# Tubular Reabsorption Rates as Related to Elevated Glomerular Filtration in Diabetic Children

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**SUMMARY**

**To study renal tubular reabsorption and tubulo-glomerular balance in diabetic children, glomerular filtration rate (GFR) and tubular reabsorption rates of sodium, glucose, ultrafilterable calcium, and phosphate were measured during fasting in 26 ambulatory type I (insulin-dependent) diabetic children without clinical signs of microangiopathy (age 7–14 yr; duration of diabetes 3–14 yr). Similar measurements were made in 28 healthy school children (age 8–14 yr). Mean GFR in the diabetic children was significantly higher than in the normal children (138 versus 109 ml/min/1.73 $m^2$, $P < 0.01$). Mean tubular reabsorption rates of sodium, glucose, and calcium were significantly increased in the diabetic subjects ($P < 0.001$). In contrast, tubular reabsorption rate of phosphate in the diabetic subjects was not enhanced. The renal threshold concentration of phosphate ($Tm_{PO_4}$/GFR) was suppressed in the diabetic compared with the healthy subjects (1.23 versus 1.73 mmol/L, $P < 0.001$). $Tm_{PO_4}$/GFR was unrelated to circulating parathyroid and growth hormone concentrations but correlated inversely with the reabsorption rate of glucose ($r = -0.53$, $P < 0.01$). Sodium reabsorption was closely correlated to GFR in both diabetic ($r = 0.99$, $P < 0.0001$) and healthy subjects ($r = 1.00$, $P < 0.0001$), and both groups showed identical regression lines. The tubular glucose reabsorption rate was independent of GFR in the diabetics. Tubular calcium and phosphate reabsorptions correlated equally well with sodium reabsorption and with GFR in the diabetic and healthy subjects ($P < 0.001$). The maximal reabsorption of phosphate relative to GFR was lowered in the diabetic children. Thus, in the diabetic subjects, the tubulo-glomerular balance was maintained for sodium, but not for phosphate.**

**These findings can be interpreted as a consequence of increased plasma (and ultrafilterate) glucose concentration inhibiting maximal phosphate reabsorption, leading to a stimulation of sodium coupled glucose reabsorption (cotransport), and thereby of solute-linked water reabsorption. The normalization of absolute phosphate reabsorption may be a consequence of the increased reabsorption of sodium. The excess sodium/solute-linked reabsorption is likely to be basic for the mechanism leading to the elevated GFR in the diabetic subjects.** DIABETES *32* (Suppl. 2):28–33, 1983.

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In type I diabetic subjects, functional glomerular changes are known to occur from the early onset of the disease. The glomerular filtration rate (GFR) and the filtration fraction (FF) are significantly increased compared with healthy subjects.[1–5] These functional changes in glomerular hemodynamics are readily reversible with optimal glucose regulation.[4–6] Functional changes in the renal tubular system may also be present from the onset of type I diabetes. Fasting urinary phosphate excretion is increased and the threshold concentration of phosphate per liter glomerular filtrate ($Tm_{PO_4}$/GFR) is significantly decreased.[7–10] These tubular abnormalities are also reversible and related to blood glucose control.[10–12]

The underlying mechanism leading to the increase in GFR and FF in short-term diabetic subjects is unknown. Both an increased surface area of the glomerular membrane[13] and/or an elevated effective glomerular filtration pressure,[4] in accordance with the classical theory by Homer Smith, have been proposed. There is, however, growing evidence that glomerular hemodynamics are under control of the tubular rate of reabsorption rather than vice versa, i.e., via a tubulo-glomerular feedback operating close to the early distal tubules. The unique structure of the nephron, with its ascending limb of Henle making close contact with both the afferent and efferent arterioles of its originating glomerulus (macula densa and juxtaglomerular apparatus), is worthy of attention.[14,15] According to this "alternative hypothesis" the increase in GFR and in FF in diabetic subjects could be accounted for by the following sequence of events: in-

TABLE 1
Plasma concentrations and urinary excretion rates in diabetic and healthy children

| Plasma concentrations | Diabetic children | Healthy children | Significance |
|---|---|---|---|
| Glucose (mmol/L) | 13.2 ± 4.16 | 4.5 ± 0.25 | $P < 0.001$ |
| Sodium (mmol/L) | 139.1 ± 2.05 | 140.5 ± 1.66 | $P < 0.01$ |
| Calcium (mmol/L) | 2.36 ± 0.12 | 2.52 ± 0.10 | $P < 0.001$ |
| Inorg. phosphate (mmol/L) | 1.36 ± 0.13 | 1.48 ± 0.13 | $P < 0.005$ |
| PTH (U/L) | 2.78 ± 0.67 | 3.03 ± 1.04 | NS |
| HGH (nmol/L) | 4.7 ± 4.52 | 6.6 ± 6.79 | NS |
| Urinary excretion rates | | | |
| Glucose (mmol/h/1.73 $m^2$) | 11.0 ± 10.87 | — | — |
| Sodium | 7.71 ± 5.11 | 5.49 ± 2.63 | NS |
| Calcium | 0.102 ± 0.091 | 0.097 ± 0.097 | NS |
| Phosphate | 1.19 ± 0.36 | 0.43 ± 0.22 | $P < 0.001$ |

creased glucose delivery to the tubules leads to increased sodium reabsorption in the proximal tubules as these processes are coupled. The obligatory increase in sodium (and water) reabsorption accompanying the increase in glucose reabsorption increases GFR. To maintain tubulo-glomerular balance for sodium and water, the tubulo-glomerular feedback is activated and leads to an increase in postglomerular resistance and a decrease in afferent arteriolar resistance. As a result, the mean ultrafiltration pressure (PUF) is elevated and the increase in GFR may be out of proportion to any increase in glomerular plasma flow, i.e., the FF is increased.

We describe a study of the tubular reabsorption of sodium, glucose, ultrafilterable calcium, and phosphate as related to GFR in diabetic and healthy children in order to discuss to what extent these results would support this "alternative hypothesis."

## PATIENTS AND METHODS

Twenty-six ambulatory children with type I diabetes mellitus (17 girls and 9 boys, aged 7–14 yr, mean 11.8 yr), duration of diabetes of 3–14 yr (mean 6.8 yr), participated in the study. Twenty-eight healthy school children (13 girls and 15 boys, aged 8–14 yr, mean 11.8 yr) served as controls. Informed consent was obtained from parents for both normal and diabetic children. Arterialized capillary blood pH was normal in all (range 7.36–7.44) with mean pH of 7.40 in the two groups. None of the children had clinical signs of microangiopathy, i.e., retinopathy or nephropathy. Serum creatinine concentration was normal and proteinuria, tested by Albustix, was not detected in any of the children. During the days preceding their study, the children had consumed an unrestricted diet with respect to minerals.

All children were studied in the supine position in the morning between 0800 and 1000 h after at least 12 h fasting and

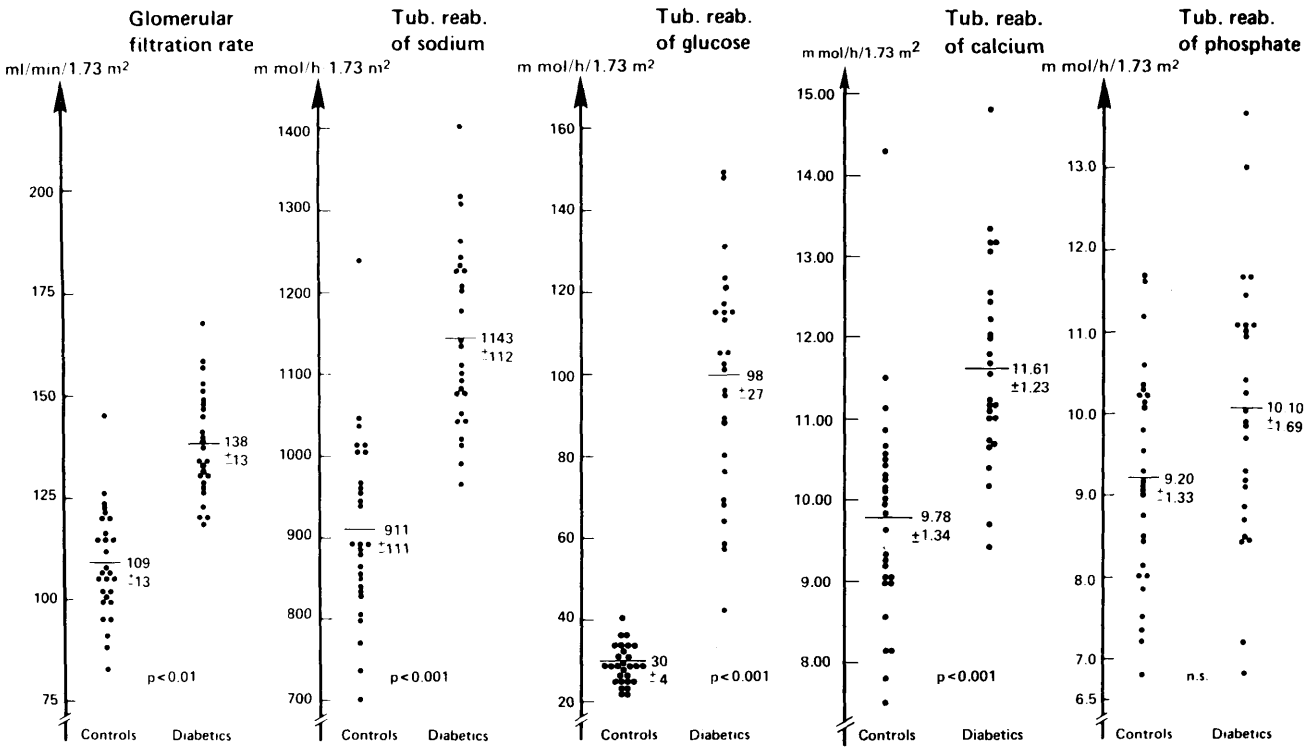


**FIGURE 1. Individual and mean values (± SD) of glomerular filtration rate. Tubular reabsorption rates of sodium, glucose, ultrafilterable calcium, and phosphate in 28 healthy and 26 diabetic children.**

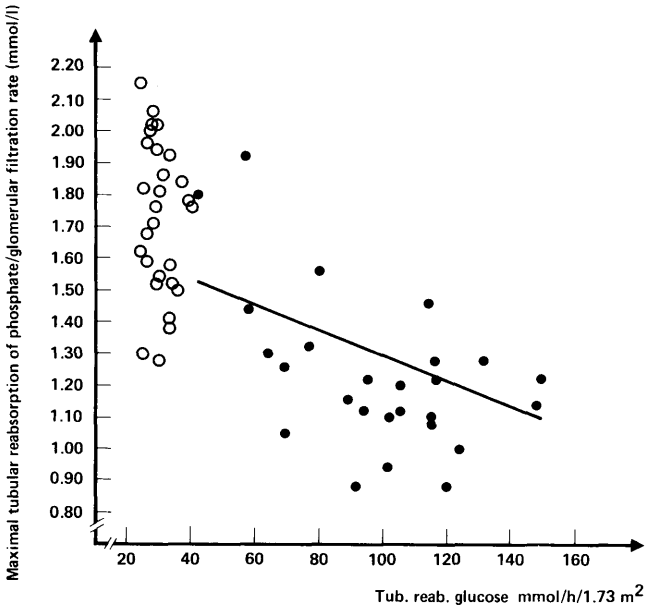


**FIGURE 2. Correlation between the threshold concentration for phosphate and the reabsorption rate of glucose in 28 healthy and 26 diabetic children. ● diabetic children y = −0.004x + 1.69; r = −0.53, P < 0.01.**

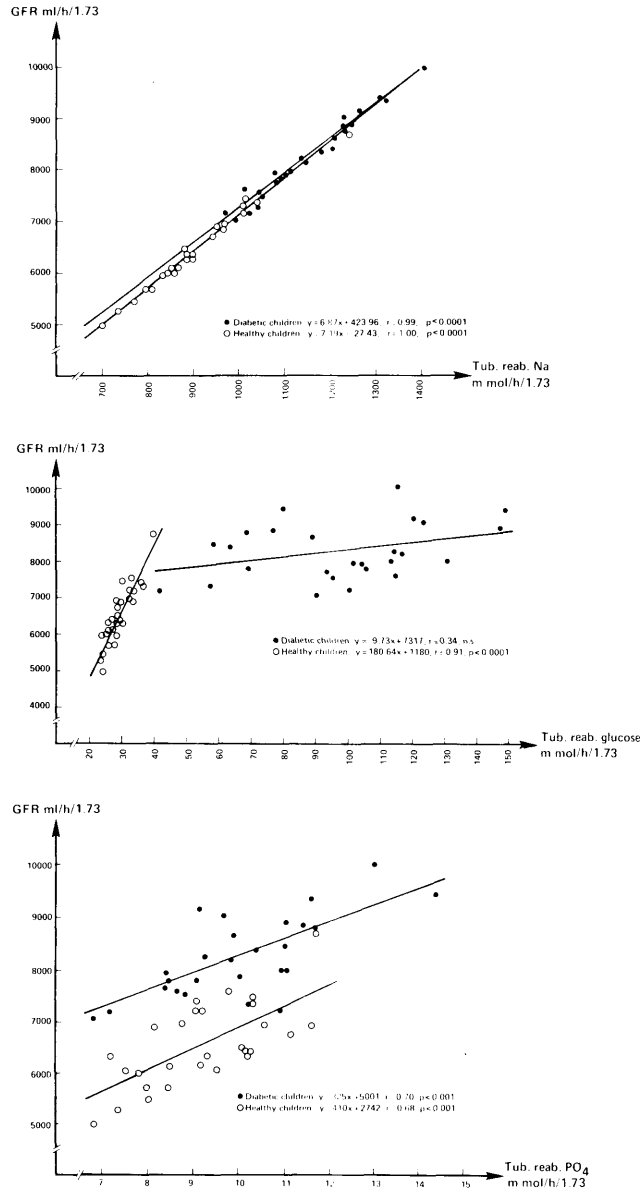


**FIGURE 3. Correlation between the reabsorption rates of sodium, glucose, and phosphate to glomerular filtration rate in 28 healthy and 26 diabetic children. ● diabetic children; ○ healthy children.**

a 30–60-min rest period, preceded by voiding urine. During the examination 200 ml water was given by mouth. The usual morning dose of insulin was deferred until the end of the test and none of the diabetic children had received insulin for at least 14 h. Glomerular filtration rate (GFR, ml/min/1.73 $m^2$) was determined from the total $^{51}Cr$ EDTA plasma clearance, measured by a simplified single injection method[16] over 2 h after i.v. injection of 3 μCi $^{51}Cr$ EDTA per kg body wt (maximum 100 μCi). A minor inaccuracy of clearance versus GFR was corrected for.[17] Fasting urine was collected for 2 h by volitional voiding. Blood samples were taken at the urine collection midpoint. The concentration of urinary and plasma sodium, glucose, calcium, and phosphorus were determined by conventional laboratory methods. Ultrafilterable plasma calcium was calculated as 60% of total plasma calcium. The $Tm_{PO_4}$/GFR was derived from the corresponding plasma phosphate value and the phosphate clearance/GFR ratio by using the nomogram by Walton and Bijvoet.[18] Serum parathyroid hormone was determined by radioimmunoassay with antibovine C-terminal PTH antisera (I.R.E., B-6220, Fleurus, Belgium), and serum growth hormone determinations were assayed by a double-antibody method[19] using appropriate antisera supplied by CEA-IRE-SOBIN.

Mann-Whitney's nonparametric test was used for all comparisons. Linear correlations in the diabetic and normal children were also tested.

## RESULTS

Plasma concentrations and urinary excretion rates of glucose ($U_{Gl}V$), sodium ($U_{Na}V$), calcium ($U_{Ca}V$), and phosphate ($U_{PO_4}V$) in the diabetic and healthy children can be seen in Table 1. In the diabetic children the plasma sodium was significantly lower than in the healthy children (139.1 versus 140.5 mmol/L, $P < 0.01$) as was plasma calcium (2.36 versus 2.52 mmol/L, $P < 0.001$) and phosphate (1.36 versus 1.48 mmol/L, $P < 0.005$).

While urinary excretion rates of sodium ($U_{Na}V$) and $U_{Ca}V$ of the diabetic subjects were not different from that of the healthy subjects, $U_{PO_4}V$ was significantly increased in the diabetics (1.19 versus 0.43 mmol/h/1.73 $m^2$, $P < 0.001$). In this group, $U_{PO_4}$ correlated both to $U_{Gl}V$ ($r = 0.53$, $P < 0.01$) and to $U_{Na}V$ ($r = 0.71$, $P < 0.001$).

Figure 1 presents individual values of GFR and tubular reabsorption rates of sodium, glucose, ultrafilterable calcium, and inorganic phosphate in healthy and diabetic children. It is noted that the mean GFR of the diabetic children was significantly increased (138 versus 109 ml/min/1.73 $m^2$, $P < 0.01$). The reabsorption rates of sodium, glucose, and calcium were also significantly higher in the diabetics (sodium: 1143 versus 911 mmol/h, $P < 0.001$; glucose: 98 versus 30 mmol/h, $P < 0.001$; and calcium: 11.6 versus 9.8 mmol/h, $P < 0.001$). In contrast mean tubular reabsorption

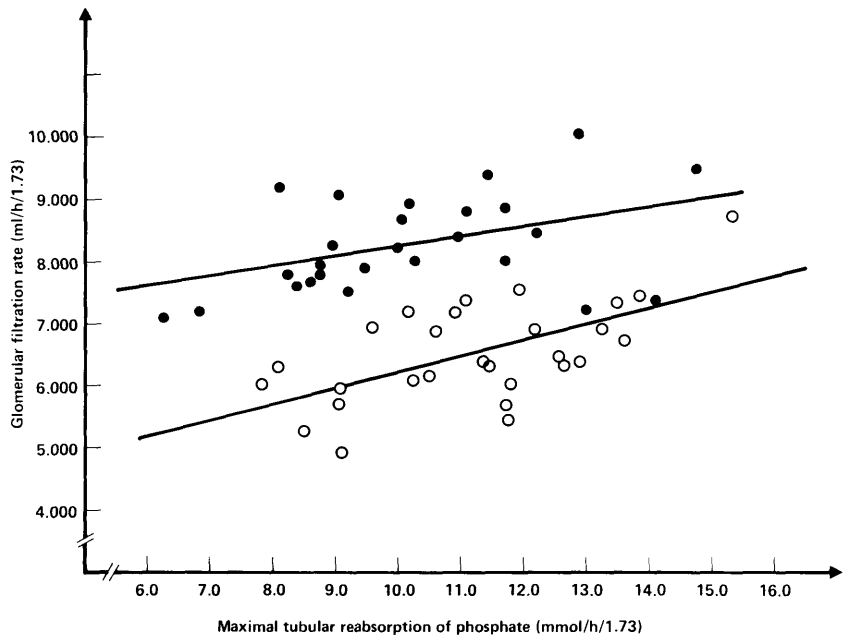


**FIGURE 4. Correlation of the maximal phosphate reabsorption rate to glomerular filtration rate in 28 healthy and 26 diabetic children. ● diabetic children y = 0.15x + 6.72; r = 0.41, P < 0.05; ○ healthy children y = 0.25x + 3.66; r = 0.59, P < 0.01.**

rate of phosphate was not increased but identical with that of the healthy children.

The renal threshold concentration for phosphate ($Tm_{PO_4}$/GFR), according to the method of Walton and Bijvoet, was markedly decreased in the diabetic children as compared with the healthy children (1.23 versus 1.73 mmol/L, $P < 0.001$) and, as indicated in Figure 2, the $Tm_{PO_4}$/GFR correlated inversely to the rate of glucose reabsorption ($r = -0.53$, $P < 0.01$). From Table 1, it is noted that plasma parathyroid hormone (PTH) and human growth hormone (HGH) concentrations were not significantly different in the diabetic and healthy subjects and PTH did not correlate with $Tm_{PO_4}$/GFR.

Figure 3 shows the relationship of the reabsorption rates of sodium, glucose, and phosphate to GFR. It can be seen that GFR and reabsorption of sodium was closely correlated both in diabetic ($r = 0.99$, $P < 0.0001$) and healthy children ($r = 1.00$, $P < 0.0001$), and their regression lines were identical. Glucose reabsorption was strongly correlated to GFR (and sodium) in the healthy children ($r = 0.91$, $P < 0.0001$), but no such correlation was present in the diabetic children. Calcium reabsorption rates were correlated to GFR both in the diabetic ($r = 0.88$, $P < 0.0001$) and the healthy children ($r = 0.95$, $P < 0.0001$). Also the reabsorption rate of phosphate correlated to GFR (and sodium reabsorption) in both diabetic and healthy children, but the regression lines were different (Figure 3). The maximal reabsorption of phosphate relative to GFR was also lowered in the diabetic children (Figure 4).

Table 2 shows the fractional reabsorption of sodium, ultrafilterable calcium, and phosphate in the diabetic and healthy children. The fractional reabsorption of sodium and calcium were identical in the two groups, whereas the fractional reabsorption of phosphate in the diabetic children was significantly suppressed.

## DISCUSSION

The present study, performed in similar age groups of diabetic and healthy children, indicates that significant changes take place both in the glomerular and tubular functions of juvenile diabetic subjects during their early disease.

The mean GFR of the diabetic children was increased by 25–30% compared with normal children (Figure 1). This result is similar to several previous studies of the GFR in adult short-term type I diabetics.[2–6] This elevation was not linearly correlated with the actual blood glucose concentration,[4,12] and the present study indicates that GFR in the diabetic children is not related to the tubular reabsorption rate of glucose (Figure 3). There was an extremely close correlation beween the GFR and the rate of sodium reabsorption in both diabetic and healthy children and their regression lines were identical (Figure 3). GFR also correlated with the reabsorp-

TABLE 2
Fractional tubular reabsorption in ambulatory diabetic and healthy children

| Fractional tubular reabsorption | Diabetic children (%) | Healthy children (%) | Significance |
|---|---|---|---|
| Sodium | 99.1 ±0.62 | 99.2 ±0.30 | NS |
| Calcium | 99.1 ±0.75 | 99.0 ±0.90 | NS |
| Phosphate | 85.4 ±4.57 | 94.1 ±2.57 | $P < 0.0001$ |

tion rates of ultrafilterable calcium and phosphate (Figure 3). However, both the absolute and maximal phosphate reabsorption relative to GFR were significantly lowered in the diabetic compared with the healthy children (Figure 4). These data applied to the concept of tubulo-glomerular balance indicate that such a balance is fully maintained for sodium in the diabetic children while there seems to be a tubulo-glomerular disequilibrium for phosphate. This disequilibrium was also apparent in the present study by the significantly lowered threshold concentration for phosphate ($Tm_{PO_4}$/GFR) in the diabetic children. This suppression in $Tm_{PO_4}$/GFR was not found to be related to the plasma concentrations of parathyroid hormone or human growth hormone, whereas there was a distinct inverse relationship between $Tm_{PO_4}$/GFR and the tubular reabsorption rate of glucose (Figure 2). The higher the reabsorption rate of glucose the more suppressed was $Tm_{PO_4}$/GFR. These data clearly indicate the presence of a glucose-mediated inhibition of phosphate reabsorption in diabetic children. As a consequence the diabetic children excreted more than twice the amount of phosphate per time unit in the urine compared with the healthy children in the fasting state (Table 1). Such increased renal phosphate excretion has previously been reported to follow hyperglycemia in man,[20–22] dog, and rat.[23–25] Considering the markedly lowered $Tm_{PO_4}$/GFR in the diabetic children it was noteworthy that the difference between the plasma $PO_4$ in the diabetic and healthy children was not more striking. Apparently a compensatory change occurs in the diabetic children, leading to a normalization of the absolute and maximal tubular reabsorption rates of phosphate. In the diabetic children, these phosphate reabsorption rates were correlated with GFR (Figures 3 and 4). Despite the fact that GFR was elevated, total phosphate reabsorption became equivalent to that of the healthy children. There are several possible explanations for the glucose-mediated inhibition of $Tm_{PO_4}$, including competition for energy or competition for sites on a carrier in the proximal tubules. The inhibitory effect of glucose appears linked to glucose reabsorption per se and not to a nonspecific osmotic intraluminal effect. Experimental work has shown that when mannitol is substituted for glucose, no change in phosphate reabsorption occurs.[22,25] This effect of glucose is also not secondary to an effect of circulating insulin.[22,26] The inhibitory effect of glucose is localized at the luminal site of the proximal tubules probably in the brush-border membrane in which the transport of phosphate, glucose, and amino acids is active and secondary to sodium transport. Accordingly, the inhibitory effect of glucose on phosphate reabsorption may be explained if one assumes that in the proximal tubule an increase in reabsorption of glucose raises intracellular sodium concentration, which in turn reduces the phosphate entry rate (and vice versa). Such a hypothesis is compatible with our observations as well as those of De Fronzo et al.,[26] who demonstrated by micropuncture that glucose inhibited phosphate reabsorption in the proximal tubules. Moreover, it is consistent with the observation by Pitts and Alexander[27] that phlorizin, which prevents glucose reabsorption, enhances phosphate reabsorption.

According to the classical theory formulated by Homer Smith, the rate of proximal reabsorption automatically adjusts for changes in GFR, thereby preserving tubulo-glomerular balance. Mogensen has shown that tubulo-glomerular balance is preserved for glucose in patients with type I diabetes of short duration.[28] In this study, we have demonstrated that such an equilibrium was also present for sodium in diabetic children. However, it is difficult to incorporate into classical theory the present finding of a disequilibrium in tubulo-glomerular balance for phosphate and the observation that the sodium (and solute) reabsorption should selectively be increased to such a degree that the absolute phosphate reabsorption becomes equivalent to that of the healthy children.

The alternative hypothesis, the distal tubular feedback hypothesis, for the relationship between GFR and tubular function postulates that the proximal reabsorption capacity is the primary variable and that significant changes in GFR are secondary to alterations in proximal tubular reabsorption rate.[15,29] The findings in the present study adapt themselves more easily to this "alternative hypothesis." According to this hypothesis and other accepted concepts concerning the processes of reabsorption of glucose, solute, and water, the sequence of events observed in the diabetic subjects would be as follows: the increased plasma (and ultrafiltrate) glucose concentration selectively stimulates that part of the sodium reabsorption that is coupled to glucose (sodium-glucose cotransport) and thereby to solute-linked water reabsorption. The net effect would be a decrease in the intratubular pressure and thereby an increase in GFR (with unchanged mean ultrafiltration pressure, PUF). This increase in GFR (without a change in renal plasma flow) will lead to an increase in filtration fraction. Due to a decrease of flow from the proximal tubules, the tubulo-glomerular feedback, probably via the renin-angiotensin system, is activated, leading to an increase in postglomerular resistance and a decrease in afferent arteriolar resistance. As a result, PUF is elevated and the increase in GFR can become disproportionate to any increase in glomerular plasma flow, i.e., the filtration fraction is increased. The increase in PUF and in angiotensin II leads in turn to a normalization of the pressure in the proximal tubules, which abolishes the stimulus to the flow-sensitive area of the distal tubules. The PUF thereby becomes normalized, whereupon the pressure in the proximal tubules will again fall. The luminal flow in the distal tubules again decreases and the vicious circle continues. While the elevated GFR is kept reasonably constant, the renal plasma flow fluctuates between normal and supernormal values. In this respect, it is interesting that Burden and Thurston[30] recently reported elevated plasma renin activity in a large number of uncomplicated diabetics and interestingly enough, Sullivan et al.[31] found that plasma angiotensin II decreased significantly with improved control in patients with nonketotic poorly regulated diabetes.

It is therefore proposed that hyperglycemia leads to marked variations in glomerular pressure and hemodynamics, which over the years may lead to degenerative glomerular lesions. The function of the glomerular apparatus will remain optimal as long as autoregulation is undisturbed. However, as soon as arteriolosclerosis prevents autoregulatory flow augmentation, the kidneys will start to fail.

The clinical implication to be drawn from these studies is that the vascular renal sequelae of long-term diabetes appear to be secondary to hyperglycemia and that utmost care to maintain glucose homeostasis should be the goal in diabetes therapy.

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