MEDICAL GRAND ROUNDS

JULY 31, 1980

PHOSPHATE METABOLISM IN DIABETIC KETOACIDOSIS

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I. TYPES OF DERANGEMENTS IN PHOSPHATE METABOLISM

Definitions

Hypophosphatemia: Low concentration of serum phosphate; normal or low intracellular phosphate.

Phosphate depletion: Loss of intracellular phosphate in excess of nitrogen (↓ P/N) for the body as a whole

Redistribution: Transfer of phosphate from certain tissues to sequestration sites (e.g., liver or muscle glycogen, growing bone, etc.). Total body phosphate is normal.

Trapping: Intracellular block in utilization of phosphate. Total body and tissue phosphate normal

(From Emmett & Seldin, 1977, Ref 16)

II. CAUSES OF HYPOPHOSPHATEMIA AND/OR PHOSPHATE DEPLETION

HYPOPHOSPHATEMIA:
CAUSES AND ASSOCIATIONS

Decreased Intake
- Antacids: binding of phosphorus in the gut
- Starvation/cachexia
- Malabsorption
- Vomiting
- Hyperalimentation: with phosphate-poor solutions

Transcellular Ionic Shifts
- Carbohydrate administration: most pronounced intravenously
- Alkalosis
- Liver disease
- Pregnancy
- Hypothyroidism
- Sepsis: gram-negative and gram-positive
- Acute myocardial infarction
- Estrogens/androgens
- Catecholamine administration

Renal Loss
- Hemodialysis: against phosphate-poor bath
- Hypokalemia
- Hypomagnesemia
- Acute gout
- Acidemia
- Renal tubular defects
- Thiazide diuretics
- Genetic hypophosphatemia
- Tumor phosphaturia

Mixed Mechanisms
- Alcoholism
- Diabetic ketoacidosis
- Hyperparathyroidism and vitamin D abnormalities

(from Fitzgerald, 1978)

Causes of Profound Hypophosphatemia
(Serum phosphorus below 1 mg/dl)

1. Treatment of alcohol withdrawal
2. Treatment of diabetic ketoacidosis
3. Administration of phosphate binding antacids
4. Recovery/diuretic phase after severe burns
5. Parenteral hyperalimentation
6. Nutritional recovery syndrome
7. Severe respiratory alkalosis

(from Knochel, 1977)

III. PATHOPHYSIOLOGIC MECHANISMS OF PHOSPHATE DEPLETION IN DIABETIC KETOACIDOSIS (Ref. 1 - 16)

A. RENAL LOSS OF PHOSPHATE (accounts for phosphate depletion)

1. Acidosis - lowers renal threshold for phosphate and increases phosphaturia
2. Glycosuria - whereas osmotic diuresis from mannitol does not alter phosphate excretion, marked glycosuria depresses renal reabsorption about 20%
3. Acetoacetate - excretion depresses phosphate reabsorption and increases phosphaturia
4. Potassium Deficiency - may be accompanied by an increase phosphate clearance. Tubular reabsorption of P(i) decreases from 90 to 55-60% despite hypophosphatemia
5. Hormonal Changes - increased aldosterone, cortisol, epinephrine, and glucagon levels all characteristic of DKA have each been reported to increase phosphaturia
6. Magnesium Deficiency - may produce phosphaturia and phosphate depletion

B. SHIFTS OF PHOSPHATE FROM ICF TO ECF (accounts for normal or high phosphate prior to treatment)

1. 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
2. Glycogen Breakdown - releases phosphate from liver and muscle
3. Tissue Wastage - gluconeogenesis for each gram of N, 0.7 mM of P(i)

IV. MAGNITUDE OF THE PHOSPHATE DEPLETION IN DIABETIC KETOACIDOSIS (From Martin et al 1958 Ref. 7)

COMPARISON OF ESTIMATED FLUID AND ELECTROLYTE REQUIREMENT IN DIABETIC ACIDOSIS

Author	Type of Study	No. of Patients	Na (mEq./Kg.)	Cl (mEq./Kg.)	HCO_3^- (mEq./Kg.)	K (mEq./Kg.)	Mg (mEq./Kg.)	P (mM/Kg.)	H_2O (L./Kg.)
Martin et al. (this study)	Retention during 12 hours of therapy of diabetic acidosis*	8	7.0	4.0	4.7	2.7†	0.16†	1.0†	0.082
Nabarro et al. [17]	Retention during therapy of diabetic acidosis and for 8 to 12 days after acute therapy on measured intake	7	7.2	5.1	...	5.0	0.56	0.5	0.087
Danowski et al. [15]	Retention during acute therapy of diabetic acidosis and up to 34 hours after acute therapy	8	10.4	9.5	...	6.0	.....	....	.....
Darrow [16]	Retention during acute therapy of diabetic acidosis and for 2 days after	1	13.3	9	...	6.1	....	....	0.114
Atchley et al. [18]	Loss during insulin withdrawal	2	5.9	2.5	...	4.9	.....	....	0.089
Butler et al. [19]	Loss during insulin withdrawal	1	5.1	4.0	...	5.6	0.8	1.3	.....
Butler*	Estimated loss 10 per cent dehydration	Estimated	5–12	4.0	...	6.0	.....	....	0.06–0.1

* Our figures might well be higher as we divided retention by 70 Kg. and this may not have represented average weight.
† This figure is too low for complete repair and only represents amount for acute therapy (see text).

PHOSPHORUS THERAPY IN DIABETIC ACIDOSIS*

Group	Type of Study	Time Period (days)	No. of Patients	P Intake (average 24 hr.)	P Intake (range, mM)	Urine Output (average, mM/24 hr.)	Urine Output (range, mM/24 hr.)	% Intake Retained (average)	% Intake Retained (range)	Estimated Requirement (mM/Kg.)
Martin et al. (this study)	Retention during acute treatment of diabetic ketoacidosis	0.5	8	44	11–86	15	3–59	72	29–95	1.0
Franks et al. [21]	Retention during acute treatment of diabetic ketoacidosis	1	10	64	42–80	25	13–46	61	44–85	0.9
Atchley et al. [18]	Insulin withdrawal	8 4	2	37.5†	33.8–41.2	38.5†	52.7–24.3	.....	0 to +41	.....
Butler et al. [19]	Insulin withdrawal	3.4	1	0		28.5‡	.....	.....	.....	1.3
Nabarro et al. [17]	Retention during acute treatment of diabetic acidosis	1	7	8	0–12	35	14–67	.....	.....	.....
.....	Retention after acute treatment	8–12	...	.....	.....	.....	.....	Mean retention 37 mM. P	.....	0.5
Darrow et al. [16]	Retention during acute treatment of diabetic acidosis	24	1	0	.....	7.5	.....	.....	.....	.....
.....	Retention after acute treatment	2	...	.....	.....	.....	.....	Retention 148.5 mM. P§	.....	5.6§

* Figures from other authors converted to mM. P for comparison with our studies.
† Last day of insulin withdrawal.
‡ Urinary P for 3.4 day period equals 94.8 mM.; this gives 28.5 mM./24 hr.
§ Patient on a very high P intake from milk diet; stools not analyzed.

Estimate of the Magnitude Of Phosphate Depletion In Diabetic Ketoacidosis

A. Based on retention during 12 - 24 hours of therapy

Franks et al (1948)	0.9 mM/kg
Martin et al (1958)	1.0 mM/kg

B. Based on loss during insulin withdrawal

Butler et al (1947) (over 3.4 days)	1.3 mM/kg

C. Based on maintaining normal serum levels during treatment

Keller et al (1980)	over 8 hours	65 mM (40-130)
Gibby et al (1978)	over 48 hours	118 mM (83-320)

V. CHANGES IN SERUM PHOSPHORUS BEFORE AND DURING TREATMENT OF DKA

A. Normal Values

	mg/dl	mM/L
Children	4.0 - 7.1	1.3 - 2.3
Adults	2.7 - 4.5	0.9 - 1.5

Reporting serum phosphate values and commercial phosphate preparations in mEq/L of phosphate is confusing since the valence of phosphate depends on pH. (From Lentz et al 1958, Ref. 75)

Effect of pH on Phosphate Milliequivalents*

pH	Molar Ratio HPO_4^{-2}:$H_2PO_4^-$	Average Valence	Number of Meq/Litre that Equals	
			1 mmol/litre	1 mg/dl
7.0	61.5:38.5	1.62	1.62	0.52
7.2	71.4:28.6	1.71	1.71	0.55
7.4	80:20	1.80	1.80	0.58
7.6	86.3:13.7	1.96	1.96	0.60

* Calculated according to Lehninger (8).

By contrast, in serum and commercial preparations the concentrations of phosphate ions in mM/L and elemental phosphorus in mg/dl are independent of pH and have a constant relationship to each other.

1 mM phosphate/L = 3.1 mg phosphorus/dl
0.32 mM phosphate/L = 1 mg/dl

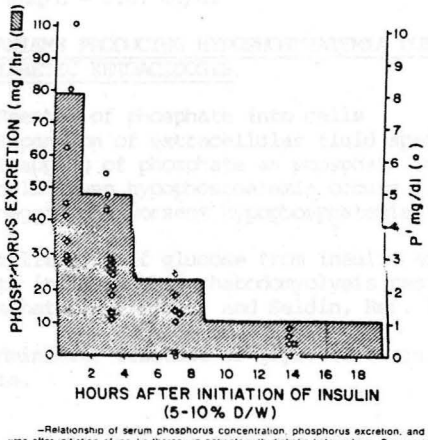
B. FINDINGS IN DIABETIC KETOACIDOSIS

SERIES	BEFORE TREATMENT Average	BEFORE TREATMENT Range	DURING TREATMENT
Franks et al (1948) Ref. 5	7.88 mg/dl	4.3 - 17.2	36% < 1mg/dl 64% < 2mg/dl
Seldin & Tarail (1950) Ref. 16	5.6 mg/dl	2.8 - 10.1	1.0 (0.16 - 2.73) (by 3 to 8 hrs)
Martin et al (1958) Ref. 7	8.6 mg/dl	2.3 - 16.2	0.7 (0.4 - 1.0) (by 12 hrs)

SERUM ELECTROLYTE LEVELS (PER CENT LOW, NORMAL OR ELEVATED) AT ENTRY AND AFTER TWELVE HOURS OF THERAPY (TWENTY-EIGHT PATIENTS)

Therapy	Entry			Twelve Hours		
	% Low	% Normal	% High	% Low	% Normal	% High
Sodium.....	67	26	7	26	41	33
Chloride.....	33	45	22	11	41	48
Bicarbonate...	100	0	0	46	50	4
Calcium.....	28	68	4	73	23	4
Potassium....	18	43	39	63	33	4
Magnesium...	7	25	68	55	24	21
Phosphate.....	11	18	71	90	10	0

(Martin et al, 1958 Ref. 7)

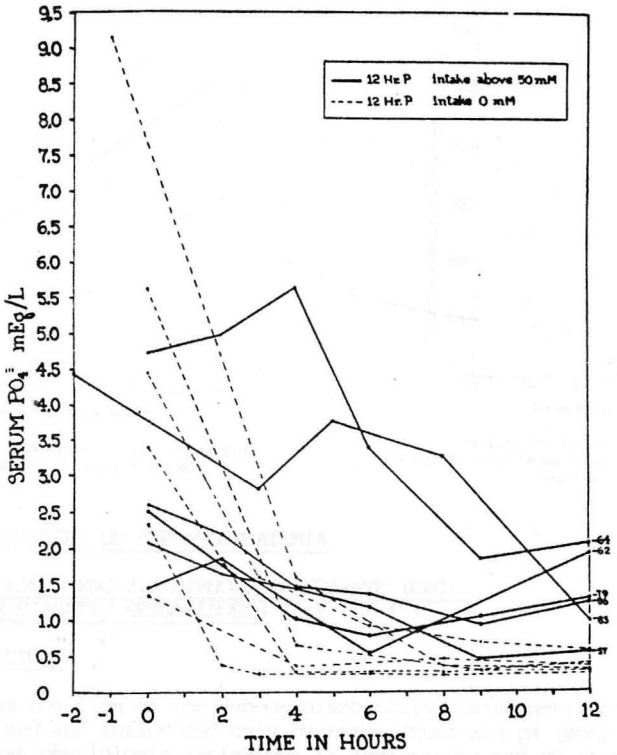


—Relationship of serum phosphorus concentration, phosphorus excretion, and time after initiation of insulin therapy in patients with diabetic ketoacidosis. Prepared from data published by Seldin and Tarail.[16]

(Adapted from Knochel 1977, Ref. 1, based on data from Seldin and Tarail, Ref. 15)

COMPARISON OF THE FALL IN SERUM PHOSPHORUS DURING TREATMENT OF DIABETIC KETOACIDOSIS WITH AND WITHOUT PHOSPHATE (Martin et al, 1958)

Therapy of Diabetic Acidosis—*Martin et al.*



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

Note: 1.00 mEq/L = 1.75 mg/dl
0.75 mEq/L = 1.31 mg/dl
0.5 mEq/L = 0.87 mg/dl

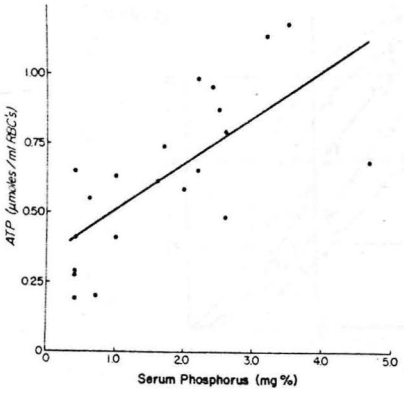
C. MECHANISMS PRODUCING HYPOPHOSPHATEMIA DURING TREATMENT OF DIABETIC KETOACIDOSIS

1. Reentry of phosphate into cells
2. Expansion of extracellular fluid space
3. Trapping of phosphate as phosphate intermediates in some cells when hypophosphatemia occurs i.e., hypophosphatemia begets and worsens hypophosphatemia

Rapid utilization of glucose from insulin administration may trap so much phosphate in liver that rhabodomyolysis results from acute fulminant hypophosphatemia. (Emmett and Seldin, Ref. 16)

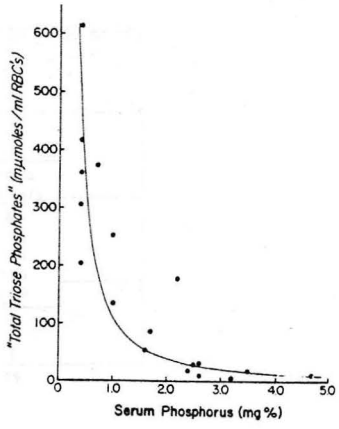
Never administer fructose or glycerol since these may produce severe trapping of phosphate.

(From Travis et al 1971, Ref. 45



Relation between Serum Phosphorus and Erythrocyte ATP (r Equal to 0.71; p Less than 0.001).

(From Travis et al 1971, Ref. 45



Relation of Serum Inorganic Phosphorus to Erythrocyte "Total Triose Phosphates" (r Equal to −0.79; p Less than 0.001).

VI. COMPLICATIONS OF HYPOPHOSPHATEMIA

A. DEPRESSED RBC 2,3 DIPHOSPHOGLYCERATE (DPG) IN DIABETIC KETOACIDOSIS (Ref. 17-43)

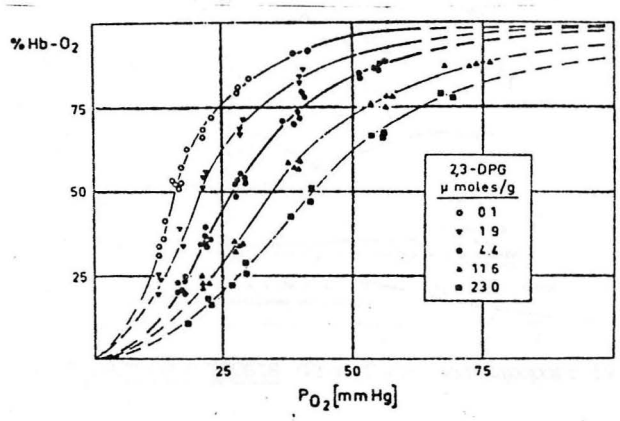
1. HISTORY

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 lead 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's 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.

2. EFFECTS OF 2,3 DPG ON P_{50} (Ref. 17-29)



(From Duhm, 1973)

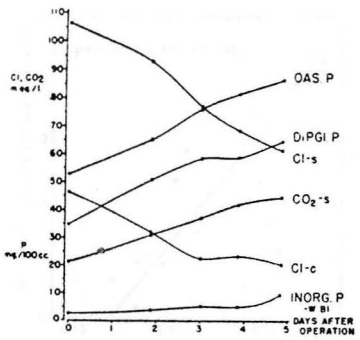
3. EFFECTS OF CHANGES IN BLOOD pH ON RBC 2,3 DPG (Ref. 17, 25, 28, 30-43)

In 1924 Haldane, Wigglesworth & Woodrow (Proc. Roy. Soc. London 96:1, 1924—1925) 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. ATP 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 solutions. 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.

EFFECT OF ALKALOSIS (From Guest and Rapoport 1939, Ref. 17)



-Changes in the blood of a dog following pyloric obstruction. (For ation of abbreviations see chart 2.)

EFFECT OF ACIDOSIS (From Guest and Rapoport 1939, Ref. 17)

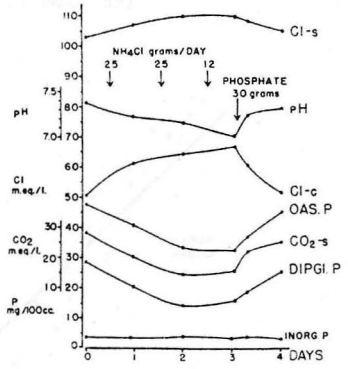


Chart 5.—Changes in the blood of a man during the development of acidosis induced by the ingestion of ammonium chloride and during recovery, after the ingestion of sodium and of potassium phosphate. (For explanation of abbreviations see chart 2.)

EFFECT OF DIABETIC KETOACIDOSIS (From Guest and Rapoport 1939, Ref. 17)

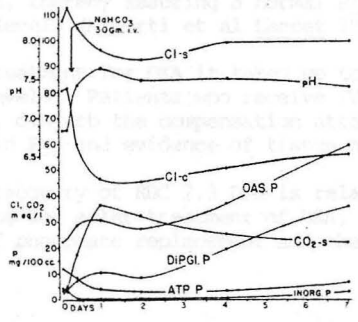
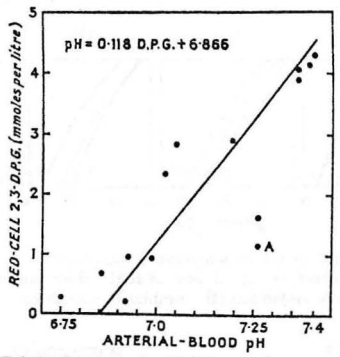


Chart 7.—Changes in the blood of a woman during recovery from the severe acidosis of diabetic coma. (For explanation of abbreviations see chart 2.)

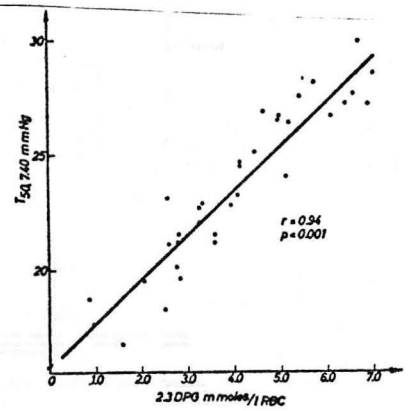
CORRELATION BETWEEN ARTERIAL pH + RBC 2,3 DPG
(From Alberti, 1972, Ref. 33)



–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.

CORRELATION BETWEEN 2,3 DPG and P_{50} (From Ditzel and Standl, 1975, Ref. 39)



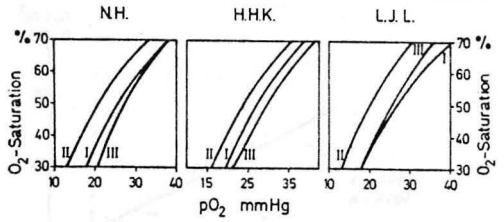
correlation of red cell 2,3-DPG content and P50 (7.40) of ODC during recovery from diabetic ketoacidosis.

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 receive IV bicarbonate for correction of arterial pH, disturb the compensation attained during acidosis, and show 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.

SHIFTS IN THE OXYGEN DISSOCIATION CURVE BEFORE, DURING AND AFTER TREATMENT OF DIABETIC KETOACIDOSIS (Ditzel and Standl 1975, Ref. 39)



The oxygen dissociation curves of the 3 most acidotic patients (N.H., H.H.K. and L.J.L.) in ketoacidosis (I), after correction of acidosis (II) and before discharge (III)

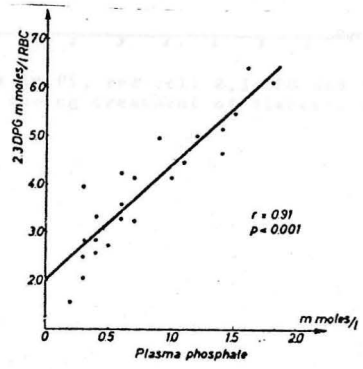
P_{50} IN VIVO AFTER CORRECTION OF KETOACIDOSIS (Ditzel 1976, Ref 40)

P_{50} at in-vivo pH in three groups of individuals.

EFFECTS OF SUDDEN CORRECTIONS OF pH ON P_{50} IN DKA (Ref 34)

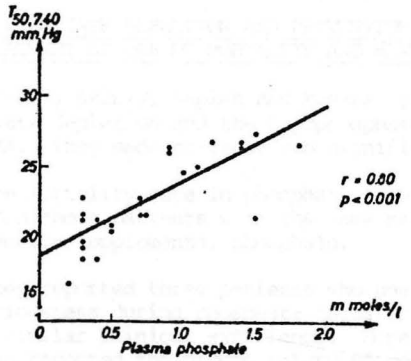
pH	P_{50} mm Hg
6.93	29.5
7.40	17.5

4. CLINICAL SIGNIFICANCE OF HYPOPHOSPHATEMIA AS RELATED TO CHANGES IN 2,3 DPG and P_{50} (Ref. 36, 37, 39)



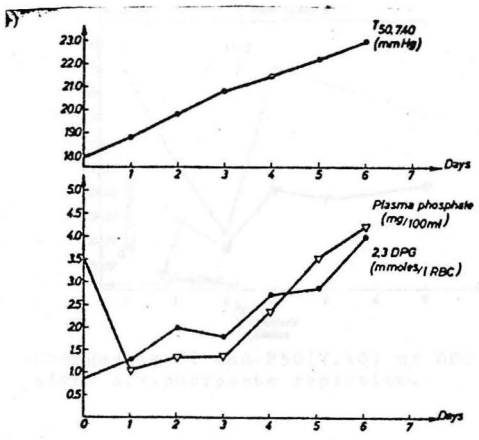
(Ditzel, 1973)

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



(Ditzel and Standl 1975)

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



(Ditzel, 1973)

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

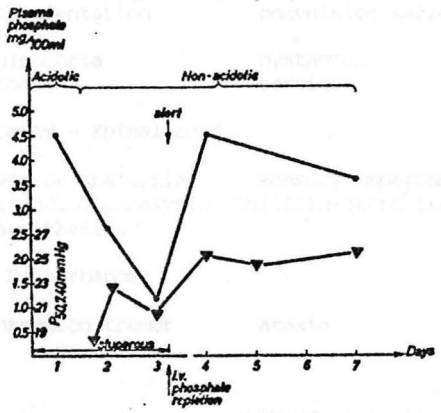
5. EFFECT OF PHOSPHATE REPLETION AND PREVENTION OF HYPOPHOSPHATEMIA IN THE TREATMENT OF DKA ON MORTALITY AND MENTAL STATUS

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. (Ref. 5)

1. The mortality rate in phosphate treated patients was 15% less than those patients with the same severity index who did not receive supplemental phosphate.

2. They reported three patients who unexpectedly regained consciousness during phosphate infusion. Guest and Rapoport had a similar clinical experience. More recently, Ditzel also has reported the prompt return of consciousness in two patients who remained stuporous long after systemic acidosis was gone.

EFFECT OF IV PHOSPHATE ON THE MENTAL STATUS AFTER RECOVERY FROM DKA
(From Ditzel 1973, Ref. 37)



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

At present there are conflicting data regarding the effects of phosphate administration on rbc 2,3 DPG and P_{50}. (Ref. 35-43)

In 1973 Ditzel and, in the same year, Andersen and Ditzel reported that in 10 cases of severe diabetic ketoacidosis intravenous phosphate therapy was able to normalize rbc 2,3 DPG within hours. Keller and Berger (1980) confirmed a rise in rbc 2,3 DPG following phosphate therapy in 12 cases of DKA compared to 12 control cases. In 1978 Bonnici reported a rise in rbc 2,3 DPG and in in vivo P_{50} plus a fall in the L/P ratio following intravenous phosphate therapy in four cases of severe DKA compared to four cases who did not receive phosphate supplementation. Although Gibby et al (1978) reported an increase in rbc 2,3 DPG over controls, they found only a small and clinically insignificant change in P_{50}.

B. THE CLINICAL SPECTRUM OF THE "LOW PHOSPHATE SYNDROMES" (Ref. 1-4, 44-66)

1. CENTRAL NERVOUS SYSTEM

A. Metabolic Encephalopathy - characterized by

memory loss	apprehension	
decreased attention	irritability	
confusion	obtundation	coma
disorientation	convulsive seizures	
anisocoria	nystagmus	nasal speech
ptosis	vertigo	dysarthria

B. Neuropathy - Spinal cord

hypo or areflexia sensory impairment
ascending paralysis (Guillain-Barré like syndrome)
paresthesias

C. Motor Disturbances

intention tremor	ataxia	ballismus

2. MUSCLE

weakness	Rhabdomyolysis	increased CPK
myopathy	EMG abnormalities	

3. ENDOCRINE

resistance to parathyroid hormone
physiologic hypoparathyroidism

insulin resistance - decrease glucose disappearance

4. RESPIRATORY (Ref. 66)

acute respiratory failure - ventilatory collapse
(5 cases reported)

5. HEPATIC

worsening of liver function from hepatic hypoxia

6. RENAL (Ref. 16)

hypercalciuria - independent of PTH
decrease tm for bicarbonate
decrease tm for glucose
impaired ammonia production

7. GASTROINTESTINAL

anorexia dysphagia

8. SKELETAL

osteomalacia - pseudofractures
rheumatologic
large joint arthralgias sacroiliitis
inflammatory arthritis aching bone pain

9. HEMATOLOGIC

A) Erythrocyte
decreased 2,3 DPG and decreased ATP
membrane rigidity - shortened life span
spherocytosis - hemolytic anemia (rare)

B) Leukocyte
depressed ATP
decrease in chemotatic, phagocytic
and bactericidal activity

C) Platelets
decreased ATP
decreased survival time → thrombocytopenia
platelet dysfunction hemorrhage (rare)

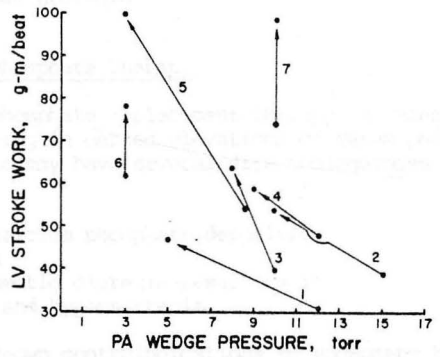
10. CARDIAC

A) Clinical (Ref. 64, 65)
1. Congestive cardiomyopathy - rapidly reversible - 3 cases
2. acute fatal cardiopulmonary failure - 2 cases

B) Experimental

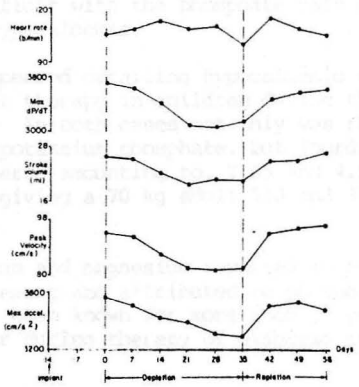
1. Myocardial performance in man before and after the correction of hypophosphatemia

Stroke work increased from an average of 49.6 to 71.7 g-m per beat during phosphate infusion with return of serum phosphate to normal (O'Connor et al 1977, Ref. 62)



Left Ventricular (LV) Stroke Work in Relation to Wedge Pressure (Preload) before and after Phosphate Repletion in Patients with Severe Hypophosphatemia.

2. Reversible depression in myocardial performance in dogs during phosphorus depletion and repletion. (Fuller et al 1978, Ref. 63)



Effects in one dog of phosphorus depletion (35 days) and repletion (21 days) on heart rate, beats per minute (b/min), Max *dP/dT*, stroke volume, and maximum ascending aortic blood flow velocity and acceleration. 14 days were allowed for postsurgical recovery before beginning the study (day 0). Recordings were obtained weekly thereafter for the duration of the study.

VII. PHOSPHATE ADMINISTRATION IN THE TREATMENT OF DIABETIC KETOACIDOSIS

A. Contraindications to Phosphate Replacement (From Knochel, 1977)

1. Hypercalcemia of any cause
2. Hyperphosphatemia
   (a) Renal failure
   (b) Hypoparathyroidism
3. Oliguria
4. Evident tissue necrosis

B. Potential Danger of Phosphate Therapy

The major danger of phosphate replacement therapy is excessive administration resulting in marked elevations of serum phosphorus. This hyperphosphatemia may have several dire consequences including:

(1) metastatic calcium phosphate deposition
(2) hypocalcemia
(3) phosphate osmotic diuresis resulting in dehydration and hypernatremia

If one observes the known contraindications to phosphate therapy and does not attempt to replace the entire potassium deficit with potassium phosphate, there should be no danger to phosphate replacement.

Since phosphate deficiency tends to parallel potassium deficiency the use of potassium phosphate has been recommended by several authors as the sole agent to correct both deficiencies. (67-70)

This is potentially dangerous since the magnitude of the deficiencies of these two ions is very different. Potassium deficiency is in the order of 5-10 mEq/Kg whereas phosphate deficiency is only about 1 mM/Kg. Replacing the entire potassium deficit with the phosphate salt can lead to pronounced hyperphosphatemia and hypocalcemia.

Recently two reports appeared detailing hypocalcemic tetany as a complication of phosphate replacement therapy in children during the treatment of diabetic ketoacidosis (71, 72). In both cases not only was the entire potassium deficit corrected with potassium phosphate, but inordinately large amounts of phosphate were administered amounting to, 7.65 and 4.5 mM of P/Kg/24 hours. This would be equal to giving a 70 kg adult 540 and 317 mM of phosphorus in 24 hours!

The fall in serum calcium and magnesium reported in other studies (71,73) during phosphate replacement and attributed to phosphate therapy must be questioned since it has been known for more than 20 years that hypocalcemia and hypomagnesemia occur during therapy of diabetic ketoacidosis even when phosphate is not given.

CHANGES IN Ca AND Mg CONCENTRATIONS DURING PHOSPHATE THERAPY WITH POTASSIUM PHOSPHATE GIVEN TO MAINTAIN A NORMAL POTASSIUM LEVEL (Zipf et al 1979, Ref. 71)

Calcium, magnesium, and pH values at time of admission, and the lowest Ca^{2+} and Mg^{2+} concentrations recorded during therapy

	Admission			Nadir during treatment			
Patient	pH	Ca^{2+} (mg/dl)	Mg^{2+} (mg/dl)	Ca^{2+} (mg/dl)	Hour	Mg^{2+} (mg/dl)	Hour
C.S.	7.01	8.3	—	4.5	30	0.6	30
S.S.$_a$	7.12	10.8	1.8	9.2	18	1.4	6
S.S.$_b$	7.05	10.6	1.9	8.6	24	1.3	12
J.M.	6.85	8.7	1.8	6.3	36	1.3	12
J.B.	6.92	9.2	—	8.6	4	—	—
S.V.	7.13	10.0	—	9.0	12	1.5	12
W.D.	7.16	11.3	1.9	10.4	24	1.6	12
J.E.	7.30	9.4	1.5	7.6	18	1.5	6
S.A.	6.92	9.3	1.8	8.7	12	1.4	12
Normal		8.8–10.9	1.5–2.7				

CHANGES IN Ca, Mg, and P CONCENTRATIONS DURING TREATMENT OF DIABETIC KETOACIDOSIS WITHOUT PHOSPHATE ADMINISTRATION (Martin et al 1958)

		%Low	%Normal	%High
Calcium	On Entry	28	68	4
	12 Hours Rx	73	23	4
Magnesium	On Entry	7	25	68
	12 Hours Rx	55	24	21
Phosphate	On Entry	11	18	71
	12 Hours Rx	90	10	0

Martin reported that when phosphate was given there was no greater change in serum or urinary calcium compared to subjects who did not receive phosphate.

MEAN PLASMA PHOSPHATE AND CALCIUM IN CONTROL AND PHOSPHATE TREATED KETOACIDOTIC PATIENTS

Keller and Berger (1980) and Gibby et al, (1978) also found no difference in serum calcium compared to controls who did not receive phosphate. (Ref. 41, 42)

Clinical and biochemical data of patients with ketoacidosis treated with phosphate infusions

Case	Age, sex	Prior therapy	Associated condition	Blood glucose (mg/dl)	pH 0 h*	pH 24 h	Plasma phosphorus (mg/dl) 0 h*	Plasma phosphorus (mg/dl) 48 h	Calcium (mg/dl) 0 h*	Calcium (mg/dl) 48 h
13	63 M	Insulin	Mesenterial and cerebral infarction	1000	7.08	—	10.0	6.9	7.8	5.4
14	21 M	Insulin	None detected	427	6.96	7.36	6.8	4.1	6.9	8.0
15	75 F	Insulin	Fever, unknown origin	796	6.87	—	6.0	2.8	10.6	9.2
16	83 M	Insulin	None detected	790	7.12	7.40	4.7	5.4	8.5	8.1
17	18 F	Insulin	Vulvitis	556	6.99	7.33	1.5	3.6	9.8	8.8
18	38 F	Insulin	Pneumonia	1190	6.72	7.36	8.2	3.2	7.3	7.0
19	34 M	Insulin	Pneumonia	950	6.89	7.43	3.1	2.0	—	—
20	36 M	Insulin	None detected	926	6.90	7.39	8.0	—	8.7	8.0
21	33 F	Insulin	Vulvitis	446	7.10	7.42	3.9	2.6	7.7	7.1
22	16 M	Oral agents	Pharyngitis	1500	7.15	7.36	2.6	4.0	—	—
23	81 M	Oral agents	Skull fracture	1000	7.22	7.45	2.2	3.0	9.5	8.4
24	41 M	Insulin	Osteomyelitis	750	6.80	7.36	8.6	2.3	10.2	8.3
Mean	45			863	6.98	7.39	5.5	3.6	8.70	7.83
± SEM	7			88	0.04	0.01	0.8	0.4	0.40	0.34

* Admission.

Clinical and biochemical data of patients with ketoacidosis without phosphate therapy

Case	Age, sex	Prior therapy	Associated conditions	Blood glucose (mg/dl)	pH 0 h*	pH 24 h	Plasma phosphorus (mg/dl) 0 h*	Plasma phosphorus (mg/dl) 48 h	Calcium (mg/dl) 0 h*	Calcium (mg/dl) 48 h
1	52 M	Insulin	Spondylitis	820	7.00	7.40	7.0	1.5	10.0	8.4
2	28 M	Insulin	Omission of insulin	685	6.96	7.41	3.3	2.0		
3	85 M	Insulin	Urinary tract infection	670	7.20	7.49	5.3	3.4	8.7	8.6
4	25 F	Insulin	Pharyngitis	770	6.90	7.30	6.5	3.7	—	—
5	26 F	Insulin	None detected	640	7.00	—	7.0	2.9	8.8	—
6	70 M	D.M. unknown	Saddle embolus aorta	1650	7.24	7.42	7.8	—	—	—
									—	—
7	75 F	Oral agents	Change of therapy (previously insulin)	1030	6.98	7.41	—	—	10.6	6.2
8	69 M	D.M. unknown	Transient ischem. attack	1020	6.93	7.48	6.1	1.2	8.6	7.8
9	46 F	D.M. unknown	Urinary tract infection	1500	7.11	7.40	6.8	2.5	—	—
10	43 F	D.M. unknown	Fever of undeterm. origin	940	6.92	7.30	9.7	1.2	—	—
11	33 M	Insulin	None detected	574	6.98	7.31	9.2	2.4	9.8	8.4
12	39 F	Insulin	None detected	952	6.92	7.40	10.0	1.7	—	—
Mean	49			938	7.00	7.39	7.2	2.2	9.4	8.3
± SEM	6			97	0.03	0.02	0.6	0.3	0.3	0.1

* Admission.

(From Gibby et al, 1978, Ref. 41)

mmol/L	Group	Time 0 h	6 h	12 h	24 h
Plasma Phosphate	Control	1.7	1.0	0.7	0.6
	Treated	1.4	1.0	1.2	1.3
				$p < 0.05$	$p < 0.01$
Plasma Calcium	Control	2.3	2.2	2.2	2.2
	Treated	2.2	2.2	2.1	2.2

C. Available Phosphate Replacement Fluids for Intravenous Use

Brand	Size/mL	Potassium mEq/ml	Phosphate mM/ml
Abbott	15	4.4	3.0
Cutter	15	4.4	3.0
Baxter	10	3.0	2.15
McGaw	30	2.0	1.12
Invenex	15	4.4	3.0

Only Abbott, Cutter*, or Invenex** Brands of Potassium Phosphate Solutions for intravenous use are currently (7/14/80) stocked by local hospitals. The following hospitals carry these brands of Potassium Phosphate with 4.4 mEq/ml of K and 3.0 mM/ml of P.

Parkland	St. Paul	Doctors Hospital	Irving Community
V.A.	Presbyterian*	Brookhaven	Garland Community**
Baylor	Medical City	Richardson Med. Ctr.	Grand Prairie Community**
Gaston	Methodist		

Hospitals carrying Sodium Phosphate for intravenous use. Only Abbott Brand stocked locally. It contains Na 4 mEq/ml
P 3 mM/ml

Parkland	St. Paul	Methodist
Doctors Hospital	Medical City	Brookhaven

Hospitals not stocking intravenous potassium phosphate solution

General Hospital of Lakewood
Forest Avenue Hospital

D. Replacement Recommendations

1. General

a. Know what brand of potassium phosphate you are using and the number of mEq of K and mM of P per ml.

b. Remember that acute replacement needs (12 to 24 hours) equal about 1 mM of phosphate/Kg.

c. Monitor serum phosphorus and potassium levels and adjust recommendations below accordingly.

2. Specific

a. If serum potassium is normal or low and serum phosphate is normal or low:

Give potassium phosphate (Abbott, Cutter, or Invenex 4.4K/3.0 P) at a concentration of 30 mEq/L of potassium which contains 20 mM of phosphate/L

Administer a total of 60-80 mM of phosphate over an 8 hour period.

If additional potassium is needed either during potassium phosphate administration or after its administration to prevent hypokalemia, it should be given as KCl.

b. If serum potassium is normal or low and phosphate level is not known:

Initial therapy should be KCl 20-40 mEq/L given at a rate of 20-40 mEq/hour.

After 3-4 hours when ECF volume is repleted and urine flow is adequate then potassium phosphate (30 mEq of K/L and 20 mM phosphate/L) should be given for a total of 60-80 mM of phosphate over an 8 hour period.

If more potassium is required, it should be given as KCl unless serum levels of phosphate are known to be low.

c. If serum potassium is initially high:

No potassium is given until ECF volume is expanded, urine flow is adequate, and serum K is falling in the normal range. This usually takes 3-4 hours.

At that time potassium phosphate can be given at the rate and for the total amount noted above.

Again, after 60-80 mM of phosphate if more potassium is needed it should be given as KCl unless serum phosphate is known to be low.

d. If the unusual circumstance occurs when potassium is high and phosphate is low:

Administer sodium phosphate (Abbott Na 4 mEq/ml, phosphate 3 mM/ml) at the rate and for the total amount noted above.

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