Tm Glucose in a Case of Congenital Intestinal and Renal Malabsorption of Monosaccharides

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Extract

Maximal rate of renal tubular reabsorption of glucose (T_{mG}) was determined in a 9-month-old girl with congenital intestinal malabsorption of glucose and galactose associated with constant glucosuria. At the time of the procedure, the patient had attained normal growth and development and was enjoying good health following a 5-month dietary regimen which excluded virtually all carbohydrates other than fructose. The standard glucose titration of renal tubules was carried out, using 4 arterial plasma glucose concentrations (P_G), each maintained over 3 consecutive 20-minute periods while the glomerular filtration rate was kept relatively constant. The following observations were made: 1. The rate of filtered glucose (F_G) was found to exceed that of reabsorption (T_G) at all P_G levels ranging from 31 to 243 mg %, revealing a very low renal plasma threshold. 2. A T_{mG} of 76.7 mg/min/1.73 m² was achieved at a P_G level of 174 mg %, when $F_G/T_G = 1.35$. This amounts to 25 % of the normal adult value, taken as 303 mg/min/1.73 m². Compared with data on premature and full-term newborns, it reflects a profound deficiency of tubular reabsorption of glucose in our patient. 3. A marked drop of T_G was recorded during the final hour of titration with prolonged elevation of F_G ; and the observation was felt to be valid. A search of the literature revealed that others have observed the same phenomenon in subjects with suboptimal tubular reabsorption of glucose relative to the filtered load.

Speculation

The finding of a low T_{mG} in our patient with documented intestinal malabsorption of glucose and galactose strengthens Crane's original concept that a common mechanism mediates active transport of glucose at the intestinal and renal tubular epithelia. The marked drop of T_G after prolonged elevation of F_G in subjects with suboptimal tubular reabsorption of glucose seems to reflect a sudden 'fatigue' or inhibition of an already strained transport mechanism. It is postulated that this propensity for 'fatigue' or inhibition, by whatever processes, may be part of the profile of defective epithelial transport of glucose in these patients.

Introduction

The active transport of glucose across mammalian small intestinal [9, 10, 40, 55] and renal tubular [4, 7, 18, 30, 31, 34, 45, 47, 51, 54] epithelia has long been a subject of intense interest. Certain parallelism between the structural [6, 39] and functional [9, 18, 30] characteristics of the epithelial cells in these organs has made it attractive to postulate a common mechanism mediating glucose transport at both sites [9, 18, 30]. With the discovery, since 1962, of a group of patients suffering congenital intestinal as well as renal malabsorption of glucose and galactose [1, 20–28, 32, 42, 43], the concept of a common epithelial glucose transport mechanism in both organs has gained credence [11].

Although all reported patients with this congenital disorder have had documented mellituria, the urinary spill of reducing substances appears to occur at varying blood sugar levels in individual patients. Several authors have commented on the apparent lowering of renal threshold for glucose in these afflicted individuals [1, 28, 32]. But, to date, there has been no published data on the renal tubular transport maxima for glucose (T_m glucose) in any of the known cases.

The present report deals with the determination of T_m glucose in an infant with congenital intestinal and renal malabsorption of monosaccharides [27, 28], using the standard method of glucose titration of the renal tubules [47].

Material and Methods

Table I summarizes the pertinent clinical data on the patient L.W. at the time of the T_m glucose determination.

The rate of glucose reabsorption (T_G) was calculated from the difference between filtered glucose (F_G) and excreted glucose (E_G), determined first at fasting arterial plasma glucose level; and again, when the latter was raised in successive stages up to 8-fold the fasting values, while the glomerular filtration rate (GFR) was kept relatively constant at each plasma glucose concentration. The highest T_G achieved during the 4-hour titration was taken as the T_{mG} . GFR was measured by means of inulin clearance (C_{in}). Plasma glucose (P_G) and inulin (P_{in}) were determined on samples obtained through an indwelling femoral artery catheter; urinary glucose (U_G), inulin (U_{in}) and volume flow (V) were measured on samples collected via an indwelling catheter in the bladder.

A constant intravenous infusion, composed of 10 % inulin (Warner-Chilcott, Morris Plains, New Jersey), 100 ml, 0.9% NaCl (USP), 200 ml and 22.3% KCl (USP), 8.6 ml, was administered to maintain an arterial plas-

ma inulin concentration between 0.31 and 0.34 mg/ml. Arterial glucose was maintained at the desired levels with 5 % Dextrose (USP) intravenously after priming with 20 % Dextrose (USP), using a constant infusion pump. Because of this baby's tendency toward massive glucosuria and osmotic diuresis when given glucose intravenously, a large volume of fluid was administered in order to balance the urine flow. Total parenteral fluid infusion rates for the 4 titration periods were 0.41 ml/min, 2.32 ml/min, 4.23 ml/min and 4.23 ml/min, respectively. In addition, water was given by gavage: 450 ml (50 ml/kg body weight) two hours before the start of period I; and 225 ml from midperiod IC through period II. The former established an adequate urine flow of 11 ml/min/1.73 m² at the outset of the titration, and the latter was found necessary for its maintenance in this patient (see Results).

Measurements of all necessary parameters were made over 3 consecutive 20-minute subperiods (A, B,

Table I. Clinical state of patient L.W. at the time of T_m glucose determination

Age	9 months
Sex	female
Height	71.8 cm (75th percentile)
Weight	8.6 kg (50th percentile)
Surface area	0.44 m ²
Glucosuria	constant
State of health and hydration	excellent. No hyperglycemia, hypertension, infection, clinically evident cardiovascular, endocrine or glomerular disease. Polyuria present. No medication given.
Interval since last gastrointestinal symptoms due to dietary glucose or galactose	5 months
Diet	1. lamb-corn oil-fructose formula [28]: a) 1200–1500 ml/24 h b) 800–1000 cal/24 h, of which 41 % was derived from fat; 38 % from CHO; and 20 % from proteins 2. Di-calcium phosphate 0.5 g twice a day 3. Zymadrops®—0.6 cc/day

C) at the low (I), and again, progressively higher plasma glucose levels (II, III, IV). Thirteen to 15 minutes were allowed for the equilibration of P_G before beginning each of the periods II, III and IV. The final two minutes of each subperiod began with urine sampling via thorough emptying of the bladder by means of Crede, washing with 20 ml of water, followed by 10 ml of air and extrusion of the last bubble from the urinary catheter, the latter signaling the initiation of a new subperiod. Arterial samplings were made exactly 10 minutes following the beginning of A, B and C.

All collected samples of urine and blood were placed on ice immediately, centrifuged, deproteinized and analyzed for glucose and inulin, using the glucose oxidase (Glucostat) [17], and modified Roe [44] methods respectively.

The patient remained recumbent, unsedated, often asleep during the procedure, but would chatter, play with toys and keep one member of the team singing, rocking and supplying entertainment while she was awake.

Calculations: Values derived from each of the 20-minute subperiods (A, B, C) were averaged to yield the representative means for periods I, II, III and IV, technically unacceptable data not being included in the calculations.

$$C_{in} = \frac{U_{in} \times V}{P_{in}}; F_G = P_G \times C_{in}; E_G = U_G \times V$$

$$C_G (\text{glucose clearance}) = \frac{U_G V}{P_G}$$

$$T_G = F_G - E_G = P_G \times C_{in} - U_G \times V$$

Results

Data and Calculations (table II)

Due to the patient's professed thirst, known tendency toward polyuria, yet small urine flow (1.32 to 1.97 ml/min/1.73 m²) in periods I_B and I_C, to circumvent dehydration and ensure adequate urine flow, a total of 225 ml of water was fed by gavage via an indwelling nasopharyngeal catheter, beginning at midperiod I_C and extending throughout period II. Water diuresis ensued and persisted through periods II and III, during which urine specific gravity fell to 1.003–1.005; urine flow averaged 16.4 ml/min/1.73 m²; and inulin U/P ratio ranged from 2.7 to 4.7. Osmotic diuresis probably began contributing to the enhanced urine flow during period III with significant rise of urine glucose; while the sustained diuresis ($V = 7.9$ to 14.2 ml/min/1.73 m²) of period IV was perhaps largely secondary to the marked glucosuria at this time. During period II_C, in addition to a 60 % increase in V , there was a concomitant 30 % drop of P_{in} , both contributing to a corresponding increase of C_{in} far above the mean value for period II. This C_{in} , derived from an unstable P_{in} , was felt to be spurious and excluded from calculations. Throughout the water diuresis of periods II and III, average C_{in} rose by 26.9 % over the mean for the entire titration without significant variation from one subperiod to another.

P_G samples from III_B and III_C were lost, but there was no reason to expect significant deviation of these values from that of III_A, since P_G for each subperiod tended to remain quite stable in this titration, and since other parameters had varied little throughout the

Table II. Measured and calculated data during glucose titration in patient L.W.¹

Period	P_G (mg/ml)	C_{in} (ml/min)	U_G (mg/ml)	V (ml/min)	F_G (mg/min)	T_G (mg/min)	Average T_G (mg/min)
I _A	0.31	8.47	0.035	4.6	2.63	2.47	2.50
I _B	0.30	9.51	0.073	0.5	2.85	2.82	
I _C	0.33	6.84	0.116	0.35	2.26	2.22	
II _A	0.65	13.1	0.125	0.75	8.52	8.42	9.91
II _B	0.70	16.9	0.094	4.13	11.8	11.4	
II _C	0.71	— ²	0.074	5.45			
III _A	1.74	15.2	1.22	5.7	26.5	19.5	19.5
III _B	— ²	17.7	2.10	5.4			
III _C	— ²	16.3	1.40	4.75			
IV _A	2.56	8.82	6.0	3.25	22.6	3.08	2.60
IV _B	2.36	9.10	9.83	2	21.5	1.82	
IV _C	2.36	11.5	6.73	3.6	27.1	2.91	

¹ Abbreviations used: P_G , arterial plasma glucose; C_{in} , inulin clearance; U_G , urine glucose; V , urine flow; F_G , filtered glucose; T_G , reabsorbed glucose.

² Data discarded because of technical error.

Table III. Tubular reabsorption of glucose by patient L.W. relative to arterial plasma and filtered glucose

Periods	Arterial plasma glucose (P _G) (mg/ml)	Filtered glucose (F _G) (mg/min)	Reabsorbed glucose (T _G) (mg/min)	F _G /T _G
I	0.31	2.58	2.50	1.03
II	0.67	10.16	9.91	1.03
III	1.74	26.40	19.50 (T _{mG})	1.35
IV	2.43	23.70	2.60	9.12

Table IV. Comparison of all measured and calculated data obtained during periods I and IV of glucose titration in patient L.W.¹

Periods	P _G (mg/ml)	C _{in} (ml/min)	U _G (mg/ml)	V (ml/min)	F _G = P _G × C _{in} (mg/min)	T _G = P _G × C _{in} - U _G × V (mg/min)	Average T _G (mg/min)
I _A	0.31	8.47	0.035	4.6	2.63	2.47	2.50
I _B	0.30	9.51	0.073	0.5	2.85	2.82	
I _C	0.33	6.84	0.116	0.35	2.26	2.22	
IV _A	2.56	8.82	6.0	3.25	22.6	3.08	2.60
IV _B	2.36	9.10	9.83	2.0	21.5	1.82	
IV _C	2.36	11.5	6.73	3.6	27.1	2.91	

¹ For abbreviations, see table II.

subperiods of III. Nevertheless, data from III_B and III_C were excluded from calculations.

Validity of T_G calculated from the mean of II_A and II_B and, again, from the single period of III_A may be verified as follows: 1. Substituting the mean C_{in} of II_A and II_B for that of II_C, the calculated mean T_G for period II would be 9.69 mg/min, compared to 9.91 mg/min derived from averaging data of II_A and II_B; 2. assuming P_G for III_B and III_C to be constant and equal to that of III_A, and using the average C_{in} of III_{A, B, C}, the calculated mean T_G of period III would be 19.53 mg/min, compared to 19.5 mg/min derived from the titration data of III_A alone. Thus, the mean values of T_G obtained for the 4 titration periods (tables II and III) may be considered valid even though data from periods II_C, III_B and III_C were excluded from the final analysis.

Tubular Reabsorption of Glucose Relative to the Filtered Load

Table III lists the mean values of the parameters essential for the characterization of tubular glucose reabsorption during the 4 test periods. It is noteworthy that 1. at all arterial plasma glucose levels (P_G), the rate of filtered glucose (F_G) always exceeded that of reabsorption (T_G); 2. in period III, when the rate of reabsorption had reached maximal efficiency (T_{mG}),

the gap between F_G and T_G had significantly widened in comparison with those found in the two previous periods, T_G now being less than 80 % of F_G, or, F_G/T_G = 1.35; and 3. when P_G and F_G had been raised to 8- and 9-folds of the initial levels respectively, T_G exhibited a marked fall to a rate found at the beginning of the procedure.

To exclude errors of observation and calculation as possible causes of such dramatic failure of T_G during period IV, the measured and calculated parameters obtained during each of the 20-minute subperiods (A, B, C) in I and IV were compared, as presented in table IV. From these data, it is clear that: 1. since the measured P_G and C_{in} and the calculated F_G and T_G remained fairly constant throughout the subperiods of I, and again, of IV, these values are valid [46, 47]; and 2. in this patient, a 9-fold rise of F_G was accompanied by essentially the same T_G during the initial and the final phases of the 4-hour-titration procedure.

A T_{mG} of 19.5 mg/min was achieved during period III (table III). Corrected for surface area, T_{mG} = 76.7 mg/min/1.73 m².

Following the procedure, this baby showed no changes in body weight, fever, dehydration or anemia. The electrolyte levels in serum were normal. Less than 4,000 colonies of *E. coli* per ml were cultured from a 'clean-catch' urine.

Table V. Fall in T_G or $\frac{T_G}{Tm_G}$ greater than 10 % concomitant with rise in F_G during Tm_G determinations

Reference	Diagnosis	Subject	ΔP_G	ΔGFR	Fall of T_G (mg/min)	Fall of	
						T_G/Tm_G^2	Fall of T_G/Tm_G (%)
GOVAERTS and MULLER 1939 [15]	diabetes mellitus (Pancreatectom- ized)	dog III	+	—	394 to 308		21.8
SMITH <i>et al.</i> 1943 [47]	essential hyper- tension with large 'splay' in titration curve ³	B.S. ♀, 44 years		+		0.96 to 0.81	15.6
		A.M. ♀, 50 years		+		1.1 to 0.69	37
						0.98 to 0.81	17.3
NIELSEN 1948 [35]	'normal' man	♂, 23 years	+	+	334 to 281		15.9
	diabetes mellitus with low Tm_G	♀, 55 years	+	—	262 to 208		20.6
BRADLEY <i>et al.</i> 1950 [2]	renal glycosuria	D.A.				1.04 to 0.92	11.1
REUBI 1951 [37]	renal glycosuria with large 'splay' ³	K.B.	+	+	304 to 268		11.8
		F.L.	+	—	144 to 103		28.5
ROBERTSON and GRAY 1953 [41]	diabetes mellitus	case 13 ♀	+		346 to 310		10.4
REUBI 1954 [38]	renal glycosuria	H.E.		0		1.31 to 1.00	23.7
		P.K.		0		1.55 to 0.45	71
LAMBERT 1954 [19]	renal glycosuria	Tim-♂	+	—	136.2 to 111.5		18.1 ¹
	mercury poisoning	♂, 20 years	+	0	9.75 to 4.63		52.5
FROESCH <i>et al.</i> 1957 [13]	renal glycosuria	E.T.			46 to 34 ²		26.1
STEIGERWALD 1957 [50]	renal glycosuria	Fl.				1.0 to 0.75	25

¹ Titration done with descending P_G

² Values derived by means of visual approximation from authors' graphs

³ 'Splay'—see [46]

Comments

During water diuresis of periods II and III, GFR exhibited a prompt and fairly stable 27 % elevation over the mean value of the entire titration period. Although C_{in} did decrease subsequently in period IV, it is important to note that this decrease was accompanied by elevated urine flow, urine glucose concentration and glucose-inulin clearance ratio, their respective values being 7.9 to 14.2 ml/min/1.73 m²; 6.0 to 9.83 mg/ml; and 0.9. As long as GFR remained sufficiently high to

ensure adequate urine flow and F_G/T_G ratio, Tm_G has been found to be independent of changes in filtration rate in normal dogs [45, 46], healthy female human adults [47], and men and women under the influence of adrenalin, caffeine and hyperemia [47].

That U_G has a finite value, even at the low P_G of 0.31 mg/ml, demonstrates a decidedly low renal plasma threshold for glucose in this patient [33]. This corroborates the earlier documentation of marked glucosuria (28.7 to 36.0 mg glucose/100 ml urine) in this patient during an asymptomatic hypoglycemic period with

Table VI. Fall in T_G , $\frac{T_G}{Tm_G}$, or $\frac{T_G}{GFR}$ less than 10 % concomitant with rise in F_G during Tm_G determinations

Reference	Diagnosis	Subject	ΔP_G	ΔGFR	Fall of T_G (mg/min)	Fall of T_G/Tm_G^2 or T_G/GFR^2	% Fall of	
							T_G	T_G/Tm_G or T_G/GFR
SMITH <i>et al.</i> 1943 [47]	essential hypertention; arteriosclerosis	S.D. ♀, 60 years				T_G/Tm_G 0.98 to 0.95		T_G/Tm_G 3
MIRSKY and NELSON 1943 [33]	renal glycosuria	R.T.	+	+	76 to 75		1.32 ¹	
	Bright's disease	L.T.	+	—	106 to 103		4.6 ¹	
CORCORAN 1948 [8]	renal glycosuria glomerulon- ephritis	case 1	+	—	240 to 236		1.67	
NIELSEN 1948 [35]	diabetes mellitus with low Tm_G	♀, 54 years	+	+	175.3 to 170.7		2.6	
GOVAERTS and LAMBERT 1949 [16]	renal glycosuria	Roul-♂	+	—	111 to 104		6.3 ¹	
REUBI 1951 [37]	renal glycosuria	P.S.	+	—	219 to 202		7.76	
		R.S.	+	—	153 to 147		3.9	
	essential hyper- tention with large 'splay' ³	E.Z.	+	+	301 to 297		1.33	
REUBI 1954 [38]	renal glycosuria with large 'splay' ³	H.M.		0		T_G/GFR 2.55 to 2.32		T_G/GFR 9.4
LAMBERT 1954 [19]	renal glycosuria	Sei-♀			108.5 to 105.7		2.58 ¹	
FROESCH <i>et al.</i> 1957 [13]	renal glycosuria	F.N.			142 to 132 ²		7.04	
LOTSPEICH and WORONKOW 1958 [29]	phlorizinized dog		—	+	102 to 94		7.84	
BRADLEY <i>et al.</i> 1961 [3]	'normal' dog	Cora	+	+	229 to 209		8.73	

¹ Titration done with descending P_G ² Values derived by means of visual approximation from authors' graphs³ 'Splay'—see [46]

arterial concentration of total reducing substance amounting to 29 mg % [28].

T_G in period III was the highest reabsorption rate attained during the titration, and it had a value less than 80 % of F_G , or $F_G/T_G > 1.25$. This T_G , then, by definition [14, 47], represents Tm_G . Thus, in our patient, $Tm_G = 76.7 \text{ mg/min}/1.73 \text{ m}^2$, which corresponds to 25 % of the normal value in adults, taken as $303 \text{ mg/min}/1.73 \text{ m}^2$ [49]. By available standards even for premature [5, 52, 53] and full-term [52] newborns, some of whom were shown to be capable of achieving 58 % [5] to 73 % [52] of adult normal Tm_G before 50 days of age, our 9-month-old patient exhibited a profound deficiency in renal tubular reabsorption of glucose. This resembles the state of her intestinal malabsorption of glucose and galactose [28], which, incidentally, exists independently of the influence of variable loading, thus representing a severe congenital membrane transport defect at both epithelial sites [1, 11, 24, 28, 32, 43].

The marked fall of T_G to approximately 3.4 % of adult normal Tm_G in the face of continuously elevated F_G in our observation was of particular interest. Even if the observed 40 % decrease in GFR could be postulated to have deprived a portion of tubules from glucose loading in period IV, such a hypothetical mechanism would fall far short of a quantitative explanation for the measured 87 % depression of T_G . Although Tm_G has been said to remain relatively constant in any one normal individual, both human [49] and canine [45, 46], documentation exists for a fall of T_G from Tm_G by as much as 1.3 % to 71 % with attainment of high F_G rise (tables V and VI). Such changes have been observed in patients with Bright's disease [8, 33], essential hypertension [37, 47], renal glycosuria [2, 8, 13, 16, 19, 33, 37, 38, 50], diabetes mellitus [35, 41], mercury poisoning [19]; in pancreatectomized [15] or phlorizinized [29] dogs; and, occasionally, in the 'normal' man [35], dog [3] and cat [12], although in the latter, there is no statistical datum. Most authors have ignored this phenomenon, usually assuming this to be an artifact of technique and calculation. Indeed, SHANNON [45, 46] had warned against insufficient hydration, inadequate elevation or rapid fluctuations of P_G during the procedure; and SMITH [48] as well as NIELSEN [36] had cautioned about titrations carried out with low urine flow. On the other hand, when properly performed, this method contains an inherent error of only $\pm 5\%$ [46, 47]. Thus, only some of the data in the literature revealing T_G drop which exceeded 10 % of Tm_G , concurrent with F_G rise, are considered significant and listed in table V. Those in table VI are included to lend qualitative support to the observations. It can be seen that: 1. Eleven of the 16 separate glucose titrations listed in table V recorded GFR changes. Of

these, 4 showed rising, 3 showed unchanged and 4 showed dropping GFR accompanying the significant T_G depression; 2. in all of the 30 titrations (tables V and VI), T_G dropped as F_G rose; and 3. with the exception of the one 'normal' man and the single 'normal' dog, the lists were composed of 27 subjects with distinctly low Tm_G , large 'splay' in the titration curve or chronically elevated F_G , 16 of whom exhibited renal glycosuria, and 4, diabetes mellitus. It is pertinent that the 'normal' man in table V had an average Tm_G of 302 mg/min and a C_{in}/Tm_G of 0.458, both of which reflect an average population of nephrons which would saturate and spill glucose at lower P_G levels than the normal [47]. Similarly, the 'normal' dog cited here had achieved a Tm_G of 12 mg/min/kg of body weight, which is in the lower range of normal values found by SHANNON [46]. Thus, it may be surmised that in certain types of kidneys, the maximal rate of tubular reabsorption of glucose may not be sustained after prolonged loading with high concentrations of filtered glucose; this need not require a drop in filtration rate, nor is it necessarily a technical artifact, in view of the number, diversity and competence of the observers enumerated. Rather, the common denominator in this phenomenon seems to be the type of subjects in whom it is most often observed, i.e., those with *suboptimal* renal tubular absorption of glucose relative to the filtered load, as if reflecting a sudden 'fatigue' or inhibition of an already strained transport mechanism. By whatever means, this propensity for 'fatigue' or inhibition may be *part of* the profile of defective epithelial transport of glucose in these patients.

Summary

Renal tubular transport maxima for glucose (Tm_G) was determined, using the standard method of glucose titration of the renal tubules, in an infant girl with congenital intestinal and renal malabsorption of monosaccharides. Her $Tm_G/1.73 \text{ m}^2$ was found to be no more than 25 % of adult normal values, with an apparent inability to maintain even this low level of function with prolonged elevation of the filtered load. It was postulated that such propensity for 'fatigue' or inhibition of the transport mechanism may be *part of* the underlying functional defect in these patients.

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