Studies on the Clearance and Tubular Reabsorption of Phosphates in Diabetes Mellitus and Some of its Complications

A. KH. ASTRUG

Internal Therapeutic Clinic, Higher Medical Institute, Sofia, Bulgaria

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Summary. From a study of the phosphate levels in the serum and urine of 106 diabetic patients and 25 controls, the following has been established: 1. Considerably increased renal elimination of phosphates in diabetics manifested by elevated values of the phosphate clearance. — 2. Lowered tubular reabsorption of phosphates mainly in patients with different forms of diabetic angiopathy. — 3. Retained normal level of the concentration of inorganic phosphorus in the serum, with the exception of its slight increase in patients with diabetic nephropathy.

Études sur la clearance et la réabsorption tubulaire des phosphates dans le diabète sucré et dans quelques unes de ses complications.

Résumé. En explorant 106 malades atteints de diabète et 25 sujets de contrôle, on a établi: 1. Augmentation considérable de l'élimination rénale de phosphates chez les diabétiques, manifestée par des valeurs élevées des clearances phosphatiques. — 2. Diminution de la réabsorption

tubulaire des phosphates surtout chez les malades accusant différentes formes d'angiopathie diabétique. — 3. Niveau normal de la concentration du phosphore inorganique dans le sérum; légère augmentation chez les malades accusant une néphropathie diabétique.

Untersuchungen der Clearance und tubulären Rückresorption von Phosphaten beim Diabetes mellitus und einigen seiner Komplikationen.

Zusammenfassung. Bei der Untersuchung von 106 Diabetikern und 25 Kontrollpersonen konnten folgende Befunde erhoben werden: 1. Beträchtlich gesteigerte renale Ausscheidung von Phosphaten bei Diabetikern, was sich durch erhöhte Werte der Phosphateclearance feststellen ließ. — 2. Eine herabgesetzte tubuläre Rückresorption von Phosphaten, hauptsächlich bei Patienten mit verschiedenen Formen der diabetischen Angiopathie. — 3. Erhaltene Normalspiegel des anorganischen Phosphors im Serum mit Ausnahme eines leichten Anstiegs der Werte bei Patienten mit diabetischer Nephropathie.

Phosphorus plays an exceedingly important role in the processes of storage, transfer and liberation of energy in the organism as well as in the intermediate metabolism of carbohydrates, fats and proteins. According to recent investigations, phosphorus, in the form of phosphates, passes into the glomerular filtrate of the kidneys from which it is largely reabsorbed together with glucose and amino acids in the proximal tubules (BLAND, 1956; NORDIN and FRASER, 1960; MAXWELL and KLEEMAN, 1962). By means of phosphate clearance and the calculated tubular reabsorption of phosphates, it is possible to follow up certain deviations of phosphorus metabolism in different pathological states (LIÈVRE and CAMUS, 1961).

It has been established that after injection of glucose, there is an increased elimination of phosphates in the urine, together with a lowering of their level in the plasma (BLAND, 1956; LEVITAN, 1957; LOTSPEICH, 1959; MARTINI, 1964). This is due to inhibition of their reabsorption in the tubules. The application of insulin results in a decrease in the phosphorus concentration in the plasma, due to increased tissue utilization of carbohydrates (CANTAROW and SCHEPARZT, 1962). On the other hand, when insulin is lacking, the phosphates cannot enter the cells due to the lowered capacity of carbohydrate utilization (GOLDBERGER, 1959). It seems that the phosphate ions and glucose have close or analogous patterns of transportation via the tubular cells (EGGLETON and SCHUSTER, 1954) under the effect

of the same enzyme systems (MAXWELL and KLEEMAN, 1962).

In uncomplicated diabetics, no changes have been established in the concentration of phosphates in the urine (SYLLABA and PLOCHAŘ, 1960) or in the values of the phosphate clearance (LIÈVRE and CAMUS, 1961). In diabetic coma the phosphates in the plasma are lowered following the fall of potassium.

The aim of the present paper is to carry out certain comparative studies on the level of phosphorus in the blood serum, and the renal clearance and tubular reabsorption of phosphates in patients with diabetes mellitus and some of its complications.

Materials and Methods

Investigations have been carried out on a series of 106 diabetic patients and 25 controls (non-diabetics). The patients were left for at least one week on a standard diet containing an almost constant quantity of phosphorus (according to CORVILAIN and ABRAMOW, 1962). The average daily intake of phosphates in the food was 2519 mg for diabetic patients and 2110 mg for the control individuals. In cases being treated with insulin, the test was performed before the administration of the drug. The concentration of phosphorus in the serum was determined photometrically by the Fiske and Subbarow method as modified by GREENBERG. The phosphate clearance was determined in two

one-hour clearance periods using the technique described by LIÈVRE and CAMUS (1961).

The test was made on subjects in a fasting condition and at rest. After emptying his bladder at 8 a.m., the subject drank 0.5 l of water. A blood sample was taken between 8 a.m. and 10 a.m. Urine specimens were obtained at 9 a.m. and 10 a.m., the quantities of both being measured. The phosphorus concentration in the blood and the urine specimens was determined. The tubular reabsorption of phosphates was estimated by means of the clearance of the endogenous creatinine, which is widely used for the evaluation of glomerular filtration (TOBIAS et al., 1962).

The diabetic patients were divided into the following 5 groups: 15 patients with uncomplicated diabetes, which was verified clinically or in the laboratory (D_o); 21 patients with diabetic acidosis, without clinical manifestations of coma (D_a); 37 diabetics with atherosclerosis in the large and medium arteries (aorta, coronary, brain and/or peripheral arteries), established clinically or with the aid of ECG, X-ray or oscillographic methods (D_s); 18 patients with signs of isolated diabetic retinopathy, without manifestations of renal impairment, i.e. without the obligatory signs and symptoms of diabetic glomerulosclerosis (D_r); 15 patients with the full clinical picture of diabetic nephropathy (D_n). The mean duration of diabetes in the patients investigated was 6.4 years.

Mean values of blood-glucose levels and excretion of glucose in urine for the different groups are given in Table 1.

Table 1. Mean values of maximal blood-glucose levels (fasting) and maximal excretion of sugar in urine

Mean Values*	D_o	D_a	D_s	D_r	D_n
Blood-Glucose (mg %)	289	382	281	303	281
Urine-Sugar (g/24h)	75	136	40	71	30

Table 2. Inorganic serum phosphorus in patients with diabetes mellitus, some of its complications and in control individuals

Inorganic phosphorus in mg %	C	D_o	D_a	D_s	D_r	D_n	D
Up to 3	8	4	6	9	5	3	27
3.1—5	15	11	15	28	13	10	77
5.1 and above	2	—	—	—	—	2	2
Total	25	15	21	37	18	15	106
Mean value (M)	3.48	3.21	3.26	3.5	3.33	3.8	3.42
Mean deviation (σ)	0.26	0.5	0.6	0.7	0.6	1.0	
Mean error (m)	0.2	0.13	0.13	0.11	0.14	0.26	

Results

The results obtained from testing of serum inorganic phosphorus, phosphate clearance (C_{PO_4}) and the degree of tubular reabsorption of phosphates (TRP) are presented separately.

The data on inorganic serum phosphorus are given in Table 2 and Figure 1.

Table 2 shows that the concentration of inorganic serum phosphorus presented no substantial changes in diabetic patients compared with controls. Patients

Fig. 1

with signs of diabetic nephropathy had the highest mean level, although the difference from the control group is not statistically significant ($t = 0.9$). Hyperphosphatemia was established only in two patients of the D_n group. Values of inorganic serum phosphorus between 2 and 3 mg % were established in 27 diabetics (25.5%) and in 8 controls (32.0%).

Fig. 2

The differences observed in studies on phosphate clearance, however, are much more significant. These are shown in Table 3 and Fig. 2.

In each of the groups of diabetics the mean value of phosphate clearance was raised in comparison with the control group. The mean C_{PO_4} of all the diabetics was approximately twice as high as that of the controls

(22.4 ml/min as against 11.5 ml/min). Patients with diabetic retinopathy showed the highest mean value (25.8 ml/min). The high statistical significance of the

The results presented give evidence of a considerable lowering of the tubular reabsorption of phosphates in the three groups of diabetic patients with different

Table 3. Phosphate clearance in patients with diabetes mellitus, some of its complications and in control individuals

Phosphate clearance in ml/min	C	D _o	D _a	D _s	D _r	D _n	D
Up to 5	5	—	—	2	2	1	5
5.1—12	11	4	7	9	5	3	28
12.1—20	5	4	3	9	3	3	22
20.1—30	1	3	5	8	4	4	24
Above 30.1	2	3	5	10	6	3	27
Total	24	14	20	38	20	14	106
Mean value (M)	11.5	20.7	21.3	22.5	25.8	21.9	22.4
Mean deviation (σ)	8.1	10.8	11.7	15.1	16.9	12.4	
Mean error (m)	1.6	2.9	2.6	2.5	3.9	3.3	

Normal values: 5—13 ml/min. (LIÈVRE and CAMUS, 1961), 5.9—17 ml/min. (SCHWARTZ, 1959).

differences between any of the diabetic groups and the control group is evident (t varies between 2.4 and 3.8, p being less than 0.01). No substantial differences were found among the separate diabetic groups. The fact that the mean value of phosphate clearance in patients with diabetic nephropathy was lower than that of patients with diabetic retinopathy, might be explained by the existence of renal insufficiency, where the elimination of phosphorus is impaired, resulting in a retention of serum phosphorus. The blood urea nitrogen was increased in 19 patients from the groups D_s, D_r and D_n. No correlation was found between BUN and the phosphate clearance. The mean C_{PO₄} in patients with renal insufficiency was 23.41 ml/min.

No correlation was established between the creatinine and phosphate clearances, nor between the creatinine concentration in the blood plasma and the phosphate clearance.

Fig. 3

Table 4. Tubular reabsorption of phosphates in patients with diabetes mellitus, some of its complications and in control individuals

Tubular reabsorption of phosphates in %	C	D _o	D _a	D _s	D _r	D _n	D
Up to 60	—	—	—	14	6	4	24
61—85	5	5	12	11	8	7	43
86—95	16	9	7	12	3	2	33
96 and over	2	—	2	1	1	1	4
Total	23	14	21	38	18	14	104
Mean value (M)	89.3	80.9	81.7	59.1	51.9	48.1	64.0
Mean deviation (σ)	7.1	8.8	11.6	21.8	27.6	31.5	
Mean error (m)	1.5	2.4	2.5	3.6	6.7	9.6	

The limits of normal values of TRP vary between 87.7 and 94.9% (LIÈVRE et CAMUS, 1961), $84.7 \pm 0.9\%$ (CHAMBERS et al., 1956), between 84 and 94% (PAUPE, 1962), $91.3 \pm 3.3\%$ (SCHAAF and KYLE, 1954).

We have not observed any case with clinically proved secondary hyperparathyroidism.

Table 4 and Fig. 3 include the data on the mean values of tubular reabsorption of phosphates.

forms of diabetic angiopathy (D_s, D_r and D_n). The greatest decrease was present in patients with diabetic nephropathy. The controls showed a mean value of $89.3 \pm 7.1\%$, which corresponds to the norms

indicated above. The differences between the mean values of TRP in the diabetics and the controls are of undoubted statistical significance (t is of the order of between 2.6 and 7.5, while p is less than 0.01 — 0.001). Almost 24% of patients with diabetic nephropathy had TRP values lower than 60%.

Discussion

The results of the tests carried out provide undoubted evidence of raised renal elimination of phosphates in diabetic patients, including those with normal renal function. The increased elimination, however, did not lead to a lowering of the phosphorus concentration in the blood serum. It would be rather difficult to present a comprehensive explanation of this interesting phenomenon, and its interpretation should be made with great caution. In the most general sense, it could be stated that in diabetic patients the metabolism of phosphorus is disturbed. It could be suggested that in diabetics the interrupted processes of the utilization of carbohydrates in the cells, including the tubular cells, also give rise to certain disturbances in the transfer of phosphates. This might be a result of an exhaustion of the enzymatic systems that play an active part in the oxidative phosphorylation of glucose in the tissues. This is due to the prolonged metabolic disturbance. Obviously phosphates and glucose compete for the same tubular reabsorption pathway (NORDIN and FRASER, 1960). MARTINI has pointed out the importance of the glucose tubular load, with saturation of the tubular reabsorptive capacity for glucose to the detriment of phosphorus. The fact that increased elimination of phosphates takes place even in unaffected kidneys, supports the notion that serious organic lesions of the kidneys are not necessary for this condition.

On the other hand, the lowering of the tubular reabsorption of phosphates is present to a greater degree in diabetics where disturbed renal function has been established. This suggests that additional renal lesions result in further blocking of phosphate reabsorption, thus enhancing the elimination of phosphate (SCHAAF and KYLE, 1954).

It seems most likely that the retention of the normal level of organic phosphorus in the serum of diabetic patients, in spite of its considerable renal elimination, is due to the retained and stable neuro-endocrinic regulatory mechanisms, which are very complex processes (YAMSHIRO and REYNOLDS, 1962). They could restore the chemoestasis of phosphates by using the considerable reserves in bones and tissues. In this respect it would be of interest to investigate further the morphology and function of the parathyroid glands in the different forms of diabetes mellitus and to examine the osteoporotic changes in the bones of the same patients.

HODGKINSON (1961) has found raised values of phosphate clearance and decreased tubular reabsorption of phosphates in 8 out of 10 patients with proved hyperparathyroidism. The administration of parathyroid hormone caused an increase of urinary phosphate due to an increase of GFR and a decrease of TRP (GOLDMAN et al., 1954).

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A. KH. ASTRUG, M.D.
Internal Therapeutic Clinic,
Higher Medical Institute,
Georgi Sofiski Str., 1
Sofia 31, Bulgaria