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Paradoxical Hypophosphaturia in Postoperative Diabetics

(surgical diabetes/phosphate reabsorption/phosphate pool size)

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Under conditions of conventional low calorie nutrition, a transient hyperphosphaturia was observed in the early postoperative period and urinary loss of phosphorus in diabetics did not exceed that in non-diabetics. To elucidate the mechanism of the increase in urinary phosphorus, we analyzed quantitative aspects of phosphorus reabsorption and found that percent phosphorus reabsorption was suppressed to a much greater extent in non-diabetics.

Size of the tissue phosphorus pool is postulated to be one of the mechanisms involved.

Phosphate is ubiquitous and abundant in biological materials and nutritional phosphate deficiency does not occur when food is ingested in amounts sufficient to meet the requirement for calories and protein. However, once total parenteral nutrition without a phosphate supplement is initiated in the case of severely wounded persons and postoperative patients with gastrointestinal disease, phosphate deficiency might occur. Moreover, in patients with burns, urinary loss of phosphorus as well as nitrogen, potassium, magnesium and so forth is remarkable as the result of hypercatabolic alteration of metabolism (1).

In the early postoperative period, carbohydrate stored as glycogen is immediately utilized so that fat and protein might be degradated as fuel, and hyperglycemia can be seen under these conditions, because some hormones including glucocorticoids and catecholamines overcome the insulin actions (2). Therefore, the posttraumatic or postoperative catabolic state is termed "stress diabetes" or "surgical diabetes". Accordingly, urinary loss of phosphorus is expectedly enhanced under conditions of surgical stress. Indeed, we noted a transient hypophosphatemia concomitant with hyperphosphaturia in postoperative patients with gastrointestinal diseases. These data prompted us to inves-

Abbreviations P.O.D. : postoperative day, y.o. : years old, P : phosphorus, Ca : total calcium, Ca^{++} : ionized calcium, S.D. : standard deviation, S.E. : standard error, Preop : preoperative period.

tigate whether urinary loss of phosphorus increases in diabetics under surgical stress.

We compared the changes of serum and urinary phosphorus and calcium contents from diabetic and non-diabetic postoperative patients under conditions of conventional low calorie nutrition.

MATERIALS AND METHODS

Patients : Fifty-one Japanese patients who had undergone surgery of the alimentary tract were divided into two groups, diabetic and non-diabetic, according to either 100 g oral glucose tolerance test or 25 g intravenous glucose tolerance test for patients with alimentary tract stenosis or obstruction (Table I). Here diabetic patients who required preoperative insulin replacement

TABLE I. *Patients and Surgery*

Type of operation	Number of patients	
	Diabetic	Non-diabetic
Esophagectomy with reconstruction of esophogus	3	3
Esophageal bypass with gastric tube	1	1
Total gastrectomy	1	2
Subtotal gastrectomy	6	11
Palliative gastrojejunostomy	1	0
Cholecystectomy	1	1
Pancreatoduodenectomy	0	1
Transduodenal papilloplasty	1	0
Colectomy	3	4
Rectosigmoidectomy	5	3
Diversion of peritoneal adhesions	0	3
	22	29

TABLE II. *Patient Groups*

	Diabetic	Non-diabetic
Number of patients	22	29
Age distribution	38–74 y.o.	25–77 y.o.
Mean ± S.D.	61± 7 y.o.	47±13 y.o.

were excluded and moreover no patient was given insulin postoperatively (Table II). Intraoperative fluid administration was carried out according to the protocol of Jenkins *et al.* (3). Peripheral venous routes were maintained for the first three postoperative days and postoperative nutrition was carried out in the same manner as is depicted in Table III. The type of operation and body weight of each patient were not factors given consideration.

TABLE III. *Postoperative Nutrition*

	0–3 P.O.D.	4–5 P.O.D.	6–7 P.O.D.	8–10 P.O.D.
Intravenous administration				
Water (ml/day)	2100	1300	800	—
Glucose (g/day)	140	110	60	—
Amino acids (g/day)	48	24	24	—
Phosphorus (mg/day)	—	—	—	—
Calcium (mg/day)	—	—	—	—
Nasogastric tube or oral administration				
Calorie (Cal/day)	—	160–480	800	1300
Phosphorus (mg/day)	—	126–377	231	375
Calcium (mg/day)	—	152–457	728	1183

Postoperative nutrition was carried out in the same manner as described previously (4) and for the purpose of this study, phosphorus and calcium contents are listed.

Experimental Methods : Blood sampling was performed as described previously (4) and following clot retraction, sera were stored at 4°C until routine analysis. Twenty-four hour urine specimens were also stored at 4°C until analysis.

Filtered phosphorus and tubular reabsorption of phosphorus determination : Filtered phosphorus was calculated by determination of serum phosphorus and glomerular filtration rate (creatinine clearance). Tubular reabsorption of phosphorus is the difference between urinary phosphorus and filtered phosphorus (creatinine clearence × serum phosphorus).

Ionized calcium determination : Serum ionized calcium was estimated with the nomogram proposed by Hanna *et al.* (5).

RESULTS

Interrelationships of Serum and Urinary Phosphorus and Calcium Pre and Postoperatively

Under the conventional low calorie postoperative nutrition, changes in the concentrations of phosphate as phosphorus and calcium in the blood and urine were investigated simultaneously in diabetic and non-diabetic patients. As depicted in Fig. 1, serum phosphorus levels from diabetic and non-diabetic patients were reduced by 23% and 15% 24 hours after surgery, respectively, and preoperative values were reverted to by the tenth day in diabetics and later in the non-diabetic group. The serum phosphorus values observed in both groups were identical throughout the experimental periods except for the preoperative period when serum phosphorus level in diabetics was rather low compared to that in non-diabetics. In contrast, the serum calcium levels observed in the non-diabetic group were always higher than the values in the diabetic group during the period of investigation. In both the diabetic and

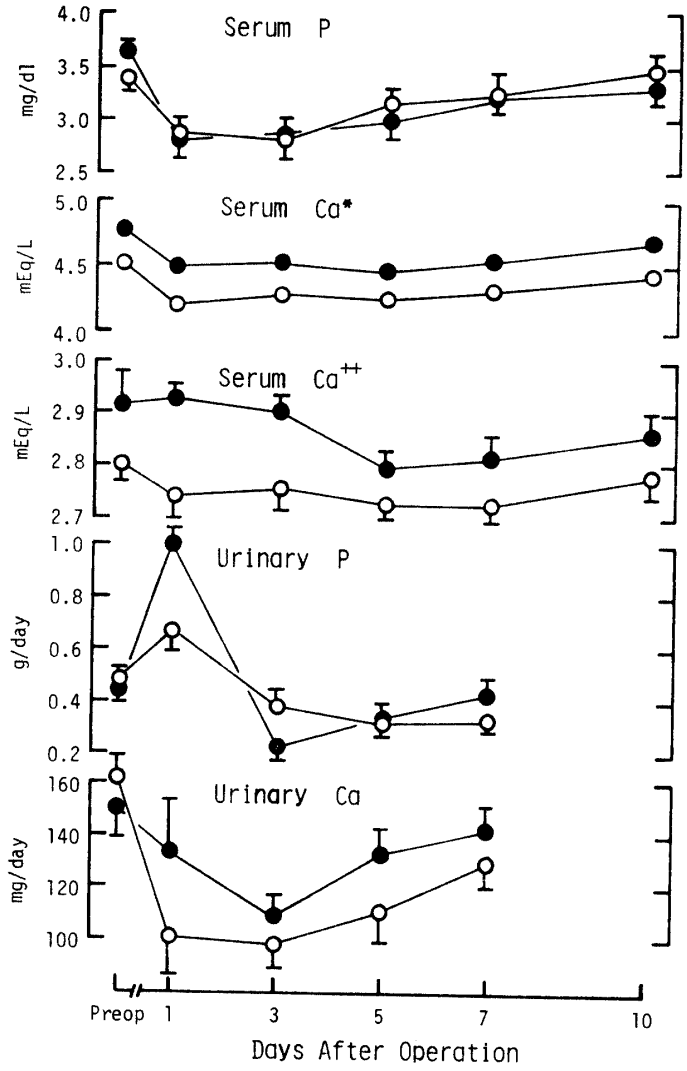

Fig. 1. Interrelationships of the serum and urinary phosphorus and calcium before and after surgery in diabetic and non-diabetic patients. ○——○ : diabetic group, ●——● : non-diabetic group. (Mean±S.E.) *Bars representing S.E. are eliminated because S.E. is not larger than each symbol.

non-diabetic groups, the serum calcium levels slightly decreased and remained low for several days.

Concerning the changes in urinary contents of phosphorus and calcium, the most striking features were evident before the turning point, that is during the catabolic phase. There was no difference between their preoperative values, but urinary phosphorus contents from diabetic and non-diabetic patients increased to 227% and 138%, respectively, as compared to their preoperative conditions. Urinary calcium contents in diabetics decreased rapidly and revealed minimum levels by the third day, whereas those in non-diabetics decreased slowly to almost the same level seen in the diabetics by the same day. Several days for non-diabetics and longer for diabetics were required for reversion to preoperative values.

TABLE IV. *Quantitative Aspects of Phosphorus Reabsorption*

	Preoperative	1 P.O.D.	3 P.O.D.	5 P.O.D.	7 P.O.D.
Non-diabetic group :					
Creatinine clearance (ml/min)	71.4±4.3	91.4±5.0	86.9±4.5	73.6±4.4	76.3±3.8
Filtered phosphorus (mg/day)	3745±223	3772±316	3838±358	3452±302	3803±228
Reabsorbed phosphorus (mg/day)	3185±228	2757±321	3459±381	3214±265	3371±158
Percent phosphorus reabsorption	86.1±1.2	67.0±2.6	90.0±2.6	88.7±1.4	87.7±1.3
Diabetic group :					
Creatinine clearance (ml/min)	80.6±5.3	79.6±5.7	79.2±5.9	75.2±5.6	78.7±3.4
Filtered phosphorus (mg/day)	3828±237	3385±380	3335±373	3456±253	3606±278
Reabsorbed phosphorus (mg/day)	3299±217	2757±340	2939±338	3119±232	3703±233
Percent phosphorus reabsorption	85.8±1.0	78.0±2.4	88.4±1.3	90.0±1.1	89.6±1.1

Values represent mean ± S. E.

Quantitative Aspects of Phosphorus Reabsorption

As shown in Table IV, the amounts of filtered phosphorus in diabetic patients were reduced during the catabolic phase ($p < 0.05$), while in non-diabetics the reduction of filtered phosphorus was not observed. However, the amounts of reabsorbed phosphorus in cases where the preoperative values were much the same in both groups decreased to much the same extent on the first postoperative day, and reached preoperative values by the third day, in both groups. Thus, 24 hours after surgery, the reduction of percent phosphorus reabsorption was greater in the non-diabetics than in the diabetic group.

DISCUSSION

Phosphate plays a variety of biological roles. Calcium phosphate or hydroxylapatite is the major constituent of skeletal structures ; organic phosphate complexes as high-energy phosphate are responsible for "energy currency" of the cells ; and, as the major buffer component of the urine, inorganic phosphate contributes to the balancing of the acid-base requirements of the body.

As the result of catabolic metabolism secondary to severe stress such as burn, injury, and surgery, phosphates are mobilized from soft-tissue and skeletal stores and thus account for conditions of hyperphosphaturia. In the present communication, we investigated whether or not urinary loss of phosphorus in diabetics is more enhanced than that in non-diabetics, under states of surgical stress by comparing the changes of serum and urinary phosphorus and calcium contents from diabetic and non-diabetic postoperative patients. We found that urinary loss of phosphorus in diabetics did not exceed that in the non-diabetics. To elucidate the mechanism of the paradoxical hypophosphaturia in diabetics, glomerular filtered phosphorus and its reabsorption fraction (percent phosphorus reabsorption) were determined and

we found that filtered phosphorus was reduced in diabetics, whereas in non-diabetics, these levels remained rather constant and that suppression of the reabsorption fraction which was seen in non-diabetic patients was diminished in diabetics. However, there were no differences between the amounts of reabsorbed phosphorus in both groups. These observations taken together with the results of our preceding report suggest that liberation of phosphate from tissue as a result of catabolism can be reduced by continuous administration of glucose at low concentrations in both groups (4). Presuming that changes in the cellular exchangeable phosphorus pool are responsible for the alterations we observed in the serum and urinary phosphorus levels, phosphorus pools in diabetic patients might have been depleted preoperatively. However, since renal excretion of phosphorus is determined by both the phosphorus load to the kidney and the capacity of the kidney to clear it, the latter possibility should be considered.

In general, the reabsorptive capacity for phosphate is poised at such a value that a slight increase or decrease in serum level results in a change in rate of excretion ; accordingly, the kidney participates in the regulation of serum phosphate concentration. The reabsorptive capacity of phosphorus is influenced significantly by body stores of phosphate and by the circulating levels of parathyroid hormones and the following factors. The major metabolite regulated by parathormone is calcium ion, which, in turn, uniquely controls hormonal secretion by the parathyroid glands. The other hormone affecting calcium ion levels is calcitonin, the secretion is also regulated by calcium ion (6). Concerning the renal functions, these two hormones reduce the reabsorption of phosphate. In our groups of patients, significant changes in serum calcium levels were observed in the early postoperative period, but their values fluctuated within normal limits. Furthermore, there was no apparent alteration of serum calcium ion during the same period (Fig. 1). Hence, among the possibile factors related to the production of hyperphosphaturia, the participation of these hormones was unlikely. The other factors responsible for the reduction of reabsorption include glucocorticoids, glucose, acidosis, alanine, acetoacetate and vitamin D (7). All of these factors except for vitamin D may be elevated in the blood from postoperative patients. In fact, blood glucose levels in diabetic and non-diabetic group reached a peak 8 hours after surgery and then decreased gradually to the respective preoperative levels by the fifth day and urinary excretion of glucocorticoid metabolites was also increased in both groups (data not shown).

Extreme hypophosphatemia is associated with clinical findings consisting of circumoral and peripheral paresthesias, lethargy, dysarthria and abnormal respiratory patterns (8). Moreover, in some patients with hypophosphatemia, a significant reduction of 2, 3-bisphosphoglycerate and adenosine triphosphate occurs (9). This in turn is accompanied by an increase in the affinity of hemoglobin for oxygen (10). These abnormalities can be readily reversed by the addition of supplemental phosphate. However, because addition of phosphate alone may sometimes result in a sharp drop in serum calcium and

thus lead to tetany, calcium and phosphate should be administrated to such patients simultaneously and with close attention to the blood chemistry.

Our observations suggest that the conventional low calorie nutrition seems to be satisfactory for maintainance of an uncomplicated postoperative course. However the supplement of phosphate to postoperative nutrition is recommended because our results imply that the phosphate pool in diabetics has already diminished preoperatively.

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