Semana de Congresos y Jornadas Nacionales 201
"Por un niño sano en un mundo mejor"
24, 25, 26, 27 y 28 de abril de 2017
Ciudad de Buenos Aires

Manejo del Coma Hiperosmolar

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Servicio de Nutrición y Diabetes.
Hospital de Niños Pedro de Elizalde.

Manejo del Coma Hiperosmolar (HHS)

- El HHS es menos frecuente en niños que en adultos pero su aparición ha ido en aumento.
- En ocasiones la CAD se presenta con alta osmolaridad y los cuadros pueden superponerse.
- Por ello muchos niños con HHS son tratados según las normas para CAD.

Zeitler P, Rosembloom A,Glaser N.Journal of Pediatrics Jan 2011: 9-14

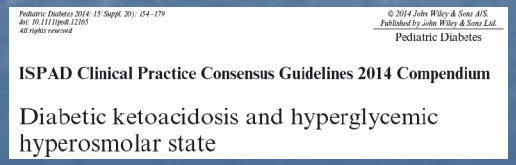
Hipótesis

Epidemiologia

Fisiopatología

Diagnostico de cetoacidosis/ *coma* hiperosmolar.

- Hiperglucemia≥ 200mg/dl
- pH ≤ a 7.30 y/o bicarbonato ≤ 15mmol/l
- Hipercetonemia o cetonuria.


Pediatric Diabetes 2014: 15 (Suppl. 20): 154–179
doi: 10.1111/pedi.12205

Pediatric Diabetes

ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Diabetic ketoacidosis and hyperglycemic hyperosmolar state

- Hiperglucemia≥600mg/dl
- pH ≥ a 7.30, bicarbonato ≥ 15mmol/l
- Cetonemia o cetonuria: ausente o negativa
- Osm:≥ a 320 mOsm/kg
- Alteracion de la conciencia.

Estado Hiperosmolar Hiperglucemico.(HHS)

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- pH ≥ a 7.30, bicarbonato ≥ 15mmol/l
- Cetonemia o cetonuria: ausente o negativa
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Pediatric Diabetes 2014: 15(Suppl. 20): 154–179

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Journal of Pediatrics 2011:158 , N 1: 9–14

Epidemiologia

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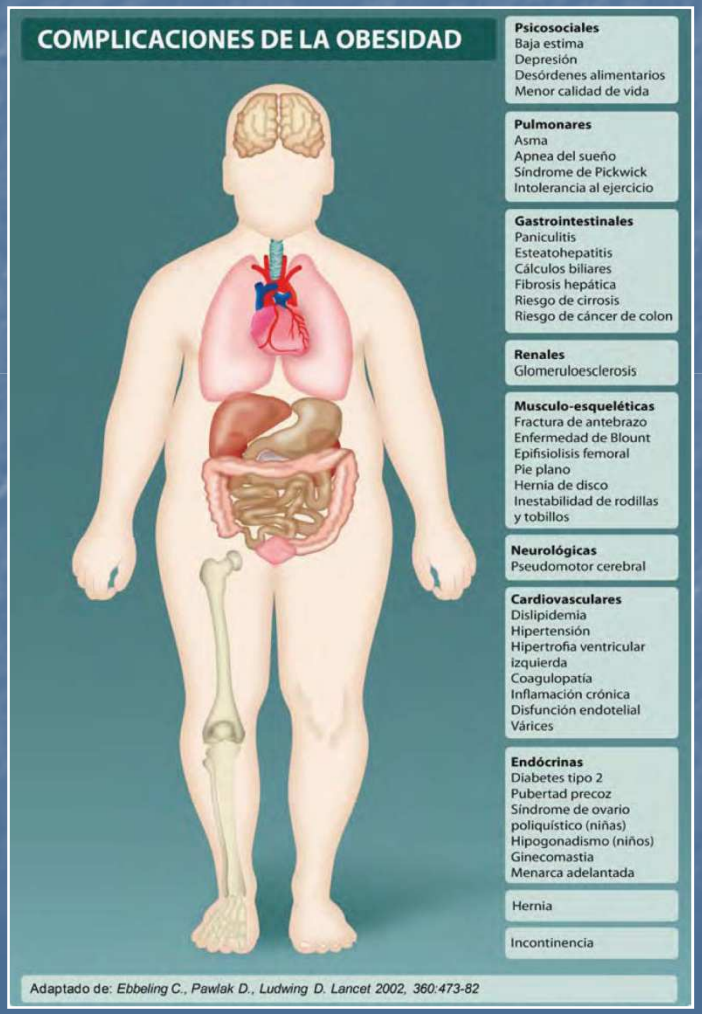
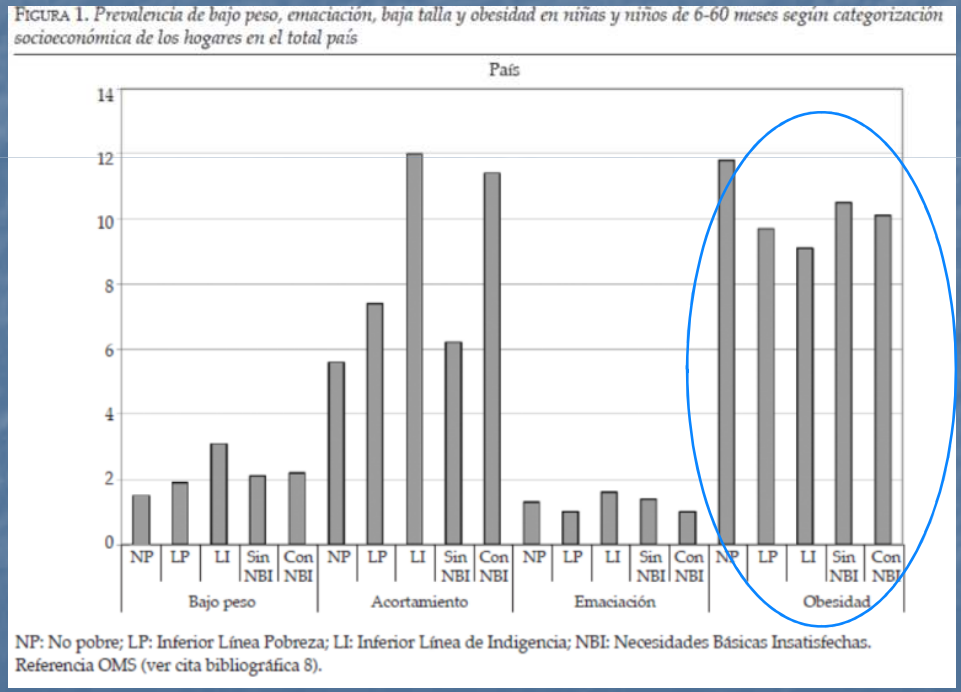
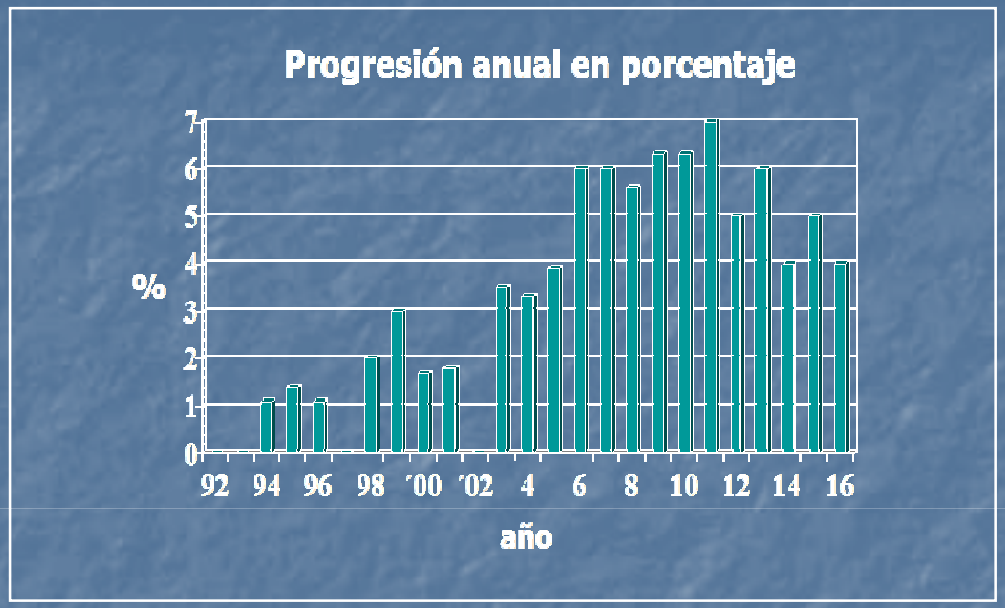
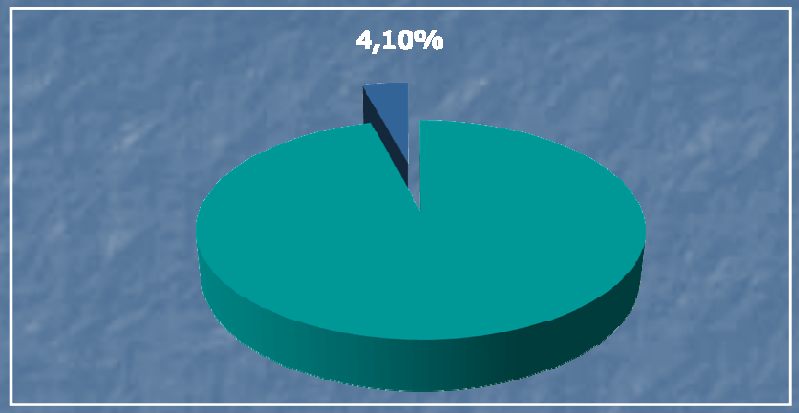




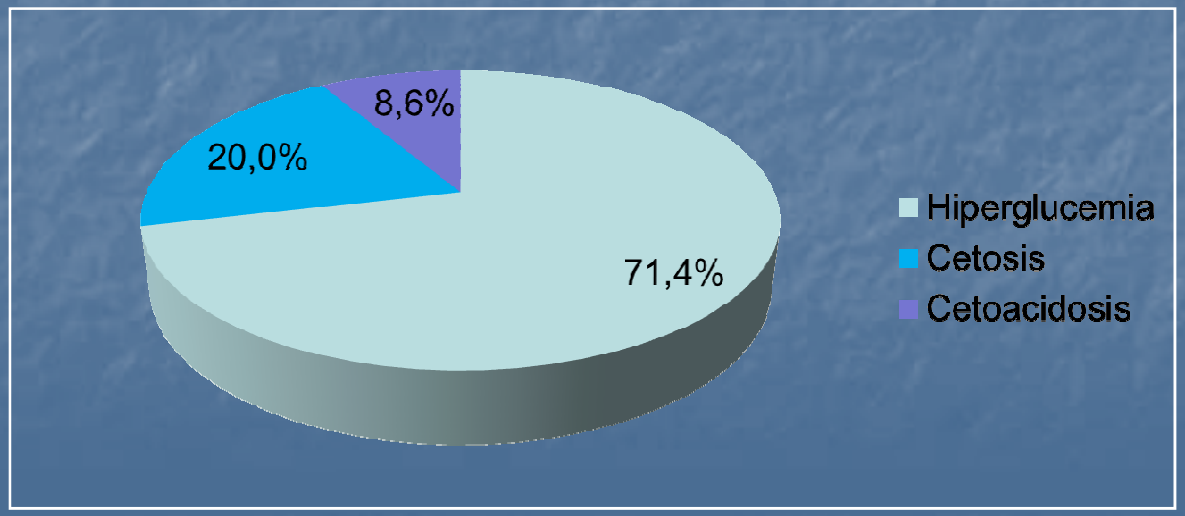
Niños 6 -72 meses.ENNyS. Arch Arg Pediatria.2009.Duran y col.

Diabetes Tipo 2. HGNPE.





2013-2016.n: 361



2006-2012.N.35

- Frecuentemente la diferenciación entre DM 2 y DM 1 es difícil ya que algunos adolescentes pueden comenzar con cuadros agudos y requerir tratamiento insulínico de urgencia.

- Diabetes autoantibody testing should be considered in overweight/obese pubertal children with a clinical picture of T1D (A).

El SEARCH for Diabetes in Youth Study, registro que un 21.2% de niños entre 10–19 años identificados por el médico como DM2 tenian GAD-65 positivo .Jama 2007

Bloqueadores Beta-Adrenérgicos

Bloqueadores de canales de calcio

Clorpromazina

Clortalidona

Cimetidina

Clozapina

Diazóxido

Ácido etacrínico

Agentes inmunosupresores

L-asparaginasa

Loxapina

Olanzapina

Fenitoina

Propranolol

Esteroides

Diuréticos tiazídicos

Metabolic Consequences of Antipsychotic Therapy: Preclinical and Clinical Perspectives on Diabetes, Diabetic Ketoacidosis, and Obesity

David J. Heal, Jane Gosden, Helen C. Jackson, Sharon C. Cheetham, and Sharon L. Smith

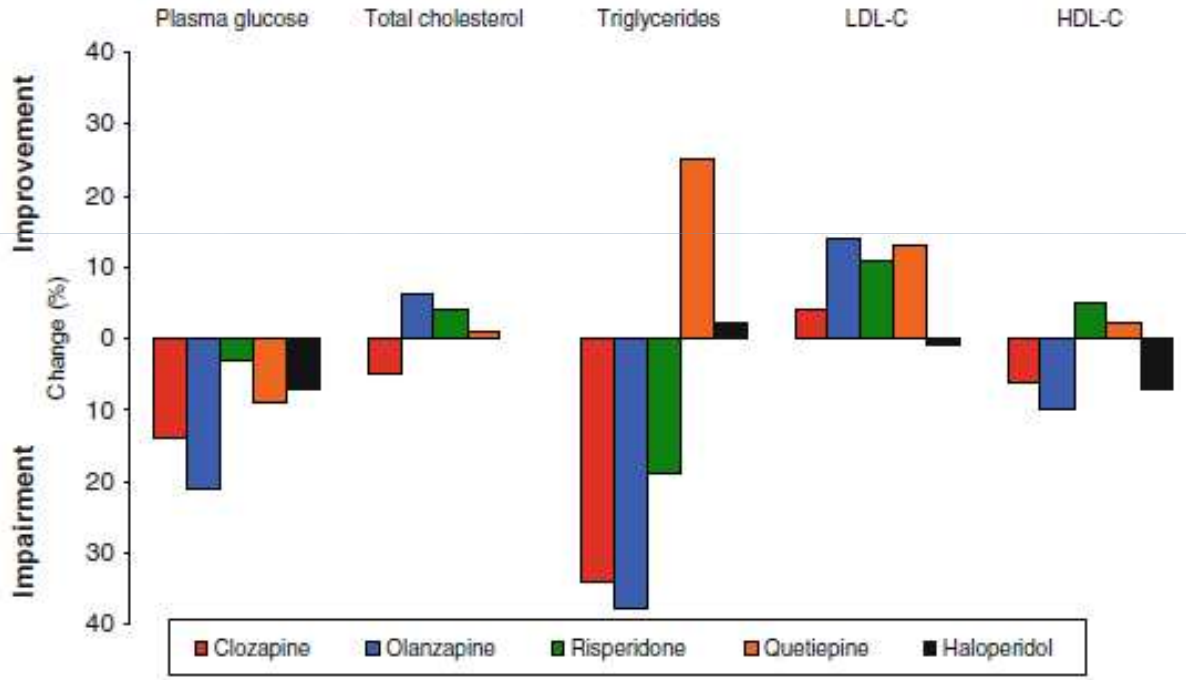


Fig. 2 Impact of various antipsychotic drugs on obesity-related cardiometabolic risk factors. Changes in the parameters are represented as percentage improvements or impairments relative to baseline. Data sourced from Wirshing et al. (2002)

Hyperglycemic hyperosmolar non-ketotic syndrome in children with type 2 diabetes*

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Patient number	Age (years)	Gender	Affected family member with type 2 diabetes mellitus (DM)	BMI (kg/m^2)	BMI percentile (%)	BMI Z-Score	Developmental delay
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7	13.5	Male	Grandmother	ND	ND	ND	Yes
Average	13.3 ± 2			32.7 ± 9.2			

BMI, body mass index; ND, not documented.

Table 2. Clinical and laboratory values at presentation

Patient number	SOsm (mOsm/L)	Glucose (mg/dL)	Urinary ketones	Serum CO_2 (mmol/L)	BUN (mg/dL)	Cr (mg/dL)	Corrected Na+* (mmol/L)	Glasgow Coma Scale (GCS)
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N:190 DM 2
HHS 3,5%

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Table 3. Clinical outcomes

Patient number	Hospital days	Days until laboratory values normalized	Days until mental status normalized	Initial infectious disease investigation	Short-term sequela	Long-term sequela
1	5	4	2	None	Arrhythmia	None
2	8	2	<1	Negative	Hypokalemia	None
3	24	6	4	Negative	Pancreatits Rhabdomyolysis Acute renal failure Candidal line infectio Central line clot	None
4	6	4	<1	None	None	None
5	8	7	7	Negative	Disequilibrium	None
6	8	6	1	Monospot+	None	None
7	4	NA	NA	Enterococcus (post-mortem)	Respiratory arrest Rhabdomyolysis Acute renal failure Pancreatitis Cerebral edema	Death
Average	10 ± 7*	5 ± 2	3 ± 2			

NA, not applicable.
*Average number of hospital days calculated for survivors.

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14% de mortalidad

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Journal of Paediatrics and Child Health

doi:10.1111/jpc.12980

ORIGINAL ARTICLE

Hyperglycaemic hyperosmolar syndrome in children: Patient characteristics, diagnostic delays and associated complications

Pacientes ≤ 18 a entre 2002 y2011 com HHS

Table 1 Demographical and Clinical Characteristics

Case number	1	2	3	4	5	6
Demographical						
Age(years)	16	6	11	11	13	11
Sex	M	M	F	F	F	F
Race	AA	AA	H	AA	AA	AA
BMI	32.1 (>97)	14.9 (18)	17.9 (55)	33.7 (>97)	32 (>97)	28 (>97)
Clinical						
FHx DM	Y	N	Y	Y	Y	Y
Days ill	6	3	14	2	1	5
Prior visits	2	1	2	0	0	Inpatient
Misdiagnosis	Constipation GE reflux	Viral illness	Dehydration Headache	NA	NA	NA
Poly-uria/dipsia	N	Y	N	N	Y	N
Presenting SX	AMS	AMS	Seizures	AMS	Vomiting	Vomiting
Acanthosis	Y	N	N	Y	Y	N
Pertinent physical examination findings						
Dry mouth	Y	N	Y	Y	Y	Y
Cool extremities	Y	Y	Y	N	N	N
Poor skin turgor	N	N	N	Y	N	Y
Intubation	Y	Y	Y	N	N	N

AA, African-American; AMS, altered mental status; BMI, body mass index-for-age percentile (percentile in parentheses); FHx DM, family history of diabetes mellitus; GE, gastroesophageal; H, Hispanic; Intubation, tracheal intubation to maintain and protect airway; NA, not applicable; N, no; SX, symptom; Y, yes.

Price A, Losek J , Jackson B.Journal of Paediatrics and Child Health **52** (2016) 80–84

Journal of Paediatrics and Child Health

doi:10.1111/jpc.12980

ORIGINAL ARTICLE

Hyperglycaemic hyperosmolar syndrome in children: Patient characteristics, diagnostic delays and associated complications

Pacientes ≤ 18 a entre 2002 y2011 com HHS

Table 1 Demographical and Clinical Characteristics

Case number	1	2	3	4	5	6
Demographical						
Age(years)	16	6	11	11	13	11
Sex	M	M	F	F	F	F
Race	AA	AA	H	AA	AA	AA
BMI	32.1 (>97)	14.9 (18)	17.9 (55)	33.7 (>97)	32 (>97)	28 (>97)
Clinical						
FHx DM	Y	N	Y	Y	Y	Y
Days ill	6	3	14	2	1	5
Prior visits	2	1	2	0	0	Inpatient
Misdiagnosis	Constipation GE reflux	Viral illness	Dehydration Headache	NA	NA	NA
Poly-uria/dipsia	N	Y	N	N	Y	N
Presenting SX	AMS	AMS	Seizures	AMS	Vomiting	Vomiting
Acanthosis	Y	N	N	Y	Y	N
Pertinent physical examination findings						
Dry mouth	Y	N	Y	Y	Y	Y
Cool extremities	Y	Y	Y	N	N	N
Poor skin turgor	N	N	N	Y	N	Y
Intubation	Y	Y	Y	N	N	N

AA, African-American; AMS, altered mental status; BMI, body mass index-for-age percentile (percentile in parentheses); FHx DM, family history of diabetes mellitus; GE, gastroesophageal; H, Hispanic; Intubation, tracheal intubation to maintain and protect airway; NA, not applicable; N, no; SX, symptom; Y, yes.

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Table 3 Morbidity and Mortality

Case number	HHS complications	Outcome
1	1 Acute renal failure 2 Malignant hyperthermia 3 Ventricular arrhythmias	Deceased
2	1 Acute renal failure	Insulin dependent
3	1 Left inferior visual field defect 2 Generalised seizures	Insulin dependent
4	1 Rhabdomyolysis 2 Compartment syndrome resulting in BKA 3 Acute renal failure requiring dialysis	Initially on insulin injections then controlled with diet
5	None	Poorly controlled on both oral hypoglycaemic agent and insulin injections
6	None	Type I diabetes mellitus, assumed secondary to tacrolimus*, expired after complications from heart transplant

*Diabetogenic effects of tacrolimus see Rangel.[16]
BKA, below knee amputation.

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16,6% de mortalidad

*Diabetogenic effects of tacrolimus see Rangel.[16]
BKA, below knee amputation.

Price A, Losek J , Jackson B.Journal of Paediatrics and Child Health **52** (2016) 80–84

Epidemiology of hyperglycemic hyperosmolar syndrome in children hospitalized in USA

Table 4. Mortality and resource utilization for hyperglycemic hyperosmolar syndrome hospitalizations

Variable	All (n = 1074)*	Type 1 diabetes (n = 758)*	Type 2 or unspecified diabetes (n = 317)*	p-Value for comparison by diabetes type
Mortality [% (n)]	2.7 (29)	2.5 (19)	3.3 (11)	0.554
Length-of-stay in days [median (IQR)]	2.6 (1.3–4.7)	2.4 (1.2–4.2)	3.3 (1.5–5.9)	<0.01
Total hospital charges [median (IQR)]	$10 882 ($4923–$23 331)	$9943 ($4623–$20 416)	$15 254 ($5815–$34 527)	<0.01

Pediatric Diabetes

Bagdurea D, Rewers A, Campagna E. PD 2012;1-7.

Fisiopatología

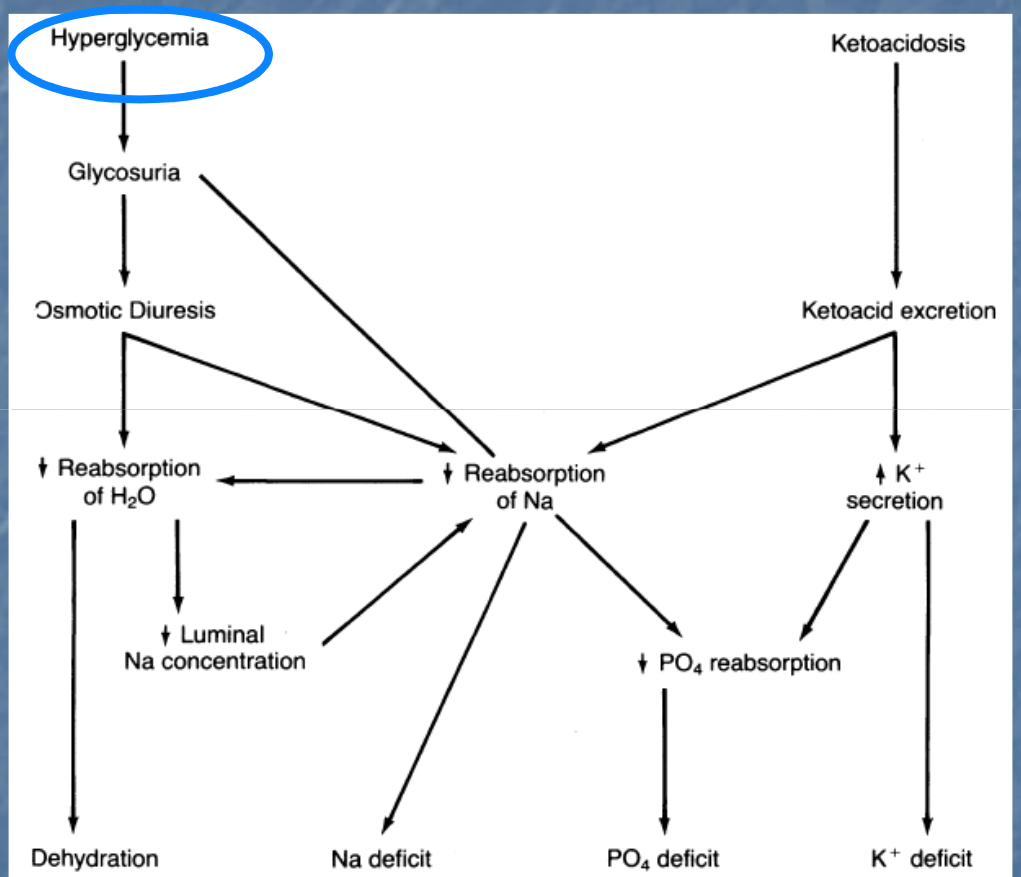


Figure 1. Pathophysiology of fluid and electrolyte disturbances in diabetic ketoacidosis.

Pediatric Clinics of North America—Vol. 37, No. 2, April 1990

CAD

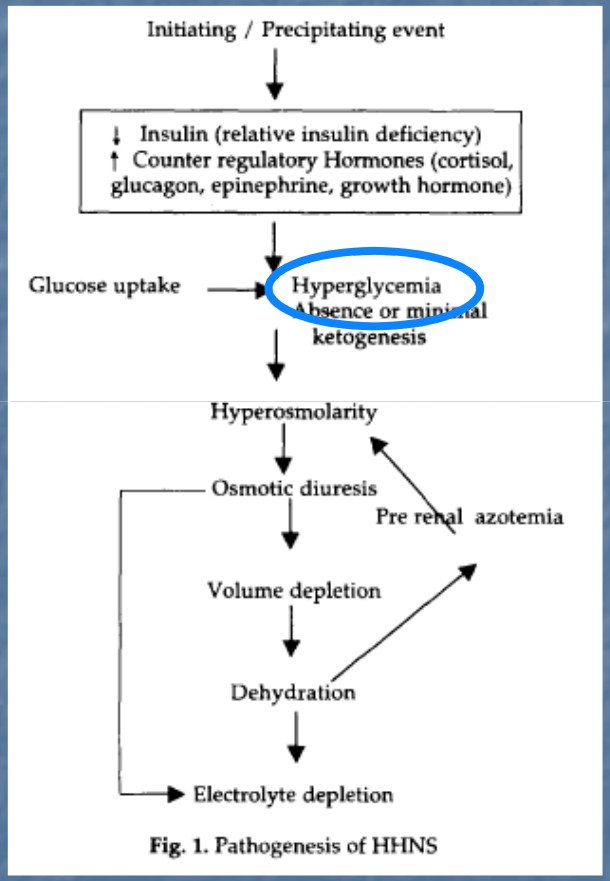
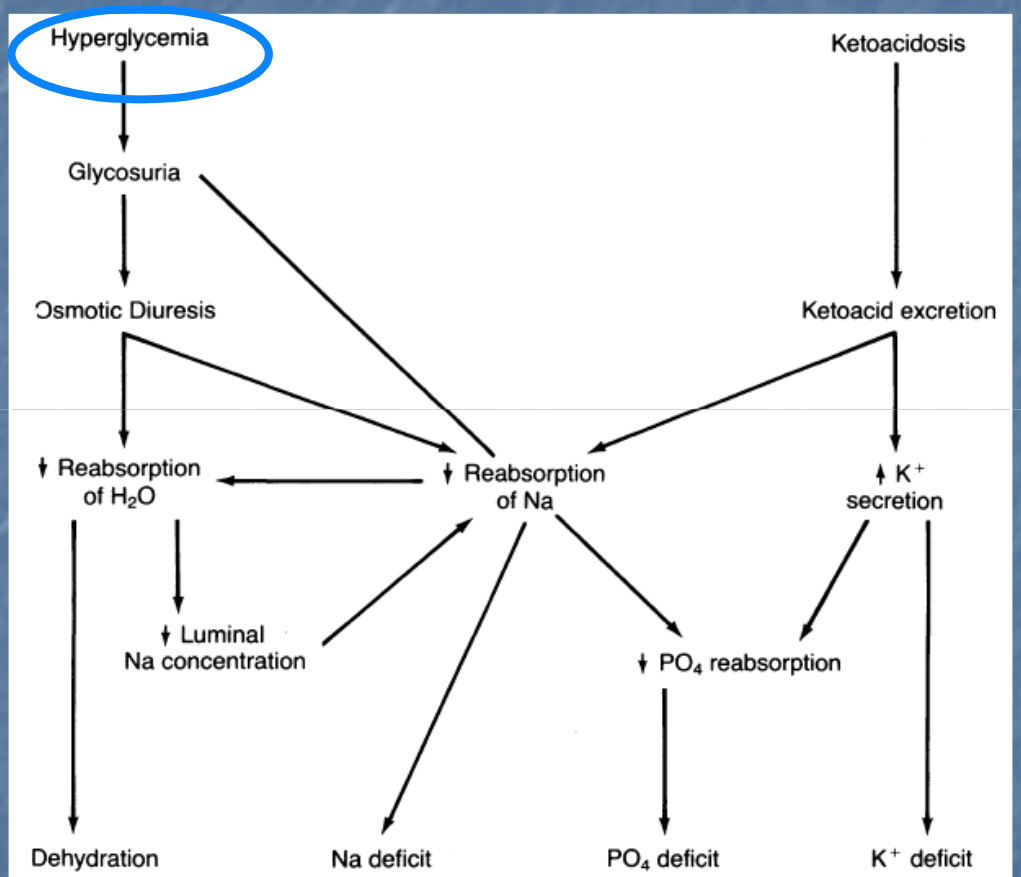


Fig. 1. Pathogenesis of HHNS

Indian Journal of Pediatrics, Volume 73—January, 2006

HHS



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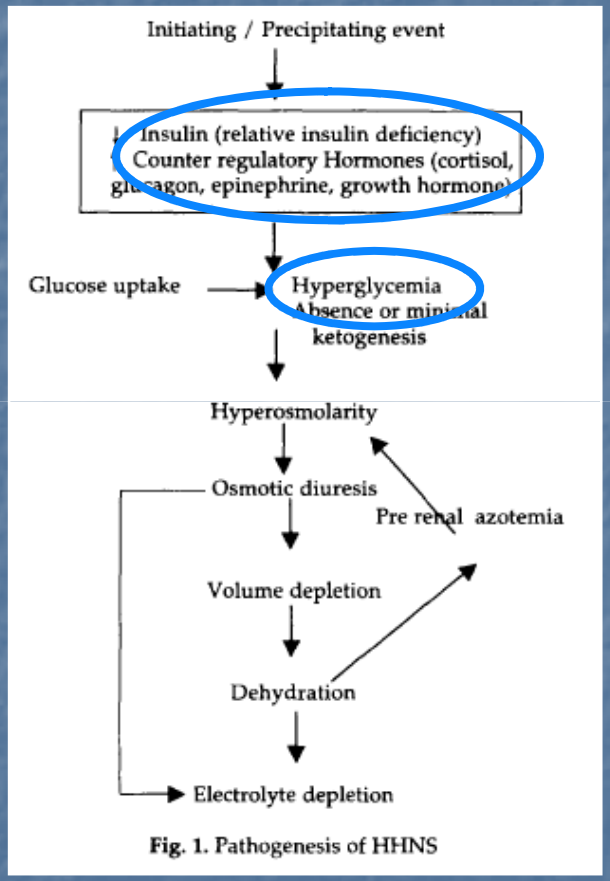

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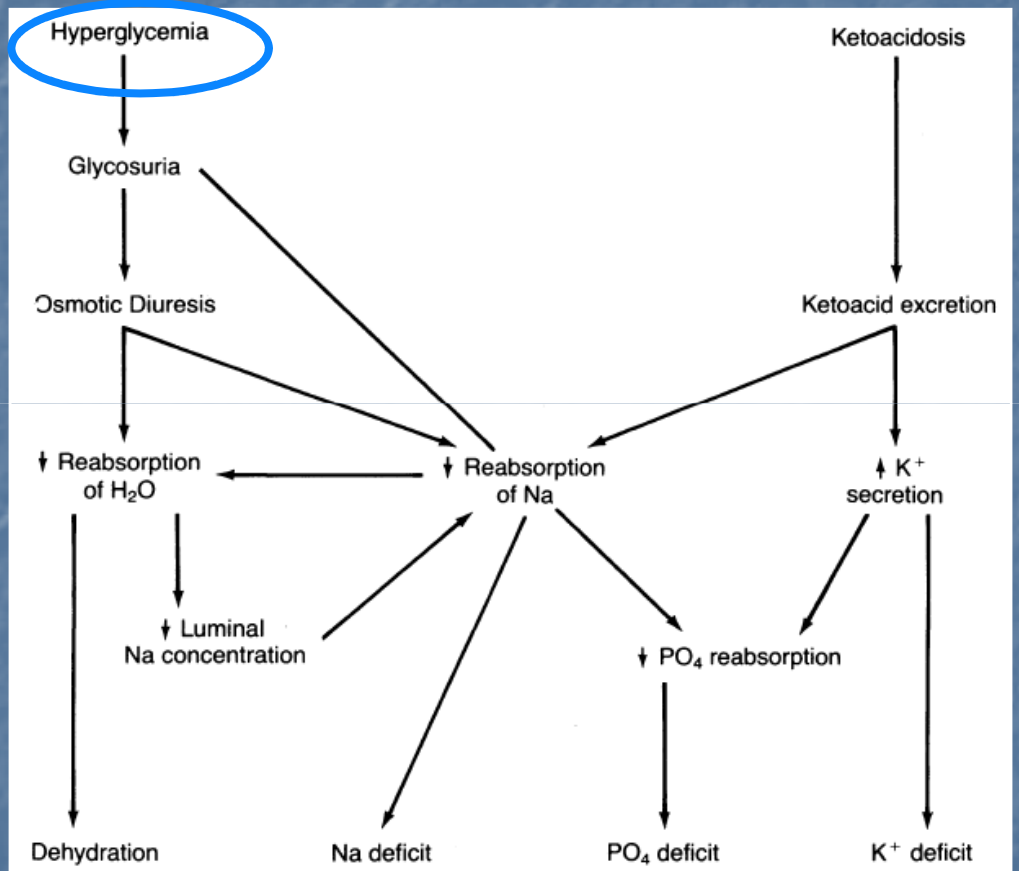

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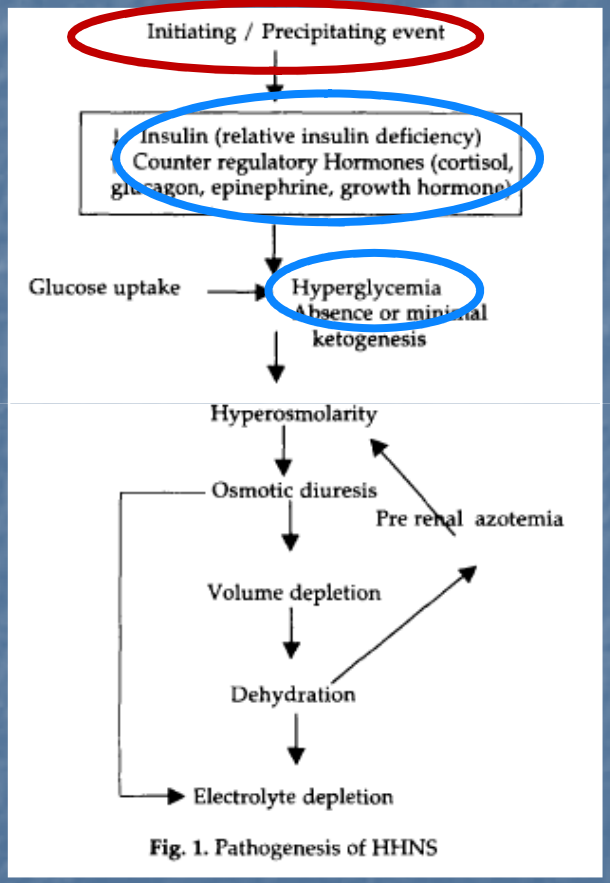

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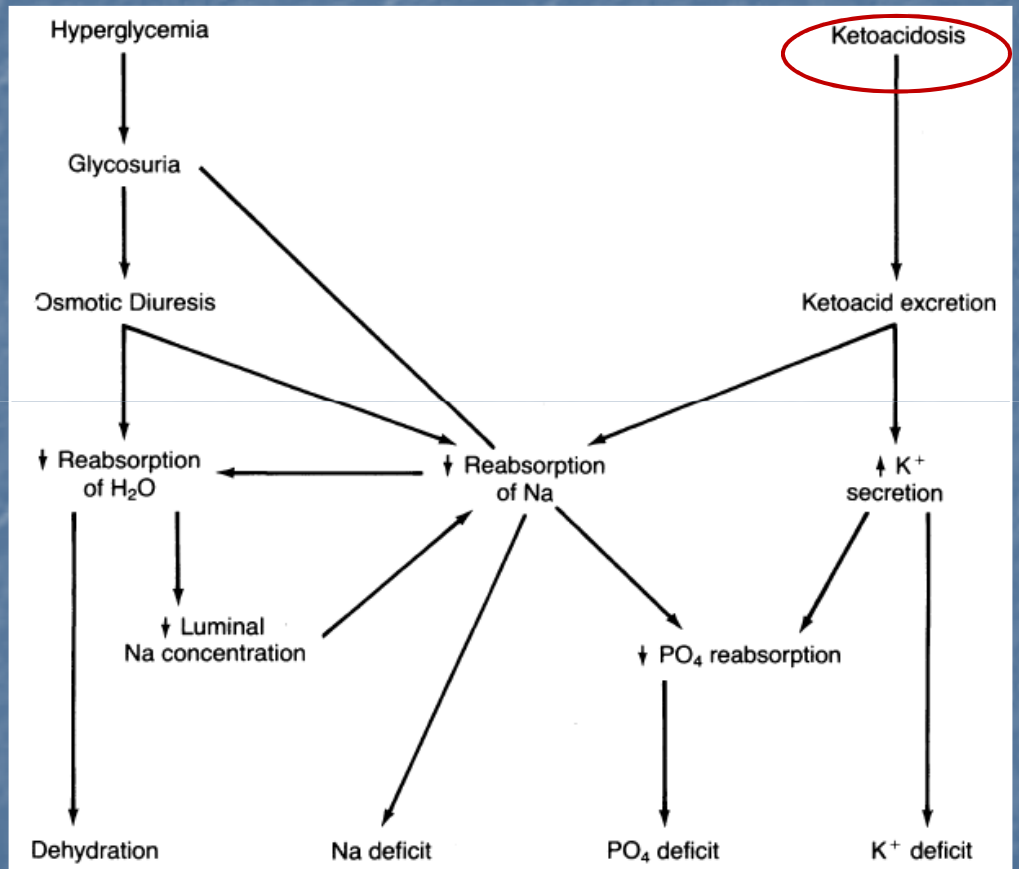

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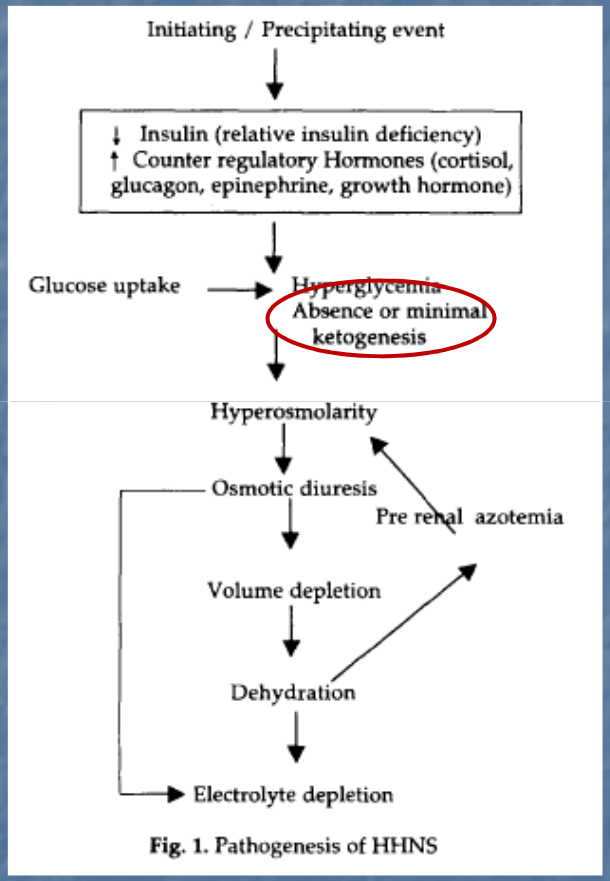

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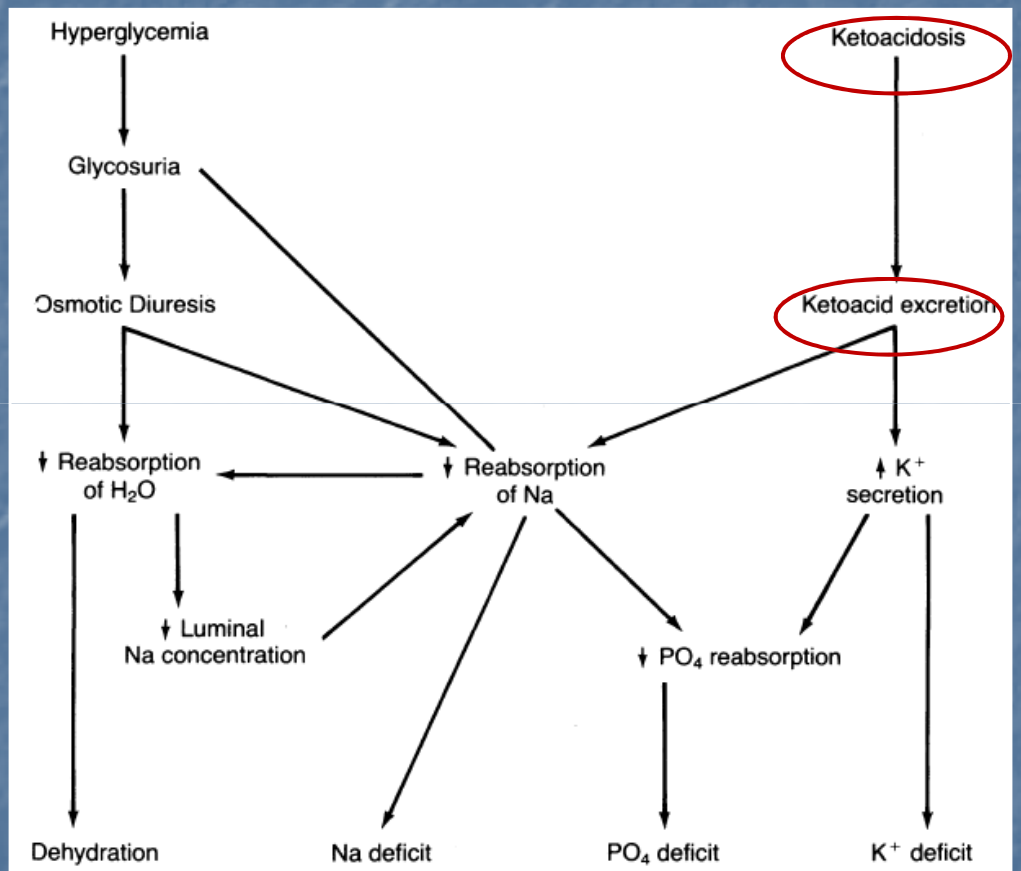

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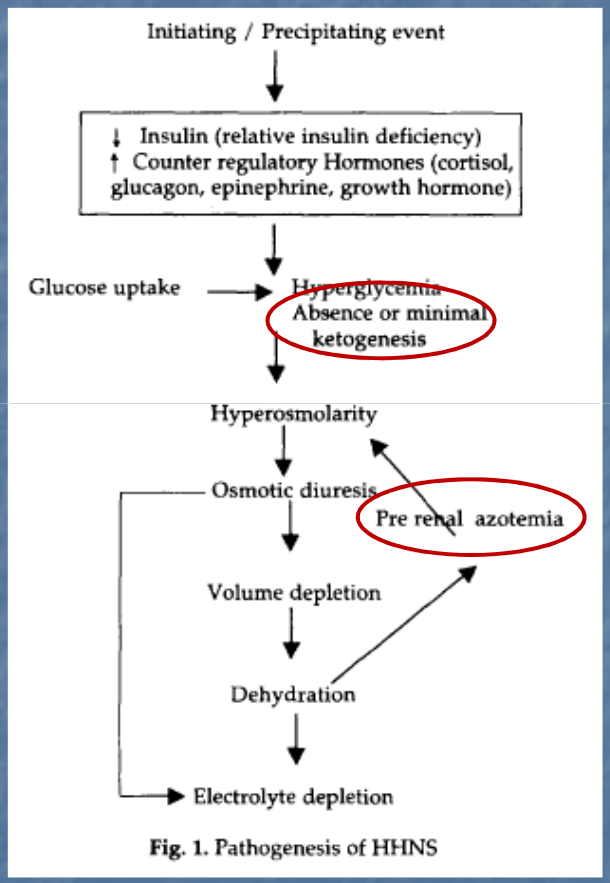

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HHS

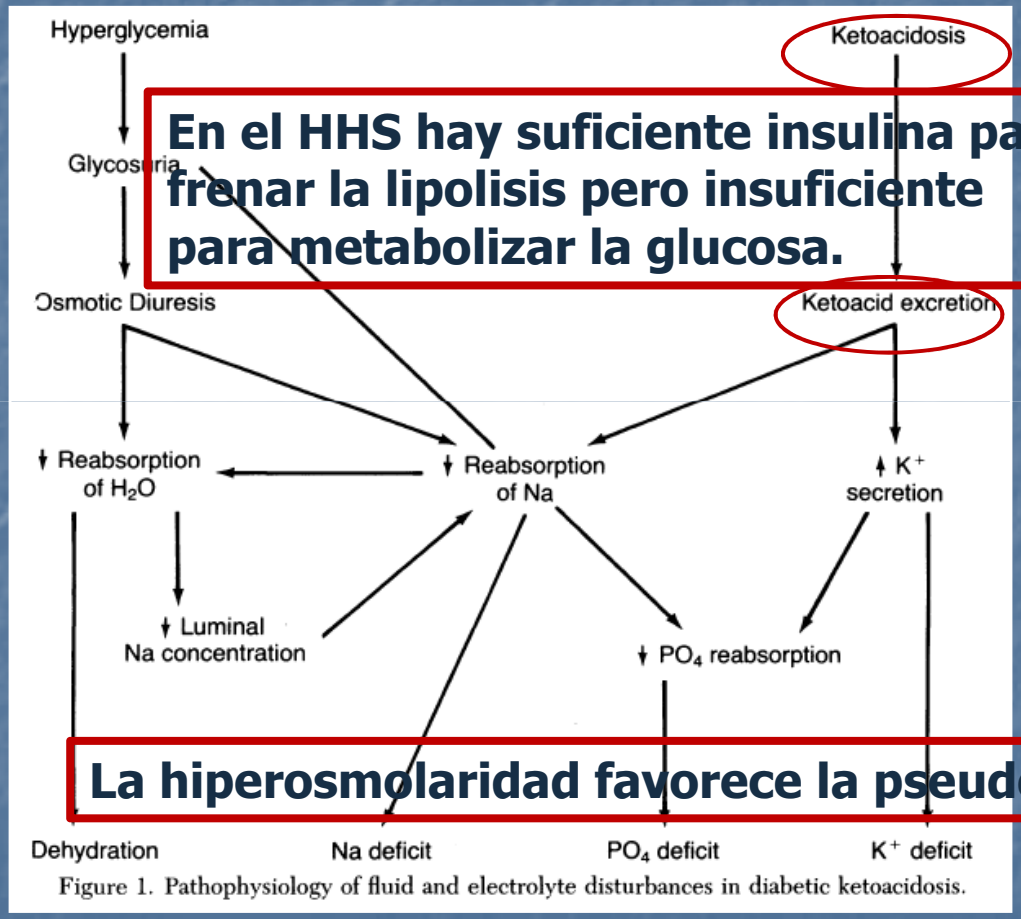
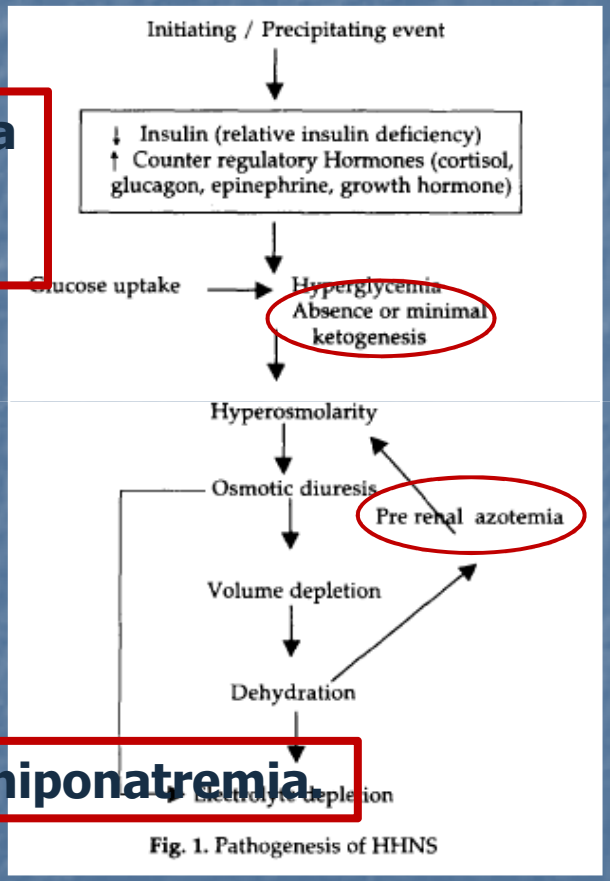


Figure 1. Pathophysiology of fluid and electrolyte disturbances in diabetic ketoacidosis.

Pediatric Clinics of North America—Vol. 37, No. 2, April 1990

En el HHS hay suficiente insulina para frenar la lipolisis pero insuficiente para metabolizar la glucosa.

La hiperosmolaridad favorece la pseudohiponatremia.



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Indian Journal of Pediatrics, Volume 73—January, 2006

CAD **HHS**

Fisiopatología

- En CAD los vómitos, la hiperventilación son síntomas mas floridos, en HHS los síntomas son mas solapados (poliuria y polidipsia intensa).

- La deshidratación y la perdida de electrolitos es mas profusa en el HHS (en adulto se calcula el doble que en la CAD).

Zeitler P, Rosembloom A,Glaser N.Journal of Pediatrics Jan 2011: 9-14

Fisiopatología

- El sobrepeso puede hacer mas difícil valorar la deshidratación por clínica.
- En jóvenes la ingesta profusa de líquidos azucarados puede condicionar el aumento de la osmolaridad.
- La hiperosmolaridad favorece la preservación del volumen intravascular con menos clínica de shock.


Tratamiento

Tratamiento

- Durante la terapia la disminución de la osmolaridad puede favorecer la disminución del volumen intravascular con riesgo de colapso.
- La hiperosmolaridad en HHS y también en la CAD es un factor de riesgo en la evolución.

Considerar en la evolución

Tratamiento

$$\text{Osmolaridad} = \text{Na} \times 2 + \frac{\text{Glucemia}}{18}$$

$$\text{Na corregido} = \text{Na} + \frac{2\,(\text{Glucemia} - 100)}{100}$$

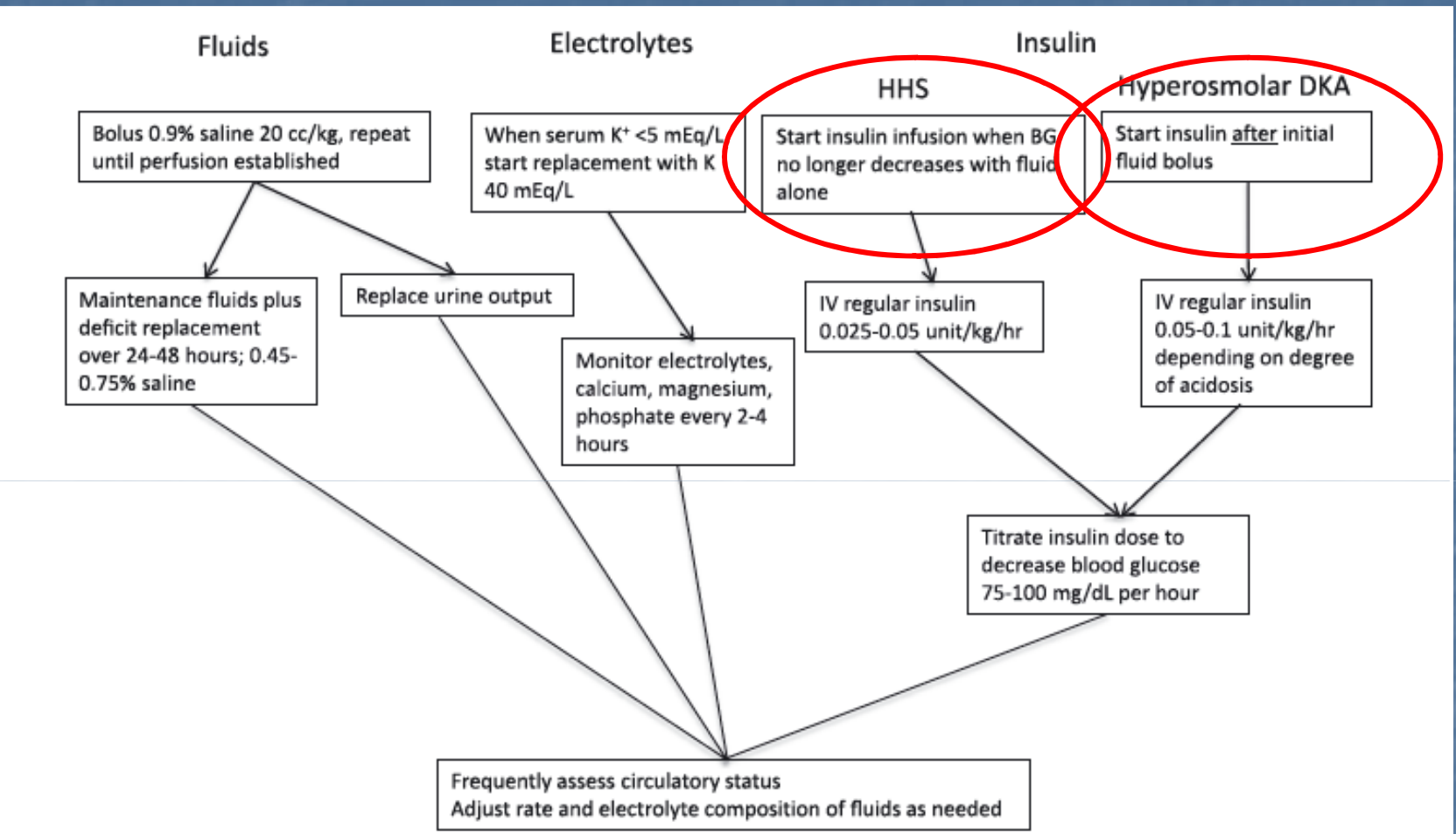

Fig. 3. Treatment of hyperglycemic hyperosmolar state (HHS). Adapted from Zeitler et al. (32).

Pediatric Diabetes 2014: 15(Suppl. 20): 154–179

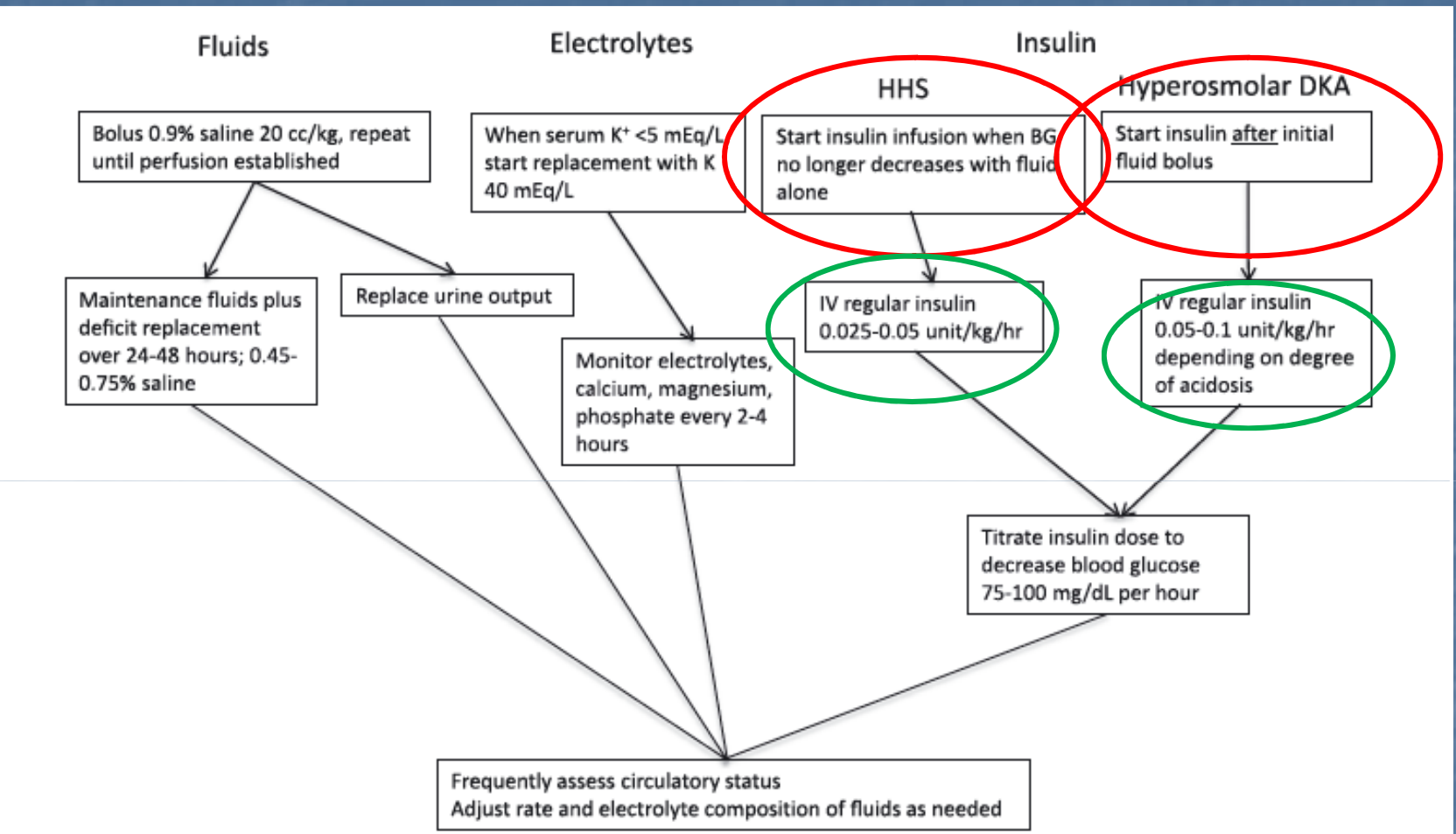

Fig. 3. Treatment of hyperglycemic hyperosmolar state (HHS). Adapted from Zeitler et al. (32).

Pediatric Diabetes 2014: 15(Suppl. 20): 154–179

- La cetosis es mínima pero puede haber acidosis láctica por mala perfusión.
- Es innecesaria la administración precoz de insulina.
- Se debe esperar el descenso paulatino de la glucemia con la hidratación.
- Se comienza con insulina cuando se frena el descenso de la glucemia.

- El aporte de liquidos se recomienda mas rapido que en la CAD calculando un deficit del 12 al 15% del peso corporal.
- Se espera un descenso de la Natremia de 0,5 meq/lt/h y de la Glucemia de 50-100 mg/dl/h.

Electrolitos. Monitoreo frecuente.

- Monitoreo de K cada 2-3 horas.
- El descenso del P puede favorecer la rabdomiolisis, anemia hemolítica y parálisis.
- El Mg tambien puede estar descendido .

Electrolitos. Monitoreo estricto.

- **K**
- **P**
- **Mg**

Electrolitos. Monitoreo estricto.

K

P

Mg

rabdomiolisis,
anemia hemolítica
parálisis.

Complicaciones

Edema cerebral, mas o menos frecuente que en la CAD?

- El efecto del edema cerebral en el cerebro puede ser diferente que en la CAD.
- La hipertonicidad de larga data determina la produccion de osmoles ideogenos.
- La hipocapnia de la CAD es el mayor condicionante de la vasoconstricción cerebral.

Complicaciones

Edema Cerebral. Fisiopatología

- Vasogenico
- Ruptura de la BHE.
- Extravasacion de proteinas
- y fluidos al intersticio (sust blanca)

- Citotoxico
- Edema celular no toxico por alteración de la bomba de Na/K/ATPasa.
- Disminucion del extravascular.
- Edema de astrocitos.

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A diferencia de los capilares periféricos en el cerebro su perfusión es continua sujeta a los aumentos o descensos de la misma.
En la misma influyen tanto las proteínas como las sales.

Edema Cerebral. Fisiopatología

- Acumulación de osmoles intracelulares
- Transportador Na/H
- Isquemia cerebral

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- Isquemia cerebral
- Transportador Na/H
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Complicaciones

- Trombosis

Profilaxis con heparina?

- Rabdomiolisis o

  Sindrome de hipertermia maligna like.

Monitoreo de CPK y creatinina
Falla renal, hipocalcemia,
paro cardiaco

Trombosis

- La trombosis es mas frecuente en el HHS que en la CAD.
- La hipertonicidad condiciona la disrupción de las células endoteliales con aumento de la tromboplastina y vasopresina que contribuyen a la hipercoagubilidad.

ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Type 2 diabetes in the child and adolescent

- Clinical testing for dysglycemia in obese at-risk youth should occur in the setting of clinical assessment of obesity-related comorbidities [non-alcoholic fatty liver disease (NAFLD), elevated triglycerides, elevated blood pressure (BP)] that are more prevalent than dysglycemia (E)

Rabdomiolsiis

- No todos los niños obesos tienen depósito de grasa en músculo y su presencia predispone a la insulinorresistencia.
- El incremento del depósito graso en músculo, que es temprano en la obesidad infantil se asocia directamente a la disminución de la sensibilidad a la insulina.

Prediabetes in obese youth: a syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning

Background—Impaired glucose tolerance is common among obese adolescents, but the changes in insulin sensitivity and secretion that lead to this prediabetic state are unknown. We investigated whether altered partitioning of myocellular and abdominal fat relates to abnormalities in glucose homoeostasis in obese adolescents with prediabetes.

Methods—We studied 14 obese children with impaired glucose tolerance and 14 with normal glucose tolerance, of similar ages, sex distribution, and degree of obesity. Insulin sensitivity and secretion were assessed by the euglycaemichyperinsulinaemic clamp and the hyperglycaemic clamp. Intramyocellular lipid was assessed by proton nuclear magnetic resonance spectroscopy and abdominal fat distribution by magnetic resonance imaging.

In summary, early in the natural history of type 2 diabetes in obese young people, altered partitioning of fat in both skeletal muscle and abdominal adipose tissues is closely linked to insulin resistance. Increased intramyocellular and intra-abdominal fat accumulation is strongly related to post-glucose hyperglycaemia in obese prediabetic young people.

Weiss R, Caprio S.Lancet. 2003 September 20; 362(9388): 951–957

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Fatal Malignant Hyperthermia-Like Syndrome With Rhabdomyolysis Complicating the Presentation of Diabetes Mellitus in Adolescent Males

ABSTRACT. *Objective.* This report describes a new fatal syndrome observed in adolescent males at the initial presentation of diabetes mellitus. The features include hyperglycemic hyperosmolar coma complicated by a malignant hyperthermia-like picture with fever, rhabdomyolysis, and severe cardiovascular instability.

Design. Case series.

Setting. Pediatric intensive care units of 3 tertiary care facilities in the United States.

Patients. Six adolescent males, 5/6 obese with acanthosis nigricans, 4/6 black.

Results. Four of 6 patients died. Four of 6 patients did not have significant ketosis. Six of 6 patients had increased temperature after the administration of insulin.

Conclusions. The underlying etiology of this syndrome remains unclear. Possibilities include an underlying metabolic disorder such as a fatty acid oxidation defect, an unrecognized infection, exposure to an unknown toxin, or a genetic predisposition to malignant hyperthermia. Evaluation for all these possibilities and empiric treatment with dantrolene should be considered for this type of patient until this syndrome is better characterized. *Pediatrics* 2003;111:1447–1452; *diabetes mellitus, rhabdomyolysis, malignant hyperthermia, obesity.*

Hipertemia maligna like

TABLE 1. Characteristics of 6 Patients With Severe Hyperglycemia, and Malignant Hyperthermia-Like Syndrome

Case	A	B	C	D	E	F
Age (y)	19	14	16	14	16	14
Sex	Male	Male	Male	Male	Male	Male
Race	Black	Black	Black	Black	White	White
Height (cm)	175	185.4	176	165	185	167
Weight (kg)	130	152.3	95.2	95	114.4	43
BMI (kg/m^2)	42.4	44.3	30.7	34.9	33.4	15.4
Acanthosis	yes	yes	yes	yes	yes	no
Family history of type 2 diabetes	Maternal aunts	Maternal grandmother	Maternal aunt	Maternal relatives	Parents, paternal grandmother, maternal great-grandfather	Maternal grandmother, (type 1 in first cousin)
Family history of MH	Not asked	Not asked	No	Not known	Not asked	No
BG (mg/dL)	1810	970	1381	1600	1680	2580
Arterial pH	7.21	7.23	7.35	7.14	7.17	7.09
Peak Pco_2 mm Hg (concurrent pH)	37 (7.30)	37 (7.02)	40 (7.25)	Not mechanically ventilated	62.3 (7.19)	30 (7.08)
Urine ketones	Trace	Large	Large	Small	Trace	Small
Sodium/potassium/ chloride/bicarbonate (mmol/L)	134/5.8/97/16	137/5.8/100/10	124/4.9*/78/29	145/5.6/103/16	141/4.3/112/19	120/26/78/7
Blood urea nitrogen/ creatinine (mg/dL)	62/7.3	11/1.0	36/2.2	50/2.2	68/4.4	76/2.8
Peak creatine phosphokinase (U/L)	473 400	N/A	79 536	101 640	6580	4706
Other	Urine myoglobin: 178 ng/mL	Urinalysis: 3+ blood, < 5 RBC. Hgb A1c: 10.7%, Serum osms 347 mOs/kg, Islet cell Abs: negative.	Urinalysis: 3+ blood, < 5 RBC. Hgb A1c: 8.1%. Throat cultures negative.	Urine myoglobin screen negative on d 1, positive on d 2	Urine myoglobin screen negative	Serum ketones: absent, Hgb A1c: 9.5%, Urine myoglobin: 596 ng/mL islet cell antibody 512 Ab <0.75 μU/mL Human Insulin Ab: < 2 μU/mL, Anti glutamic acid decarboxylase 65 Ab: 1.0 U/mL

RBC indicates red blood cells; Hgb A1c, hemoglobin A1c; Abs, antibodies; OSMS, osmolality; mOs/kg, milliosmoles/kg.
Data represents initial measurements unless otherwise noted.
* Sample drawn 5 hours after initial Na, previous samples read as "hemolyzed."

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Race	Black	Black	Black	Black	White	White
Height (cm)	175	185.4	176	165	185	167

TABLE 3. Outcomes of 6 Patients With Severe Hyperglycemia, Malignant Hyperthermia-Like Syndrome

Case	A	B	C	D	E	F
Fever	Yes	Yes	Yes	Yes	Yes	Yes
Rhabdomyolysis	Yes	Likely	Yes	Yes	Yes	Yes
Hypotension	Yes	Yes	Yes	Yes	Yes	Yes
Arrythmia		Yes	No		Yes	No
Deep venous thrombosis documented	Yes	No	Yes		No	No
Other		Seizure	Seizure			
Outcome	Recovered, renal function returned to normal, off insulin at discharge after significant weight loss during 104th hospital day	Died of intractable arrythmia	Died of saddle pulmonary embolus on third hospital day	Died of multisystem failure including cardiac failure, pulmonary edema, renal failure	Died of intractable arrythmia	Survived, discharged on insulin after 8 hospital days
Peak creatine phosphokinase (U/L)	473 400	N/A	79 536	101 640	6580	4706
Other	Urine myoglobin: 178 ng/mL	Urinalysis: 3+ blood, < 5 RBC. Hgb A1c: 10.7%, Serum osms 347 mOs/kg, Islet cell Abs: negative.	Urinalysis: 3+ blood, < 5 RBC. Hgb A1c: 8.1%. Throat cultures negative.	Urine myoglobin screen negative on d 1, positive on d 2	Urine myoglobin screen negative	Serum ketones: absent, Hgb A1c: 9.5%, Urine myoglobin: 596 ng/mL islet cell antibody 512 Ab <0.75 μU/mL Human Insulin Ab: < 2 μU/mL, Anti glutamic acid decarboxylase 65 Ab: 1.0 U/mL

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Data represents initial measurements unless otherwise noted.
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Causas de muerte

Complicaciones

- Deshidratación
- Alteraciones hidroelectroliticas severas.
- Hipertonicidad

Conclusiones . HHS vs CAD.

- Mas rápida reposición de líquidos
- Monitoreo de electrolitos mas frecuente
- Menor dosis de insulina
- Mayor monitoreo del volumen circulatorio
- Menor riesgo de edad cerebral.
- Mayor riesgo de trombosis, rabdomiolisis e hipertermia maligna.

INTERNAL MEDICINE

□ CASE REPORT □

Is This the Worst Outcome of Metabolic Syndrome? Hypophosphatemia and Resulting Cardiac Arrest during the Treatment of Diabetic Ketoacidosis with Hypertriglyceridemia

Akinori Osuka, Tetsuya Matsuoka and Koji Idoguchi

Inter Med 48: 1391-1395, 2009 DOI0.2169/internalmedicine.48.2236

INTERNAL MEDICINE

□ CASE REPORT □

Inter Med 48: 1391-1395, 2009 DOI: 10.2169/internalmedicine.48.2236

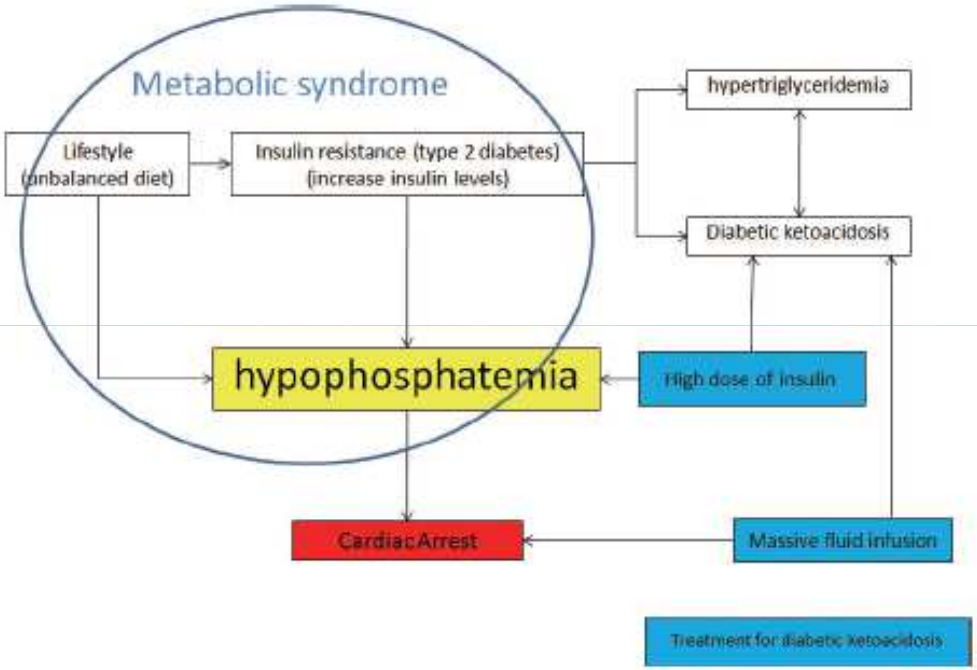

Figure 2. **The lifestyle of patients with metabolic syndrome leads to insulin resistance and hypophosphatemia. Once diabetic ketoacidosis develops, high doses of insulin and massive fluid infusion are needed to treat the patient. These therapies lead to further hypophosphatemia, cardiac overload, and cardiac arrest.**


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