Hypoxia-induced lactic acidosis. Accumulation of lactate during hypoxia, by far the most common clinical setting of the disorder, originates from impaired mitochondrial oxidative function that reduces the availability of adenosine triphosphate (ATP) and NAD^+ (oxidized nicotinamide adenine dinucleotide) within the cytosol. In turn, these changes cause cytosolic accumulation of pyruvate as a consequence of both increased production and decreased utilization. Increased production of pyruvate occurs because the reduced cytosolic supply of ATP stimulates the activity of 6-phosphofructokinase (PFK), thereby accelerating glycolysis. Decreased utilization of pyruvate reflects the fact that both pathways of its consumption depend on mitochondrial oxidative reactions: oxidative decarboxylation to acetyl coenzyme A (acetyl-CoA), a reaction catalyzed by pyruvate dehydrogenase (PDH), requires a continuous supply of NAD^+; and carboxylation of pyruvate to oxaloacetate, a reaction catalyzed by pyruvate carboxylase (PC), requires ATP. The increased [NADH]/[NAD^+] ratio (NADH refers to the reduced form of the dinucleotide) shifts the equilibrium of the lactate dehydrogenase (LDH) reaction (that catalyzes the interconversion of pyruvate and lactate) to the right. In turn, this change coupled with the accumulation of pyruvate in the cytosol results in increased accumulation of lactate. Despite the prevailing mitochondrial dysfunction, continuation of glycolysis is assured by the cytosolic regeneration of NAD^+ during the conversion of pyruvate to lactate. Provision of NAD^+ is required for the oxidation of glyceraldehyde 3-phosphate, a key step in glycolysis. Thus, lactate accumulation can be viewed as the toll paid by the organism to maintain energy production during anaerobiosis (hypoxia) [14]. ADP—adenosine diphosphate; TCA cycle—tricarboxylic acid cycle.

Conventionally, two broad types of lactic acidosis are recognized. In type A, clinical evidence exists of impaired tissue oxygenation. In type B, no such evidence is apparent. Occasionally, the distinction between the two types may be less than obvious. Thus, inadequate tissue oxygenation can at times defy clinical detection, and tissue hypoxia can be a part of the pathogenesis of certain causes of type B lactic acidosis. Most cases of lactic acidosis are caused by tissue hypoxia arising from circulatory failure [14,15].

CAUSES OF LACTIC ACIDOSIS

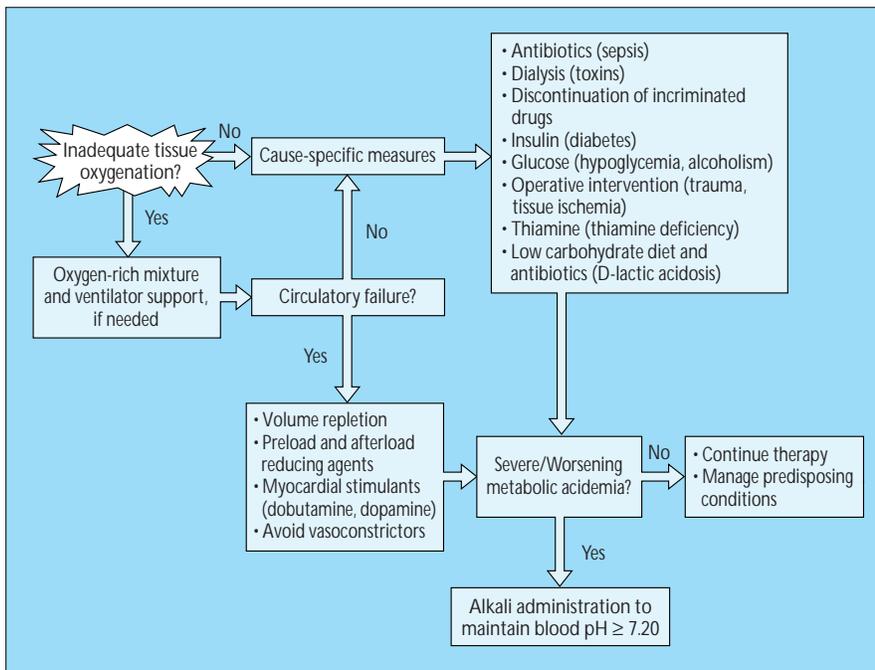| Type A: Impaired Tissue Oxygenation	Type B: Preserved Tissue Oxygenation	
	Diseases and conditions	Drugs and toxins
Shock	Diabetes mellitus	Epinephrine,
Severe hypoxemia	Hypoglycemia	norepinephrine,
Generalized convulsions	Renal failure	vasoconstrictor agents
Vigorous exercise	Hepatic failure	Salicylates
Exertional heat stroke	Severe infections	Ethanol
Hypothermic shivering	Alkaloses	Methanol
Massive pulmonary emboli	Malignancies (lymphoma,	Ethylene glycol
Severe heart failure	leukemia, sarcoma)	Biguanides
Profound anemia	Thiamine deficiency	Acetaminophen
Mesenteric ischemia	Acquired	Zidovudine
Carbon monoxide poisoning	immunodeficiency syndrome	Fructose, sorbitol,
Cyanide poisoning	Pheochromocytoma	and xylitol
	Iron deficiency	Streptozotocin
	D-Lactic acidosis	Isoniazid
	Congenital enzymatic defects	Nitroprusside
		Papaverine
		Nalidixic acid

FIGURE 6-21

Lactic acidosis management. Management of lactic acidosis should focus primarily on securing adequate tissue oxygenation and on aggressively identifying and treating the underlying cause or predisposing condition. Monitoring of the patient's hemodynamics, oxygenation, and acid-base status should be used to guide therapy. In the presence of severe or worsening metabolic acidemia, these measures should be supplemented by judicious administration of sodium bicarbonate, given as an infusion rather than a bolus. Alkali administration should be regarded as a temporizing maneuver adjunctive to cause-specific measures. Given the ominous prognosis of lactic acidosis, clinicians should strive to prevent its development by maintaining adequate fluid balance, optimizing cardiorespiratory function, managing infection, and using drugs that predispose to the disorder cautiously. Preventing the development of lactic acidosis is all the more important in patients at special risk for developing it, such as those with diabetes mellitus or advanced cardiac, respiratory, renal, or hepatic disease [1,14–16].

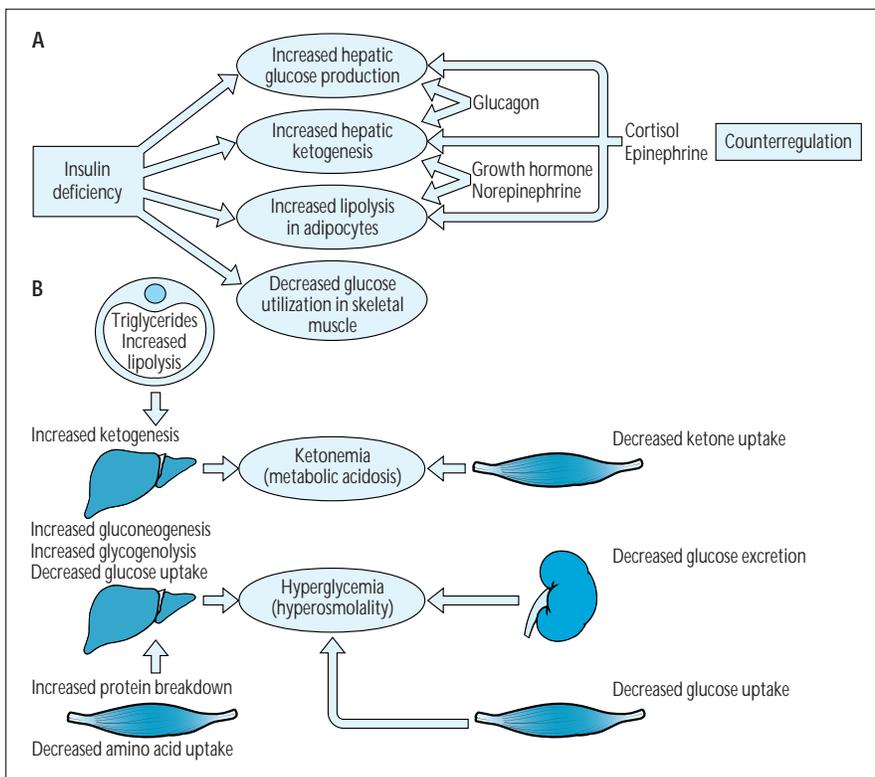# Diabetic ketoacidosis and nonketotic hyperglycemia

FIGURE 6-22

Role of insulin deficiency and the counter-regulatory hormones, and their respective sites of action, in the pathogenesis of hyperglycemia and ketosis in diabetic ketoacidosis (DKA). **A**, Metabolic processes affected by insulin deficiency, on the one hand, and excess of glucagon, cortisol, epinephrine, norepinephrine, and growth hormone, on the other. **B**, The roles of the adipose tissue, liver, skeletal muscle, and kidney in the pathogenesis of hyperglycemia and ketonemia. Impairment of glucose oxidation in most tissues and excessive hepatic production of glucose are the main determinants of hyperglycemia. Excessive counterregulation and the prevailing hypertonicity, metabolic acidosis, and electrolyte imbalance superimpose a state of insulin resistance. Prerenal azotemia caused by volume depletion can contribute significantly to severe hyperglycemia. Increased hepatic production of ketones and their reduced utilization by peripheral tissues account for the ketonemia typically observed in DKA.
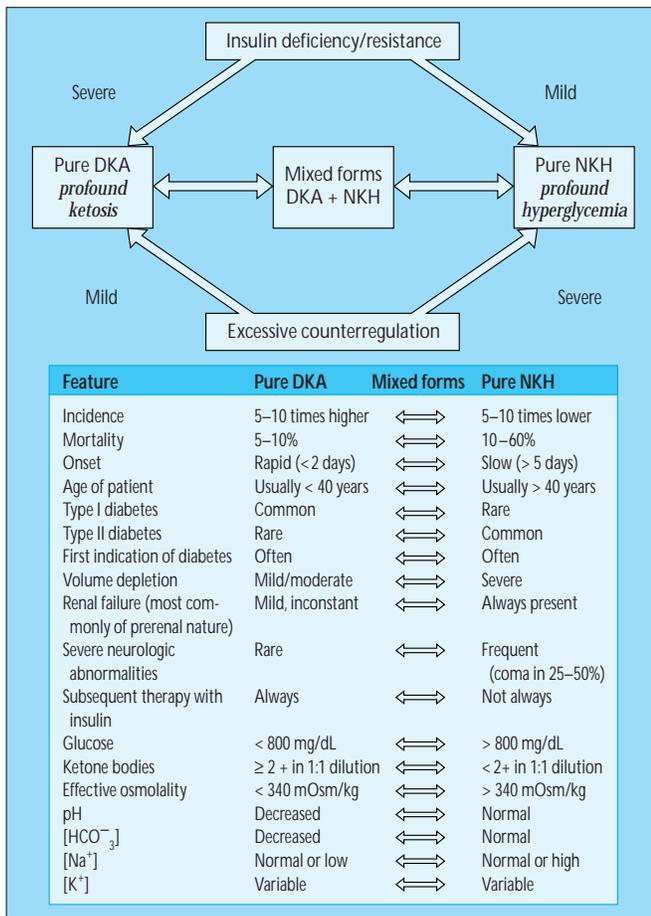
Clinical features of diabetic ketoacidosis (DKA) and nonketotic hyperglycemia (NKH). DKA and NKH are the most important acute metabolic complications of patients with uncontrolled diabetes mellitus. These disorders share the same overall pathogenesis that includes insulin deficiency and resistance and excessive counterregulation; however, the importance of each of these endocrine abnormalities differs significantly in DKA and NKH. As depicted here, pure NKH is characterized by profound hyperglycemia, the result of mild insulin deficiency and severe counterregulation (*eg*, high glucagon levels). In contrast, pure DKA is characterized by profound ketosis that largely is due to severe insulin deficiency, with counterregulation being generally of lesser importance. These pure forms define a continuum that includes mixed forms incorporating clinical and biochemical features of both DKA and NKH. Dyspnea and Kussmaul's respiration result from the metabolic acidosis of DKA, which is generally absent in NKH. Sodium and water deficits and secondary renal dysfunction are more severe in NKH than in DKA. These deficits also play a pathogenetic role in the profound hypertonicity characteristic of NKH. The severe hyperglycemia of NKH, often coupled with hypernatremia, increases serum osmolality, thereby causing the characteristic functional abnormalities of the central nervous system. Depression of the sensorium, somnolence, obtundation, and coma, are prominent manifestations of NKH. The degree of obtundation correlates with the severity of serum hypertonicity [17].

Table from figure:

Feature	Pure DKA	Mixed forms	Pure NKH
Incidence	5–10 times higher	⟺	5–10 times lower
Mortality	5–10%	⟺	10–60%
Onset	Rapid (< 2 days)	⟺	Slow (> 5 days)
Age of patient	Usually < 40 years	⟺	Usually > 40 years
Type I diabetes	Common	⟺	Rare
Type II diabetes	Rare	⟺	Common
First indication of diabetes	Often	⟺	Often
Volume depletion	Mild/moderate	⟺	Severe
Renal failure (most commonly of prerenal nature)	Mild, inconstant	⟺	Always present
Severe neurologic abnormalities	Rare	⟺	Frequent (coma in 25–50%)
Subsequent therapy with insulin	Always	⟺	Not always
Glucose	< 800 mg/dL	⟺	> 800 mg/dL
Ketone bodies	≥ 2 + in 1:1 dilution	⟺	< 2+ in 1:1 dilution
Effective osmolality	< 340 mOsm/kg	⟺	> 340 mOsm/kg
pH	Decreased	⟺	Normal
[HCO_3^-]	Decreased	⟺	Normal
[Na^+]	Normal or low	⟺	Normal or high
[K^+]	Variable	⟺	Variable

MANAGEMENT OF DIABETIC KETOACIDOSIS AND NONKETOTIC HYPERGLYCEMIA

Insulin	Fluid Administration	Potassium repletion	Alkali
1. Give initial IV bolus of 0.2 U/kg actual body weight. 2. Add 100 U of regular insulin to 1 L of normal saline (0.1 U/mL), and follow with continuous IV drip of 0.1 U/kg actual body weight per h until correction of ketosis. 3. Give double rate of infusion if the blood glucose level does not decrease in a 2-h interval (expected decrease is 40–80 mg/dL/h or 10% of the initial value.) 4. Give SQ dose (10–30 U) of regular insulin when ketosis is corrected and the blood glucose level decreases to 300 mg/dL, and continue with SQ insulin injection every 4 h on a sliding scale (*ie,* 5 U if below 150, 10 U if 150–200, 15 U if 200–250, and 20 U if 250–300 mg/dL).	Shock absent: Normal saline (0.9% NaCl) at 7 mL/kg/h for 4 h, and half this rate thereafter Shock present: Normal saline and plasma expanders (*ie,*albumin, low molecular weight dextran) at maximal possible rate Start a glucose-containing solution (*eg,* 5% dextrose in water) when blood glucose level decreases to 250 mg/dL.	Potassium chloride should be added to the third liter of IV infusion and subsequently if urinary output is at least 30–60 mL/h and plasma [K^+] < 5 mEq/L. Add K^+ to the initial 2 L of IV fluids if initial plasma [K^+] < 4 mEq/L and adequate diuresis is secured.	Half-normal saline (0.45% NaCl) plus 1–2 ampules (44-88 mEq) $NaHCO_3$ per liter when blood pH < 7.0 or total CO_2 < 5 mmol/L; in hyperchloremic acidosis, add $NaHCO_3$ when pH < 7.20; discontinue $NaHCO_3$ in IV infusion when total CO_2>8–10 mmol/L.

CO_2—carbon dioxide; IV—intravenous; K^+—potassium ion; NaCl—sodium chloride; $NaHCO_3$—sodium bicarbonate; SQ—subcutaneous.

Diabetic ketoacidosis (DKA) and nonketotic hyperglycemia (NKH) management. Administration of insulin is the cornerstone of management for both DKA and NKH. Replacement of the prevailing water, sodium, and potassium deficits is also required. Alkali are administered only under certain circumstances in DKA and virtually never in NKH, in which ketoacidosis is generally absent. Because the fluid deficit is generally severe in patients with NKH, many of whom have preexisting heart disease and are relatively old, safe fluid replacement may require monitoring of central venous pressure, pulmonary capillary wedge pressure, or both [1,17,18].