ΟΞΕΙΕΣ ΥΠΕΡΓΛΥΚΑΙΜΙΚΕΣ ΚΑΤΑΣΤΑΣΕΙΣ

ΚΑΛΛΙΟΠΗ ΚΩΤΣΑ
ΛΕΚΤΟΡΑΣ ΕΝΔΟΚΡΙΝΟΛΟΓΙΑΣ
ΤΜΗΜΑ ΕΝΔΟΚΡΙΝΟΛΟΓΙΑΣ, ΔΙΑΒΗΤΗ, ΜΕΤΑΒΟΛΙΣΜΟΥ
Α' ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ
ΝΟΣΟΚΟΜΕΙΟ ΑΧΕΠΑ

ΔΙΑΒΗΤΙΚΗ ΚΕΤΟΞΕΩΣΗ
ΥΠΕΡΓΛΥΚΑΙΜΙΚΟ ΥΠΕΡΩΣΜΩΤΙΚΟ ΚΩΜΑ - ΟΡΙΣΜΟΣ

- ΚΕΤΟΝΑΙΜΙΑ
- ΥΠΕΡΓΛΥΚΑΙΜΙΑ
- ΟΞΕΩΣΗ

Ketonaemia 3 mmol/L and over **or** significant ketonuria (more than 2+ on standard urine sticks)
Blood glucose over 11 mmol/L or known diabetes mellitus
Bicarbonate (HCO_3^-) below 15 mmol/L **and/or** venous pH less than 7.3

Characteristic features of a person with HHS:

Hypovolaemia

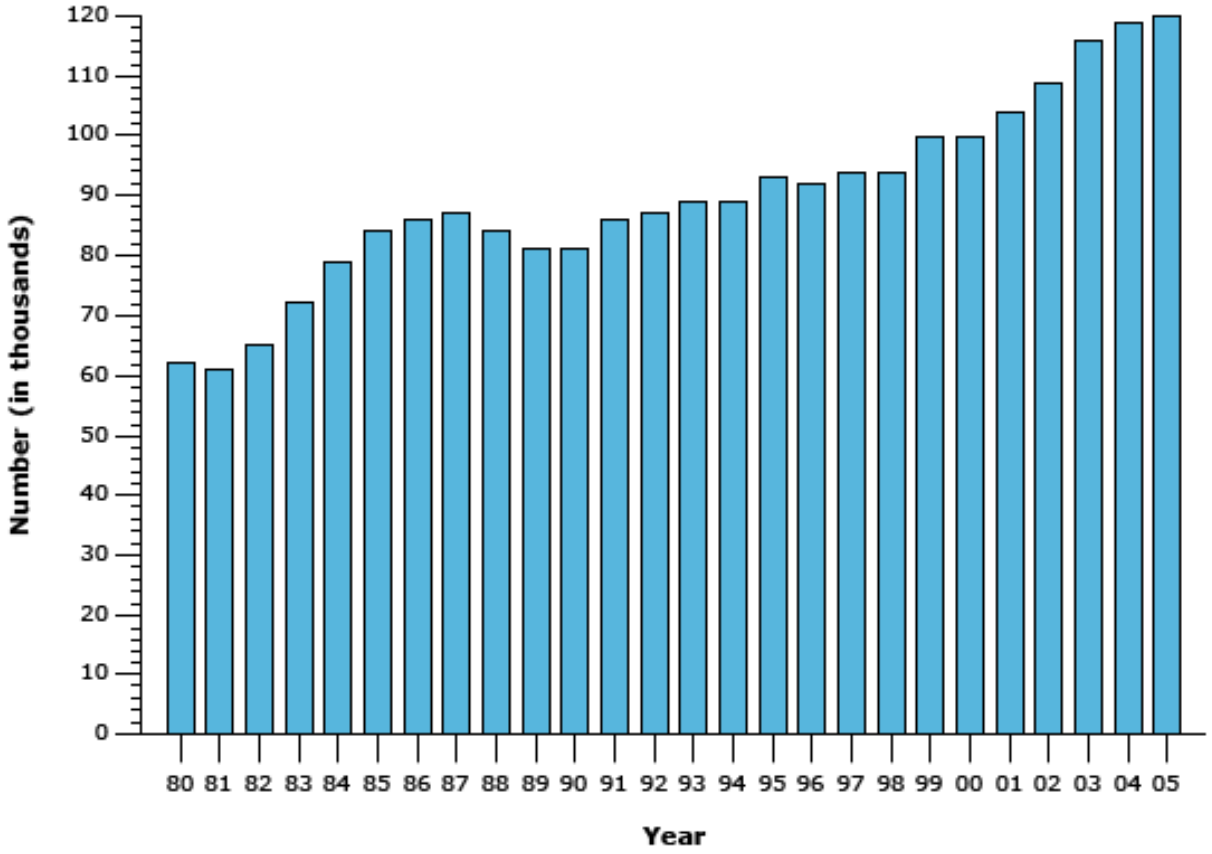
+

Marked hyperglycaemia (>30 mmol/L) without significant hyperketonaemia (<3.0 mmol/L) or acidosis (pH>7.3, bicarbonate >15 mmol/L)

+

Osmolality >320 mosmol/kg

Number (in thousands) of hospital discharges with diabetic ketoacidosis as first-listed diagnosis, United States, 1980-2005



The number of hospital discharges with diabetic ketoacidosis (DKA) as the first-listed diagnosis increased between 1980 and 2005, with about 62,000 discharges in 1980 with DKA as the first-listed diagnosis and about 120,000 in 2005.

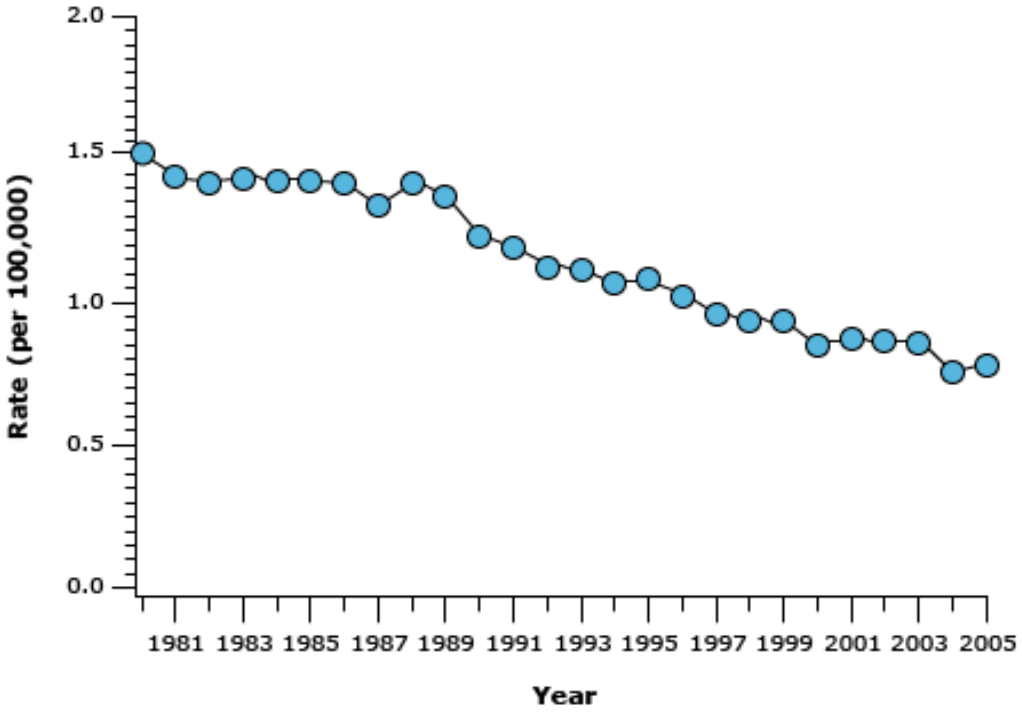
Reproduced from: Centers for Disease Control and Prevention: Diabetes Data & Trends. Retreived from http://www.cdc.gov/diabetes/statistics/dkafirst/fig1.htm on March 1, 2011.

Epidemiology

The true incidence is difficult to establish. Population-based studies range from 4.6 to 8 episodes per 1,000 patients with diabetes (Johnson 1980, Faich 1983). DKA remains a significant clinical problem in spite of improvements in diabetes care (Fishbein 1995, Umpierrez 1997).

In those previously diagnosed, the disease may have been managed by diet, oral hypoglycaemic agents or insulin. It is uncommon, but has a higher mortality than DKA (Delaney 2000). There are no recent publications from the UK of mortality in HHS, but reported series suggest mortality may have improved though remains high at between 15-20% (Piniés 1994, Rolfe 1995, MacIsaac 2002, Kitabachi 2006, Chung 2006).

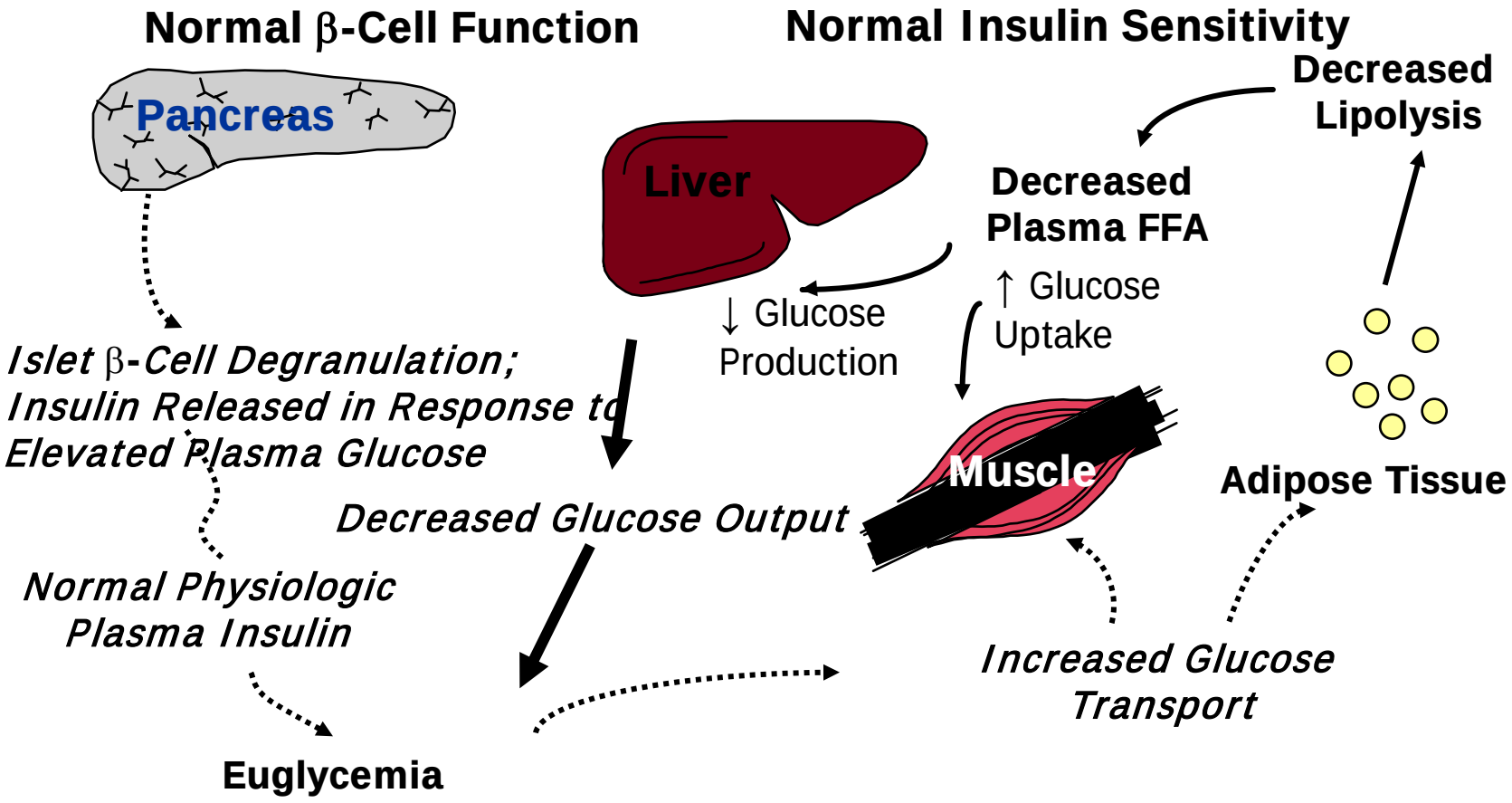
Age-adjusted death rates for diabetic hyperglycemic crises as underlying cause per 100,000 general population, United States, 1980-2005



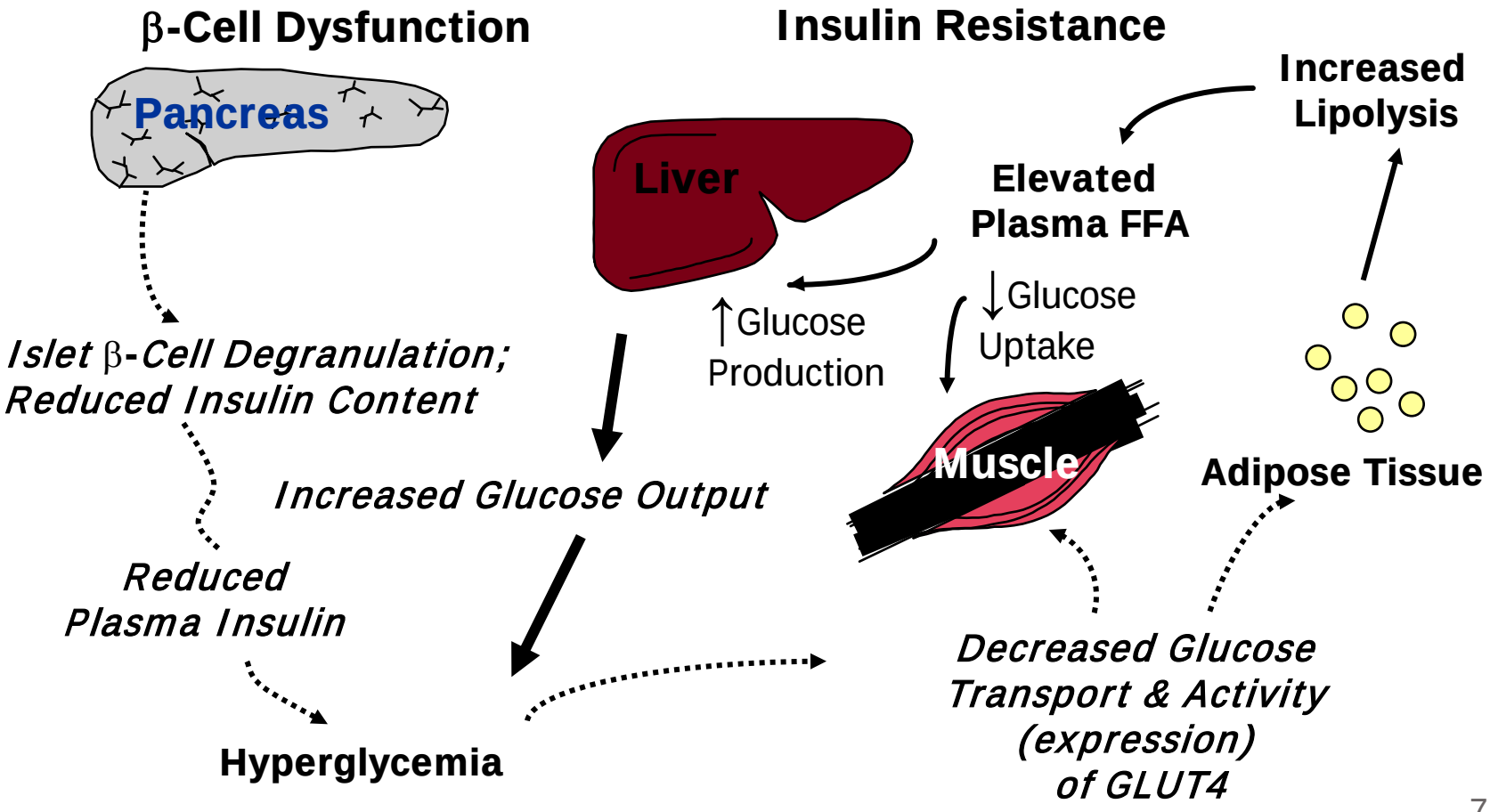
Between 1980 and 2005, the age-adjusted death rate for hyperglycemic crises in the general population declined. In 2005, the age-adjusted death rate for hyperglycemic crises was 0.8 per 100,000 general population, almost half the rate in 1980 (1.5 per 100,000).

Reproduced from: Centers for Disease Control and Prevention: Diabetes Data & Trends. Retreived from http://www.cdc.gov/diabetes/statistics/mortalitydka/fRateDKAGenAgeAdjusted.htm on February 23, 2011.

Φυσιολογική λειτουργία β-κυττάρου=Ευγλυκαιμία



Δυσλειτουργία β-κυττάρου και αντίσταση στην ινσουλίνη = Υπεργλυκαιμία



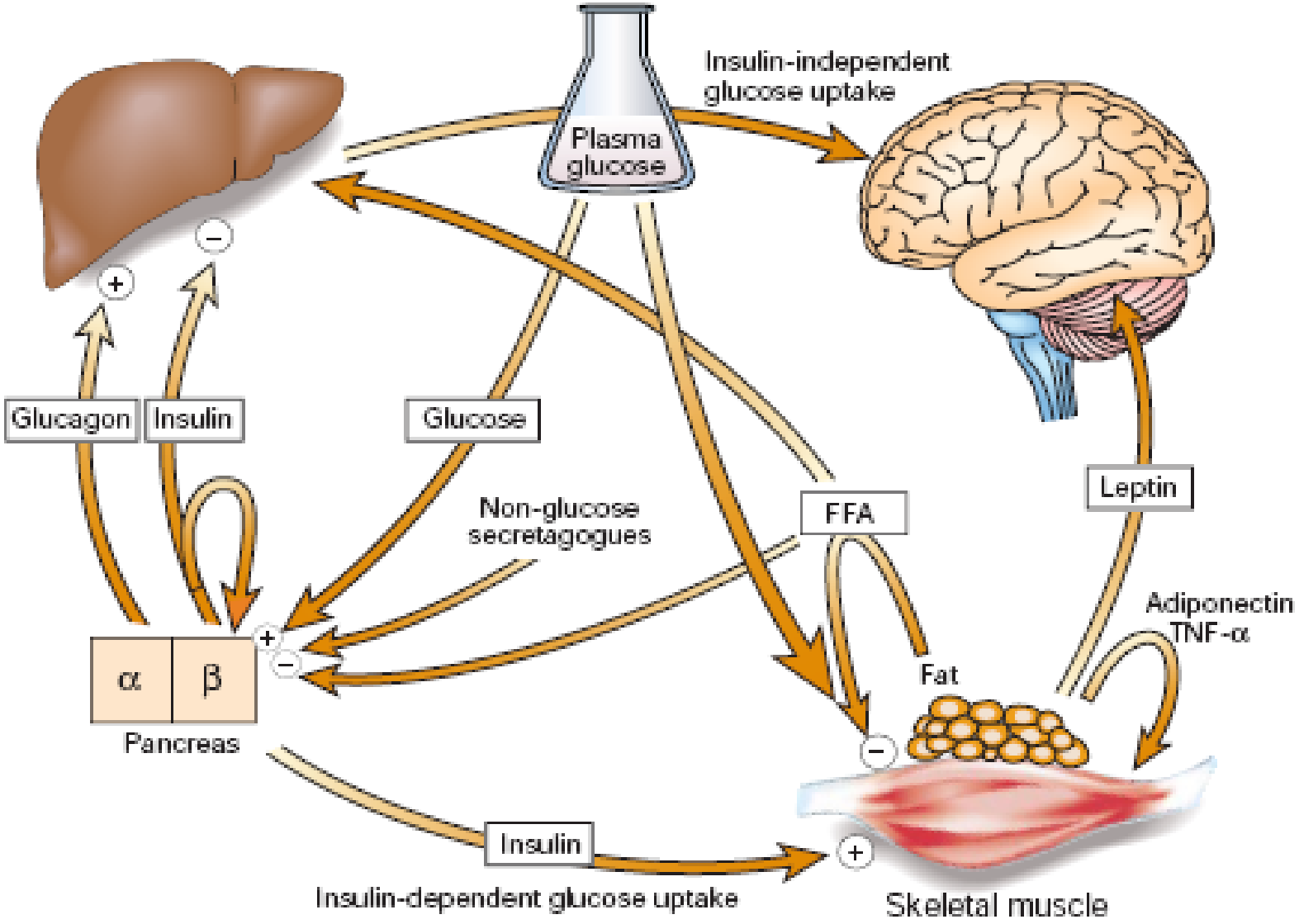
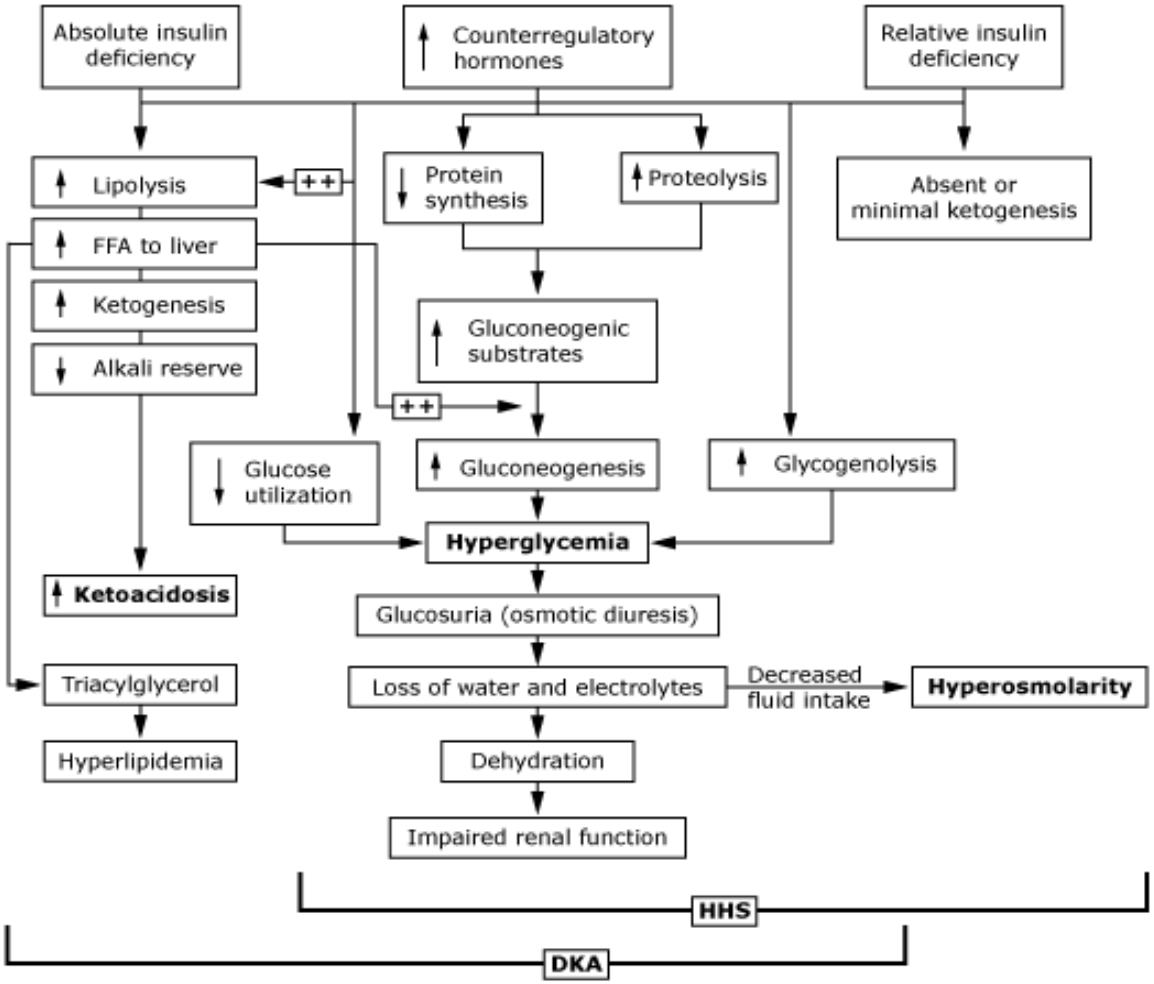


Figure taken from:
http://www.smbs.buffalo.edu/bch/Courses/bch404/GW_Nature_InsulinSig.pdf#search=%22GLUT4%20vesicles%20micrograph%22

Pathogenesis of diabetic ketoacidosis and hyperosmolar hyperglycemic state



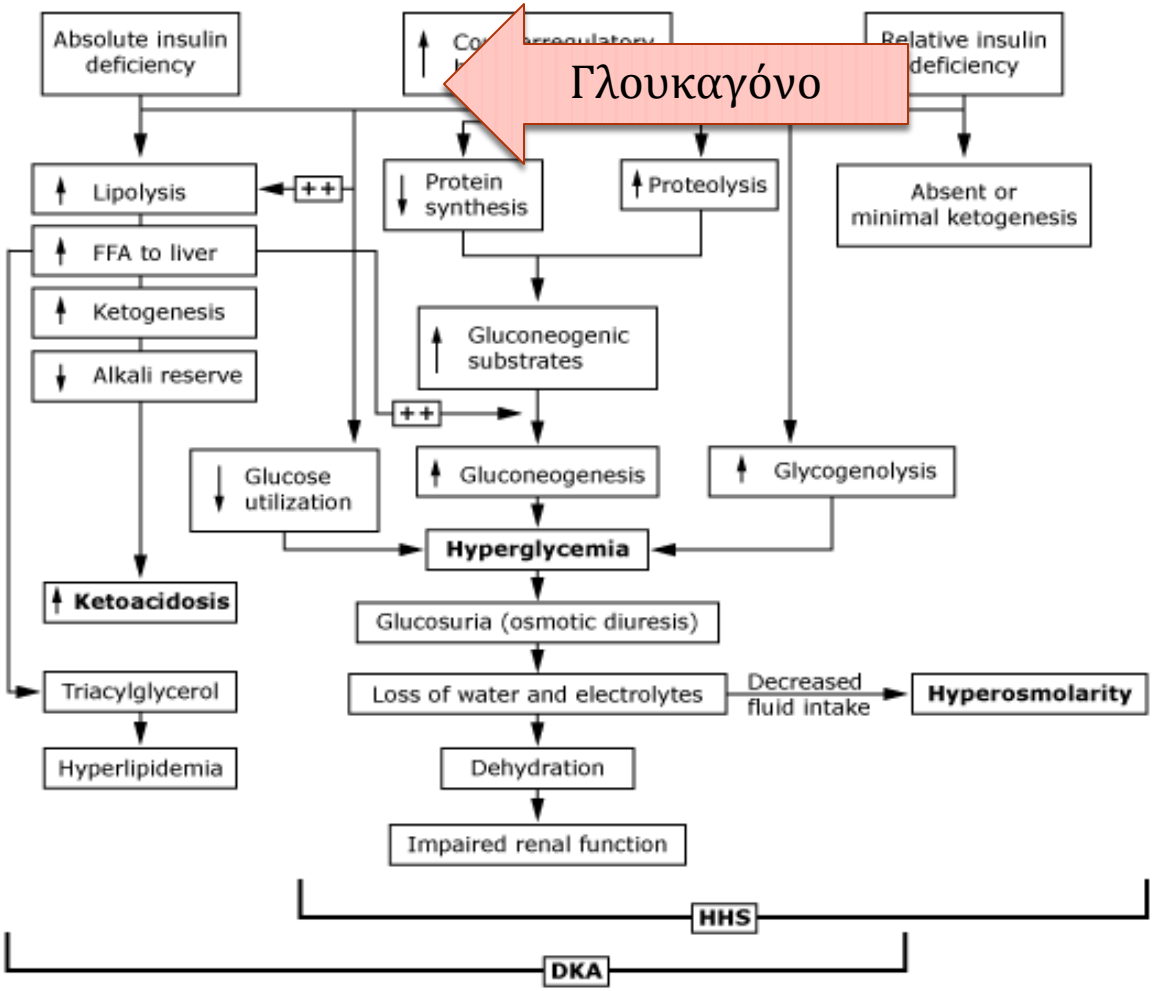
++: Accelerated pathway.

Diagnostic criteria for diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS)

	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10	>18
Urine ketones*	Positive	Positive	Positive	Small
Serum ketones*	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)•	Variable	Variable	Variable	>320
Anion gapΔ	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

* Nitroprusside reaction method.
• Calculation: 2[measured Na (mEq/L)] + glucose (mg/dL)/18.
Δ Calculation: (Na+) - (Cl- + HCO3-) (mEq/L). See text for details.

Pathogenesis of diabetic ketoacidosis and hyperosmolar hyperglycemic state



++: Accelerated pathway.

Insulin regulation of glucose metabolism in the liver

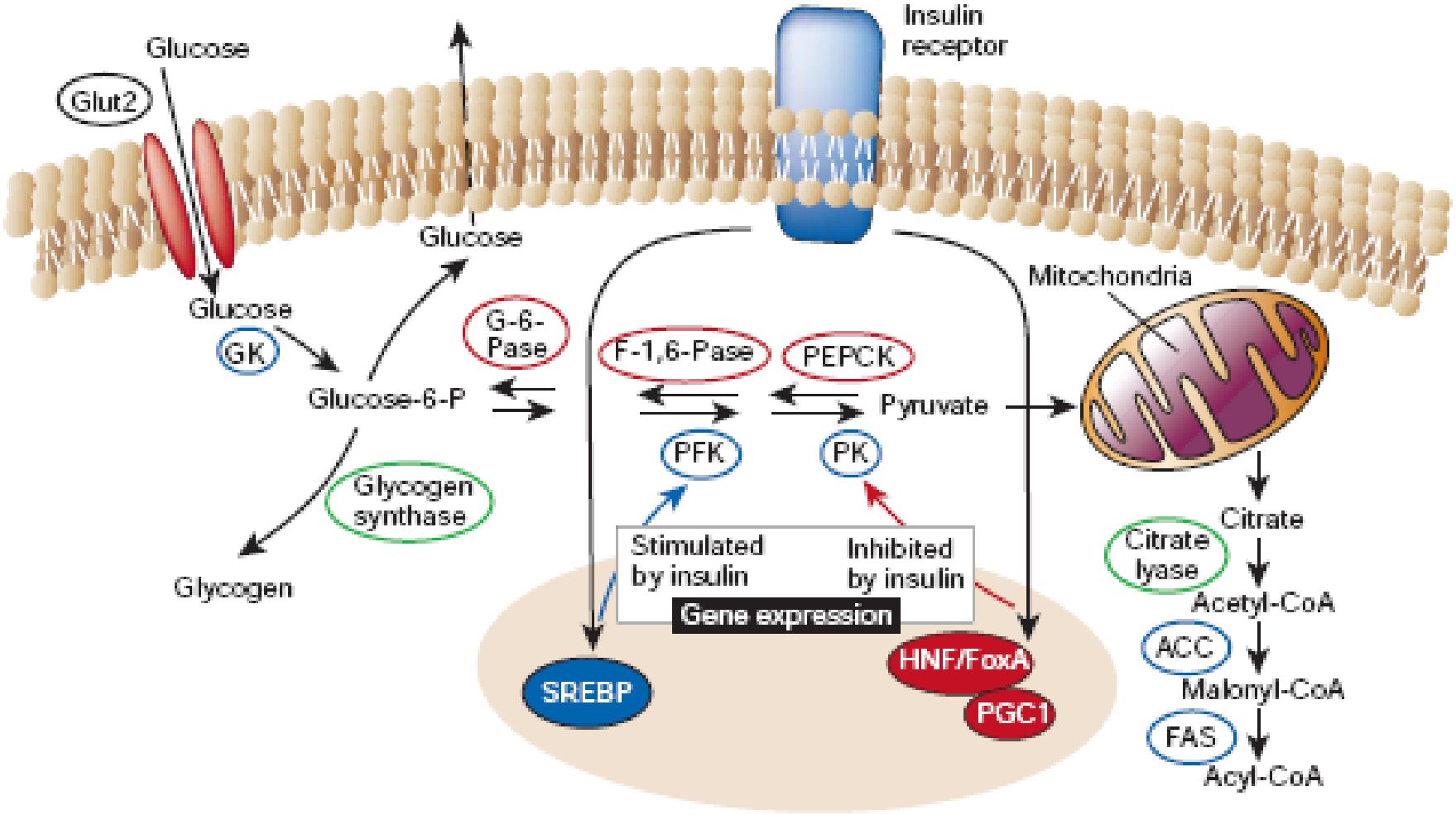


Figure taken from:
http://www.smbs.buffalo.edu/bch/Courses/bch404/GW_Nature_InsulinSig.pdf#search=%22GLUT4%20vesicles%20micrograph%22

Παθογένεια

- Η ινσουλίνη προωθεί τη σύνθεση τριγλυκεριδίων και αναστέλλει την οξείδωση των ελεύθερων λιπαρών οξέων και την παραγωγή κετονικών σωμάτων.
- Σε απουσία ινσουλίνης παράγονται κετονικά σώματα
- Αυτά είναι- acetoacetate, 3-hydroxybutyrate, acetone
- Φυσιολογικά μπορούν να χρησιμοποιηθούν σαν ενεργειακό υπόστρωμα όταν παράγονται σε μικρές ποσότητες.
- Σε ΔΚΟ η παραγωγή υπερβαίνει τη δυνατότητα χρησιμοποίησης και αποβάλλονται με τα ούρα.

Διαγνωστικά κριτήρια ΔΚ και ΥΥΚ όπως προτείνονται από την American Diabetes Association *[Clinical Diabetes, 2001;19(2):82]*

	ΔΚ			ΥΥΚ
	Ήπια	*Μέτρια*	*Σοβαρή*	
Γλυκόζη πλάσματος (mg/dl)	>250	>250	>250	>600
Αρτηριακό pH	7.25 - 7.30	7.00 - 7.25	<7.00	>7.30
Διττανθρακικά (mEq/l)	15 - 18	10 - <15	<10	>15
Κετόνες ούρων*	θετικό	θετικό	θετικό	ήπια
Κετόνες ορού*	θετικό	θετικό	θετικό	ήπια
Δραστική ωσμωτικότης ορού (mOsm/kg)**	μεταβλητή	μεταβλητή	μεταβλητή	>320
Χάσμα ανιόντων***	>10	>12	>12	>12
Διαταραχές αισθήσεων ή διανοητική άμβλυνση	εγρήγορση	εγρήγορση / υπνηλία	stupor / κώμα	stupor / κώμα

*μέθοδος: nitroprussidereaction

**υπολογισμός: 2 [Na^+ (mEq/l)] + γλυκόζη (mg/dl) /18

***υπολογισμός: (Na^+) – (Cl^- + $HCO3^-$) (mEq/l)

Joint British Diabetes Societies Inpatient Care Group

Definition and Diagnosis

DKA consists of the biochemical triad of ketonaemia, hyperglycaemia, and acidaemia.

Definition and diagnosis

A precise definition of HHS does not exist and would be inappropriate, but there are characteristic features that differentiate it from other hyperglycaemic states such as DKA. These are:

- Hypovolaemia
- Marked hyperglycaemia (30 mmol/L or more) without significant hyperketonaemia (<3 mmol/L) or acidosis (pH>7.3, bicarbonate >15 mmol/L)
- Osmolality usually 320 mosmol/kg or more

N.B. A mixed picture of HHS and DKA may occur.

Predisposing or precipitating factors for diabetic ketoacidosis and hyperosmolar hyperglycemic state

DKA	HHS
Inadequate insulin treatment or noncompliance	**Inadequate insulin treatment or noncompliance (21 to 41 percent)**
New onset diabetes (20 to 25 percent)	**Acute illness**
Acute illness	Infection (32 to 60 percent)
Infection (30 to 40 percent)	Pneumonia
Cerebral vascular accident	Urinary tract infection
Myocardial infarction	Sepsis
Acute pancreatitis	Cerebral vascular accident
Drugs	Myocardial infarction
Clozapine or olanzapine	Acute pancreatitis
Cocaine	Acute pulmonary embolus
Lithium	Intestinal obstruction
Terbutaline	Dialysis, peritoneal
	Mesenteric thrombosis
	Renal failure
	Heat stroke
	Hypothermia
	Subdural hematoma
	Severe burns
	Endocrine
	Acromegaly
	Thyrotoxicosis
	Cushing's syndrome
	Drugs/therapy
	Beta-Adrenergic blockers
	Calcium-channel blockers
	Chlorpromazine
	Chlorthalidone
	Cimetidine
	Clozepine
	Diazoxide
	Ethacrynic acid
	Immunosuppressive agents
	L-asparaginase
	Loxapine
	Olanzapine
	Phenytoin
	Propranolol
	Steroids
	Thiazide diuretics
	Total parenteral nutrition
	Previously undiagnosed diabetes

Data from: Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes mellitus (Technical Review). Diabetes Care 2001; 24:131.

ΚΛΙΝΙΚΑ ΧΑΡΑΚΤΗΡΙΣΤΙΚΑ

- Αρχικά πολυουρία – τελικά ολιγοανουρία
- Αφυδάτωση, δίψα
- Υπόταση, ταχυκαρδία
- Κένωση, οξέωση
- Υπεραερισμός (ABC)
- Έμμετοι
- Κοιλιακό άλγος
- Πτώση επιπέδου συνείδησης, κώμα

ΑΡΧΙΚΗ ΑΝΤΙΜΕΤΩΠΙΣΗ

ΙΣΤΟΡΙΚΟ-ΚΛΙΝΙΚΗ ΕΚΤΙΜΗΣΗ

- Αερισμός, αναπνοή, κυκλοφορία
- Διανοητική κατάσταση
- Πιθανές επιβαρυντικές καταστάσεις

  (ΟΕΜ, λοιμώξεις)
- Υποογκαιμία

Table 338-4 Laboratory Values in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS) (Representative Ranges at Presentation)

	DKA	HHS
Glucose,[a] mmol/L (mg/dL)	13.9–33.3 (250–600)	33.3–66.6 (600–1200)
Sodium, meq/L	125–135	135–145
Potassium[a]	Normal to ↑	Normal
Magnesium[a]	Normal[b]	Normal
Chloride[a]	Normal	Normal
Phosphate[a]	↓	Normal
Creatinine	Slightly ↑	Moderately ↑
Osmolality (mOsm/mL)	300–320	330–380
Plasma ketones[a]	++++	+/–
Serum bicarbonate,[a] meq/L	<15 meq/L	Normal to slightly ↓
Arterial pH	6.8–7.3	>7.3
Arterial P_{CO_2},[a] mmHg	20–30	Normal
Anion gap[a][Na - (Cl + HCO_3)]	↑	Normal to slightly ↑

Effective serum osmolality:

$$2 \times [\,Na\ (mEq/L)] + glucose(mg/dL) / 18$$

ç : 275-285 mOsm/L

anion gap :

$$(Na+) - (\,Cl- + HCO3-)\ (mEq/L)$$

Τυπικό έλλειμμα υγρών και ηλεκτρολυτών σε ΔΚ και ΥΥΚ. *[Clinical Diabetes, 2001;19(2):83]*

	ΔΚ	ΥΥΚ
Σύνολο υγρών (liters)	6	9
Υγρά (ml/kg βάρους σώματος)	100	100 - 200
Na^{+} (mEq/kg)	7 - 10	5 - 13
Cl^{-} (mEq/kg)	3 - 5	5 - 15
K^{+} (mEq/kg)	3 - 5	4 - 6
PO4 (mmol/kg)	5 - 7	3 - 7
Mg^{++} (mEq/kg)	1 - 2	1 - 2
Ca^{++} (mEq/kg)	1 - 2	1 - 2

Εργαστηριακός έλεγχος

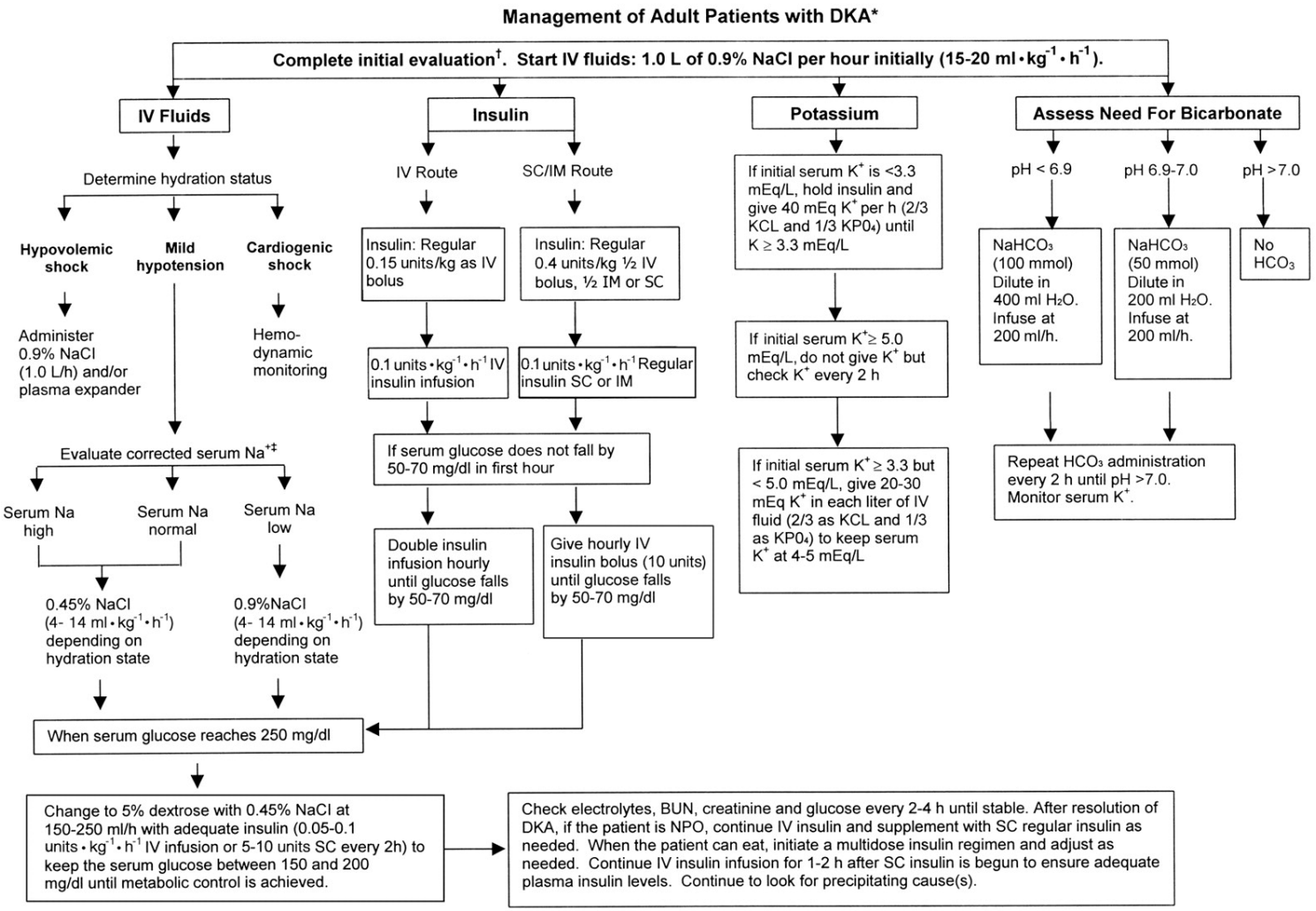
1. **Σάκχαρο αίματος**(250- 600 mg/dl)
2. Αέρια αίματος (PH 6.8 – 7.3)
3. Διττανθρακικά< 12 mmol/l = σοβαρή οξέωση
4. Κετόνες πλάσματος, ούρων= ++++
5. Νεφρική λειτουργία :ουρία, κρεατινίνη, ηλεκτρολύτες
6. Ωσμωτικότητα 300 – 320 mosm/l
7. Χάσμα ανιόντων= Αυξημένο
8. ΗΚΓ
9. Λοιμώξεις : Γεν. αίματος, καλλιέργειες αίματος και ούρων, ΤΚΕ,CRP

Παρακολούθηση

Ωσμωτικότητα = [2 x (Να + Κ) + glucose (mg/dL)/18 + (BUN/2.8)]

	0	1ω	2ω	3ω	6ω	12ω	24ω
Γλυκόζη	✓	✓	✓	✓	✓	✓	✓
Ουρία, Κ, Να	✓	✓	✓	✓	✓		✓
Κρεατινίνη	✓				✓	✓	✓
Διττανθρ	✓	✓	✓	✓	✓	✓	✓
pH	✓		✓		✓		

Protocol for the management of adult patients with DKA. *DKA diagnostic criteria: blood glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15 mEq/l, and moderate ketonuria or ketonemia.



American Diabetes Association et al. Dia Care 2004;27:s94-s102

American Diabetes Association.

Fluid administration and deficits

There is universal agreement that the most important initial therapeutic intervention in DKA is appropriate fluid replacement followed by insulin administration. The main aims for fluid replacement are:

- Restoration of circulatory volume
- Clearance of ketones
- Correction of electrolyte imbalance

The typical fluid and electrolyte deficits are shown in the table below. For example, an adult weighing 70kg presenting with DKA may be up to 7 litres in deficit. This should be replaced as crystalloid. In patients with kidney failure or heart failure, as well as the elderly and adolescents, the rate and volume of fluid replacement may need to be modified. The aim of the first few litres of fluid is to correct any hypotension, replenish the intravascular deficit, and counteract the effects of the osmotic diuresis with correction of electrolyte disturbance.

Typical Deficits in DKA:

Water (ml/kg)	100
Sodium (mmol/kg)	7-10
Chloride (mmol/kg)	3-5
Potassium (mmol/kg))	3-5

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3. Colloid versus crystalloid?

Many guidelines suggest that in hypotensive patients initial fluid resuscitation should be with colloid. However, the hypotension results from a loss of electrolyte solution and it is more physiological to replace with crystalloid. Moreover, a recent Cochrane review did not support the use of colloid in preference to crystalloid fluid (Perel 2007).

4. Rate of fluid replacement?

There is concern that rapid fluid replacement may lead to cerebral oedema in children and young adults. National and international paediatric guidelines recommend cautious fluid replacement over 48 hours. Existing adult guidelines (ADA, ABCD, SIGN) all recommend rapid initial fluid replacement in the first few hours. No randomised controlled trials exist to guide decision making in this area. We therefore recommend cautious fluid replacement in small young adults who are not shocked at presentation.

Intravenous glucose concentration

The management should be focussed on clearing ketones as well as normalising blood glucose. It is often necessary to administer an intravenous infusion of 10% glucose in order to avoid hypoglycaemia and permit the continuation of a fixed rate IVI to suppress ketogenesis. Introduction of 10% glucose is recommended when the blood glucose falls below 14 mmol/L. It is important to continue 0.9% sodium chloride solution to correct circulatory volume. It may be necessary to infuse these solutions concurrently (Section B, Action 2). Glucose should not be discontinued until the patient is eating and drinking normally.

Insulin therapy

A fixed rate IVI calculated on 0.1 units/ per kilogram infusion is recommended. It may be necessary to estimate the weight of the patient. See *Controversial Areas*. Insulin has the following effects:

- Suppression of ketogenesis
- Reduction of blood glucose
- Correction of electrolyte imbalance

Metabolic treatment targets

The recommended targets are

- Reduction of the blood ketone concentration by 0.5 mmol/L/hour
- Increase the venous bicarbonate by 3 mmol/L/hour
- Reduce capillary blood glucose by 3 mmol/L/hour
- Potassium should be maintained between 4.0 and 5.0 mmol/L

If these rates are not achieved then the fixed rate IVI rate should be increased (see *Management of DKA* Section B, Action 2).

6. Continuation of long-acting insulin analogues?

In the last few years the use of long acting basal insulin analogues (Levemir®, Lantus®) has become widespread. Continuation of subcutaneous analogues during the initial management of DKA provides background insulin when the IV insulin is discontinued. This avoids rebound hyperglycaemia when IV insulin is stopped and should avoid excess length of stay. This only applies to long acting analogues and does not obviate the need to give short acting insulin before discontinuing the intravenous insulin infusion.

7. Fixed-rate intravenous insulin infusion (fixed rate IVII) versus variable rate?

Patient demographics are changing and patients with DKA are now more likely to be obese or suffering with other insulin-resistant states including pregnancy. Evidence has led to the re-emergence of fixed rate IVII in adults in the USA and international paediatric practice (Kitabchi 2009, BSPED 2009, ISPAD 2009). Fixed dose(s) per kilogram body weight enable rapid blood ketone clearance, which is readily monitored using bed-side ketone measurement. The fixed rate may need to be adjusted in insulin resistant states if the ketone concentration is not falling fast enough, and/or the bicarbonate level is not rising fast enough.

8. Initiating treatment with a priming dose (bolus) of insulin?

A priming dose of insulin in the treatment in DKA is not necessary provided that the insulin infusion is started promptly at a dose of at least 0.1 unit/kg/hour (Kitabchi 2008).

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Inpatient Care Group

9. Intravenous bicarbonate?

Adequate fluid and insulin therapy will resolve the acidosis in DKA and the use of bicarbonate is not indicated (Morris 1986, Hale 1984). The acidosis may be an adaptive response as it improves oxygen delivery to the tissues by causing a right shift of the oxygen dissociation curve. Excessive bicarbonate may cause a rise in the CO2 partial pressure in the cerebro-spinal fluid (CSF) and may lead to a paradoxical increase in CSF acidosis (Ohman 1971). In addition, the use of bicarbonate in DKA may delay the fall in blood lactate: pyruvate ratio and ketones when compared to intravenous 0.9% sodium chloride infusion (Hale 1984). There is some evidence to suggest that bicarbonate treatment may be implicated in the development of cerebral oedema in children and young adults (Glaser 2001).

10. Use of intravenous phosphate?

Whole-body phosphate deficits in DKA are substantial, averaging 1 mmol/kg of body weight. There is no evidence of benefit of phosphate replacement (Wilson 1982) thus we do not recommend the routine measurement or replacement of phosphate. However, in the presence of respiratory and skeletal muscle weakness, phosphate measurement and replacement should be considered (Liu 2004).

1. Arterial or venous measurements?

Recent evidence shows that the difference between venous and arterial pH is 0.02-0.15 pH units and the difference between arterial and venous bicarbonate is 1.88 mmol/L (Kelly 2006, Gokel 2000). This will change neither diagnosis nor management of DKA and it is not necessary to use arterial blood to measure acid base status (Ma 2003). Venous blood can be used in portable and fixed blood gas analysers and therefore venous measurements (bicarbonate, pH and potassium) are easily obtained in most admitting units. Arterial line insertion should only be performed if its use will influence management i.e. for frequent arterial oxygen level measurements or monitoring blood pressure in the critically unwell patient.

2. Blood ketone measurement?

Ketonaemia is the hallmark of DKA. Frequent repeated measurement of blood 3-beta-hydroxybutyrate has only recently become a practical option due to the availability of meters which can measure blood ketone levels. Compelling evidence supports the use of this technology for diagnosis and management of DKA (Sheikh-Ali 2008, Bektas 2004, Vaneli 2003, Naunheim 2006). The resolution of DKA depends upon the suppression of ketonaemia and measurement of blood ketones now represents best practice in monitoring the response to treatment.

Recommendations

1. Measure venous rather than arterial bicarbonate and pH
2. Blood ketone meters should be used for near patient testing
3. Crystalloid rather than colloid solutions are recommended for fluid resuscitation
4. Cautious fluid replacement in young adults
5. 0.9% sodium chloride solution is the recommended fluid of choice
6. Subcutaneous long-acting analogue insulin should be continued
7. Insulin should be administered at a fixed rate IVII calculated on body weight
8. Do not use a priming dose (bolus) of insulin
9. Bicarbonate administration is not recommended routinely
10. Phosphate should not be supplemented routinely

DKA/HHS flowsheet for the documentation of clinical parameters, fluid and electrolytes, laboratory values, insulin therapy, and urinary output.

SUGGESTED
DKA/HHS FLOWSHEET

DATE: HOUR:	ER												
Weight (daily)													
Mental Status*													
Temperature													
Pulse													
Respiration/Depth**													
Blood Pressure													
Serum Glucose (mg/dl)													
Serum Ketones													
Urine Ketones													
ELECTROLYTES													
Serum Na^+ (mEq/L)													
Serum K^+ (mEq/L)													
Serum Cl^- (mEq/L)													
Serum HCO_3^- (mEq/L)													
Serum BUN (mg/dl)													
Effective Osmolality													
2[measured Na(mEq/L)]													
+Glucose (mg/dl)/18													
Anion Gap													
A.B.G.													
pH Venous(V) Arterial(A)													
pO_2													
pCO_2													
O_2 SAT													
INSULIN													
Units Past Hour													
Route													
INTAKE FLUID/METABOLITES													
0.45% NaCl(ml) past hour													
0.9% NaCl(ml) past hour													
5% Dextrose(ml) past hour													
KCL (mEq) past hour													
PO_4 (mMOLES) past hour													
Other (e.g., HCO_3^-)													
OUTPUT													
Urine (ml)													
Other													

* A-ALERT D-DROWSY S-STUPOROUS C-COMATOSE
** D-DEEP S-SHALLOW N-NORMAL

American Diabetes Association et al. Dia Care 2004;27:s94-s102

American Diabetes Association.

Βασικές αρχές θεραπείας

- Χορήγηση υγρών
- Χορήγηση ινσουλίνης ταχείας δράσης
- Χορήγηση Κ
- Χορήγηση αντιβιοτικών σε λοίμωξη

Χορήγηση υγρών

- 0.9% NaCl i.v.
  - 1 l σε 30 λεπτά
  - 1 l σε 1 ώρα
  - 1 l σε 2 ώρες
  - 1 l σε 4 ώρες
- ‘Οταν η γλυκόζη < 250 mg/dl,
  - Αλλαγή σε 5% dextrose, 1 l ανά 8 ώρες
  - Αν συνυπάρχει αφυδάτωση συνεχίζεται η έγχυση 0.9% NaCl και προστίθεται 5% dextrose 1 l ανά 12 ώρες
- Συνήθως απαιτούνται περίπου 6 l τις πρώτες 24 ώρες αλλά χρειάζεται προσοχή σε ηλικιωμένους αλλά και νέους.

Ινσουλίνη

- 50 μονάδες σε 50 ml 0.9% NaCl i.v. δια μέσου αντλίας
  - 6 units/ώρα αρχικά
  - 3 units/ώρα όταν η γλυκόζη < 270 mg/dl
  - 2 units/ώρα όταν η γλυκόζη <180 mg/dl
- Έλεγχος γλυκόζης ανά ώρα και αύξηση του ρυθμού αν δεν έχουμε μείωση στην πρώτη ώρα
- Στόχος η μείωση κατά ~55-110 mg/dl ανά ώρα

Κάλιο

- K< 3.5 mmol/l, χορήγηση 40 mmol K
- Ρυθμός χορήγησης < 20 mmol/hr
- K = 3.5-5.5 mmol/l, χορήγηση 20 mmol K
- K > 5.5 mmol/l (ή ανουρία) δεν χορηγείται K
- Επανεκτίμηση αργότερα (εργαστηριακός έλεγχος).
- Προσοχή =Αν αρχικά K+ < 3.3 mmol/l τότε διακόπτεται η χορήγηση ινσουλίνης έως K+ > 3.3mmol/l.

Hypokalaemia and hyperkalaemia

Hypokalaemia and hyperkalaemia are potentially life-threatening conditions during the management of DKA. There is a risk of acute pre-renal failure associated with severe dehydration and it is therefore recommended that no potassium be prescribed with the initial fluid resuscitation or if the serum potassium level remains above 5.5 mmol/L. However, potassium will almost always fall as the DKA is treated with insulin, thus it is recommended that 0.9% sodium chloride solution with potassium 40 mmol/L (ready-mixed) is prescribed as long as the serum potassium level is below 5.5 mmol/L and the patient is passing urine. If the serum potassium level falls below 3.5 mmol/L the potassium regimen needs review. Where fluid balance permits, an increase in rate of 0.9% sodium chloride solution with potassium 40 mmol/L infusion is possible. Otherwise, a more concentrated potassium infusion will be needed and to ensure safe practice, all aspects of its use must comply with local and national guidance (NPSA 2002, 2009). Trusts need to ensure that they have local protocols in place which allow for the safe administration of concentrated potassium solutions. This may require transfer to a higher care environment. Electrolyte measurements can be obtained from most modern blood gas analysers and should be used to monitor sodium, potassium and bicarbonate levels.

Hypoglycaemia

The blood glucose may fall very rapidly as ketoacidosis is corrected and a common mistake is to allow the blood glucose to drop to hypoglycaemic levels. This may result in a rebound ketosis driven by counter-regulatory hormones. Rebound ketosis lengthens duration of treatment. Severe hypoglycaemia is also associated with cardiac arrhythmias, acute brain injury and death. Once the blood glucose falls to 14 mmol/L intravenous glucose 10% needs to be commenced to prevent hypoglycaemia.

Cerebral oedema

Cerebral oedema causing symptoms is relatively uncommon in adults during DKA although asymptomatic cerel
occurrence (Rosenb
that cerebral oeder
hours of initiation c
speculation that it i
However, this is dis
oedema may be pr
started (Hoffmann
phenomenon is unl
that cerebral hypop
perfusion may be tl
2001, Glaser 2008,

Cerebral oedema a
common in childre
around 70 to 80%
children under 12 y
result of cerebral o
case control study
complicating DKA
developed cerebral
and, after severity
insulin administrati
of fluid administere
associated with inc

The presence of one or more of the following may indicate severe DKA and admission to a Level 2/HDU (High Dependency Unit) environment, insertion of a central line and immediate senior review should be considered:

- Blood ketones over 6 mmol/L
- Bicarbonate level below 5 mmol/L
- Venous/arterial pH below 7.1
- Hypokalaemia on admission (under 3.5 mmol/L)
- GCS less than 12 or abnormal AVPU scale
- Oxygen saturation below 92% on air (assuming normal baseline respiratory function)
- Systolic BP below 90 mmHg
- Pulse over 100 or below 60 bpm
- Anion gap above16 **[Anion Gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$]**

Pulmonary oedema

Pulmonary oedema has only been rarely reported in DKA. As with cerebral oedema, the observation
usually occurs within a
treatment has led to the
plication is iatrogenic and
stalloids over a short
the likelihood of this
5). Elderly patients and
iac function are at
oring of central venous
dered.

A. Hour 1: Immediate management upon diagnosis: 0 to 60 minutes.

T=0 at time intravenous fluids are commenced
If there is a problem with intravenous access critical care support should be requested immediately

Aims

- Commence IV 0.9% sodium chloride solution
- Commence a fixed rate IVII but only after fluid therapy has been commenced
- Establish monitoring regime appropriate to patient; generally hourly blood glucose (BG) and hourly ketone measurement, with at least 2 hourly serum potassium for the first six hours
- Clinical and biochemical assessment of the patient
- Involvement of the diabetes specialist diabetes team at the earliest possible stage

Action 1 - Intravenous access and initial investigations

- Rapid ABC (Airway, Breathing, Circulation)
- Large bore iv cannulae and commence iv fluid replacement (See action 2)
- Clinical assessment
  - o Respiratory rate; temperature; blood pressure; pulse; oxygen saturation
  - o Glasgow Coma Scale. NB: a drowsy patient in the context of DKA is serious and the patient requires critical care input. Consider NG tube with airway protection to prevent aspiration
  - o Full clinical examination
- Initial investigations should include:
  - o Blood ketones
  - o Capillary blood glucose
  - o Venous plasma glucose
  - o Urea and electrolytes
  - o Venous blood gases
  - o Full blood count
  - o Blood cultures
  - o ECG
  - o Chest radiograph
  - o Urinalysis and culture
- Continuous cardiac monitoring
- Continuous pulse oximetry
- Consider precipitating causes and treat appropriately
- Establish usual medication for diabetes

Action 2 – Restoration of circulating volume

Assess the severity of dehydration using pulse and blood pressure. As a guide 90mmHg may be used as a measure of hydration but take age, gender and concomitant medication into account.

Systolic BP (SBP) on admission below 90mmHg

Hypotension is likely to be due to low circulating volume, but consider other causes such as heart failure, sepsis, etc.

- Give 500 ml of 0.9% sodium chloride solution over 10-15 minutes. If SBP remains below 90mmHg this may be repeated **whilst awaiting senior input**. In practice most patients require between 500 to 1000 ml given rapidly.
- If there has been no clinical improvement re-consider other causes of hypotension and seek **immediate senior assessment**. Consider involving the ITU/critical care team.
- Once SBP above 90mmHg follow fluid replacement as below

Exercise caution in the following patients

- Young people aged 18-25 years
- Elderly
- Pregnant
- Heart or kidney failure
- Other serious co-morbidities

Systolic BP on admission 90 mmHg and over

Below is a table outlining a typical fluid replacement regimen for a previously well 70kg adult. This is an illustrative guide only. A slower infusion rate should be considered in young adults (see Controversial Areas).

Fluid	Volume
0.9% sodium chloride 1L *	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours
Re-assessment of cardiovascular status at 12 hours is mandatory, further fluid may be required	

*Potassium chloride may be required if more than 1 litre of sodium chloride has been given already to resuscitate hypotensive patients

Action 3 - Potassium replacement

Hypokalaemia and hyperkalaemia are life threatening conditions and are common in DKA. Serum potassium is often high on admission (although total body potassium is low) but falls precipitously upon treatment with insulin. Regular monitoring is mandatory.

Potassium level in first 24 hours (mmol/L)	Potassium replacement in mmol /L of infusion solution
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given (see serious complications section)

Action 4 - Commence a fixed rate intravenous insulin infusion (IVII)

- If weight not available from patient, estimate patient weight (in kg)
- If pregnant use present weight and consider calling for senior obstetric help as well.
- Start continuous fixed rate IVII via an infusion pump. 50units human soluble insulin (Actrapid®, Humulin S®) made up to 50ml with 0.9% sodium chloride solution. Ideally this should be provided as a ready-made infusion
- Infuse at a fixed rate of 0.1unit/kg/hr (i.e. 7ml/hr if weight is 70kg)
- Only give a stat dose of intramuscular insulin (0.1 unit/kg) if there is a delay in setting up a fixed rate IVII.
- If the patient normally takes insulin Lantus® or Levemir® subcutaneously continue this at the usual dose and usual time
- Insulin may be infused in the same line as the intravenous replacement fluid provided that a Y connector with a one way, anti-syphon valve is used and a large-bore cannula has been placed

B. 60 minutes to 6 hours

Aims:

- Clear the blood of ketones and suppress ketogenesis
- Achieve a rate of fall of ketones of at least 0.5 mmol/L/hr
- In the absence of ketone measurement, bicarbonate should rise by 3 mmol/L/hr and blood glucose should fall by 3 mmol/L/hr
- Maintain serum potassium in normal range
- Avoid hypoglycaemia

Action 1 – Re-assess patient, monitor vital signs

- Consider urinary catheterisation if incontinent or anuric (i.e. not passed urine by 60 minutes)
- Consider naso-gastric tube if patient obtunded or if persistently vomiting
- If oxygen saturation falling perform arterial blood gases and request repeat chest radiograph
- Regular observations and Early Warning Score (EWS) charting as appropriate
- Accurate fluid balance chart, minimum urine output 0.5ml/kg/hr
- Continuous cardiac monitoring in those with severe DKA
- Give low molecular weight heparin as per NICE guidance (CG 92 Jan 2010)

Action 2 – Review metabolic parameters

- Measure blood ketones and capillary glucose hourly (note: if meter reads "blood glucose over 20 mmol/L" or "HI" venous blood should be sent to the laboratory hourly or measured using venous blood in a blood gas analyser until the bedside meter is within its QA range)
- Review patient's response to fixed rate IVII hourly by calculating rate of change of ketone level fall (or rise in bicarbonate or fall in glucose).
- Assess resolution of ketoacidosis

o If blood ketone measurement available and blood ketones not falling by at least 0.5 mmol/L/hr call a prescribing clinician to increase insulin infusion rate by 1 unit/hr increments hourly until ketones falling at target rates (also check infusion**)

o If blood ketone measurement not available use venous bicarbonate. If the bicarbonate is not rising by at least 3 mmol/L/hr call a prescribing clinician to increase insulin infusion rate by 1 unit/hr increments hourly until bicarbonate is rising at this rate**

o Alternatively use plasma glucose. If glucose is not falling by at least 3 mmol/L/hr call a prescribing clinician to increase insulin infusion rate by 1 unit/hr increments hourly until glucose falls at this rate. Glucose level is not an accurate indicator of resolution of acidosis in euglycaemic ketoacidosis, so the acidosis resolution should be verified by venous gas analysis**

**** If ketones and glucose are not falling as expected always check the insulin infusion pump is working and connected and that the correct insulin residual volume is present (to check for pump malfunction)**

- Measure venous blood gas for pH, bicarbonate and potassium at 60 minutes and 2 hours and 2 hourly thereafter.
- If the potassium is outside the reference range, assess the appropriateness of potassium replacement and check it hourly. If it is abnormal next hour seek immediate senior medical advice. (See Action 3 p14).
- Continue fixed rate IVII until ketones less than 0.3 mmol/L, venous pH over 7.3 and/or venous bicarbonate over 18 mmol/L. (See section C)
- Do not rely on urinary ketone clearance to indicate resolution of DKA, because these will still be present when DKA has resolved.
- If glucose falls below 14 mmol/L commence 10% glucose given at 125mls/hour alongside the 0.9% sodium chloride solution.
- Monitor and replace potassium as it may fall rapidly.

Action 3 – Identify and treat precipitating factors

C. 6 to 12 hours.

Aim: The aim within this time period is to:

- Ensure that clinical and biochemical parameters are improving
- Continue IV fluid replacement
- Continue insulin administration
- Assess for complications of treatment e.g. fluid overload, cerebral oedema
- Continue to treat precipitating factors as necessary
- Avoid hypoglycaemia

Action 1 – Re-assess patient, monitor vital signs

- If patient not improving seek senior advice
- Ensure referral has been made to diabetes team

Action 2 – Review biochemical and metabolic parameters

- At 6 hours check venous pH, bicarbonate, potassium, as well as blood ketones and glucose
- Resolution is defined as ketones less than 0.3mmol/L, venous pH over 7.3 (do not use bicarbonate as a surrogate at this stage – see box Section D).

D. 12 to 24 HOURS

Expectation: By 24 hours the ketonaemia and acidosis should have resolved

Aim:

- Ensure that clinical and biochemical parameters are improving or have normalised
- Continue IV fluids if not eating and drinking.
- If patient is not eating and drinking and there is no ketonaemia move to a variable rate IVII as per local guidelines
- Re-assess for complications of treatment e.g. fluid overload, cerebral oedema
- Continue to treat precipitating factors as necessary
- Transfer to subcutaneous insulin if patient is eating and drinking normally. Ensure subcutaneous insulin is started before IV insulin is discontinued. Ideally give subcutaneous fast acting insulin and a meal and discontinue IV insulin one hour later.

Action 1 – Re-assess patient, monitor vital signs

NB: Do not rely on bicarbonate to assess resolution of DKA at this point due to possible hyperchloraemia secondary to high volumes of 0.9% sodium chloride solution. The hyperchloraemic acidosis may cause renal vasoconstriction and be a cause of oliguria. However, there is no evidence that the hyperchloraemic acidosis causes significant morbidity or prolongs length of stay.

Action 2 – Review biochemical and metabolic parameters

- At 12 hours check venous pH, bicarbonate, potassium, as well as blood ketones and glucose
- Resolution is defined as ketones <0.3mmol/L, venous pH>7.3

Expectation: Patients should be eating and drinking and back on normal insulin.

If expectation is not met within this time period it is important to identify and treat the reasons for the failure to respond to treatment. **This situation is unusual** and requires senior and specialist input.

E. Conversion to subcutaneous insulin.

- Convert back to an appropriate subcutaneous regime when biochemically stable (blood ketones less than 0.3, pH over 7.3) and the patient is ready and able to eat.

Conversion to subcutaneous insulin is ideally managed by the Specialist Diabetes Team. If the team is not available see Appendix 1. If the patient is newly diagnosed it is essential they are seen by a member of the specialist team prior to discharge.

Complication of DKA

21.20 Complications of diabetic ketoacidosis

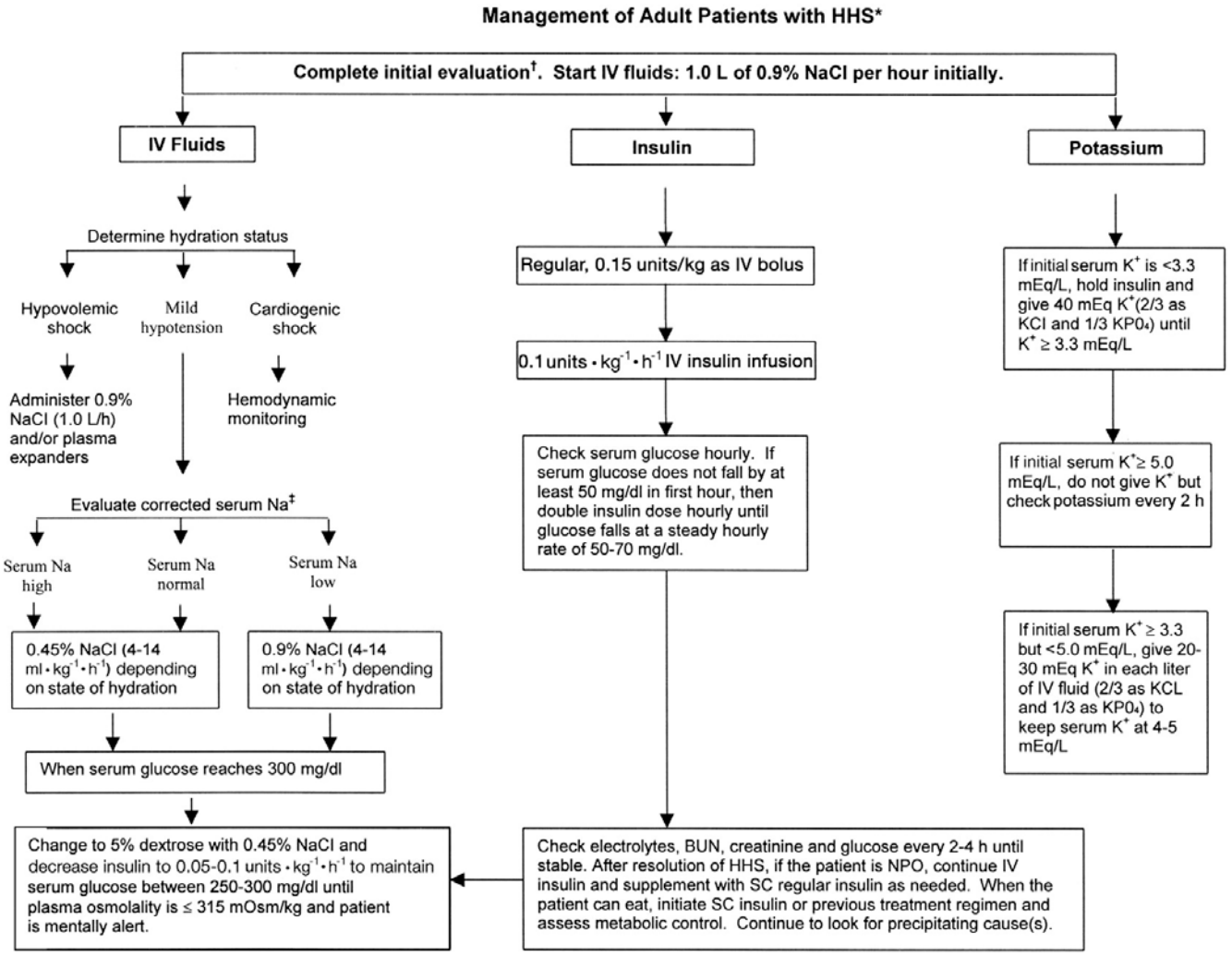
- Cerebral oedema
  - May be caused by very rapid reduction of blood glucose, use of hypotonic fluids and/or bicarbonate
  - High mortality
  - Treat with mannitol, oxygen
- Acute respiratory distress syndrome (p. 187)
- Thromboembolism
- Disseminated intravascular coagulation (rare)
- Acute circulatory failure

Laboratory evaluation of metabolic causes of acidosis and coma

	Starvation or high fat intake	DKA	Lactic acidosis	Uremic acidosis	Alcoholic ketosis (starvation)	Salicylate intoxication	Methanol or ethylene glycol intoxication	Hyperosmolar coma	Hypoglycemic coma	Rhabdomyolysis
pH	Normal	↓	↓	Mild ↓	↓↑	↓↑*	↓	Normal	Normal	Mild ↓ may be ↓↓
Plasma glucose	Normal	↑	Normal	Normal	↓ or normal	Normal or ↓	Normal	↑↑ >500mg/dL	↓↓ <30 mg/dL	Normal
Glycosuria	Negative	++	Negative	Negative	Negative	Negative•	Negative	++	Negative	Negative
Total plasma ketonesΔ	Slight ↑	↑↑	Normal	Normal	Slight to moderate ↑	Normal	Normal	Normal or slight ↑	Normal or slight ↑	Normal
Anion gap	Slight ↑	↑	↑	Slight ↑	↑	↑	↑	Normal	Normal or slight ↑	↑↑
Osmolality	Normal	↑	Normal	↑	Normal	Normal	↑↑	↑↑ >330 mOsm/kg	Normal	Normal or slight ↑
Uric acid	Mild (starvation)	↑	Normal	Normal	↑	Normal	Normal	Normal	Normal	↑
Miscellaneous		May give false-positive for ethylene glycol◇	Serum lactate >7 mmol/l	BUN >200 mg/dL		Serum salicylate positive	Serum levels positive			Myoglobinuria hemoglobinuria

+: positive.
* Acetest and Ketostix measure acetoacetic acid only: thus, misleading low values may be obtained because the majority of "ketone bodies" are β-hydroxybutyrate.
• Respiratory alkalosis/metabolic acidosis.
Δ May get false-positive or false-negative urinary glucose caused by the presence of salicylate or its metabolites.

Protocol for the management of adult patients with HHS. *Diagnostic criteria: blood glucose >600 mg/dl, arterial pH >7.3, bicarbonate >15 mEq/l, mild ketonuria or ketonemia, and effective serum osmolality >320 mOsm/kg H2O.



American Diabetes Association et al. Dia Care 2004;27:s94-s102

American Diabetes Association.

Treatment of HHS

Treatment goals

The goals of treatment of HHS are to treat the underlying cause and to gradually and safely:

- Normalise the osmolality
- Replace fluid and electrolyte losses
- Normalise blood glucose

Other goals include prevention of:

- Arterial or venous thrombosis
- Other potential complications e.g. cerebral oedema/ central pontine myelinolysis
- Foot ulceration

Table 1 – Typical fluid and electrolyte losses in HHS (Kitabachi 2009)

		For 60 kg patient	For 100 kg patient
Water	100-220 ml/kg	6-13 litres	10-22 litres
Na+	5-13 mmol/kg	300-780 mmol	500-1300 mmol
Cl-	5-15 mmol/kg	300-900 mmol	500-1500 mmol
K+	4-6 mmol/kg	240-360 mmol	400-600 mmol

Biochemical

HHS should not be diagnosed from biochemical parameters alone. However, the blood glucose is markedly raised (usually 30 mmol/L or more), as is the osmolality.

Osmolality is useful, both as an indicator of severity and for monitoring the rate of change with treatment. As frequent measurement of osmolality is not usually available in UK hospitals, osmolarity should be calculated as a surrogate using the formula $2Na^+$ + glucose + urea.

This gives the best approximation to measured osmolality, though a more accurate formula has been derived (Bhagat 1984). *(For the sake of clarity, calculated osmolarity and measured osmolality will be referred to as osmolality in the rest of this guideline).* Urea is not an effective osmolyte but including it in the calculation is important in the hyperosmolar state, as it is one of the indicators of severe dehydration.

Clinical

Acute impairment in cognitive function may be associated with dehydration but is not specific to the condition and is not necessarily present. Alterations in mental status are common with osmolalities over 330 mosmol/kg. The constellation of sunken eyes, longitudinal furrows on the tongue and extremity weakness correlates well with raised blood urea (Gross 1992, Sinert 2005). Severe hypovolaemia may manifest as tachycardia (pulse >100 bpm) and/or hypotension (systolic blood pressure <100 mmHg), (Lapides 1965, Delaney 2000, Kavouras 2002). Patients will usually be identified as being at high risk by use of a validated triage Early Warning Scoring systems (EWS).

Despite these severe electrolyte losses and total body volume depletion, the typical patient with HHS, may not look as dehydrated as they are, because the hypertonicity leads to preservation of intravascular volume, causing movement of water from intracellular to extracellular – see Figure 1 (Coller 1935, Mange 1997, Bartoli 2009).

High-dependency / level 2 care

Patients with HHS are complex and often have multiple co-morbidities so require intensive monitoring. The JBDS suggest that the presence of one or more of the following may indicate the need for admission to a high-dependency unit / level 2 environment, where the insertion of a central venous catheter to aid assessment of fluid status and immediate senior review by a clinician skilled in the management of HHS should be considered:

- Osmolality greater than 350 mosmol/kg
- Sodium above 160 mmol/L
- Venous/arterial pH below 7.1
- Hypokalaemia (less than 3.5 mmol/L) or hyperkalaemia (more than 6 mmol/L) on admission
- Glasgow Coma Scale (GCS) less than 12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale
- Oxygen saturation below 92% on air (assuming normal baseline respiratory function)
- Systolic blood pressure below 90 mmHg
- Urine output less than 0.5 ml/kg/hr
- Serum creatinine > 200 µmol/L
- Hypothermia
- Macrovascular event such as myocardial infarction or stroke
- Other serious co-morbidity

Isotonic versus hypotonic fluid replacement

- Rapid changes in osmolality may be harmful. Use 0.9% sodium chloride solution as the principle fluid to restore circulating volume and reverse dehydration.
- Measurement or calculation of osmolality should be undertaken every hour initially and the rate of fluid replacement adjusted to ensure a positive fluid balance sufficient to promote a gradual decline in osmolality.
- Fluid replacement alone (without insulin) will lower blood glucose which will reduce osmolality causing

Water replacement and hypotonic (0.45% sodium chloride solution) fluid

Ideally patients will recover quickly enough to replace the water deficit themselves by taking fluids orally. There is no experimental evidence to justify using hypotonic fluids less than 0.45% sodium chloride solution. However, if the osmolality is no longer declining despite adequate fluid replacement with 0.9% sodium chloride solution AND an adequate rate of fall of plasma glucose is not being achieved then 0.45% sodium chloride solution should be substituted.

hours and the remainder in the following 12 hours though this will in part be determined by the initial severity, degree of renal impairment and co-morbidities such as heart failure, which may limit the speed of correction.

- A target blood glucose of between 10 and 15 mmol/L is a reasonable goal. Complete normalisation of electrolytes and osmolality may take up to 72 hours.

Insulin dose and timing

- If significant ketonaemia is present (3β-hydroxy butyrate is more than 1 mmol/L) this indicates relative hypoinsulinaemia and insulin should be started at time zero.
- If significant ketonaemia is not present (3β-hydroxy butyrate is less than 1 mmol/L) do NOT start insulin.
- Fluid replacement alone with 0.9% sodium chloride solution will result in falling blood glucose and because most patients with HHS are insulin sensitive there is a risk of lowering the osmolality precipitously. Insulin treatment prior to adequate fluid replacement may result in cardiovascular collapse as water moves out of the intravascular space, with a resulting decline in intravascular volume (a consequence of insulin-mediated glucose uptake and a diuresis from urinary glucose excretion) (see Figure 2).
- The recommended insulin dose is a fixed rate intravenous insulin infusion (FRIII) given at 0.05 units per kg per hour (e.g. 4 units/hr in an 80 kg man) is used. A fall of glucose at a rate of up to 5 mmol/L per hour is ideal and once the blood glucose has ceased to fall following initial fluid resuscitation, reassessment of fluid intake and evaluation of renal function must be undertaken. **Insulin may be started at this point**, or, if already in place, the infusion rate increased by 1 unit/hr. As with DKA, a FRIII is preferred, though generally lower doses are required.

Potassium

Patients with HHS are potassium deplete but less acidotic than those with DKA so potassium shifts are less pronounced, the dose of insulin is lower, and there is often co-existing renal failure. Hyperkalaemia can be present with acute kidney injury and patients on diuretics may be profoundly hypokalaemic. Potassium should be replaced or omitted as required (see Table 2).

Table 2 – Potassium replacement in HHS

Potassium level in first 24 hr (mmol/L)	Potassium replacement in infusion solution
Over 5.5	Nil
3.5 – 5.5	40 mmol/L
Below 3.5	Senior review as additional potassium required (via central line in HDU)

Anti-infective therapy

As with all acutely ill patients, sepsis may not be accompanied by pyrexia. An infective source should be sought on clinical history and examination and C-reactive protein may be helpful (Gogos 2001). Antibiotics should be given when there are clinical signs of infection or imaging and/or laboratory tests suggest its presence.

Anticoagulation

Patients in HHS have an increased risk of arterial and venous thromboembolism (Whelton 1971, Keller 1975). Previous studies have estimated that patients with diabetes and hyperosmolality have an increased risk of venous thromboembolism (VTE) similar to patients with acute renal failure, acute sepsis or acute connective tissue disease (Paton 1981, Keenan 2007). The risk of venous thromboembolism is greater than in DKA (Petrauskiene 2005). Hypernatraemia and increasing antidiuretic hormone concentrations can promote thrombogenesis by producing changes in haemostatic function consistent with a hypercoagulable state (Carr 2001).

All patients should receive prophylactic low molecular weight heparin (LMWH) for the full duration of admission unless contraindicated. In a survey of UK hospitals (unpublished) of guidelines for the treatment of HHS, some have recommended the use of full treatment dose anticoagulation. However, patients with HHS are often elderly and at increased risk of haemorrhage and we could not find evidence to support this approach. Full anticoagulation should only be considered in patients with suspected thrombosis or acute coronary syndrome. One study has suggested that patients with HHS have an increased risk of VTE for three months after discharge (Keenan 2007). Consideration should be given to extending prophylaxis beyond the duration of admission in patients deemed to be at high risk.


Thank You