Uzhhorod National University

Medical Faculty 2

Feysa S.V., Tovt-Korshynska M.I., Shushman I.V.

Management of acute complications of diabetes mellitus

Guidelines for workshops

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Preface.

In guidelines set out basic information about the etiology, pathogenesis, clinical symptoms, diagnosis, differential diagnosis, treatment and prevention of acute complications of Diabetes Mellitus. Recommended as a supplementary educational footage for students of IV, VI course of Medical faculty.

Рецензенти:

- Ганич Т.М. – завідувач кафедри факультетської терапії медичного факультету Ужгородського національного університету, д.мед.н., професор
- Рудакова С.О. – доцент кафедри терапії та сімейної медицини факультету післядипломної освіти Ужгородського національного університету, к.мед.н., доцент

Розглянуто на засіданні кафедри внутрішніх хвороб медичного факультету №2 ДВНЗ «Ужгородський національний університет» 14 квітня 2017 р. (протокол №9) та рекомендовано як методичні рекомендації для проведення практичних занять з ендокринології для студентів медичного факультету №2

CONTENT

CLASSIFICATION OF ACUTE COMPLICATIONS OF DM

1. Hyperglycemic coma:
   - diabetic ketoacidosis (DKA);
   - non-ketonic hyperglycemic-hyperosmolar coma (NKHHC);
   - lactoacidosis (LA).
2. Hypoglycemic coma (HC).

DIABETIC KETOACIDOSIS (DKA)

Before the area of insulin therapy, ketosis was the leading cause of death of patients with DM. Since insulin deficiency worsens the clinical picture and leads to metabolic abnormalities, complication is more common in young diabetics. Despite insulin usage, mortality remains high (6 -10 %).

DKA results from grossly deficient insulin modulation of glucose and lipid metabolism.

Precipitating factors:

1) newly diagnosed diabetes (presenting manifestation);
2) inadequate administration of exogenous insulin;
3) increased requirements for insulin caused by the presence of an underlying stressful condition:
   - intercurrent infections (pneumonia, cholecyctitis);
   - vascular disorders (myocardial infarction, stroke);
   - endocrine disorders(hyperthyroidism, pheochromocytoma);
   - trauma;
   - pregnancy;
   - surgery.

Clinical presentation.

Diabetic ketosis.

It is a status which is characterized by increased level of ketones in blood, without clinical signs of dehydration and can be corrected by diet (fat restriction) and regular insulin injections.

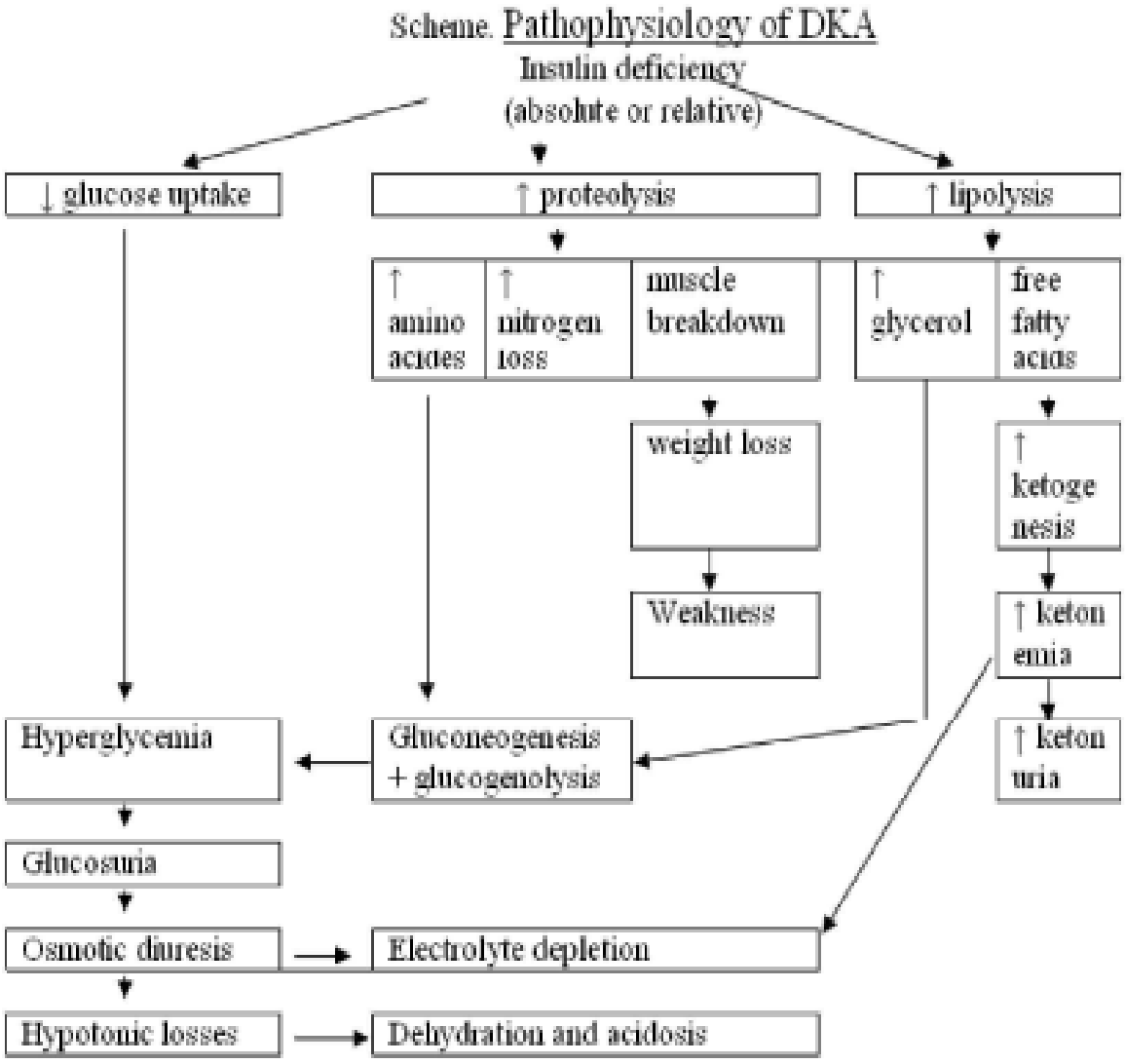
DKA develops over a period of days or weeks.

Signs and symptoms.

1. Polydipsia, polyuria and weakness are the most common presenting complaints.
2. Anorexia, nausea, vomiting, abdominal pain may be present and mimic an abdominal emergency.
3. Ileus and gastric dilatation may occur and predispose to aspiration.
4. Kussmaul breathing (deep, sighing respiration) is present as respiratory compensation for the metabolic acidosis and is obvious when the pH is less than 7.2.
5. Symptoms of central nervous system involvement include headache, drowsiness, lassitude, stupor and coma (only 10 % patients are unconscious).

Physical examination.

1. Hypothermia is common in DKA. A fever should be taken as strong evidence of infection.
2. Hyperpnea or Kussmaul respiration are present and related to decrease acidosis, acetone maybe detected on the breath (musty (fruity) odor to the breath).
3. Tachycardia frequently is present, but blood pressure is usually normal unless profound dehydration is present.
4. Poor skin turgor may be prominent depending on the degree of hydration.
5. Hyporeflexia (associated with low serum potassium) can be elicited.
6. Signs consistent with a "surgical abdomen" but which follow severe ketonemia can confuse the clinical picture.
7. In extreme cases of DKA one can see hypotonia, stupor, coma, discoordination of ocular movements, field dilated pupils and finally death.
8. Other signs from a precipitating illness can be present.



Laboratory findings.

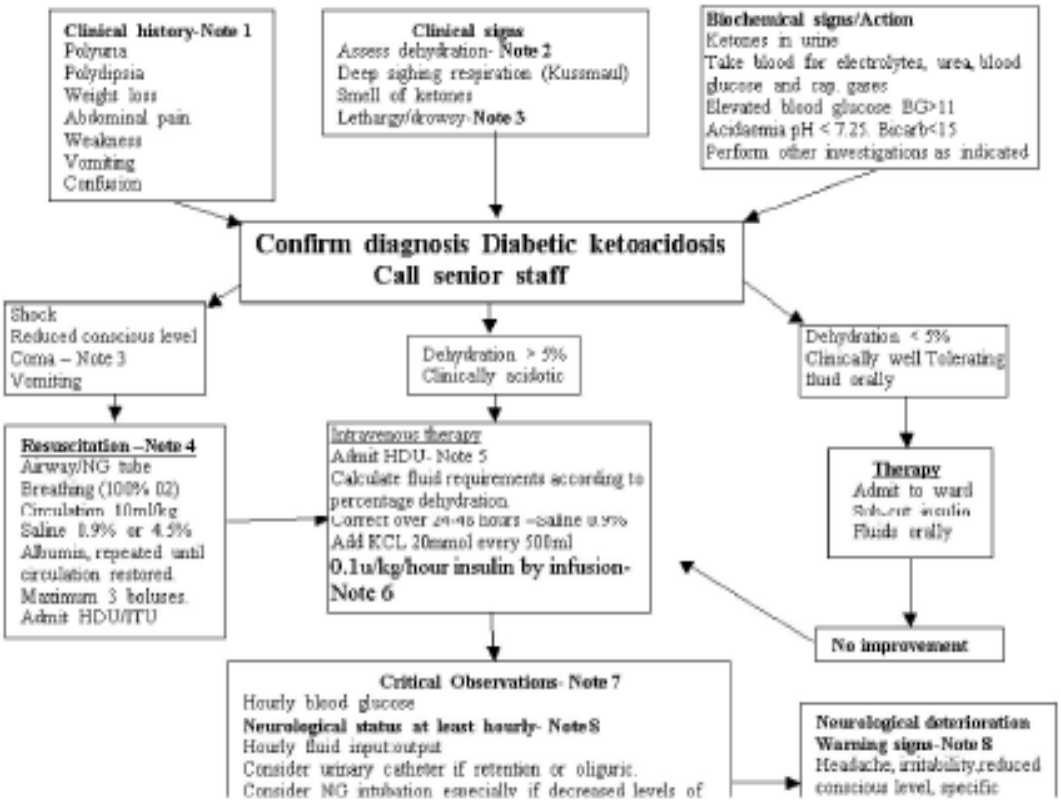
1. The hallmark of DKA is the finding of:
   - hyperglycemia;
   - ketonemia;

- metabolic acidosis (plasma pH and bicarbonates are decreased).

2. A presumptive bedside diagnosis is justified if the urine is strongly positive for both glucose and ketones.
3. Different changes of electrolyte levels in the blood can be observed and does not reflect the actual total body deficits.
4. Serum amylase and transaminases can be elevated.
5. Leukocytosis occurs frequently in DKA and therefore cannot be used as a sole indication ofinfectious process.

Types of DKA:

- abdominal;
- vascular collapse;
- cerebral (encephalopathic);
- renal;
- mixed.



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Differential diagnosis.
DKA must be distinguished from the variety of clinical conditions, particularly those in which central nervous system function is altered and also associated with metabolic acidosis. Patient's history and physical examination often are adequate diagnostic techniques.

Treatment.

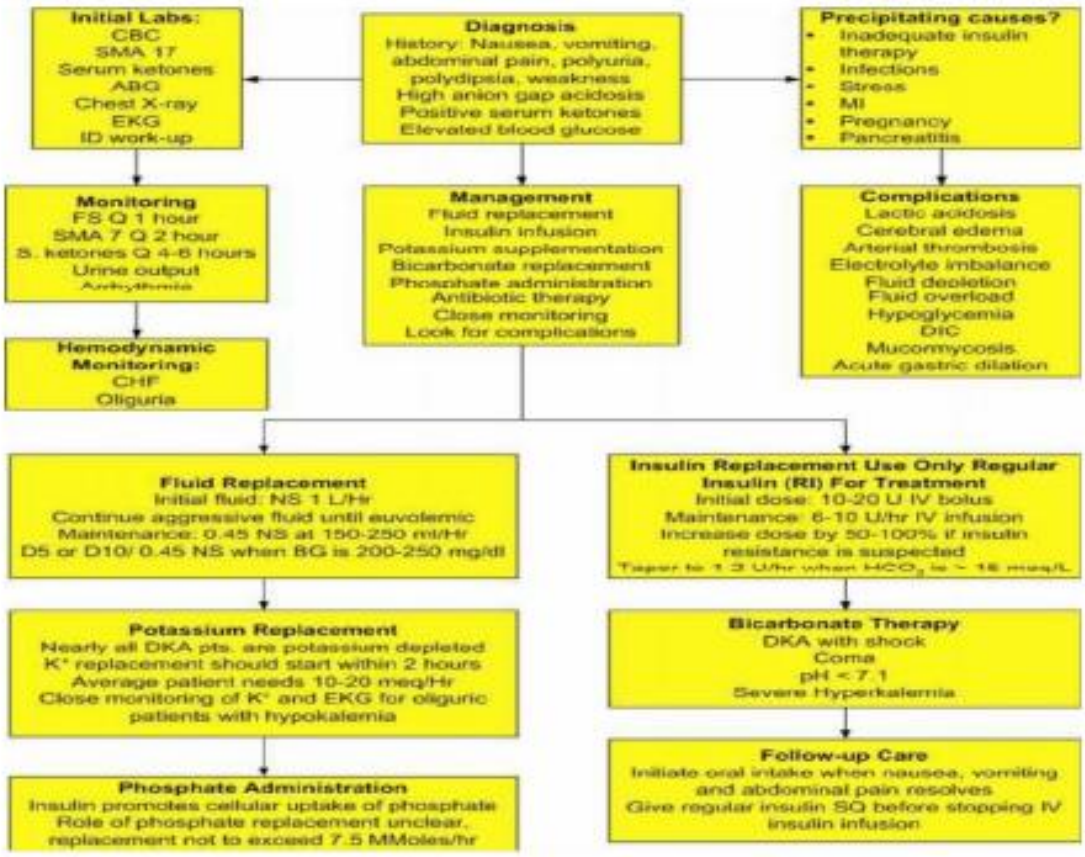
The goals of therapy include:
1. Rehydration.
2. Reduction of hyperglycemia.
3. Correction of: a) acid-base and b) electrolyte imbalance.
4. Investigation of precipitating factors, treatment of complications.

The most important factor to emphasize is frequent monitoring of patient both clinically and chemically. Initially, laboratory data should be obtained every 1 – 3 hours and less frequently once clinical improvement is noted. If patient is in shock, stupor or coma, a nasogastric tube (especially if vomiting) and urinary catheter are recommended.

Frequent assessment of potassium status is vital. II lead of electrocardiogram (ECG) can be provided rapid assessment of hyperkalemia (peaked T-waves) and hypokalemia (flat T-waves and presenceof U waves). Careful observation of neurological status is vital to detect the infrequent but devastating presence of cerebral edema.

Rehydration

The average fluid deficit in adults with DKA is 3 to 5 l. Rapid infusion of 0,9 % sodium chloride (e.g., 1 l/h for the first 1 to 2 hours) is given and then reduced to 0,5 – 0,3 l/h if blood pressure is stable. After the initial infusion, intravenous fluid therapy must be adjusted individually on the basis of urine output, clinical assessments of hydrationand circulation, determination of plasma electrolytes and glucose. When serum glucose level is about 11 – 13 mmoll/l administration of 5 % glucose with insulin can be performed (1 or 2 unites of insulin on each 100 ml of 5 % glucose solution). Addition of glucose to the intravenous solutions necessary for correction of tissue lipolysis and acidosis.



Insulin treatment.

DKA can be treated with low dose insulin regimens; e.g., initial intravenous administration of 10 - 20 units of regular insulin followed by continuous intravenous infusion of 0,1 unit/kg/hour in 0,9 % sodium chloride infusion. (50 units of insulin can be added to a 500 ml bottle of 0,9 % sodium chloride solution to give 1 insulin unite/10 ml of solution).

If glucose level does not improve after an hour of infusion, the rate of insulin is doubled until response is noted. But if there is a tendency for decreasing the level of glycemia we have to decrease the dose of insulin in two times.

When the serum glucose concentration reaches 11-13 mmol/l, insulin can be given subcutaneously (if plasma and urine persistently negative for ketones). Blood glucose level should be maintained at about 11 mmol /l during intravenous therapy. Improvement usually is noted in 8 – 24 hours. Following stabilization of the clinical condition,patients are placed in insulin regimen consisting of five injections of regular insulin.

Treatment of electrolyte disorders.

As a rule, potassium should never be given until the state of renal function is known and until serum potassium concentration is available. In most patients the initial serum potassium is high-normal or elevated and the initiation of K replacement (20 to 40 mmol/h) usually can be deferred for 2 hours, using hourly serum measurements as a guide.

Potassium should be infused at a rate of ml of 1,5 g/h during 3 – 5 hours.

Correction of metabolic acidosis.

The metabolic acidosis occurs due to insulin deficiency and dehydration. So ketone bodies are themselves metabolized to bicarbonate once proper therapy is begun (fluids, electrolytes, insulin) and exogenous administration of bicarbonate can overcorrect to alkalosis.

The use of bicarbonate can be recommended only in the following cases:

- if life-threatening hyperkalemia;
- when severe lactic acidosis complicates DKA;
- with severe acidosis (pH<7), especially when complicated by shock that is not responsive to appropriate fluid resuscitative measures in an attempt to improve cardiac output.

Bicarbonate would be to infuse at rate of 100 to 300 ml of 2,5 % solution.

Other therapeutic consideration:

- since infection is one of the leading precipitating events of DKA, it should be looked for and, if found, treated appropriately;
- vascular thrombosis (it is secondary to severe dehydration, high serum viscosity, and low cardiac output) – heparin (5000 unites 4 times a day);
- vascular collapse can be treated by mezatone (1 – 2 ml); glucocorticoids (dexametasone 4 mg two times a day). You must remember that development of vascular collapse after initiation of therapy should suggest the presence of gram-negative sepsis or silent myocardial infarction;
- cerebral edema - it is rare but frequently fatal complication. Some physicians believe that rapid osmotic reduction of plasma glucose should be avoided to minimize rapid osmotic changes. Some patients have premonitory symptoms (e.g., sudden headache, rapid decrease of the level of consciousness), but in others acute respiratory arrest is the initial manifestation. If cerebral edema is diagnosed, therapeutic maneuvers might include the use of: mannitol (1 – 2 g/kg intravenous over 20 min), dexametasone (0,25 – 0,50 mg/kg/day divided q 4 – 6 h). But they are usually ineffective after the onset of respiratory arrest.

NONKETONIC HYPERGLYCEMIC-HYPEROSMOLAR COMA (NKHHC OR HNC).

HNC is a syndrome characterized by impaired consciousness, sometimes accompanied by seizures, extreme dehydration, and extreme hyperglycemia that is not accompanied by ketoacidosis.

The syndrome usually occurs in patients with type II DM, who are treated with a diet or oralhypoglycemic agents, sometimes it is a complication of previously undiagnosed or medically neglected DM (type II).

In contrast to ketoacidosis, mortality in patients with HNC has been very high (50 %) in most cases. Mortality has been associated with convulsions, deep vein thrombosis, pulmonary embolus,pancreatitis and renal failure. Death is usually due to an associated severe medical condition and not to the hyperosmolality.

The pathophysiology of HNC is similar to that of ketoacidosis, except that ketoacids do not accumulate in blood. The reason of this phenomenon is unclear. Initially it was thought that patients with HNC produced enough insulin to prevent lipolysis and ketogenesis but not enough to prevent hyperglycemia. The concept was invalidated by finding similar inappropriately low plasma insulin concentrations in patients with two syndromes. The finding of lower plasma free fatty acids, as well as cortisol and growth-hormone concentrations, in patients with ketoacidosis has raised the possibility that the absence of ketosis may be the result of decreased cortisol and growth-hormone effects on lipolysis. Suppression of lipolysis by hyperosmolality also has been proposed.

HNC usually develops after a period of symptomatic hyperglycemia in which fluid intake is inadequate to prevent extreme dehydration from the hyperglycemia-induced osmotic diuresis.

<u>Predisposing factors.</u>

1. HNC seems to occur spontaneously in about 5 – 7 % of patients.
2. In 90 % of patients some degree of renal insufficiency seems to coexist.
3. Infection (e.g., pneumonia, urinary tract infections, gram-negative sepsis) is underlying frequent precipitating cause.
4. Use of certain drugs has been associated with this condition:
   - steroids increase gluconeogenesis and antagonize the action of insulin;
   - potassium-wasting diuretics (hypokalemia decreases insulin secretion), e.g., thiazides,
   - furosemide;
   - other drugs, e.g., propranolol, azathioprine, diazoxide.
5. Other medical conditions such as cerebrovascular accident, subdural hematoma, acute pancreatitis and severe burns have been associated with HNC.
6. Use of concentrated glucose solutions, such as used in peripheral hyperalimentation or renal dialysis, has been associated with HNC.
7. HNC can be induced by peritoneal or hemodialysis, tube feeding.
8. Endocrine disorders such as acromegaly, Cushing disease and thyrotoxicosis have been also associated with HNC.

Clinical presentation. Signs and symptoms.

1. Polyuria, polydipsia, weight loss, weakness and progressive changes in state of consciousness from mental cloudiness to coma (present in 50 % of patients) occur over a number of days to weeks.
2. Because other underlying conditions (such as cerebrovascular accident and subdural hematoma) can coexist, other causes of coma should be kept in mind, especially in the elderly.
3. Seizures occur in 5 % of patients and may be either focal or generalized.

Physical examination.

1. Severe dehydration is invariably present.
2. Various neurologic deficits (such as coma, transient hemiparesis, hyperreflexia, and generalized areflexia) are commonly present. Altered states of consciousness from lethargy to coma are observed.
3. Findings associated with coexisting medical problems (e.g., renal disease, cardiovascular disease) may be evident.

Laboratory findings.

1. Extreme hyperglycemia (blood glucose levels from 30 mmol/l and over are common).
2. Markedly elevated serum osmolality is present, usually in excess of 350 mOsm/l. (Normal =290 mOsm/l). The osmolality can be calculated by the following formula: mOsm/l = 2(Na + K) = blood glucose/18 + BUN/2.8.
3. The initial plasma bicarbonate averaged.
4. Serum ketones are usually not detectable, and patients are not acidic.
5. Serum sodium may be high (if severe degree of dehydration is present), normal, or high (when the marked shift of water from the intracellular to the extracellular space due to the marked hyperglycemia is present).
6. Serum potassium levels may be high (secondary to the effects of hyperosmolality as it draws potassium from cells), normal, or low (from marked urinary losses from the osmotic diuresis). But potassium deficiency exists.

Treatment.

This condition is a medical emergency and patient should be placed in an intensive care unit.Many of the management techniques recommended for a patient with DKA are applicable here aswell.

The goals of therapy include:

- rehydration;
- reduction of hyperglycemia;
- electrolytes replacement;
- investigation of precipitating factors, treatment of complications.

Rehydration.The average fluid deficit is 10 liters, and acute circulatory collapse is a common terminal event in HNC. The immediate aims of treatment are to expand rapidly the contracted intravascular volume in order to stabilize the blood pressure, improve the circulation, and improve the rate of urine production. *It is important to remember that it is the severe hyperglycemia and the concomitant obligatory shift of water from the intracellular to the intravascular compartment that prevents this latter space from collapsing at the time of severe fluid depletion. With too rapid correction of hyperglycemia, potential hypovolemic shock (as fluid moves from the extracellular space back into the intracellular space) may occurs*.
Treatment is starting by infusion 1 to 3 liters of 0,9 % sodium chloride over 1 to 2 hours; if this suffices to stabilize the blood pressure, circulation and restore good urine flow, the intravenous fluid can be changed to 0,45 % sodium chloride to provide some free water. 0,45 % sodium chloride is used at a rate of 150 to 500 ml/hour depending on the state of hydration, previous clinical response and the balance between fluid input and output. The aim of this phase of intravenous fluid therapy is not to attempt rapidly correct the total fluid deficit or the hyperosmolality, but rather to maintain stable circulation and renal function and to progressively replenish water and sodium at rates that do not threaten or cause acute fluid overload. Generally, half of the loss is replaced in the first 12 hours and the rest in the subsequent 24 hours.

Insulin therapy.
Insulin treatment in HNC is started by 10 to 20 unites of regular insulin intravenously as a bolus dose prior to starting the insulin infusion and then giving intravenously regular insulin in a dose of 0,05 – 0,10 unites/kg/hour (many authorities routinely use the same insulin treatment regimens as for treating DKA, other authorities recommend smaller doses of insulin, because they believe that patients with type II DM are very sensitive to insulin, but this view is not universally accepted, and many obesed type II diabetics with NHC require larger insulin doses to induce a progressive decrease in their marked hyperglycemia. *It is important to remember that because of insulin therapy causes blood glucose levels to fall, water shifts into the cells and existing hypotension and oliguria can further aggravated. Thus, initially some advocate delaying insulin therapy while infusion normal saline until vital signs have improved.*
When the plasma glucose reaches the range 11 to 13 mmol/l, 5 % glucose should be added to the intravenous fluids to avoid the risk of hypoglycemia. Following recovery the acute episode, patients are usually switched to adjusted doses of subcutaneous regular insulin at 4 to 6-hour intervals.
When they are able to eat, this is changed to 1 or 2 injection regimen.

Treatment of electrolyte disorders.
Once urine flow has been reestablished, potassium should be added to begin repletion of the total body deficits. Potassium replacement is usually started by adding 20 mmol/l to the initial liter of the intravenously-infused 0,45 % sodium chloride with careful serum potassium and ECG monitoring.

LACTIC ACIDOSIS (LA).

DM is one of the major causes of LA, a serious condition characterized by excessive accumulationof lactic acid and metabolic acidosis.
The hallmark of LA is the presence of tissue hypoxemia, which leads to enhanced anaerobic glycolysis and to increased lactic acid formation.

Pyruvic acid	Lactic acid
NADH	NAD
Acetoacetic	Beta-hydroxybutyric

Piruvic acid is converted into lactic acid by lactic dehydrogenase (LDH) in the presence of reduced nicotinamide adenine dinucleotide (NADH), which, in turn, is converted into NAD. The reaction is reversible and involves LDH in both directions. The conversion of acetoacetic acid into beta-hydroxybutyric acid also requires the oxydation of NADH. LA results from decreased availability of NAD caused by lack of oxygen. Likewise, the deficiency of NAD impairs the conversion of beta-hydroxybutyric into acetoacetic acid. Thus, LA predisposes to accumulation of beta-hydroxybutyricacid, which does not react with ACE-test tablet, so, the reaction for ketone bodies may be negative or slightly positive. The normal blood lactic acid concentration is 1 mmol/l, and the pyruvic to lactic ratio is 10:1. An increase in lactic acid without concomitant rise in pyruvate leads to LA of clinical importance.

Predisposing factors.

1. Heart and pulmonary failure (which leads to hypoxia).
2. Usage of biguanide, phenformin therapy.
3. Alcohol intoxication.
4. Ketoacidosis (it is important to have a very high index of suspection with respect to presence of LA).

Clinical presentation.

Signs and symptoms.

1. Kussmaul breathing (deep, sighing respiration) is present as respiratory compensation for the metabolic acidosis and is obvious when the pH is less than 7.2.
2. Symptoms of central nervous system involvement include headache, drowsiness, lassitude.
3. Anorexia, nausea, vomiting, and abdominal pain may be present.
4. Myalgia is common.

Physical examination.

1. Acrocyanosis is common.
2. Tachycardia frequently is present, blood pressure is decreased.
3. Poor skin turgor and dry skin may be prominent.
4. Hypothermia is common in LA.

5. Hyperpnea or Kussmaul respiration are present and related to degree of acidosis.
6. Findings associated with coexisting medical problems (e.g., renal disease, cardiovascular disease) may be evident.

Laboratory findings.

1. Blood glucose level is not high
2. Glucosuria is absent.
3. Blood lactic acid is high.

Treatment of LA.

LA is treated by correcting the underlying cause. In severe cases, bicarbonate therapy should be used (intravenously-infused 2,5 % sodiumbicarbonates 1 to 2 l/day).

LA can be treated with low dose insulin regimens with 5 % glucose solution infusion. Volume expanders and oxygen therapy are helpful treatment as well.

Comparison of DCA, HNC and LA.

	DKA	HNC	LA
Age	Below 40	Above 40	Above 40
Type of DM	Type I	Type II	Type II
Predisposing factor	Insulin deficiency	Dehydration	Hypoxia
Prodromes	Several days duration or less than 1 day	Several days duration	Less than 1 day
Underlying renal, cardiovascular or pulmonary disease	About 15 %	About 85 %	About 90 %
General	More acidic and less dehydrated, hyperventilation	More dehydrated and less acidic, no hyperventilation	More acidic and less dehydrated, hyperventilation
Neurologic symptoms and signs	Rare	Very common	Very common
Laboratory findings:			
- blood glucose	High (about 20–30 mmol/l)	Very high (about 40–50 mmol/l)	Normal or about 10–11 mmol/l
- plasma ketones	+	-	-

- serum sodium	Normal, elevated or low	Normal, elevated or low	Normal
- serum potassium	Normal, elevated or low	Normal, elevated or low	Normal
- serum bicarbonate	Low	Normal	Low
- blood pH	Less than 7,35	Normal	Less than 7,35
- serum osmolality	Less than 330 mOsm/l	Over 350 mOsm/l	Normal
- free fatty acids	↑	↓ or normal	Normal
Complications: - Thrombosis - Mortality	Rare 1–10 %	Frequent 20–50 %	Very rare About 90 %
Diabetes treatment after recovery	Always insulin	Diet alone or oral agents, sometimes insulin	Diet alone or oral agents, sometimes insulin

HYPOGLYCEMIA

It is a syndrome characterized by symptoms of sympathetic nervous system stimulation or central nervous system dysfunction that are provoked by an abnormally low plasma glucose level. Hypoglycemia represents insulin excess and it can occur at any time.

Precipitating factors.

- irregular ingestion of food;
- extreme activity;
- alcohol ingestion;
- drug interaction;
- liver or renal disease;
- hypopituitarism and adrenal insufficiency.

Clinical presentation. Signs and symptoms.

Two distinct patterns are distinguished:

1. adrenergic symptoms (they are attributed to increased sympathetic activity and epinephrine release): sweating, nervousness, tremulousness, faintness, palpitation, and hunger sometimes;
2. cerebral nervous system manifestations: confusion, inappropriate behavior (which can be mistaken for inebriation); visual disturbances, stupor, coma or seizures. (Improvement in the cerebral nervous system manifestations will be with a rise in blood glucose.)

A common symptom of hypoglycemia is the early morning headache, which is usually present when the patient awakes.

Patients should be familiar with the symptoms of the hypoglycemia but some of them are not heralded by symptoms.

Physical examination.

1. The skin is cold, moist.
2. Hyperreflexia can be elicited.
3. Hypoglycemic coma is commonly associated with abnormally low body temperature
4. Patient may be unconsciousness.

Laboratory findings. Low level of blood glucose

Treatment. Insulin–treated patients are advised to carry sugar lumps, candy, or glucose tablets at all time.

If symptoms of hypoglycemia develop, patients have to eat candy or to drink glass of fruit juice or water with 3 tbsp. of sugar. Family members of patients with diabetes should be taught to give such treatment if patient suddenly exhibit confusion or inappropriate behavior:

1) glucagon 0,5 – 1 units (0,5 – 1 ml) s/c, i/m or i/v. If patient does not respond to 1 unit of glucagon within 25 minutes, further injections are unlikely to be effective, and are not recommended;

2) an i/v injection of 20 or 100 ml of 40 % glucose, followed by a continuous infusion of 5 % glucose (10 % glucose may be needed) until it clearly can be stopped safely;
3) glucocorticoids and adrenaline are helpful as well.

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