Acute complications of DM

- Dehydration
- Ketoacidosis
- Hypoglycemia

Diabetic ketoacidosis (DKA)

- DKA occurs more commonly in type 1 diabetes because the insulin deficiency is more severe, though it can occur rarely in type 2 diabetes.
- In about a quarter of young people who develop type 1 diabetes, the insulin deficiency and hyperglycemia lead to ketoacidosis before the disease is recognized and treated.
- This can occur at the onset of type 2 diabetes as well, especially in young people. When a person is known to have diabetes and is being adequately treated, DKA usually results from omission of insulin, mismanagement of acute gastroenteritis (the "flu"), or an overwhelming new health problem (e.g., bacterial infection, myocardial infarction).

DEFINITION OF DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is caused by a decrease in effective circulating insulin associated with increases in counter regulatory hormones including glucagon, catecholamines, cortisol, and growth hormone.

- ✓ **This leads to increased glucose production by the liver and kidney and impaired peripheral glucose utilisation with resultant hyperglycaemia, and hyperosmolality.**
- ✓ **Increased lipolysis, with ketone body (beta-hydroxybutyrate, acetoacetate) production causes ketonaemia and metabolic acidosis.**
- ✓ **Hyperglycaemia and acidosis result in osmotic diuresis, dehydration, and obligate loss of electrolytes.**

The biochemical criteria for the diagnosis of DKA include hyperglycaemia

- ✓ **(blood glucose >11 mmol/l (~200 mg/dl)) with a venous pH <7.3 and/or bicarbonate <15 mmol/l.**
- ✓ **There is associated glycosuria, ketonuria, and ketonaemia.**
- ✓ **Rarely, young or partially treated children as well as pregnant adolescents may present with near normal glucose values ("euglycaemic ketoacidosis").**

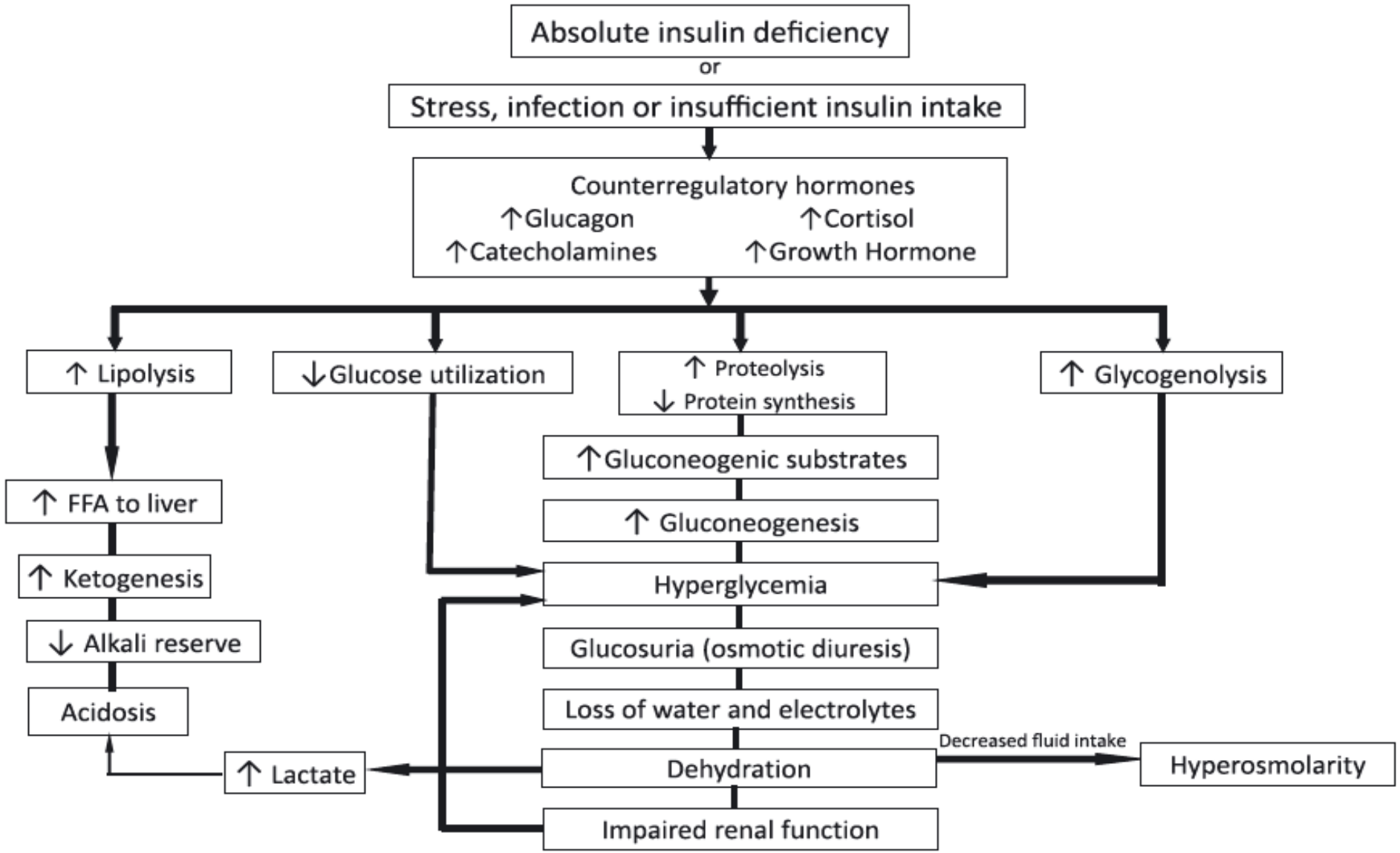
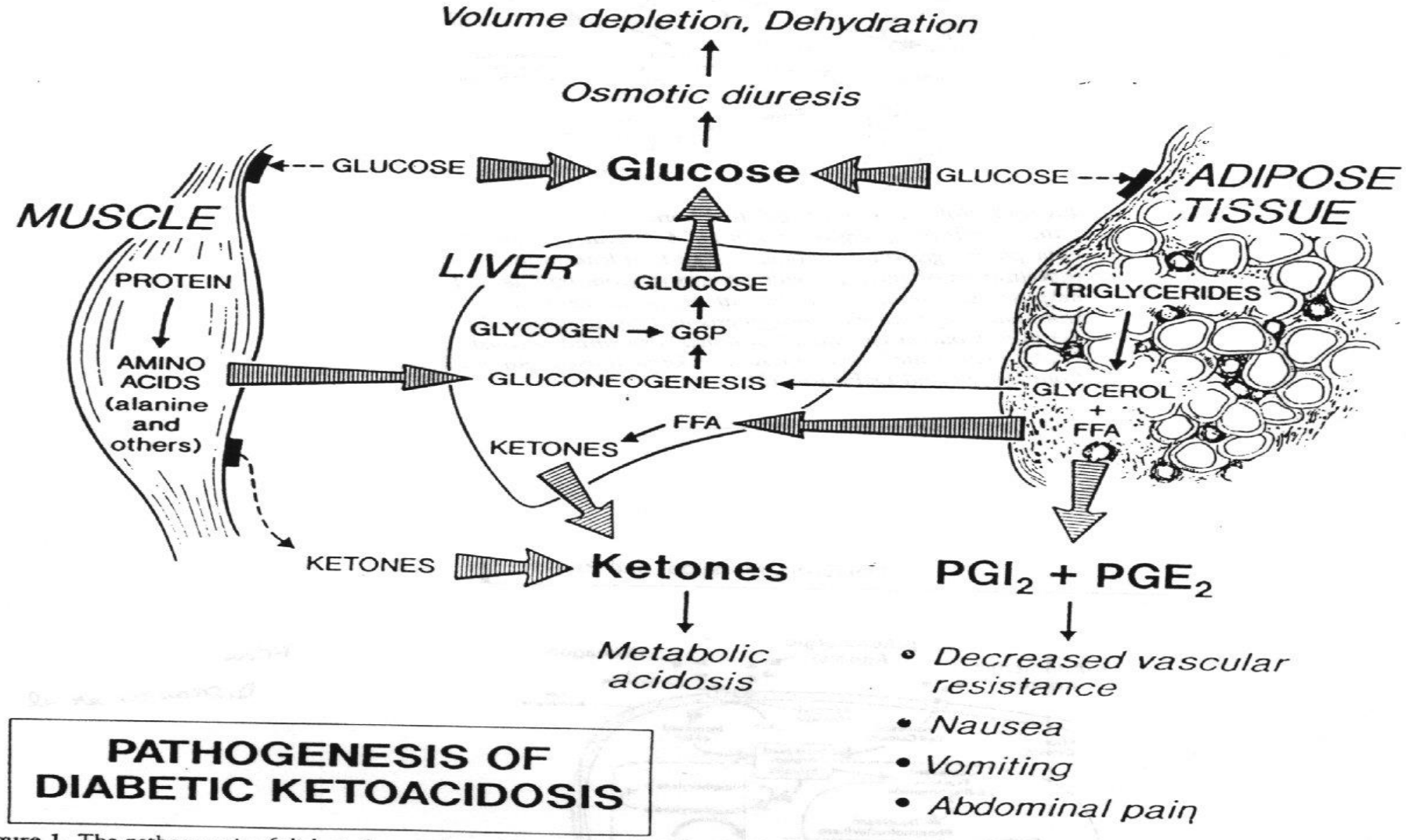


Fig. 1. Pathophysiology of diabetic ketoacidosis. Reprinted with permission from Wolfsdorf et al. (232).



PATHOGENESIS OF DIABETIC KETOACIDOSIS

Figure 1. The pathogenesis of diabetic ketoacidosis. Severe insulin deficiency causes hyperglycemia, ketosis, and increased production of PGI_2 and PGE_2. Hyperglycemia is due to increased gluconeogenesis from amino acids, glycerol, and lactate and to decreased peripheral utilization of glucose. Ketosis is due to increased triglyceride lipolysis and increased FFA release from adipose tissue, to preferential utilization of FFAs for ketogenesis in the liver, and to deceased peripheral utilization of ketones. Increased PGI_2 and PGE_2 production by adipose tissue is due to accelerated triglyceride lipolysis and enhanced production of PGI_2 and PGE_2 in adipose tissue. Hyperglycemia causes an osmotic diuresis, volume depletion, hypotension, and dehydration. Ketosis causes an anion gap metabolic acidosis due to the dissociation of the ketoacids in the circulation and/or a hyperchloremic metabolic acidosis due to the loss of potential bicarbonate in the urine in the form of ketone bodies and the retention of chloride. Increased production of PGI_2 and PGE_2 causes decreased peripheral vascular resistance, hypotension, tachycardia, nausea, vomiting, and abdominal pain. Black rectangles denote impaired peripheral utilization of glucose and ketones, as indicated.


Urine test
A.D.A.M.

DKA is generally categorised

DKA is categorised by the severity of the acidosis; varying from

- **mild (venous pH <7.30, bicarbonate concentration <15 mmol/l),**
- **moderate (pH <7.2, bicarbonate <10),**
- **severe (pH <7.1, bicarbonate <5).**

The risk of DKA

In children with established TIDM the risk of DKA in established TIDM is 1–10% per patient per year.

Risk is increased in children with:

- poor metabolic control

- or previous episodes of DKA;

- peripubertal and adolescent children;

- children with psychiatric disorders,

including those with eating disorders; and those with difficult family circumstances,

including lower socioeconomic status and lack of appropriate health insurance.

Inappropriate interruption of insulin pump therapy also leads to DKA.

Children whose insulin is administered by a responsible adult rarely have episodes of DKA, and 75% of episodes of DKA beyond diagnosis are probably associated with insulin omission or treatment error.

The remainder are due to inadequate insulin therapy during intercurrent illness

MORBIDITY AND MORTALITY OF DKA IN CHILDREN

Reported mortality rates from DKA in national population based studies are reasonably constant:

- **0.15% (USA),**
- **0.18% (Canada) - 0.25% (Canada),**
- **and 0.31% (UK)**

In places with less developed medical facilities, the risk of dying from DKA is greater, and children may die before receiving treatment.

MORBIDITY AND MORTALITY OF DKA IN CHILDREN

Cerebral oedema

- Cerebral oedema accounts for 57–87% of all DKA deaths.

The incidence of cerebral oedema has been fairly consistent between national population based studies:

-0.46%(Canada), 0.68% (UK), and 0.87% (USA).

Single centre studies often report higher frequencies because of ascertainment bias arising from secondary referral patterns: 1.1% (USA) to 4.6%(USA).

MORBIDITY AND MORTALITY OF DKA IN CHILDREN

Other possible causes of mortality and morbidity include:

- hypokalaemia, hyperkalaemia, hypoglycaemia, other CNS complications; haematoma, thrombosis
- sepsis and infections (including rhinocerebral mucormycosis), aspiration pneumonia, pulmonary oedema, adult respiratory distress syndrome (ARDS), pneumomediastinum and subcutaneous emphysema and rhabdomyolysis.

Late sequelae relate to cerebral oedema and other CNS complications; these include hypothalamopituitary insufficiency,isolated growth hormone deficiency,and combined GH and TSH deficiency

CEREBRAL OEDEMA

- **Presentation**

Cerebral oedema typically occurs 4–12 hours after treatment is activated, but can be present before treatment has begun, or may develop any time during treatment for DKA. Symptoms and signs of cerebral oedema are variable and include onset of headache, gradual decrease or deterioration in level of consciousness, inappropriate slowing of the pulse rate, and an increase in blood pressure.

CEREBRAL OEDEMA
Risk factors [1]

- **Several potential risk factors, at diagnosis or during treatment, have been identified through epidemiological studies**

- attenuated rise in measured serum sodium

- severity of acidosis

- greater hypocapnia

- increased serum urea nitrogen

ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents

Water and salt deficits must be replaced.
Intravenous or oral fluids that may have been given before the child presents for treatment and prior to assessment should be factored into calculation of deficit
and repair.

Initial intravenous fluid administration and, *if needed*, volume expansion, should begin immediately with an isotonic solution
(0.9% Saline or balanced salt solutions such as Ringer's lactate).

- **Water and salt replacement in DKA**

The volume and rate of administration depends on circulatory status and, where it is clinically indicated, the volume is typically 10–20 ml/kg over 1–2 hours, repeated if necessary.

Use crystalloid and *not* colloid.

Table 3. Glasgow coma scale or score (GCS)

Best eye response	Best verbal response	Best verbal response (non-verbal children)	Best motor response
1. No eye opening	1. No verbal response	1. No response	1. No motor response
2. Eyes open to pain	2. No words, only incomprehensible sounds; moaning	2. Inconsolable, irritable, restless, cries	2. Extension to pain (decerebrate posture)
3. Eyes open to verbal command	3. Words, but incoherent*	3. Inconsistently consolable and moans; makes vocal sounds	3. Flexion to pain (decorticate posture)
4. Eyes open spontaneously	4. Confused, disoriented conversation†	4. Consolable when crying and interacts inappropriately	4. Withdrawal from pain
	5. Oriented, normal conversation	5. Smiles, oriented to sound, follows objects and interacts	5. Localizes pain
			6. Obeys commands

The GCS consists of three parameters and is scored between 3 and 15; 3 being the worst and 15 the best (63). One of the components of the GCS is the best verbal response, which cannot be assessed in non-verbal young children. A modification of the GCS was created for children too young to talk.

*Inappropriate words, random or exclamatory articulated speech, but no sustained conversational exchange.

†Attention can be held; patient responds to questions coherently, but there is some disorientation and confusion.

Table 1. Losses of fluids and electrolytes in diabetic ketoacidosis and maintenance requirements in normal children

	Average (range) losses per kg		24-h maintenance requirements
Water	70 mL (30–100)	≤10 kg*	100 mL/kg/24 h
		11–20 kg	1000 mL + 50 mL/kg/24 h for each kg from 11–20
		>20 kg	1500 mL + 20 mL/kg/24 h for each kg >20
Sodium	6 mmol (5–13)		2–4 mmol†
Potassium	5 mmol (3–6)		2–3 mmol
Chloride	4 mmol (3–9)		2–3 mmol
Phosphate	(0.5–2.5) mmol		1–2 mmol

Data are from measurements in only a few children and adolescents (8–12). In any individual patient, actual losses may be less or greater than the ranges shown in Table 1.

Three methods for determining maintenance water requirements in children are commonly used: *the Holliday-Segar formula (13) (shown in Table 1), a simplified Holliday-Segar formula (Simplified method based on Holliday-Segar: <10 kg 4 mL/kg/h; 11–20 kg 40 + 2 mL/kg/h for each kg between 11 and 20; >20 kg 60 + 1 mL/kg/h for each kg >20), and a formula based on body surface area for children more than 10 kg (1500 mL/m^2/24 h) (14).

†Maintenance electrolyte requirements in children are per 100 mL of maintenance IV fluid (14, 15).

Example of volumes needed to replace fluid and provide maintenance for a 10% deficit to be given evenly over 48 hours (if deficit is estimated at <10%, then the infusion rate needs to be appropriately reduced).

Weight (kg)	Infusion rate for maintenance and a 10% deficit (ml/kg/h)
4 – 9	6
10 – 19	5
20 – 39	4
40 - 59	3.5
60 - 80	3

Insulin

- Physiological studies indicate that intravenous insulin at a dose of

0,05-0,1 unit/kg/hour, which achieves steady state plasma insulin levels of around 100–200 μU/ml within 60 minutes, is effective. Such plasma insulin levels are able to offset insulin resistance and, in most circumstances, inhibit lipolysis and ketogenesis; exerting maximal or near maximal effects on suppression of glucose production and stimulated peripheral glucose uptake.The resolution of acidaemia invariably takes longer than normalisation of blood glucose concentrations

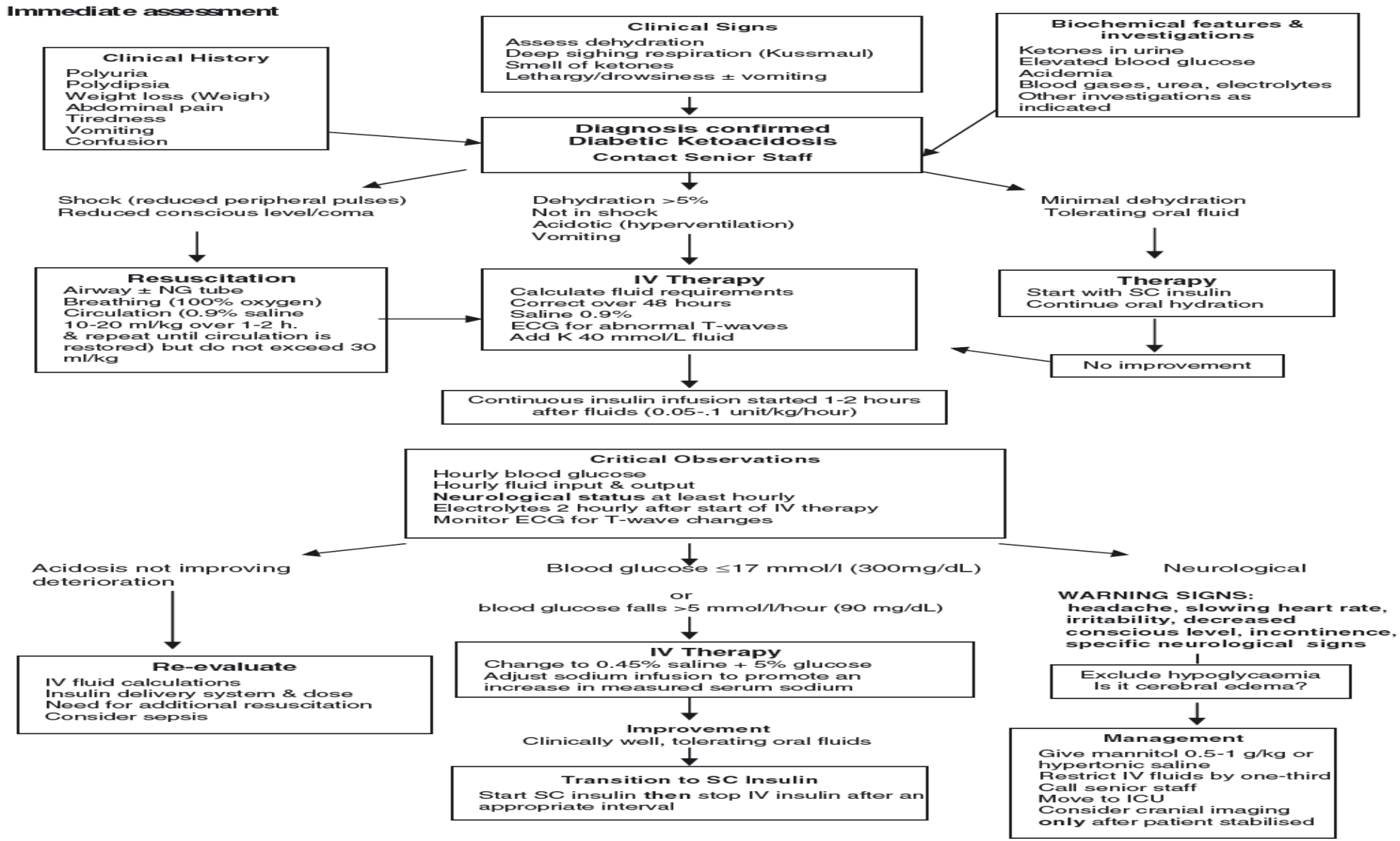
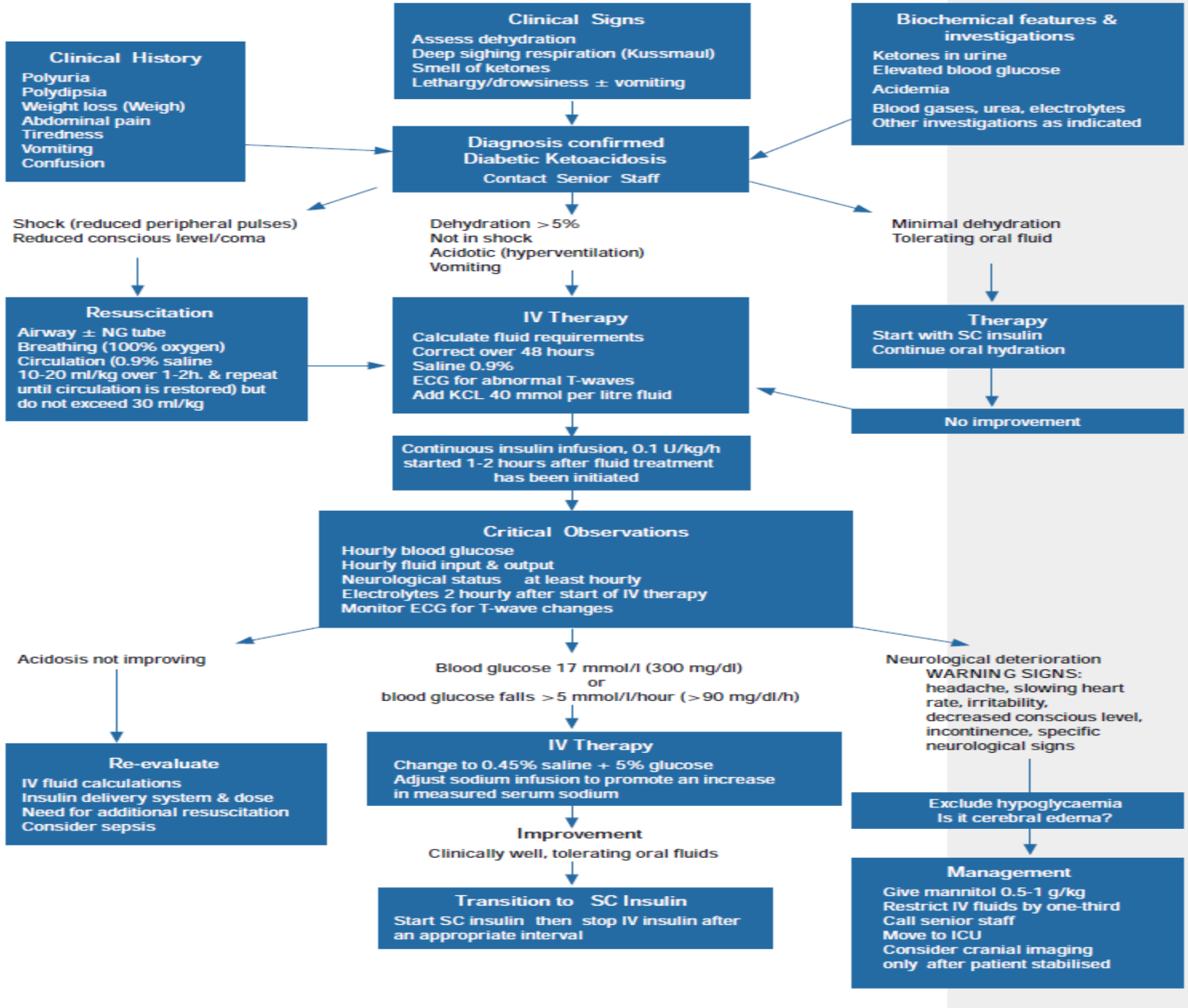


Fig. 2. Algorithm for the management of diabetic ketoacidosis. Adapted from Dunger et al. (233). NG, nasogastric; SC, subcutaneous.

Figure 1
DKA Management – Recommended Care



Insulin therapy for DKA

Correction of insulin deficiency:

– Dose: 0.05-0,1 units/kg/hour

– Route of administration: intravenous

The dose of insulin should remain at 0,05-0,1 U/kg/hour at least until resolution of ketoacidosis (pH >7.30, HCO3>15 mmol/l and/or closure of anion gap). To prevent an unduly rapid decrease in plasma glucose concentration and possible development of hypoglycemia, glucose should be added to the intravenous fluid when the plasma glucose falls to ~14–17 mmol/l (250–300 mg/dl).

Potassium

- The major loss of potassium is from the intracellular pool as a result of hypertonicity, insulin deficiency, and buffering of hydrogen ions within the cell.
- Serum potassium levels at the time of presentation may be normal, increased or decreased: hypokalaemia at presentation may be related to prolonged duration of disease, whereas hyperkalaemia primarily results from reduced renal function.
- Administration of insulin and the correction of acidosis will drive potassium back into the cells, decreasing serum levels.

Potassium, phosphate, and acid base management

Potassium

- ***Replacement is required.***
- ***Replacement therapy should be based on serum potassium measurements.***
- ***Start potassium replacement immediately if the patient is hypokalaemic; otherwise, start potassium concurrent with starting insulin therapy. If the patient is hyperkalaemic, defer potassium until urine output is documented.***
- ***Starting potassium concentration in the infusate should be 40 mmol/l and potassium replacement should continue throughout intravenous fluid therapy.***

Acidosis

- **In DKA there is an increased anion gap. The major retained anion is beta-hydoxybutyrate (β-OHB) and acetoacetate.**

  anion gap=[Na^+]-([Cl^-]+[$HCO3^-$]) normally 12 ± 2 mmol/l

- **The indications for bicarbonate therapy in DKA are unclear. Several controlled trials of sodium bicarbonate in small numbers of children and adults have been unable to show clinical benefit or any important difference in the rate of rise in the plasma bicarbonate concentration.**

- **<u>In children we used bicarbonate when pH is<7.0</u>**

Diabetes and illness

Infections associated with hyperglycemia with or without ketosis

- Recommend additional doses of short or rapid-acting insulins with careful monitoring to reduce BG, prevent ketoacidosis and avoid hospital admission
- The dose and frequency of injection will depend on the age of the child, the level and duration of hyperglycemia, the severity of ketosis and previous experience with alterations of insulin

- **Example** Sick child, BG 15–20 mmol/l (± ketosis): advise 10–20% of total daily insulin dose (or 0.1 U/kg) as short or rapid-acting insulin every 2–4 h until BG falls to <15 mmol/l. Thereafter any additional doses might be 5–10% of the total daily dose

Hypoglycemia

Definition

There is no consistent or agreed definition of hypoglycemia for the diabetic child

- In theory, hypoglycemia is the level of BG at which physiological neurological dysfunction begins
- In practice, neurological dysfunction can be symptomatic or asymptomatic, and the level at which it occurs
  - varies between individuals
  - may vary with time and circumstances
  - is affected by antecedent hypoglycemia

Clinical hypoglycemia alert

- A glucose value of ≤3.9 mmol/L (70 mg/dL) is an alert value that requires attention to prevent hypoglycemia. The alert can be used as the threshold value for identifying and treating hypoglycemia in children with diabetes because of the potential for glucose levels to drop further

Clinically important or serious hypoglycemia

- A glucose value of <3.0 mmol/l (54 mg/dl) indicates serious, clinically important hypoglycemia. These low levels may lead to defective hormonal counterregulation and impaired awareness of hypoglycemia.
- Neurogenic symptoms and cognitive dysfunction occur below this level with subsequent increased risk of severe hypoglycemia. This level should be recorded in routine clinical care and reported in audit and in clinical trials of interventions directed towards reducing hypoglycemia as recommended by the International Hypoglycemia Study Group.

Severe hypoglycemia

Severe hypoglycemia is defined as an event associated with severe cognitive impairment (including coma and convulsions) requiring external assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions

Hypoglycemia

Hypoglycemia is the most frequent acute complication in type 1 diabetes

- Mild hypoglycemia may cause a variety of reversible signs and symptoms characteristic of neurological dysfunction, from transient dizziness or cognitive impairment to excitation of peripheral nerves or even temporary hemiplegia
- Severe prolonged hypoglycemia with convulsions has the potential, particularly in young children, to cause permanent CNS impairment
- Hypoglycemia provokes significant anxiety in children, adolescents, parents and other care givers
- Hypoglycemia is an important limiting factor in attempts to achieve near-normoglycemia

Hypoglycemia

Infections associated with hypoglycemia

- These infections are often associated with nausea, vomiting ± diarrhea. Advise replacing meals with frequent small volumes of sugary drinks and careful BG monitoring
- Reduction of insulin dose by 20–50% may be required
- If hypoglycemia (and nausea or food refusal) persists, an injection of glucagon may reverse the hypoglycemia and enable oral fluids to be re-established

Signs and symptoms of hypoglycemia. Clinically causes

Clinically, hypoglycemia causes signs and symptoms of

Autonomic activation (hunger, trembling of hands or legs, palpitations, anxiety, pallor, sweating)

Neuroglycopenia (impaired thinking, change of mood, irritability, dizziness, headache, tiredness, confusion and later convulsions and coma)

Neuroglycopenia may occur before autonomic activation (causing hypoglycemic unawareness)

Recommendation
The level of BG should be maintained above 4 mmol/l

Hypoglycemia Predisposing factors

Hypoglycemia is the result of a mismatch between insulin, food and exercise

- Altered routine (missed or erratic meals, changes in physical activity, alterations or errors in insulin dosage or absorption)
- Younger age (<6 years)
- Lower HbA1c
- Total deficiency of endogenous insulin
- Antecedent hypoglycemic episodes
- Hypoglycemic unawareness
- Defective glucagon and catecholamine counter-regulation (longer duration)
- Alcohol ingestion

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- Alcohol ingestion

Grading of severity
Mild (grade 1)

Hypoglycemia

- Child or adolescent is aware of, responds to and self-treats the hypoglycemia
- Children aged below 5–6 years can rarely be classified as grade 1 hypoglycemia because they are usually unable to help themselves

Moderate (grade 2)

- Child or adolescent cannot respond to hypoglycemia and requires help from someone else, but oral treatment is successful

Severe (grade 3)

- Child or adolescent is semi-conscious or unconscious or in coma ± convulsions and may require parenteral therapy (glucagon or IV glucose)

Hypoglycemia - Consequences

- ***Brain dysfunction***
- Severe prolonged episodes with convulsions
- Transient episodes have important implications for school and social wellbeing.
- ***Nocturnal hypoglycemia***

Hypoglycemia Mild or moderate (grade 1 or 2)

Treatment

- Immediate oral rapidly absorbed simple carbohydrate e.g.
  - 5–15 g glucose or sucrose (tablets/sugar lumps)
  - 100 ml sweet drink (glucose/sucrose drinks, cola, etc)
- Wait 10–15 min … if no response …
- Repeat oral intake as above
- As symptoms improve or normoglycemia is restored, the next meal or oral complex carbohydrate should be ingested (e.g. fruit, bread, cereal, milk)

BG measurements are the only way to confirm hypoglycemia if the diagnosis is uncertain, for example in children who may mimic the symptoms of hypoglycemia in order to be allowed to eat sweet foods. BG measurements also confirm the return of BG towards normal after hypoglycemia

Severe (grade 3)

Treatment is urgent

- Severe hypoglycemia with loss of consciousness ± convulsions (particularly if there is vomiting) is most safely and rapidly reversed by injection of **Glucagon**
  - 0.5 mg for age <12 years
  - 1.0 mg for age 12+ years
  - [or 0.1–0.2 mg/10 kg body weight]
- best given IM (or deep SC)
- If glucagon is unavailable or recovery is inadequate … **IV glucose** should be administered slowly by trained personnel over several minutes to reverse the hypoglycaemia
  e.g. glucose 10–30% at a dose of 200–500 mg/kg (glucose 10% is 100 mg/ml)
- If the hypoglycemia is not associated with vomiting nor severe enough to remove the swallowing, spitting or gag reflexes, it is usually effective to give concentrated sugar as glucose gel/syrup/honey/jam carefully by mouth The evidence is not strong that massaging the outside of the cheek against the gum facilitates buccal absorption of glucose. It is likely that some of the sugar is swallowed and absorbed lower in the gastrointestinal tract.

Recommendations hypo

- Equipment for BG measurement must be available to all young people with diabetes for immediate confirmation and safe management of hypoglycemia
- Children, adolescents, parents, schoolteachers and other care givers should receive education on the recognition and management of hypoglycemia
- Glucagon should be readily accessible to all parents and care givers, especially when there is a high risk of severe hypoglycemia. Education on administration of glucagon is essential
- Children and adolescents with diabetes should wear some form of identification

Vascular complications

Microvascular complications

- Children and adolescents with diabetes are at risk from progressive microvascular damage
- Early vascular changes are subclinical but can be detected by sensitive testing methods
- The prepubertal phase of diabetes contributes to the risk of vascular damage
- Puberty accelerates the progression of microvascular complications
- Improvements in glycemic control reduce the risk of retinopathy, nephropathy and neuropathy

Vascular complications

Risk factors for the development of microvascular complications

- Younger age at onset
- Longer duration of diabetes
- Poor glycemic control
- Family history of diabetes complications
- Higher blood pressure (not necessarily to hypertensive levels)
- Smoking
- Abnormal lipid levels

Recommendation Awareness in families, children and adolescents of potential long-term complications is a fundamental part of diabetes education. Such information should be provided to children at a rate appropriate to their level of understanding and maturity

Diabetic eye disease *Retinopathy*

Vascular complications

- Diabetic retinopathy remains the most common cause of acquired blindness in young and older adults
- Early retinopathy is asymptomatic but may be detected by sensitive methods (e.g. fundus photography or fluorescein angiography) in a large proportion of young people with diabetes duration of more than 10 years
- Fluorescein angiography is not performed in many pediatric centers but is a sensitive method of detecting early functional vascular abnormalities of the retina which are potentially reversible by improvements in metabolic control. There is good evidence that serial fundus photography, which is less invasive, is equally effective in the monitoring of retinopathy

Retinopathy

Types of retinopathy

- Early or background retinopathy
- Microaneurysms
- Hemorrhages
- Hard and soft exudates
- Intra-retinal microvascular abnormalities (IRMA)

Diabetic kidney disease *Nephropathy*

Diabetic nephropathy and end-stage renal failure have been a major cause of mortality amongst young adults with type 1 diabetes

- Increasing and persistently elevated urinary albumin excretion may predict later diabetic nephropathy
- Elevated blood pressure is an associated feature of diabetic kidney disease

Microalbuminuria

- The 95th centile for albumin excretion in non-diabetic children is 7.2–7.6 μg/min
- Persistent microalbuminuria is defined in a minimum of two out of three consecutive urine specimens
  Albumin excretion rate (AER) 20–200 μg/min in timed overnight urine collections
  or
  AER 30–300 mg/24 h in 24-h urine collections

Nephropathy

Nephropathy

Recommendation

- **Age of microalbumin screening**
  - **Prepubertal onset of diabetes: 5 years after onset or at age 11 years, or at puberty (whichever is earlier), and annually thereafter (every year)**
  - **Pubertal onset of diabetes: 2 years after onset, and annually thereafter**

Diabetic nerve disease *Neuropathy*

Vascular complications

- Clinical neuropathy is rare in children and adolescents with satisfactory glycemic control
- Sensitive tests can detect subclinical neurological abnormalities, the natural history of these being unclear
- In the presence of poor diabetic control young people should be questioned and examined in relation to
  - symptoms of numbness, pain, cramps and paresthesia
  - skin sensation, vibration sense and light touch
  - ankle reflexes

Macrovascular complications

Vascular complications

- Large vessel disease such as coronary artery atherosclerotic disease does not often manifest in children or adolescents but has its beginnings in early childhood
- Macrovascular disease is accelerated by diabetes, dyslipidemia, raised blood pressure and smoking, and is associated with obesity
- Macrovascular complications are the commonest cause of premature death in adults with diabetes

The evolution of macrovascular disease may be reduced by

- Improved metabolic control of diabetes
- Blood pressure control
- Treatment of dyslipidemia (e.g. familial hypercholesterolemia)
- Not smoking
- Participation in healthy exercise

Growth and development

Associated conditions and other complications

Impaired growth and delayed pubertal development may occur in the following circumstances

- Poor metabolic control
- Inadequate nutritional intake
- Hypothyroidism
- Celiac disease
- Other conditions not associated with diabetes

Recommendation Regular monitoring and assessment of growth are an essential part of good diabetes management


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