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Originals

Variations in renal threshold for glucose in Type 1 (insulin-dependent) diabetes mellitus

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Summary. The blood glucose/urinary glucose relationship was studied in 23 patients with Type 1 (insulin-dependent) diabetes. Glucose was infused intravenously in order to increase blood glucose concentration slowly and gradually. The renal threshold was recorded at the slightest trace of glycosuria and varied by a factor of 2 (from 6.0 to 14.3 mmol/l). The rise in blood glucose required to change the urinary output (0–1.1 mmol glucose/20 min) varied by a factor of 7 (1.1–7.6 mmol/l). The maximal rate of tubular glucose reabsorption varied by a factor of 2 (0.93–1.98 mmol/min). The renal threshold was negatively correlated with the creatinine clearance ($r = -0.52$, $p < 0.05$), but was not correlated with diabetic control, age or duration of diabetes. The maximal rate of glucose reabsorption was negatively correlated with age ($r = -0.47$, $p < 0.05$) and duration of diabetes ($r = -0.54$, $p < 0.05$). In conclusion, urinary glucose excretion is dependent on both renal threshold and the splay and the slope of the blood glucose/urinary glucose excretion curve. Thus, the degree of glycosuria is of value as an index of diabetic control only when the blood glucose/urinary glucose relationship is known. The inverse correlation between renal threshold and creatinine clearance limits the usefulness of measuring glycosuria in patients with nephropathy.

Key words: Renal threshold, splay, creatinine clearance, maximal rate of renal tubule glucose absorption, glycosuria, nephropathy, Type 1 diabetes, diabetic control.

The degree of glycosuria is still the most universally used measure of diabetic control. Glucose is freely filtered at the glomerulus and reabsorbed in the proximal convoluted tubule. The amount of glucose reabsorbed increases linearly with rising plasma glucose concentration until a maximum value (Tm_G) is reached. Any further increase in the filtered glucose load is excreted in the urine. The concentration in plasma at which glucose appears in the urine is the renal threshold for glucose (RT_G). Therefore, in order to use urinary glucose excretion as an index of diabetic control, the blood glucose/urinary glucose relationship must be known. Deviations in RT_G above or below the normal threshold of 10 mmol/l are commonly found.

More recent studies of the relationship between the degree of glycosuria and the blood glucose level show their poor correlation [1–5]. Among the reasons for this discrepancy are the time lag between the filtration of glucose in the glomeruli and emptying of the bladder, incomplete urine collection, differences in renal threshold and the fact that urine tests give no information about blood glucose levels below the renal threshold.

The aim of the present work was to study the differences in RT_G and its relationship to creatinine clearance, Tm_G, age, duration of diabetes and metabolic control in patients with Type 1.

Patients and methods

Thirty-five patients with Type 1 diabetes were studied after informed consent. Twelve of these patients were later excluded, nine because of insufficient bladder emptying (shown by a coefficient of variation of creatinine clearance of > 10%) and three due to other technical problems. Thus, 23 patients with Type 1 diabetes (Table 1) were studied in the morning, fasting and with omission of their morning insulin. Seven of the patients had persistent proteinuria and decreased creatinine clearance. Short-acting insulin was infused IV (Infusomat) until the patients were aglycosuric. Infusion of isotonic glucose (5.5%) was then started at a rate causing the blood glucose to rise slowly and gradually at 1 mmol $\cdot l^{-1} \cdot 20\ min^{-1}$. Urine was collected in 20-min periods and the glucose concentration measured quantitatively. Capillary whole blood glucose was measured every 10 min. In order to ensure a high diuresis, 1000 ml of tap water was taken orally during the hour before the test and 100–200 ml/20 min during the study. Measurements were carried out with the patients in the supine position.

The RT_G was defined as the blood glucose concentration at the

Table 1. Clinical details of 23 patients with Type 1 diabetes

Sex M:F	Age (years)	Duration of diabetes (years)	M-value (arbitrary units) ($n = 23$)	HbA_{1c} (%) ($n = 13$)
18:5	32 ± 14 (15–64)	11 ± 10 (0–36)	50 ± 29 (8–127)	9.3 ± 1.4 (7.4–11.6)

Expressed as mean ± SD with range in parentheses

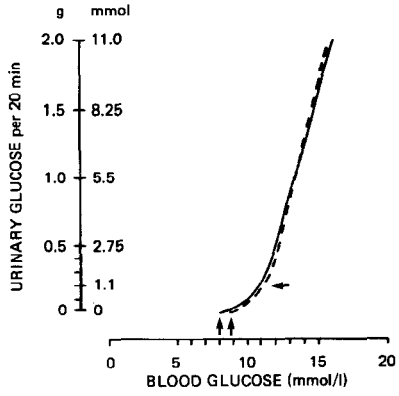

Fig. 1. Blood glucose/urinary glucose titration curves in one patient determined on two occasions 3 months apart. The splay is defined as that part of the curves from the renal threshold (↑↑) to a glucose excretion of 1.1 mmol/20 min (←)

Fig. 2. Distribution of renal threshold in 23 patients with Type 1 diabetes. The hatched bars indicate patients with persistent proteinuria and decreased creatinine clearance

start of the 20-min period where the first trace of glycosuria was found (0.56 mmol/l). The 'splay' (the curved part of the blood glucose/urinary glucose titration curve, i. e. that part of the curve between the renal threshold and the linear part) was arbitrarily defined as the rise in blood glucose level required to increase urinary glucose excretion from 0 to 1.1 mmol/20 min (Fig. 1) [6].

For comparison, RT_G was also calculated from correlations between the mean blood glucose concentrations (five blood glucose values/day at 08.00, 11.00, 14.00, 17.00, 22.00 h) and the 24-h glucose excretion during three admission days before the infusion study. In three patients, this method was unapplicable due to a high RT_G and no glycosuria.

Creatinine clearance was measured during the last three to four 20-min periods. Tm_G was calculated from the straight part of the urinary glucose/blood glucose titration curve using the formula: Tm_G = creatinine clearance × plasma glucose (blood glucose × 1.15) minus urinary excretion rate (urine flow × urinary glucose concentration).

Blood and urinary glucose levels were measured with a glucose oxidase method [7]. The sensitivity of the test for urinary glucose was 0.55 mmol/l. Glycosylated haemoglobin (stable HbA_{1c}) was determined as described previously [8]. The M-value was calculated according to Schlichtkrull et al. [9].

Conventional parametric correlation coefficients were calculated.

Results

The correlation between mean blood glucose and urinary glucose excretion 3 days before the RT_G study was low ($r = 0.51$, $p < 0.05$).

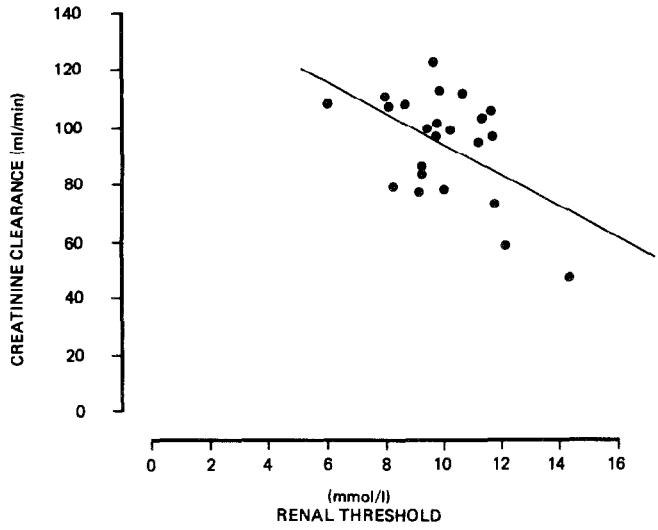

Fig. 3. Correlation between threshold and creatinine clearance. $r = -0.52$, $p < 0.05$, $y = -5.5x + 148.9$, $n = 23$

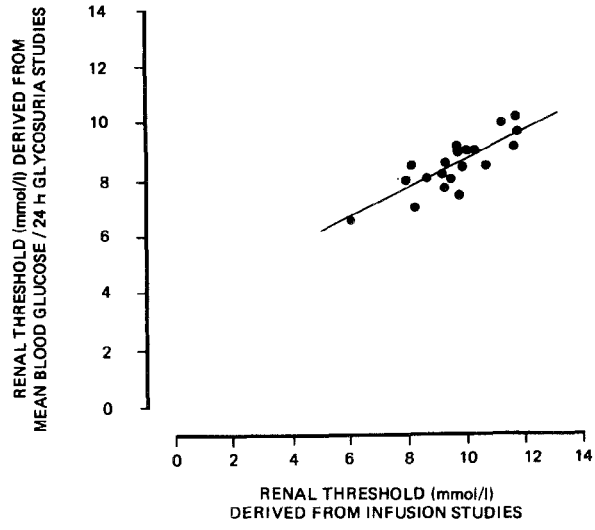

Fig. 4. Correlation between renal threshold estimated from mean blood glucose/24 h glycosuria and from infusion studies. $r = 0.84$, $p < 0.001$, $y = 0.56x + 3.14$, $n = 20$

During the RT_G study, the urinary flow during the first period with glycosuria varied from 88 to 479 ml/20 min (281 ± 109 ml/20 min, mean ± SD) and the amount of glucose excretion varied from 0.46 to 7.74 mmol (mean 1.70 ± 1.81 mmol/l). The rise in blood glucose during the 20-min period preceding the first period with glycosuria varied from 0.2 to 1.9 mmol/l (mean 1.1 ± 0.5 mmol/l).

Mean creatinine clearance was 100 ± 22 ml/min (range 47–140 ml/min), the mean renal threshold was 10.0 mmol/l (6.0–14.3 mmol/l) (Fig. 2), the mean splay 2.7 mmol/l (1.1–7.6 mmol/l) and the mean Tm_G 1.37 mmol/min (0.93–1.98 mmol/min).

RT_G as well as the splay were correlated with creatinine clearance, although these correlations were weak ($r = -0.52$, $p < 0.05$ and -0.53, $p < 0.05$, respectively (Fig. 3). There was no correlation between renal threshold and age, duration of diabetes, HbA_{1c}, M-value, uri-

nary flow or splay. The coefficient of variation of RT_G in six patients studied twice with a 3-month interval was 12%.

The Tm_G was negatively correlated with age ($r = -0.47$, $p < 0.05$) and with duration of diabetes ($r = -0.54$, $p < 0.05$). Tm_G was not correlated with RT_G, urinary flow, splay, or M-value.

Figure 4 shows the correlation between the two methods of estimating the renal threshold ($r = 0.84$, $p < 0.001$). There was good agreement in the low range, but RT_G values based on infusion experiments were higher than those based on correlations between mean blood glucose and 24-h glycosuria in the medium and high ranges.

Discussion

The present study demonstrates that the RT_G and the splay vary greatly and are negatively correlated with creatinine clearance in Type 1 diabetes. It has previously been shown that diabetic glomerulosclerosis in long-term diabetes is associated with a raised renal threshold for glucose [10, 11]. This means that the assessment of control of patients with Type 1 diabetes based on urinary glucose excretion is difficult, particularly in those with nephropathy, unless the blood glucose/urinary glucose excretion relationship is known. The sensitivity of the method for urinary glucose obviously influences the results. The sensitivity of the method used in the present work was 0.55 mmol/l, which is in the order of magnitude of many commercial strip methods used by patients. In the present study, variation in urinary glucose excretion only explained 26% of the variation in mean blood glucose during 3 days before the RT_G study. However, it is not feasible to perform blood glucose/urinary glucose titration curves in all patients with Type 1 diabetes. In a recent paper, Walford et al. [12] found the renal threshold of diabetic patients to vary from 3 to 10 mmol/l (mean 7.2 mmol/l). The study was based on home measurements of blood glucose (Stat-Tek system) and urinary glucose (Diastix). RT_G was defined as the mean of the blood glucose concentration 1 h before and at the time when the urine changed from 0% to 0.1% or 0.25% glycosuria (5.5 or 13.8 mmol/l). This degree of glycosuria is much higher than the degree of glycosuria in the first period of urine collection in the present study. This would tend to give a higher RT_G than the study of Walford et al., but the opposite was the case. The rise in blood glucose in the study of Walford et al. may have been from a concentration far below RT_G and, thereby, the use of too low a blood glucose level for defining RT_G may explain the lower RT_G values in their study.

In our study, RT_G was not related to age, duration of diabetes, metabolic control, or splay. RT_G measured on two occasions with a 3- to 4-month interval showed no significant change. Walford et al. found that RT_G was weakly correlated with age ($r = 0.30$, $p < 0.02$) and with mean blood glucose ($r = 0.50$, $p < 0.01$) when they excluded patients with proteinuria.

The inverse correlation between Tm_G and age and duration of diabetes may be explained by the falling creatinine clearance with age and duration of diabetes. Tm_G was not correlated with RT_G, splay or metabolic control.

We found no correlation between urinary flow and RT_G and Tm_G, suggesting that water loading does not influence RT_G.

It is not practical to perform infusion studies in all diabetic patients in order to determine RT_G. A rough estimate of RT_G can be obtained by correlating the mean blood glucose levels and the 24-h urinary glucose excretion. The method is, however, not feasible in patients with a high threshold and no glycosuria and, in the higher range, it gives lower values than RT_G estimated from infusion studies.

Having documented the limitations testing for glycosuria, in assessing metabolic control, we think they should be used only when blood glucose monitoring is impossible for practical or economic reasons. In 'super-regulated' patients with no glycosuria this is obviously a conditio sine qua non.

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