MEDICAL GRAND ROUNDS

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THE PATHOPHYSIOLOGIC RATIONALE IN THE TREATMENT OF DIABETIC KETOACIDOSIS: A REVIEW OF RECENT ADVANCES AND NEW CONCEPTS

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I. FACTORS AFFECTING MORTALITY

TABLE I

FACTORS AFFECTING MORTALITY IN DKA
(Soler, FitzGerald, Bennett, Malins 1973)

258 Cases - Overall Mortality 6.2% (1968-1972)

	Mortality Rate
1. Age: 10-19 years	0.0%
20-59 years	4.8%
Greater than 59 years	15.7%
2. State of Consciousness	
Non-comatose	3.7%
Comatose	19.0%
3. Initial Blood Sugar - mg/100 ml	
Less than 500	0.0%
500-999	8.6%
Greater than 1000	19.0%
4. Initial Blood Urea N - mg/100 ml	
Less than 19	0.0%
20-44	3.8%
45 or greater	21.0%
5. Presence of Complications	
Myocardial Infarction	50.0%
Infection	10.0%

Ref. 1

TABLE II

FINDINGS IN DIABETIC ACIDOSIS

	Beigelmans Series		PMH
	Fatal(32)	Non Fatal(308)	88
*AGE	54	36	38
Men	59%	44%	38%
Women	31%	56%	62%
CHEMICAL DATA-SERUM			
*Glucose	995	657	475
*Urea N	62	32	25
*Osmolality	357	323	
Bicarbonate	7	6	<10.
Ketone-dilution	1/16	1/16	1/5
Potassium	5.4	5.3	4.8
Sodium	132	131	132
PHYSICAL FINDINGS			
Respiration	29	30	
*Pulse	100	117	121
Systolic pressure	110	125	129
*Diastolic pressure	58	71	76
*Comatose	31%	3%	

* significant difference Ref. 2-4

II. THE CLINICAL SPECTRUM OF DIABETIC KETOACIDOSIS (Ref. 5-8)

A) EUGLYCEMIC KETOACIDOSIS (Ref. 5,6)
B) HYPERGLYCEMIC, NON-HYPEROSMOLAR KETOACIDOSIS
C) HYPERGLYCEMIC HYPEROSMOLAR KETOACIDOSIS (Ref. (8)
D) COMBINED KETOACIDOSIS AND LACTIC ACIDOSIS (Ref. 90-101)

A) Euglycemic Diabetic Ketoacidosis

Severe dehydration and volume depletion are generally characteristic of DKA. However when ketoacidosis supervenes rapidly, especially in children, there may be very little or no significant volume depletion and no increase in tonicity (Ref. 5 Nabarro et al). Recently (1973) Munro and co-workers (Ref. 6) described a group of 16 patients (mean age 18.6; range 10-28 yrs) with low or near normal blood glucose with severe ketoacidosis (mean $BHCO_3$ 7.0 mEq/L) but with no evidence of volume depletion or hyperosmolality. In 44% of the patients mean blood glucose was 66 mg% and serum sodium 139 mEq/L. The other 56% had a mean blood glucose of 183 mg% (143-199) with a concomitant mean serum sodium of 137 mEq/L. They all gave a history of persistent vomiting and/or inability to eat while continuing their usual insulin dose.

B) Hyperglycemic Non-hypertonic Ketoacidosis

Many patients in diabetic ketoacidosis are seen who are severely ECF volume depleted and ketoacidotic but are not hypertonic as a consequence of their adequately replacing osmotically driven water loss by polydypsia. In the PMH series of 83 patients analyzed by Dr. Dan Foster (Medical Grand Rounds - PMH Nov. 3, 1966) 83% had serum sodium $[Na]_S$ corrected for glucose ranging between 130-149 mEq/L. In 25 percent mean $[Na]_S$ corrected for glucose ranged between 130-139 mEq/L, and in the remaining 53% corrected $[Na]_S$ varied between 140-149 mEq/L.

In Fulup's series of 70 patients, 11% had a measured serum osmolality of less than 300 mOsm/L and 24% had an osmolality less than 310 mOsm/L. Mean measured osmolality of the entire group was 332 (range 285-450) with 41% 320 mOsm/L or less.

C) Ketotic Hyperosmolar Coma

In Fulup, Tannenbaum and Dreyers series (Ref. 7) of 70 episodes of DKA where serum osmolality was measured, serum osmolality was

330 mOsm/L or greater in 43%
340 mOsm/L or greater in 27%
360 mOsm/L or greater in 14%

In Beigelman's series of 340 cases of DKA, serum osmolality in the fatal cases averaged 357 and in the non-fatal cases 323 mOsm/L (Ref. 2) Gerich, Martin and Recant (Ref. 8) reported a series of non-ketotic hyperosmolar coma where serum osmolality ranged between 327-416 and averaged 373 mOsm/L. The overlap in osmolality between ketoacidosis and non-ketotic hyperosmolar coma is obvious.

D) Combined Ketoacidosis and Lactic Acidosis

See Section G pg 25-32

III. DEVELOPMENT OF THE PATHOPHYSIOLOGIC DEFECTS IN DIABETIC KETOACIDOSIS

TABLE III

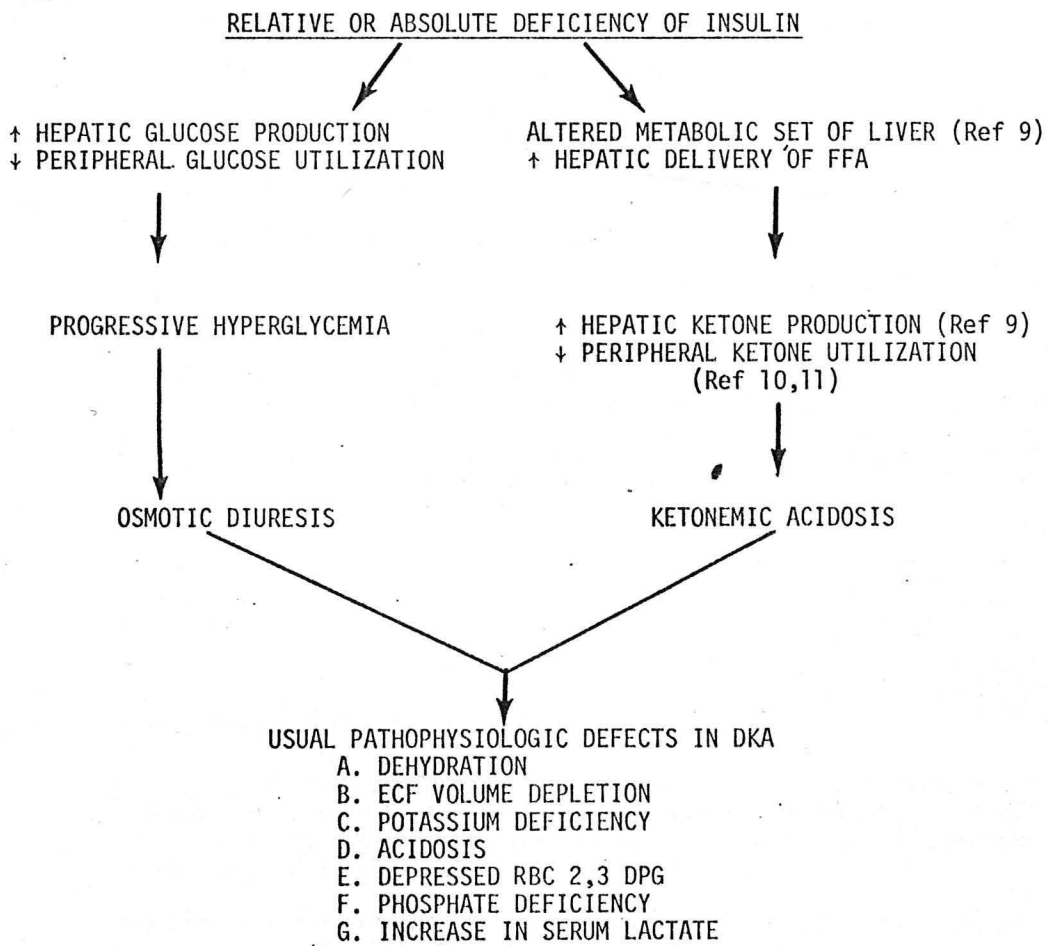


TABLE IV

USUAL PATHOPHYSIOLOGIC DEFECTS IN DKA

I. DEHYDRATION-HYPERTONICITY - with
Low, normal or high serum sodium
Presence of idiogenic osmols within brain cells and a propensity to cerebral edema on rapid ↓ in plasma osmolality

II. ECF VOLUME DEPLETION - with ECF volume partially sustained by the hyperglycemia

III. POTASSIUM DEFICIENCY - with initial high, low or normal serum K and propensity to hypokalemia during treatment

IV. ACIDOSIS - Ketoacidosis with potential bicarbonate

V. DEPRESSED RBC 2,3 DPG - with normal P_{50} secondary to right shift of Hgb-O_2 dissociation curve by acidosis

VI. PHOSPHATE DEFICIENCY - with initial high, normal or low serum P(i) and hypophosphatemia during treatment

VII. INCREASED SERUM LACTATE - with propensity to lactate acidosis both early and late in treatment

A & B - DEHYDRATION AND ECF VOLUME DEFICIT (Ref. 12-19)

1. OSMOTIC DIURESIS - produces a loss of water in excess of salt. Although urine osmolality is slightly hypertonic to plasma, most of the osmotically active particles are glucose and the urine contains at the most 50-70 mEq/L of sodium (Ref. 14,15).

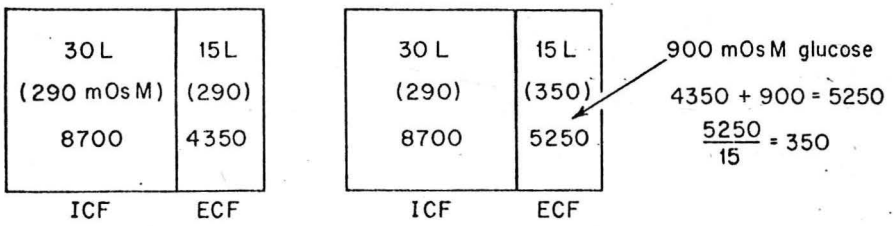
The loss via polyuria of 9 L of such a urine containing 50 mEq/L of Na is equivalent to the loss of
(1) 3 L of ECF (450 mEq Na)
(2) 6 L of Water

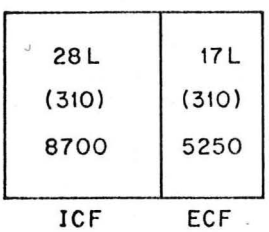
2. MECHANISM OF HYPERTONICITY WITH LOW $[Na]_S$ AND DECREASE IN ECF VOLUME WITH RAPID DECREASE IN BLOOD GLUCOSE

Fig. 1

FLUID SHIFTS AND APPARENT HYPONATREMIA IN DKA

75 Kg ♂ 0.6 BW = 45L 30 ICF 15 ECF





a) CHANGE IN VOLUME

$8700 + 5250 = \frac{13950}{45} = 310$

$\frac{5250}{310} = 17$ Liters

b) CHANGE IN Na CONCENTRATION

$140 \times 15 = 2100$ mEq

$\frac{2100}{17} = 124$ mEq/L

3. OVERVIEW

The average loss of ECF is about 3L and for water about 4L. The magnitude of the ECF volume deficit is mainly a clinical judgement (aided by changes in hematocrit and serum proteins) whereas the water loss can be estimated from:

(a) the plasma osmolality - the normal osmolality is 290 mOsm/L. The average osmolality in DKA is 320 mOsm/L

290 x 42L (60% of 70 kg) = 12,180

12180/320 = 38L i.e. Loss of 4L of H_2O

(b) in the absence of significant hyperlipemia hypertonicity (water loss) can be estimated from the "corrected serum Na" by use of the formula (Ref. 16)

Corrected Serum Na = Measured $[Na]_S$ + [(Plasma glucose - 100) x 0.016]

Example

a) Plasma glucose 1000 mg%, $[Na]_S$ 145 mEq/L
Corrected $[Na]_S$ = 145 + 14.4 = 159 mEq/L

b) Plasma glucose 1200 mg%, $[Na]_S$ 120 mEq/L
Corrected $[Na]_S$ = 120 + 17.6 = 137 mEq/L

While it is imperative to correct ECF volume rapidly, the correction of hypertonicity should be slow and gradual in order to prevent cerebral swelling (Ref. 11, 12). The initial 3 liters of fluid should in almost all instances be isotonic rather than hypotonic saline.

4. DANGERS OF TOO RAPID LOWERING OF BLOOD GLUCOSE DURING TREATMENT OF DKA

A) Decrease in Effective ECF Volume

May reduce effective ECF volume by 1-2 liters and thereby worsen collapse and precipitate lactic acidosis. Make certain that ECF volume repletion takes into account the decrease in ECF volume attendant on the fall in blood sugar and on the extent of osmotic diuresis continuing during ECF replacement.

B) Production of Osmotic Dysequilibrium in the Brain with Increased Propensity to Cerebral Edema

Clements et al have reported an increase in cerebrospinal fuild pressure in 5 patients during treatment of DKA (Ref. 13,18) which they postulated may be related to increased polyol pathway activity in the brain. Assal and co-workers however failed to find any increase in CSF pressure in 9 patients during treatment of DKA (Ref. 19).

C) Late Hypoglycemia

When blood glucose falls during treatment to around 270-300 mg%, glucose infusion must be started for several reasons i.e. to prevent late hypoglycemia, to minimize osmotic dysequilibrium in the brain and finally to permit continuation of insulin therapy until ketosis breaks, since blood sugar falls more rapidly than the control of ketosis.

Glucose must be infused at a rate (mg/min) adequate to maintain blood glucose between 250-300 mg% yet not producing an osmotic diuresis. During maximum insulinization the rate of glucose utilization may vary from 280-600 mg/min. The appropriate rate for a given patient must be determined by noting the response to a known rate of infusion (i.e. 400 mg/min). Just hanging up a bottle of D_5W can be catastrophic. The patient may die of hypoglycemia if 5% glucose is running at 3cc/min (150 mg/min) and his rate of peripheral glucose utilization is 500 mg/min.

C - POTASSIUM METABOLISM IN DKA (Ref. 20-34)

1. LOSS OF POTASSIUM FROM BODY - 5 to 10 mEq/Kg/Body Wt (mean 300 mEq)

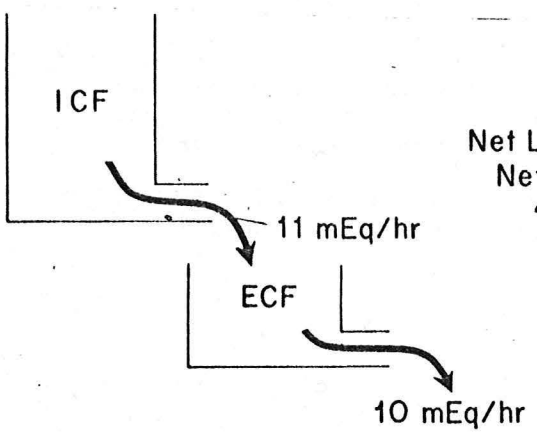
   A) RENAL LOSS
      1. Acidosis
      2. Osmotic diuresis
      3. ↑ Cortisol
      4. ↑ Aldosterone (Ref. 20)

   B) VOMITING - frequent
      6-25 mEq/L (as high as 40 mEq/L)

2. SHIFTS OF POTASSIUM FROM ICF TO ECF

   A) Dehydration
   B) Acidosis - for each ↓ 0.1 pH an ↑ 0.6-1.0 mEq/L
   C) Deglycogenation
   D) Tissue Wastage - Gluconeogenesis
      for each gram N - 2.7 mEq of K, 0.7 mM of P(i) and 0.6 mEq Mg

3. MECHANISM OF HYPERKALEMIA IN THE PRESENCE OF K DEFICIENCY IN DKA



IN 24 HOURS

Net Loss From Body = 240 mEq

Net Gain Into ECF = 24 mEq

4 mEq/L x 15 L = 60 mEq

$60 + 24 = \frac{84}{12} = 7$ mEq/L

4. MECHANISM OF HYPOKALEMIA DURING TREATMENT OF DKA

A) CONTINUED URINARY LOSS (Ref. 21)
If no K given - 67 mEq in 1st 24 hours (Danowski)
With K replacement - 135 lost in urine of 238 mEq infused

B) SHIFTS OF K FROM ECF TO ICF

C) EXPANSION OF ECF

5. INITIAL VALUES FOR SERUM K ON ADMISSION (Ref 21-25)

A) Below Normal 4-15% cases
B) Normal 45-63% cases
C) High 22-40% cases

Despite the not infrequent (22-40%) cases of hyperkalemia in the presence of K deficiency, remember that hypokalemia (4-15%) or normal serum K (45-63%) are often present on admission. During the first hour of therapy serum K can fall > 1 mEq/L. Where serum K is low or normal, K therapy should be started almost at once and therapy should be vigorous. Potassium phosphate rather than KCl should be used.

D - KETOACIDOSIS

1 - DANGERS OF ACIDOSIS (Ref. 35-38)

A. CARDIAC
1. Increased risk of arrhythmias
2. Impairs cardiac contractility
3. Decreases C-V response to catecholamines
4. Increases propensity to pulmonary edema during volume replacement

B. METABOLIC
1. Increases insulin resistance
2. Slight decrease in $NaHCO_3$ when buffer capacity is low produces a large decrease in pH

C. RESPIRATORY - May impair ventilatory compensation with severe acidosis (Ref. 40)

EFFECT OF SMALL CHANGES IN $NaHCO_3$
ON pH WHEN BUFFERING CAPACITY IS LOW

pCO_2	$NaHCO_3$	$\Delta NaHCO_3$	pH	ΔpH
25	10		7.23	
25	2	-2	7.14	+0.09
20	5		7.03	
20	3	-2	6.81	+0.22

EFFECT OF pH ON VENTILATORY RESPONSE

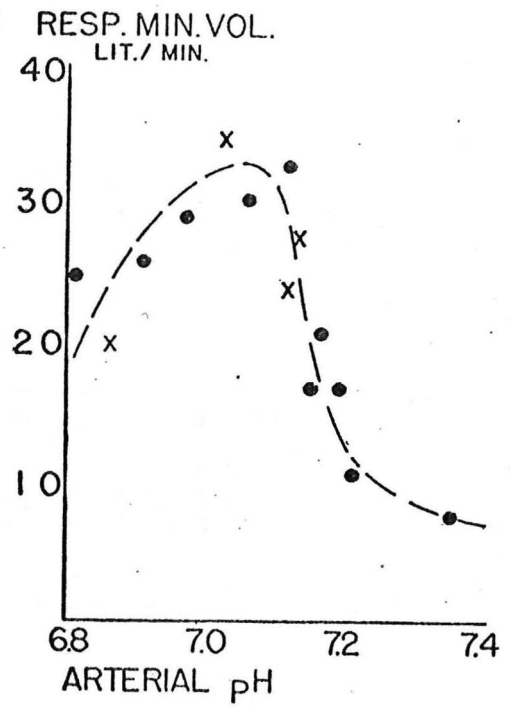


FIG. 1. THE RELATIONSHIP BETWEEN RESPIRATORY MINUTE VOLUME AND ARTERIAL pH

CASE 1

Biochemical changes and insulin given in Case I

Time	pH	Pco_2 (mmHg)	Standard bicarbonate (mEq l)	Base deficit (mEq l)	Bicarbonate given (mEq)	Blood sugar (mg/100 ml)	Soluble insulin units
10.30 hours	7·02	23	8	27	100	1250	100
11.00 hours	7·29	11	11·1	20	50	1300	
14.00 hours	7·30	23	14·5	13·5	50	670	50
17.00 hours	7·48	16	19·7	6			
22.00 hours	7·42	25	21·2	4		400	10
21.00 hours	7·43	32·5	22·5	1·5		210	

(from Kuzemko et al)

Note - ONLY 3.1 mEq/L ↑ in $NaHCO_3$ but a marked decrease in pCO_2 (indicating improved ventilation) from 23 to 11 mm Hg and a disproportionate rise in pH from 7.02 to 7.29

2 - PROPENSITY FOR THE DEVELOPMENT OF ALKALOSIS WITH $NaHCO_3$ TREATMENT (Ref. 39-41)

A - KETOACIDOSIS WITH POTENTIAL BICARBONATE

The usual findings in DKA include the following organic metabolizable acids

Na-AcAc	=	3.0 mM/L
Na-BOH	=	11.0 mM/L
Na-Lactate	=	2.5 mM/L
Na-FFA	=	2.5 mM/L
		18.0

When these are metabolized 18.0 mEq/L of $NaHCO_3$ is regenerated.

Example

$NaHCO_3$ + Ketone Acid → Na-Ketone + H_2O + CO_2

Na-Ketone $\xrightarrow{\text{Krebs cycle}}$ $NaHCO_3$

B - HYPERVENTILATION PERSISTS despite rising bicarbonate producing normal or elevated pH despite reduced bicarbonate levels

C - INCREASED VENTILATORY RESPONSE with lowering of pCO_2 and inordinate rise in pH may occur with bicarbonate administration in severely acidotic patients whose ventilatory response previously was not maximal (Case 1 & 2)

CASE 2 - [redacted]

This 37 year old [redacted] man, a known heroin addict, was brought to the hospital in a comatose state, with Kussmaul respirations and an odor of ketones on his breath. On a previous admission blood sugars were 174 and 186 mg%. A diagnosis of diabetic ketoacidosis was made. He was treated with insulin, IV fluids and recovered.

Time	pH	pCO_2	$BHCO_3$	Gluc.	$BHCO_3$ Admin.
0	6.87	17	>3.0	650	
1	7.11	23	6.8	588	↑ 440 mEq ↓
2	7.04	19	5.3	510	
3	7.11	16.5	5.4	390	
4	7.35	16	9.0	390	
6	7.41	15	9.2	372	
8	7.45	15	10.0	336	
12	7.58	19	17.5	314	
18	7.57	23	21	360	

Note:
1. Decrease in pCO_2 from 17 to 15 with bicarb administration indicating improved ventilatory response.
2. Normal pH 7.41 with a $BHCO_3$ of 9.2
3. Note alkalosis (pH 7.58) with bicarb of 17.5

3 - DANGERS OF ALKALOSIS DURING TREATMENT OF DIABETIC KETOACIDOSIS

A. ACUTE WORSENING OF HYPOKALEMIA (Ref. 20-34)

1) Inordinately large changes in pH may occur with small increments in bicarbonate (see Case I, pg 12; Case II, pg 13). For each 0.1 u increase in pH, serum K will fall from 0.6 - 1.0 mEq/L

2) Even without bicarbonate therapy serum K usually falls within one hour of starting therapy by 1.1 to 1.5 mEq/L (Alberti; Beigelman)

3) Hypokalemia may worsen hypophosphatemia (Vianna; Anderson) (Ref. 72,73)

4) Hypokalemia may precipitate a large spectrum of atrial, junctional or ventricular arrhythmias, at times fatal.

B. PRODUCTION OF PARADOXICAL CSF ACIDOSIS (Ref 44-48)

The problem of the production of CFS acidosis by the administration of bicarbonate during the treatment of diabetic ketoacidosis was raised by Posner and Plum's publication in 1967 (Ref. 44-48). Since pCO_2 was thought to equilibrate rapidly between blood and CSF whereas bicarbonate had to be actively secreted, it was anticipated that bicarbonate administration would raise CSF pCO_2, whereas CSF bicarbonate would remain unchanged and a CSF acidosis would ensue, a state thought to produce deterioration of cerebral function. In 1974 Assal and co-workers reported measuring CSF pH before and after correction of systemic acidosis with bicarbonate infusions in diabetic ketoacidosis (Ref. 46). CSF pH indeed did fall from 7.35 to 7.27 (normal CSF pH = 7.26-7.36) but it did not fall below normal levels. Moreover, it fell to no greater extent with bicarbonate than it did with saline. Although all patients were stupoprous on admission, all showed definite and progressive improvement in levels on consciousness.

Most important is the recent meticulous study of Plum and Price who compared cisternal and lumbar CSF in 59 cases. A consistent difference between the two CSF compartments was found, with the pH lower and pCO_2 higher in the lumbar region. They concluded that sampling of lumbar CSF fluid in acutely ill patients provided unreliable information about cerebral acid-base status (Ref.48).

C. PRODUCTION OF TISSUE AND CEREBRAL HYPOXIA (Ref. 61A-63)

↓ P_{50} by shift of the Hbg-O_2 dessociation curve from the right to the left and unmasking of the low RBC 2,3 DPG, previously compensated for by the Bohr effect of acidosis

4 - RATIONAL USE OF BICARBONATE IN DKA

Under ordinary circumstances bicarbonate therapy is contraindicated. However severe acidosis (pH less than 7.0 or 7.1) or dangerously low serum bicarbonate (5 mEq/L or less) may dictate the use of bicarbonate. It must be given slowly and pH monitored frequently (since a small rise in bicarbonate if associated with an improved ventilatory response and a fall in pCO_2 may cause an inordinate rise in pH). DO NOT RAISE pH ABOVE 7.15.

Moreover if initial serum K is low (4-15% of cases) or normal (45-63% of cases) then K should be included in the initial (if low) infusion.

E - DEPRESSED RBC 2,3 DIPHOSPHOGLYCERATE (DPG) IN DIABETIC KEOTACIDOSIS (Ref. 49-63)

1. HISTORY

The position of the Hgb-O_2 dissociation curve until recently was regarded as fixed and influenced only by temperature and pH (Bohr Effect). The fact that physiologic variations in temperature and pH seemed too limited to provide an effective control mechanism for release of O_2 from Hgb led Barcroft (1921) to postulate a "third substance" which formed an integral part of the Hgb-O_2 complex and regulated O_2 release.

In 1967 Barcroft's postulated "third substance" was shown by Benesch & Benesch and by Chanutin and Curnish to be the organic polyphosphates of rbc's, especially 2,3 DPG and ATP. The former was more important quantitatively since its molar concentration was 3-4 x that of ATP. The studies of these two groups firmly established that the levels of 2,3 DPG and ATP in the RBC are the metabolic controlling factors capable of regulating O_2 unloading at the tissue level in physiologic and pathologic condition.

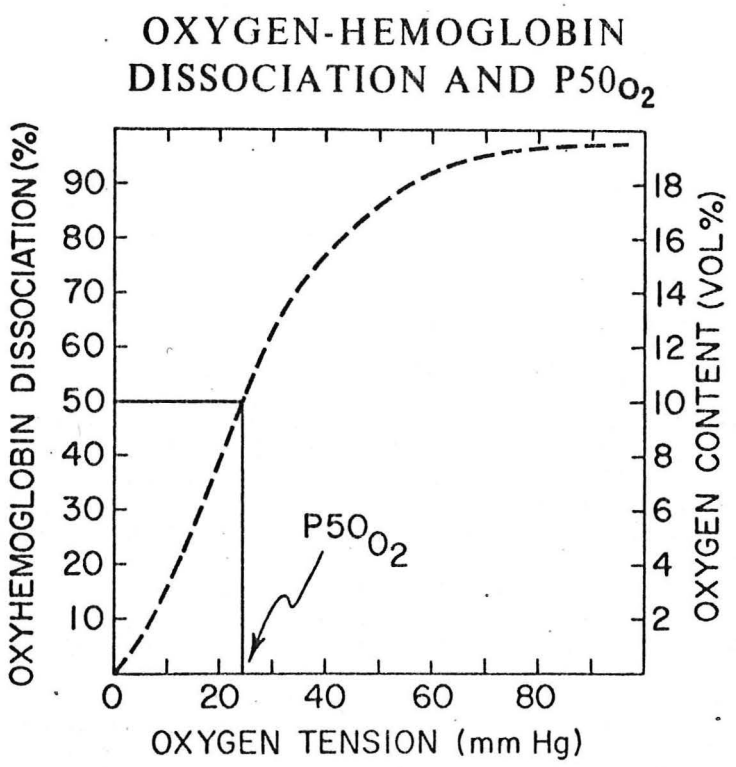
Their studies showed that levels of 2,3 DPG in concentrations present in RBC's can decrease the oxygen affinity of Hgb about thirty fold, thereby facilitating O_2 unloading from Hgb i.e. in effect shifting the Hgb-O_2 curve to the right.

Recent studies have shown (J. Duhm) that 2,3 DPG has at least two effects on the O_2 affinity of human rbc's. (Ref. 59)

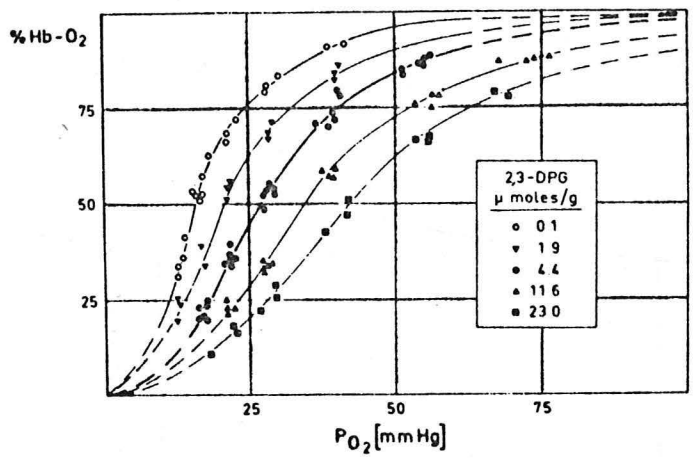
(1) It decreases the affinity of Hgb for O_2 by combining with deoxyhemoglobin, thereby shifting the Hgb-O_2 dissociation curve to the right and increasing P_{50}.

(2) 2,3 DPG also changes intraerythrocyte pH relative to plasma pH. In accord with the Gibbs-Donnon equilibrium an increase in rbc 2,3 DPG decreases intra-rbc pH and thereby alters the Bohr Effect of Hgb.

2. Hgb-O_2 DISSOCIATION CURVE AND P_{50}



3. EFFECTS OF 2,3 DPG ON P_{50}



4. EFFECTS OF CHANGES IN BLOOD pH ON RBC 2,3 DPG

In 1924 Haldane, Wigglesworth & Woodrow (Proc Roy Soc London 96:1, 1924-25) reported that NH_4Cl acidosis produced a fall in organic acid-soluble phosphorus in blood. In 1929 Byrom (Brit J Exper Path 10:10, 1929) described a reduction in organic acid-soluble phosphorus in the blood in diabetic ketoacidosis. Rapoport (1937) identified diphosphoglycerate as that fraction of organic acid-soluble P in the rbc that decreased during acidosis. In 1939 Guest and Rapoport reported a decrease in RBC 2,3 DPG in DKA, along with evidence of marked phosphaturia and phosphate depletion. Moreover they showed that following treatment for DKA marked hypophosphatemia and also a fall in RBC ATP supervened. Levels remained low until after 2,3 DPG reached normal concentrations. As long ago as 1924 Haldane et al prophetically suggested that some of the ill effects of acidosis might be the consequence of depletion of labile phosphate stores and advised that phosphate

administration seemed rational and advisable. Guest in 1939 on the basis of his above described studies routinely treated DKA with phosphorus containing solution. It has taken about 30 years for the medical profession to realize the clinical importance of severe hypophosphatemia and phosphate depletion and to return to a previously used therapy.

CORRELATION BETWEEN ARTERIAL pH + RBC 2,3 DPG

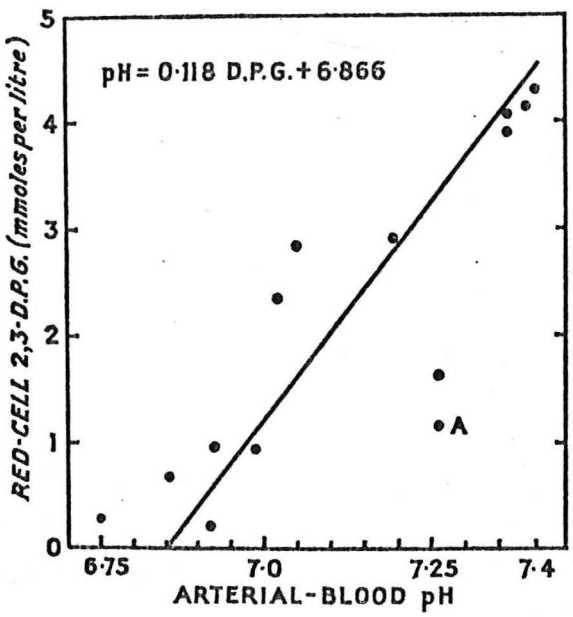
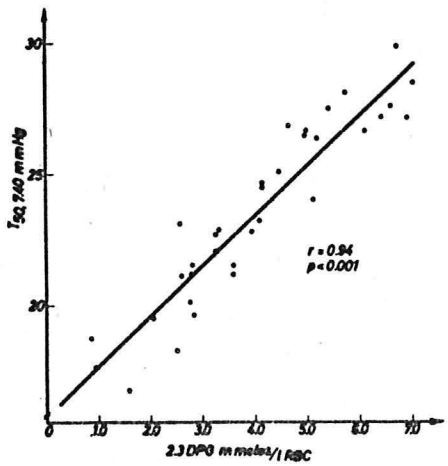


Fig. 1—Relation between red-cell 2,3-D.P.G. and arterial-blood pH in patients with uncontrolled diabetes before treatment.

A, subject who received bicarbonate before treatment with insulin.

(from Alberti et al. Lancet, 26 Aug, 1972)

CORRELATION BETWEEN 2,3 DPG AND P_{50}



Correlation of red cell 2,3-DPG content and P50(7.40) of ODC during recovery from diabetic ketoacidosis.

The low 2,3 DPG seen in DKA prior to therapy (↓ from 4.5 to 2.2 mm/L) is balanced by the systemic acidosis which shifts to Hgb-O_2 dissociation curve to the right, thereby assuring a normal P_{50} (mean 28.8) and O_2 release at the tissue level (Alberti et al, Lancet 1972; Ditzel 1973).

Following treatment for DKA it takes up to 5-7 days for 2,3 DPG to return to normal levels. Patients who received IV bicarbonate for correction of arterial pH, disturbed the compensation attained during acidosis, and showed an acute fall in P_{50} and evidence of tissue hypoxia.

Since slow recovery of RBC 2,3 DPG is related to the hypophosphatemia that occurs during and after treatment of DKA, rational therapy dictates the early use of phosphate replacement and the exclusion of bicarbonate whenever possible.

EFFECTS OF SUDDEN CORRECTION
OF pH IN DKA

pH	P_{50} mm Hg
6.93	29.5
7.40	17.5

F - PHOSPHATE DEPLETION IN DKA (Ref. 64-74)

1 - RENAL LOSS OF PHOSPHATE

a) Acidosis - lowers renal threshold for phosphate and increases phosphaturia
b) Glycosuria - whereas osmotic diuresis from mannitol does not alter phosphate excretion, marked glycosuria depresses renal reabsorption about 20% (Ref. 67-69)
c) Acetoacetate - excretion depresses phosphate reabsorption and increases phosphaturia (Ref. 69)
d) Potassium Deficiency - may be accompanied by an increase phosphate clearance. Tubular reabsorption of P(i) decreases from 90 to 55-60% despite hypophosphatemia (Ref. 72,73)
e) Hormonal Changes - Increased aldosterone, cortisol and glucagon levels all characteristic of DKA have each been reported to increase phosphaturia (Ref. 20,67,71)

2 - SHIFTS OF PHOSPHATE FROM ICF TO ECF

a) Acidosis - results in breakdown of organic polyphosphates in many tissue cells in addition to the RBC. The percent lost from RBC is greater than other tissues. P(i) is lost in excess of Nitrogen
b) Glycogen breakdown
c) Tissue Wastage - gluconeogenesis for each gram of N, 0.7 mM of P(i)

3 - MECHANISM OF HYPERPHOSPHATEMIA IN PRESENCE OF PHOSPHATE DEPLETION IN DKA

Similar to that for potassium

4 - MECHANISM OF HYPOPHOSPHATEMIA DURING AND AFTER THERAPY (may last 5 days or more without specific Rx)

a) Cessation of renal loss
b) Reentry into cells
c) Expansion of ECF

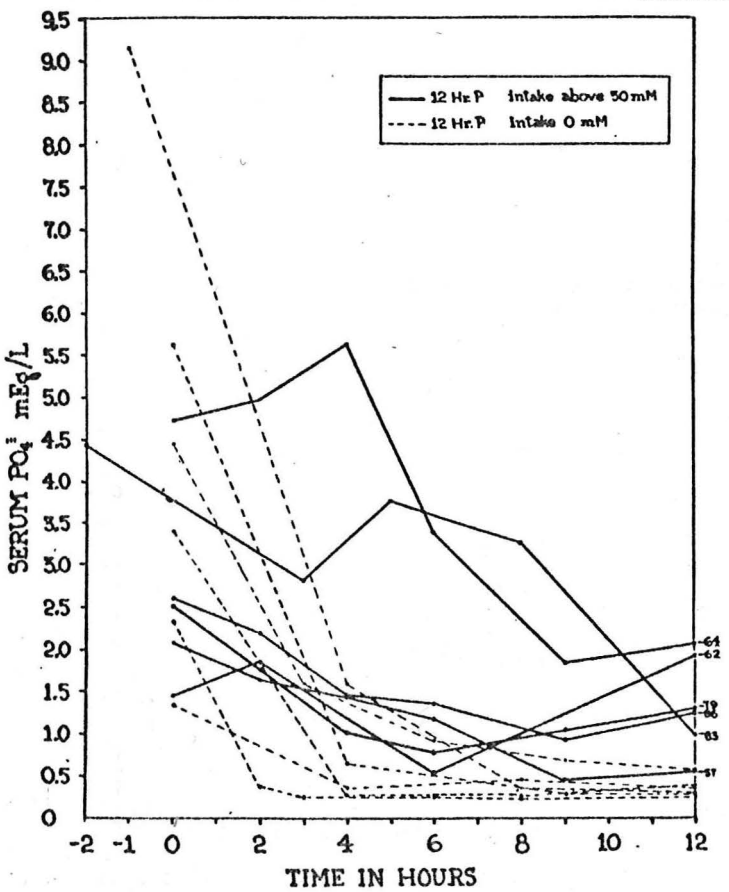
5 - MAGNITUDE OF PHOSPHATE DEPLETION

Varies from 0.5 to 1.2 mM/kg body wt.
Averages about 70-100 mM

6 - SERUM PHOSPHATE LEVELS BEFORE AND DURING TREATMENT (mg/100 ml)

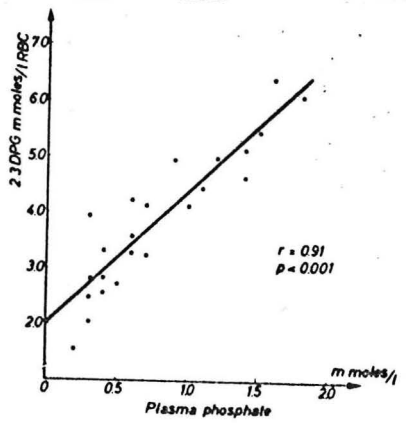
Series	Before	During Rx
Seldin & Tarail	5.6 (2.8 - 10)	1.0 (0.1 - 2.7)
Martin et al	elevated in 71%	below normal 90%
Franks et al	7.88 (4.3 - 17.2)	36% < 1 mg% 64% between 1-2 mg%

In 1948 Franks, Berris, Kaplan and Meyers systematically studied and treated the phosphate depletion and the hypophosphatemia which ensues during treatment of DKA. They made at least two significant observations. First the mortality rate in phosphate treated patients was 15% less than those patients with the same severity index who did not receive supplemental phosphate. Second, they reported three patients who unexpectedly regained consciousness during phosphate infusion. Guest and Rapoport had similar clinical experience. More recently Ditzel also has reported the prompt return of consciousness in a patient who remained stuporous long after systemic acidosis was gone.

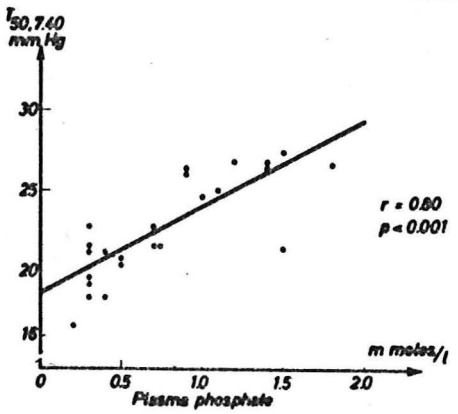


Therapy of Diabetic Acidosis - Martin et al (Ref. 66)

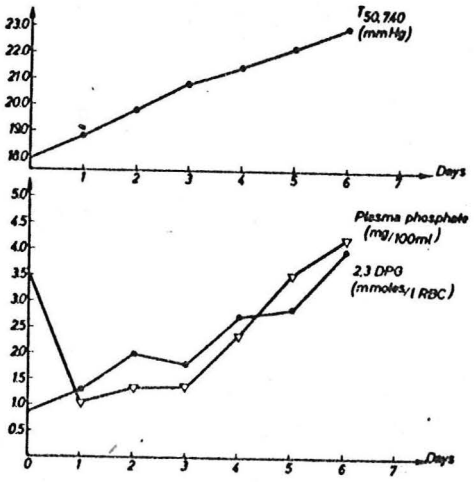
Effect of phosphate * therapy on serum phosphate level in diabetic ketoacidosis.



Correlation of Pi and red cell 2,3-DPG after insulin administration during recovery from diabetic ketoacidosis.

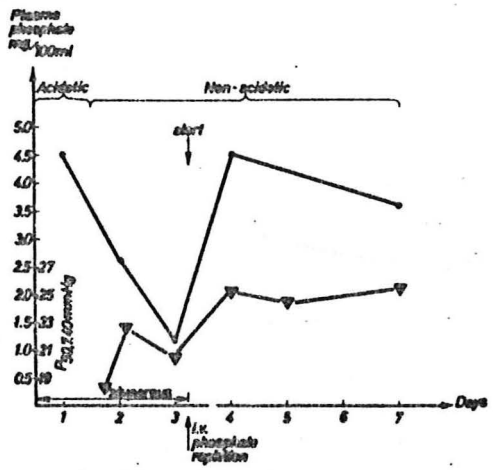


Correlation of Pi and P50(7.40) of ODC after insulin administration during recovery from diabetic ketoacidosis.



Changes in Pi, red cell 2,3-DPG and P50(7.40) of ODC during treatment of diabetic ketoacidosis.

EFFECT OF IV PHOSPHATE ON THE MENTAL STATUS AFTER RECOVERY FROM DKA



Changes in Pi and P50(7.40) of ODC before and after i.v.phosphate repletion.

Other studies (Travis et al; Lichtman et al) indicate that in vivo RBC glucose metabolism is regulated by the plasma concentration of inorganic phosphates. The regulation appears mainly at the glyceraldehyde-3-P step. Hypophosphatemia results in a decrease in RBC 2,3 DPG and ATP with an increase in total trioses. Not only is oxygen delivery impaired but ATP may be depressed enough to produce an hemolytic anemia. Severe hypophosphatemia even in the absence of phosphate depletion (i.e. trapped phosphate in body cells) can lead to the many clinical manifestations of the "low phosphate syndrome".

MEAN ATP, 2,3 DPG AND P_{50} IN PATIENTS WITH SERUM PHOSPHATE BELOW 1 mg%

	P(i) mg%	ATP µm/ml rbc	2.3 DPG µm/ml rbc	P_{50} mm Hg
5 Patients				
Mean	0.50	0.41	2.6	19.5
Range	0.4 - 0.7	0.20 - 0.65	2.2 - 3.2	16.5 - 23.3
20 Normals	3.4 ± 1.0	1.1 ± 0.2	5.1 ± 0.8	27 ± 2.2

8 - THE CLINICAL SPECTRUM OF THE LOW PHOSPHATE SYNDROME (Ref. 75-89)

a) ACUTE HEMOLYTIC ANEMIA WITH RIGID RBC's

b) IMPAIRED PHAGOCYTIC FUNCTION OF GRANULOCYTES WITH PROPENSITY TO INFECTION

c) IMPAIRED PLATELET FUNCTION WITH HEMORRHAGE

d) CNS DYSFUNCTION WITH PARESTHESIAS, WEAKNESS, CONVULSIONS AND COMA

e) HEART FAILURE

f) MYOPATHY WITH RHABDOMYOLYSIS AND MYOGLOBINURIA

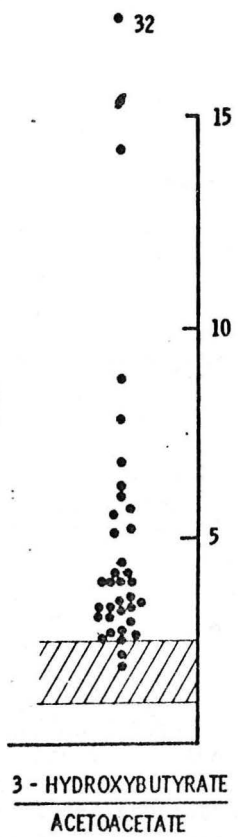
g) HEPATIC HYPOXIA

h) RHEUMATIC MANIFESTATIONS

G - COMBINED DIABETIC KETOACIDOSIS AND LACTIC ACIDOSIS (Ref 90-102)

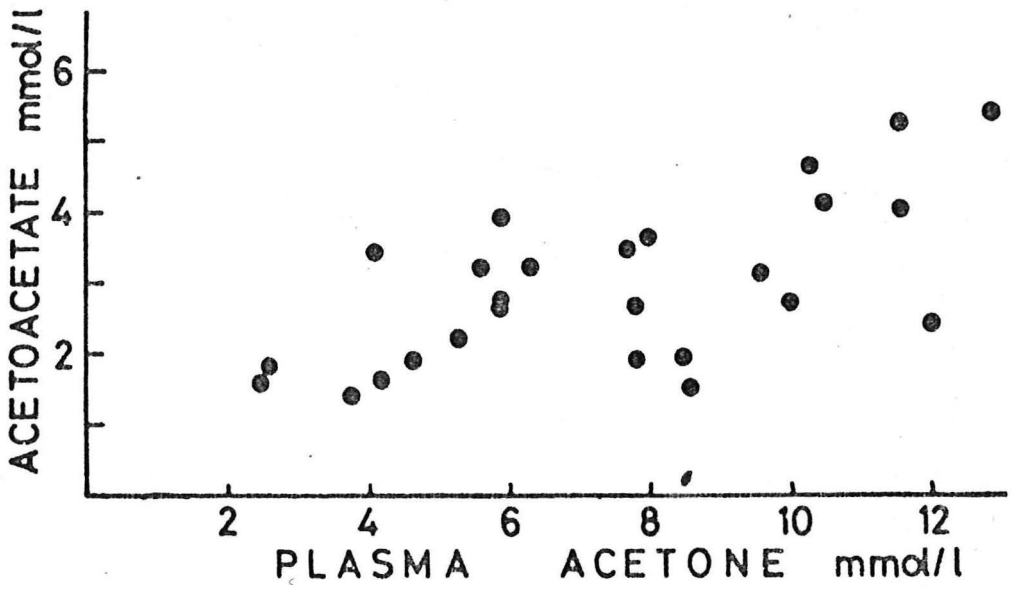
1. KETONE PRODUCTION AND KETONE BODIES IN BODY

During the development of progressive ketoacidosis, accelerated fatty acid oxidation in the mitochondria of liver cells results not only in accelerated acetoacetate production but also in the generation of large amounts of $NADH+H^+$. This shifts the redox potential and most of the acetoacetic acid (AA) is reduced to betahydroxybutyric acid (BOH). As a consequence most of the ketone acids present are in the form of BOH. In normal, non-diabetic subjects the mean BOH/AA ratio is 1.5 (Alberti & Hockaday 1972, Ref. 92). In contrast, in diabetic ketoacidosis the mean ratio found by Alberti & Hockaday in 50 patients was 5.2 ± 0.9 (range 1.9 - 31.7). In 18 milder cases of DKA Stephens, Sulway and Watkins (1971) reported a mean BOH/AA of only 2.7. (The total ketones (AA+BOH) in this study were less than 7 mM/L in all cases.) The higher ratio reported by Alberti & Hockaday may represent not only accelerated fatty acid oxidation with alteration of the redox potential in the mitochondria favoring reduction to BOH but also associated lactic acidosis, since the higher ratios were all found in severely ill patients.



Ratio of blood 3-hydroxybutyrate to acetoacetate in diabetic coma. (Shaded section indicates normal range).

Not only are AA and BOH present in the plasma and body fluids in DKA but recent studies indicate that acetone is also present in large concentrations, averaging 7.3 mM/L (range 2.5 - 12.9) (Sulway and Malins). In most studies where AA was measured by specific enzymatic methods in DKA, acetoacetate levels average about 3 mM/L, a figure similar to the mean value of 3.02 mM/L reported by Sulway and Malins in 41 cases of DKA.



RELATION BETWEEN BLOOD-ACETOACETATE AND PLASMA-ACETONE IN 26 PATIENTS IN KETOACIDOSIS, BEFORE TREATMENT.

This varying BOH/AA ratio and the presence of acetone in high concentrations has important clinical implications, not only in the diagnosis of DKA but also in following the course of treatment.

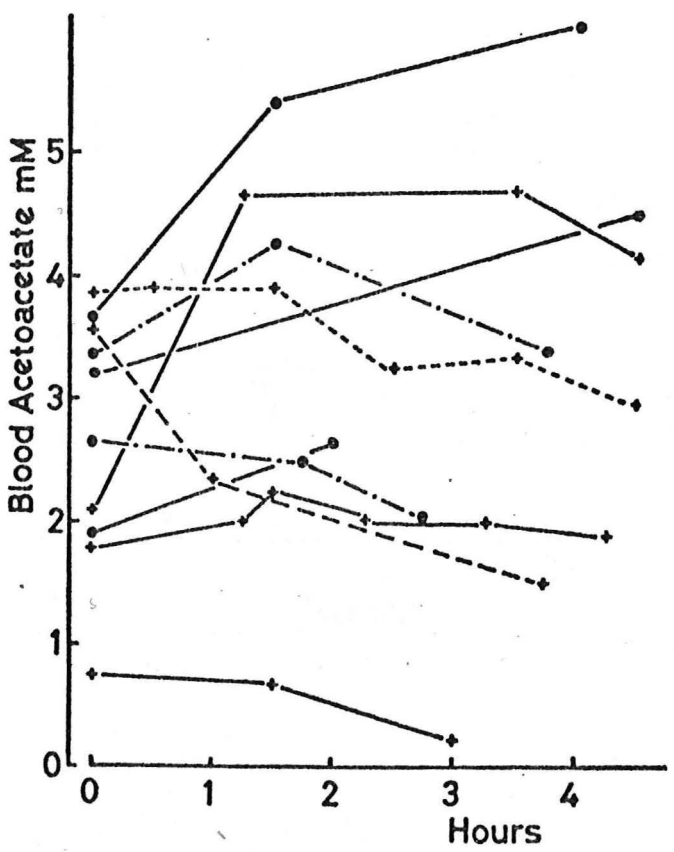
It is critical to remember that the usual tests for ketone bodies in plasma and urine (Acetest, Ketostix*) utilize the nitroprusside reaction which does not react with BOH, reacts mainly with AA, and

* Ketostix should not be used routinely to determine plasma ketones in DKA. It has been found unreliable in many studies because of early decomposition of reagents after the bottle is opened. It is more sensitive to acetone than the Acetest tablets. Its use initially would seem rational when combined DKA and lactic acidosis is suspected since AA may be very low whilst BOH is high. The high acetone associated with this would more likely be positive with the Ketostix and alert one to the possibility of combined DKA and lactic acidosis.

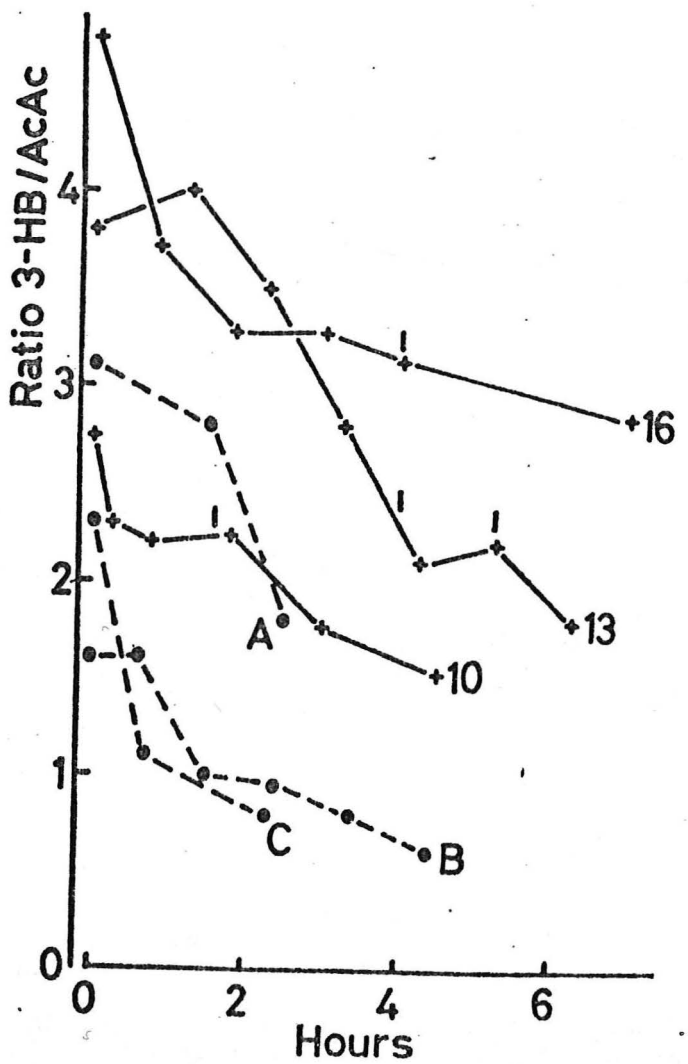
only weakly with acetone. In essence one is measuring AA only, a small fraction of the total ketones, therefore the degree of ketonemia may be underestimated before therapy is started if the ratio of BOH/AA is high. This is especially true when an element of lactic acidosis is present. Under these circumstances the test for ketones may even be negative.

Moreover during treatment, when free fatty acid oxidation is decreased and ECF volume is expanded (reducing or ending any associated lactic acidosis) "ketones" may appear to increase in plasma when in fact total ketones are reduced but the percent of AA has increased. Intelligent interpretation of such an "apparent but not real" increase in ketones can be made by noting changes in pH and bicarbonate concentration.

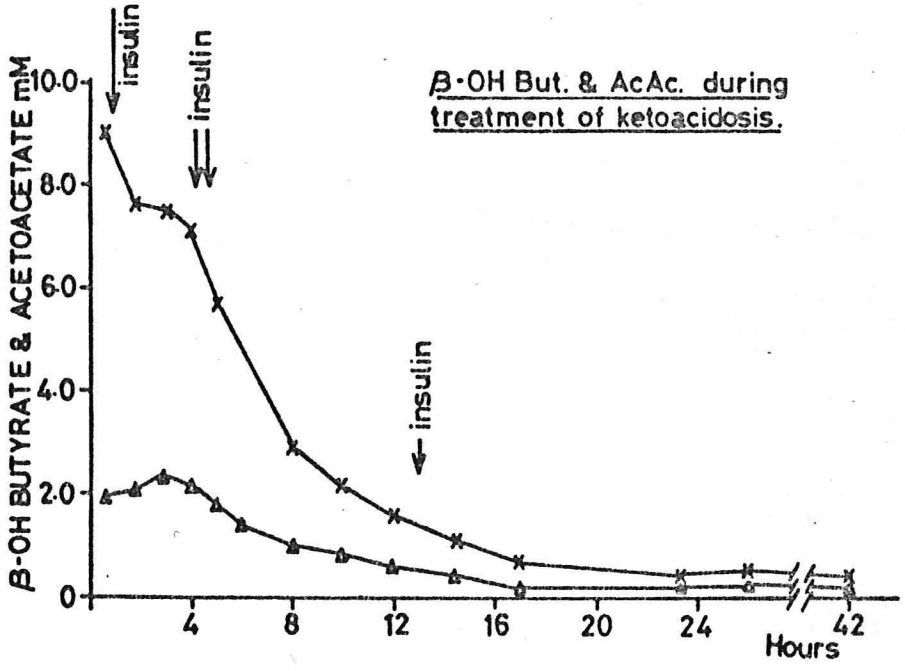
CHANGES IN BLOOD ACETOACETATE
DURING TREATMENT OF DKA



CHANGES IN THE BOH/AA RATIO
DURING TREATMENT OF DKA



CHANGES IN BOH AND AA DURING
TREATMENT OF DKA



2. LACTIC ACIDOSIS COMBINED WITH KETOACIDOSIS

Lactic acidosis combined with diabetic ketoacidosis was considered rare until the studies of Watkins, Smith, FitzGerald and Malins were reported in 1969. Since patients with diabetic ketoacidosis are dehydrated, volume depleted and often show evidence of peripheral circulatory collapse it should make one suspect on a priori grounds that the two should occur together frequently.

In the 27 patients with DKA reported by Watkins et al the mean lactate in patients with total BOH less than 10 mM/L was 1.88 mEq/L whereas in those with BOH greater than 13 mM/L mean lactate was 3.7 mEq/L.

LACTATE LEVELS IN DKA

(Watkins, Smith, FitzGerald, Malins 1969)

Patient With Blood BOH Levels Greater Than 7 mEq/L

MEAN	BOH 14.5 mEq/L	BOH 8.9 mEq/L
Blood Lactate mEq/L	3.7	1.8
Blood Glucose mg %	1072	556
Blood pH	6.94	7.15
Percent of Group	29%	71%

In a larger series of 50 patients with DKA, Hockaday and Alberti found 7.3% with lactate levels in excess of 7 mEq/L (Ref. 96)

BLOOD LACTATE, PYRUVATE & L/P RATIO
IN DIABETIC KETOACIDOSIS

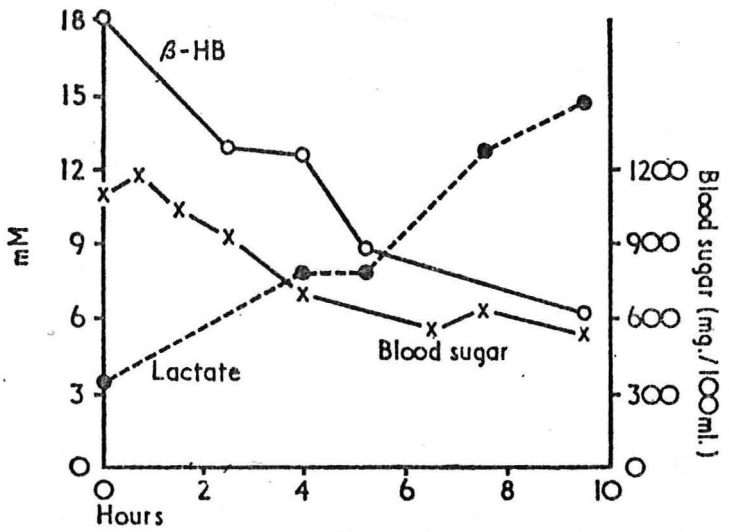
	33 Percent Lactate greater than 2.0 mEq/L	64 Percent Lactate less than 2.0 mEq/L
MEAN		
Lactate	4.67 mEq/L	1.79 mEq/L
L/P	25	17
pH	7.03	7.22
Glucose	824 mg %	631 mg %
Ketone	14 mEq/L	8.4 mEq/L

REDOX PAIRS

Cytoplasmic

Mitochondrial

Not only is lactate elevated early in 33 percent of Alberti and Hockaday's patients with DKA, but lactate may rise later in the course of treatment, frequently due to progressive collapse, and mask the ketonemia since under these conditions AA will decrease and BOH increase. The patient's "apparent ketones" will diminish sharply or disappear while acidosis may worsen. Again changes in "ketones" must be interpreted in the light of changes in arterial blood pH and plasma bicarbonate. Such circumstances are shown in the next figure.



Marliss amd co-workers (1970) have stressed the fact that the altered redox state associated with lactic acidosis may obscure the ketoacidosis which is also present. (Ref. 95)

H - INSULIN TREATMENT OF DIABETIC KETOACIDOSIS

There has been a flurry of recent reports (Ref. 103-106) promulgating the use of continuous intravenous infusions of small doses of insulin (6.5 to 8 units per hour after a small initial intravenous priming dose of about 6-8 units). These reports have constituted a major attack on the usual insulin therapy advised in ketoacidosis. However to date only about 62 patients with DKA have been studied by this technic. Moreover it should be noted that in one report 6 out of the 14 (43%) of patients had plasma pH 7.34 or greater (Ref. 103); in another 2 of 13 patients (15%) had pH 7.34 or greater (Ref. 105) and in a third series (Ref. 104) 5 of 11 patients (45%) had pH's greater than 7.34, indeed (11%) had pH greater than 7.40. In all series they make the point that these small doses produced maximal insulinization (with serum insulin levels circa 100 μU/ml) and that the danger of hypoglycemia was negligible since cessation of infusion led to prompt cessation of insulin action.

I have no doubt that a great many patients in diabetic ketoacidosis will respond to small doses of IV insulin as described above. However the object of insulin therapy in DKA is to provide adequate insulin to stop the ketotic and gluconeogenic processes. The precise amount required in any given individual is unknown and at best is an educated guess. While we agree with their criticism of the use of large subcutaneous doses of insulin, these objections are really not valid for intermittent, hourly IV administration of insulin (50-100 U). Since the dose of insulin required in the treatment of DKA is a biologic titration with the end points of controlling ketogenesis and hyperglycemia and since a not insignificant percentage of patients require large amounts of insulin to effect this, it is rational to use large IV doses. The only proven danger of insulin is hypoglycemia. No matter what dose is used (large or minute) if it is enough to produce maximum insulinization then the danger of late hypoglycemia is equal in both circumstances. Our experience at PMH dictate the use of what others would term "large doses" (i.e. 50-100 U IV insulin) at hourly intervals until hyperglycemia and ketonemia break. We prefer to consider these doses as that amount necessary to achieve the results mentioned above. Within a one week period in March while this protocol was being prepared, three patients entered in DKA who required (not just received) inordinately large doses of insulin for control of their DKA. These cases are briefly described below. Finally the problem in reducing mortality in DKA have never been that of too much insulin but rather of too little too late.

[redacted] - a 17 year old girl with known diabetes since age 8 had been doing well on 40 U of NPH daily until about [redacted] 1975 when glycosuria increased and her physician gradually increased her insulin to 75 U/NPH/day. She had a sore throat without fever 2 weeks prior to admission which receded in one week. Following this glycosuria increased, for which she

took an extra 60 U of regular insulin daily and increased her NPH to 80/day for 2 days prior to admission. Despite an increase in insulin from 75 U/day to 140 U/day, on the day of admission she was brought to the emergency room in full blown diabetic ketoacidosis with Kussmaul respiration. Blood sugar was 711 mg%, creat 2.2, Na 142, K 4.1, bicarb < 10 mEq/L and art. pH 6.98.

In this case who went progressively and rapidly into ketoacidosis despite increasing her daily insulin from 75 to 140 U/day, it would have been irrational at best to have treated her with small continuous IV insulin (circa 6-8 U/hr). Indeed she required 840 U of insulin before ketosis broke.

[redacted] is a 51 year old [redacted] woman who had over the years been treated at times with insulin, then with oral agents, followed again by insulin and then oral agents. A perfect history for the eventual development of increasing antibodies. On [redacted]/75 she developed a flu like syndrome and because of a rise in FPS to 479 mg% was again restarted on insulin (20 U NPH/day). Nevertheless she developed progressive weakness, nocturia, and was on [redacted]/75 in ketoacidosis with a blood glucose of 570, Na 134, K 4.3, bicarboante 6 mEq/L, serum ketones positive 1:16 and an arterial pH of 7.16. She made an initial salutory response to 475 units of insulin over about 12 hours with a rise in arterial pH to 7.36. Within another 12 hours she lapsed back into progressive hyperketonemia, which required another 850 units to control. Following this, insulin requirements increased progressively requiring as much as 750-1125 U/day for control of her diabetes. Following institution of steroid therapy, insulin requirements have decreased to around 180-200 U/day.

The folly of even considering small dose therapy in such a patient is too apparent for further comment.

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