose metabolite, that is degraded by the glyoxalase system to produce d-lactate. Methylglyoxal (and thereby d-lactate) is also formed directly in the plasma via an interaction between glucose and proteins and via aminoacetone degradation directly in the plasma.

J Crit Care 2012;27:132-7

Metformine and Lactic Acidosis

Attending Rounds

Lactic Acidosis in a Patient with Type 2 Diabetes Mellitus

Lawrence S. Weisberg

Abstract

Lactic acidosis occurs when lactate production exceeds its metabolism. There are many possible causes of lactic acidosis, and in any given patient, several causes may coexist. This Attending Rounds presents a case in point. Metformin's role in the pathogenesis of lactic acidosis in patients with diabetes mellitus is complex, as the present case illustrates. The treatment of lactic acidosis is controversial, except for the imperative to remedy its underlying cause. The use of sodium bicarbonate to treat the often alarming metabolic derangements may be quite efficacious in that regard but is of questionable benefit to patients. Renal replacement therapies (RRTs) have particular appeal in this setting for a variety of reasons, but their effect on clinical outcomes is untested.

Clin J Am Soc Nephrol 10: 1476–1483, 2015. doi: 10.2215/CJN.10871014

MALA is an extremely rare event with an estimated incidence

of 0.03 to 0.06 per 1000 patient-years.

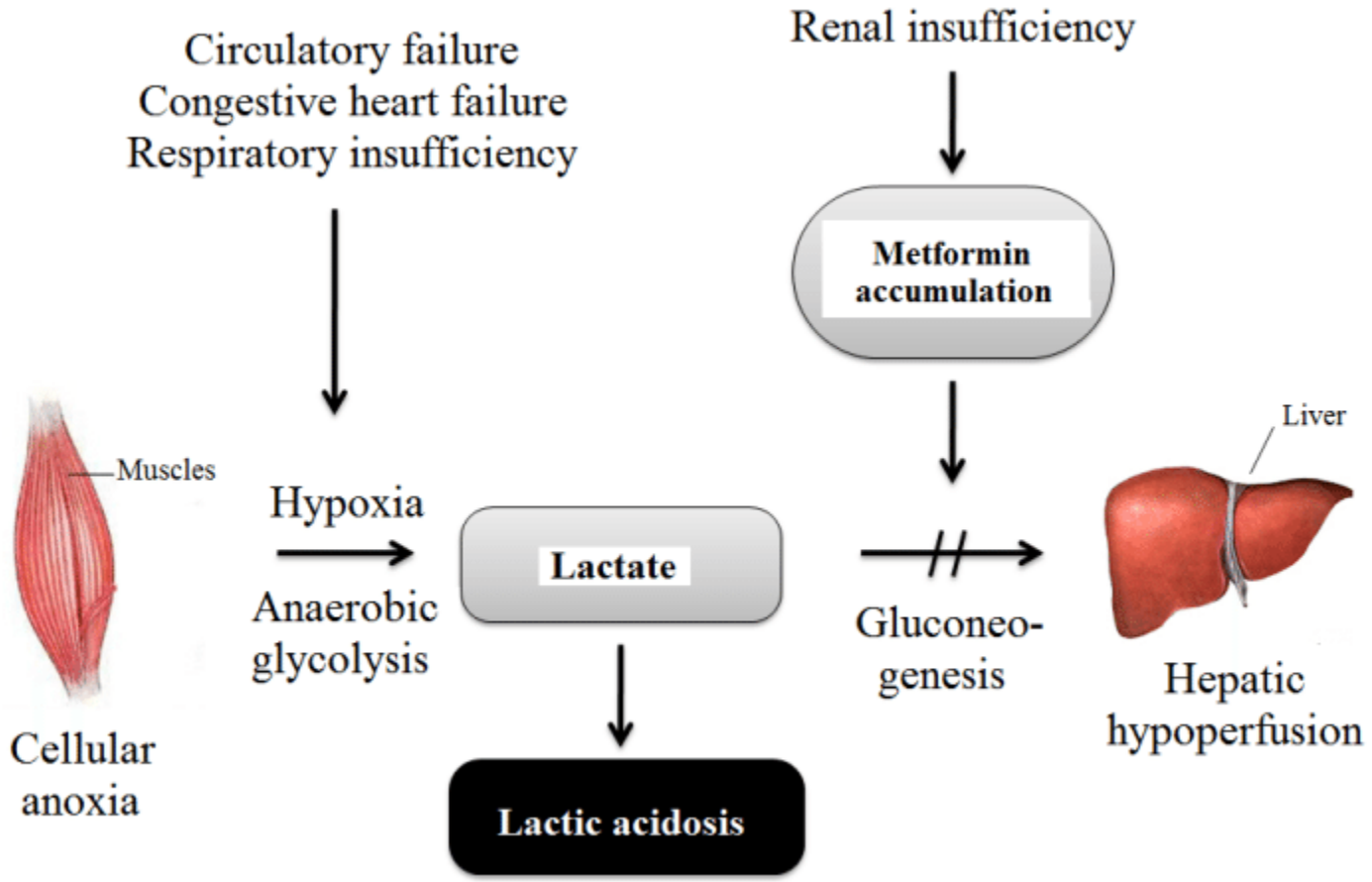
Metformin plasma level of at least 40mg/L (10 times the therapeutic level)

may be necessary to cause lactic acidosis.

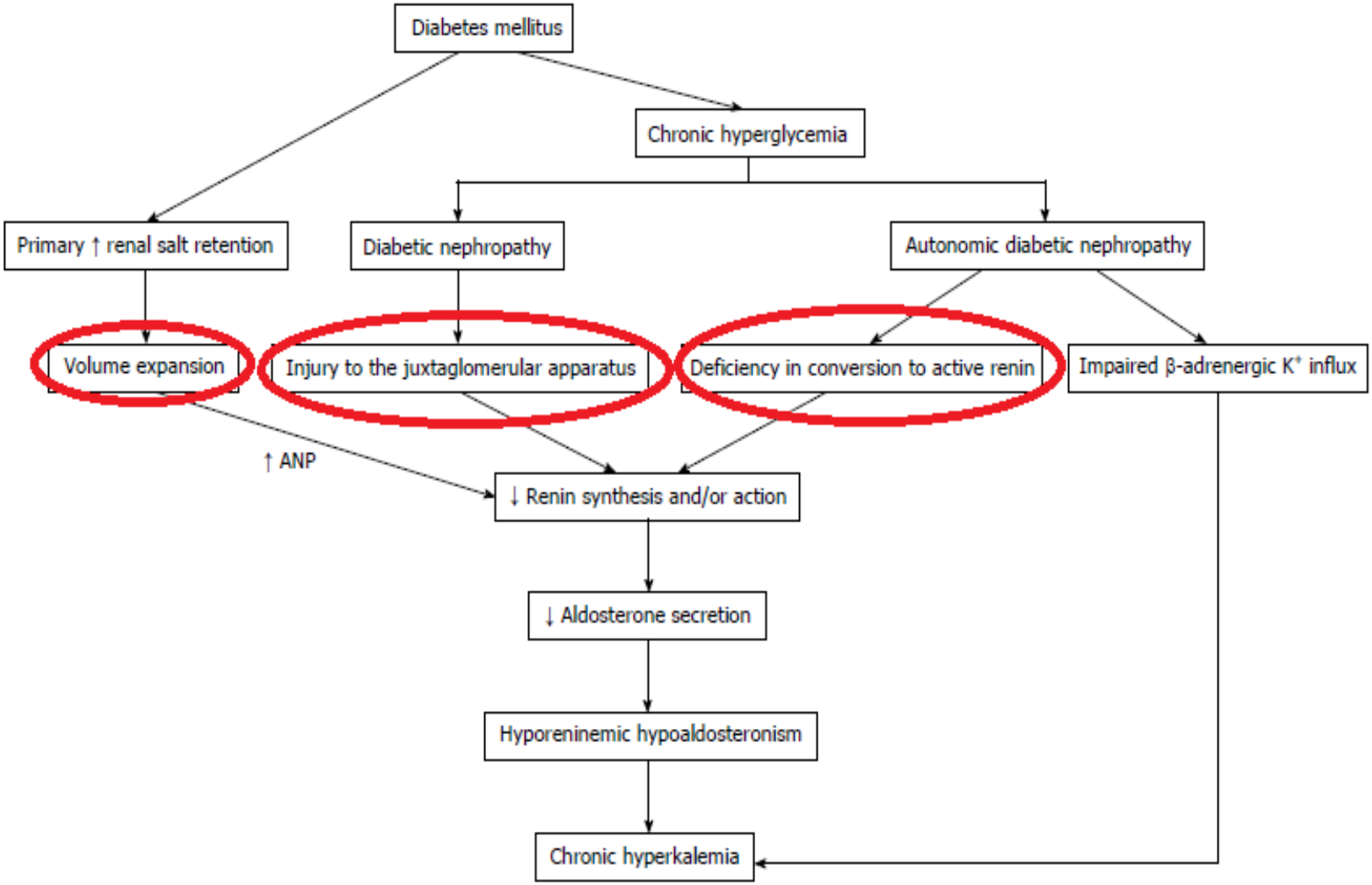
The increase in plasma lactate concentration observed with metformin

exposure correlates with the inhibition of mitochondrial oxidative

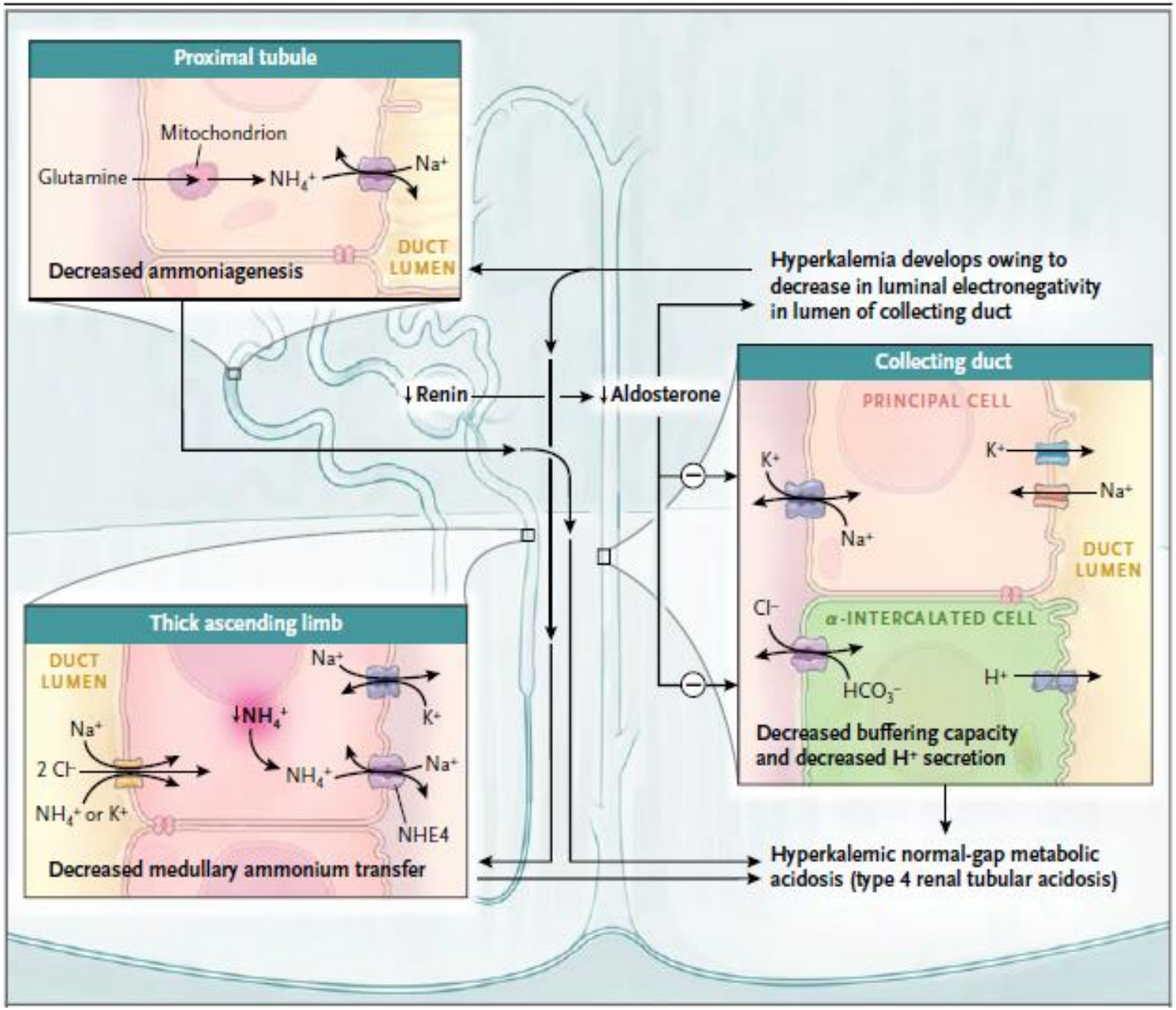
phosphorylation .


Circulatory failure
Congestive heart failure
Respiratory insufficiency
Renal insufficiency
Metformin accumulation
Muscles
Liver
Hypoxia
Anaerobic glycolysis
Lactate
Gluconeo-genesis
Hepatic hypoperfusion
Cellular anoxia
Lactic acidosis

Sousa AGP *et al*. Hyporeninemic hypoaldosteronism and diabetes mellitus



World J Diabetes 2016 March 10; 7(5): 101-111



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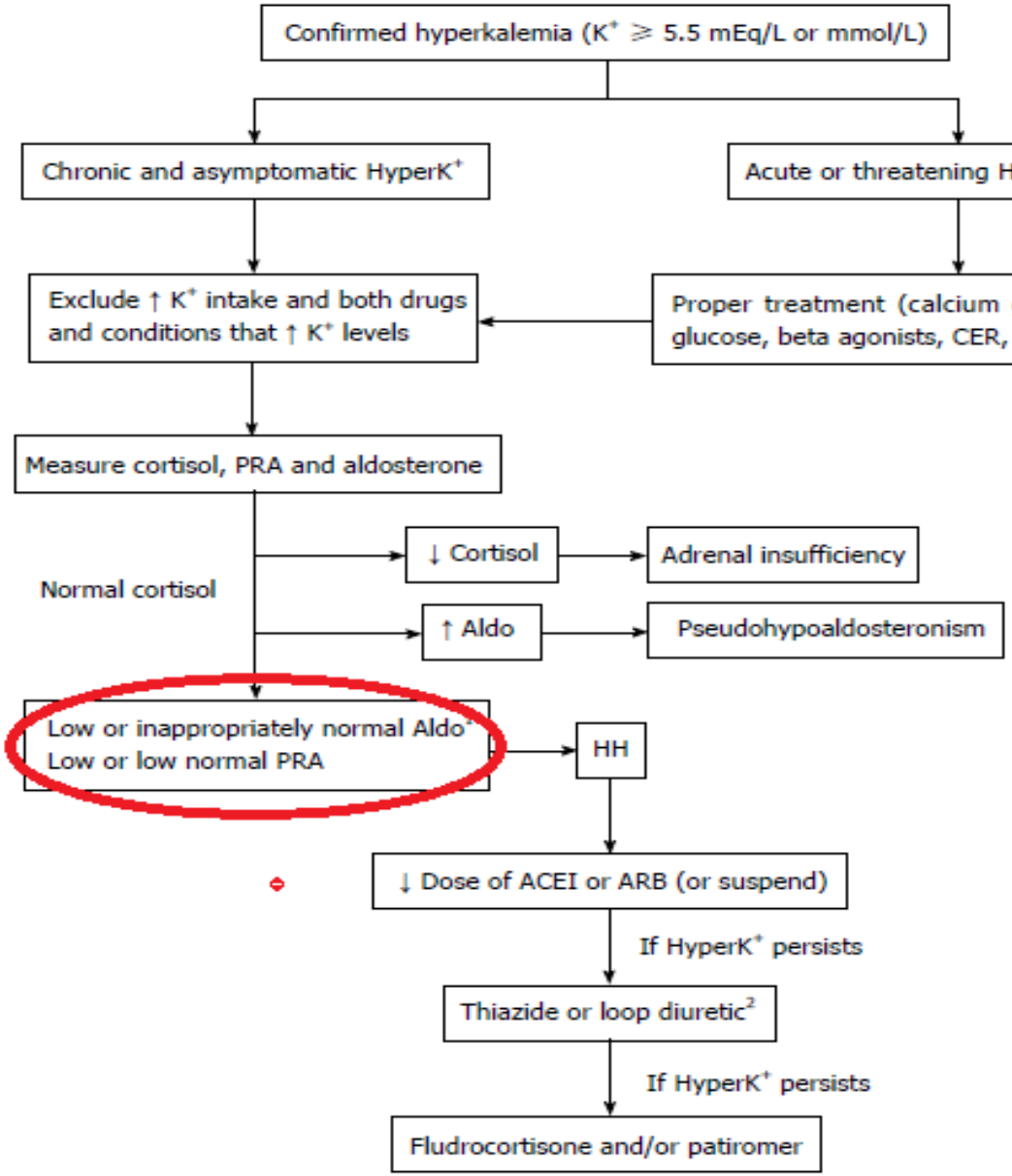

World J Diabetes 2016 March 10; 7(5): 101-111

Hypochloremic metabolic alkalosis

- **Vomitting**
- **Use of diuretic**
- **Acidosis induced alkalosis:**

[Cl−] was markedly decreased in patients with DKA. Hypochloraemia in DKA is generally explained by plasma dilution. However, the [Na+]/[Cl−] ratio was increased compared to the healthy control subjects, indicating a lack of [Cl−], relative to [Na+].

Hypochloraemia implies hypochloraemic alkalosis, which could be a metabolic compensation for metabolic acidosis in DKA.

The inverse correlation of [Cl−] and [XA−] supports this assumption: The more ketoacids, the less chloride .

Adjusting [Cl−] and [XA−] for [Na+] is an established tool to appreciate and quantitate an excess or deficit of a certain plasma ion, when plasma dilution is present.

It hase been suggested that hypochloremia caused by chloride moving into the intracellular compartment ,could be a response to accumulating anions in blood. Also chloride channels activated by acidic exteracellular PH,and enhanced renal chloride excretion be possible.

Adult respiratory distress syndrome

Adult respiratory distress syndrome, or noncardiogenic pulmonary edema, is a potentially fatal complication of DKA that fortunately occurs rarely. This change is believed to be due to increased water in the lungs and reduced lung compliance and may be similar to those occurring in brain cells leading to cerebral edema, which suggests that it is a common biological phenomenon in tissues.

Respiratory muscle weakness due to hypokalemia,hypophosphatemia ,hypomagnesemia ,acidosis, pulmonary infection,……