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Hyperfiltration and renal disease in glycogen storage disease, type I

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Hyperfiltration and renal disease in glycogen storage disease, type I. A prospective study of 14 patients (ages 6 months to 33 years) with glycogen storage disease, Type I (GSD-I) was carried out in order to define the character and frequency of renal dysfunction. A marked increase in the glomerular filtration rate (GFR) was documented in virtually all subjects, with the mean GFR raised by approximately 50%, to the range of 170 ml/min/1.73 m^2. While this constituted the only renal abnormality found in the younger patients, a significant increase in urinary albumin excretion was seen in three teen-aged individuals; three patients over 20 years of age exhibited frank proteinuria (2 to 8 g/day). Renal biopsy on two of the proteinuric subjects revealed focal and global glomerulosclerosis and interstitial fibrosis. Evaluation of factors known to cause an increase in GFR did not define the precise etiology for its elevation in GSD-I. These studies suggest that: (1) glomerular damage and chronic renal disease are common in older patients with GSD-I; (2) the renal injury appears to be specifically related to GSD-I and is not secondary to the treatment of the disease; and (3) the natural history of the renal lesion in GSD-I may be analogous to that seen in insulin-dependent diabetes, with a "silent" period where hyperfiltration is the only demonstrable renal abnormality, followed by evidence of increasing glomerular damage progressing from microalbuminuria to frank proteinuria.

Type I glycogen storage disease (GSD-I) is caused by a congenital in vivo deficiency of glucose-6-phosphatase activity, normally present in the liver, kidney and intestine. The glucose-6-phosphatase enzyme is absent in type IA GSD; microsomal translocase enzymes are absent in types IB and IC [1–3]. Glucose-6-phosphatase normally liberates free glucose from the glucose-6-phosphate produced via gluconeogenic and glycogenolytic pathways. Prominent clinical features of GSD-I include hypoglycemia on brief fasting, lactic acidosis, hypertriglyceridemia, hyperuricemia, growth failure, hepatomegaly, renal enlargement, and bleeding diathesis [1]. These abnormalities are reversed or markedly improved when fasting is avoided [4].

Several patients with GSD-I have been noted to develop renal dysfunction [5–7]. This problem was initially felt to be a complication of chronic hyperuricemia since necropsy findings were interpreted as diagnostic of uric acid nephropathy [5]. However, the use of xanthine oxidase inhibitors, together with the improved metabolic control brought about by frequent feeding plus overnight intragastric glucose infusion and cornstarch regimens, has resulted in normal to near-normal levels of serum uric acid [4]. Urate nephropathy as a complication of GSD-I might then have been expected to be eliminated. In addition, the entity of chronic uric acid nephropathy as a cause of renal insufficiency has itself been questioned [8].

The problem of chronic renal disease in GSD-I has received new interest; a recent report [9] showed that ten of eleven patients over 20 years of age had evidence of significant renal damage (proteinuria, hypertension, or decreased creatinine clearance). Three of the patients had died because of renal failure. Hyperuricemia had been controlled in recent years, and urinary tract infections were not unusually common. Renal biopsies in three patients demonstrated focal segmental glomerulosclerosis and interstitial fibrosis.

In evaluating one of our patients with GSD-I and proteinuria, an extremely high glomerular filtration rate (GFR) was found. The renal biopsy of this patient also showed focal glomerulosclerosis and interstitial fibrosis. These pathological findings are consistent with the renal lesion seen when glomerular hyperfiltration is induced in experimental animal models [10]. Preliminary studies on several other GSD-I patients revealed elevated creatinine clearance, reflecting glomerular hyperfiltration. A prospective study was then initiated, the purpose of which was to define the character and frequency of renal dysfunction in a population of GSD-I patients of varying ages, with particular emphasis on the prevalence of glomerular hyperfiltration in this population.

Methods

Subjects

Fourteen patients with GSD-I are followed at Children's Hospital of Philadelphia. They all were contacted and agreed to participate in this study. The patients ranged in age from 6 months to 33-2/12 years. Two of the patients were related (brothers). The study protocol was approved by the Committee for Protection of Human Subjects of The Children's Hospital of Philadelphia. Informed consent was obtained from all patients capable of understanding and from all parents.

Experimental protocol

All studies were carried out in the Clinical Research Center of The Children's Hospital of Philadelphia. The patients were

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Table 1. Clinical characteristics of the GSD-I patients

Pt.	Sex	Type GSD-I	Age at time of study *yr*	Overnight feedings started *yr*	Overnight program at time of study	Weight *%IBW*	Height *%ile*	Blood pressure	Prot. intake *% RDA for age*
1	F	A	0.6	Just	Infusion	93	<5	98/64	120
2	F	B	3.1	<1	Infusion	103	<5	90/58	240
3	F	A	3.9	<1	Infusion	93	<5	98/48	300
4	M	A	3.9	<1	Infusion	103	5	110/72	230
5	F	A	6.0	<1	Infusion	110	5	110/60	160
6	M	A	7.3	<1	Infusion	136	20	100/62	110
7	F	B	9.6	<1	Infusion[a]	76	<5	104/70	90
8	F	A	11.2	<1	Infusion	109	50	128/72	60
9	M	A	15.1	4	Infusion	103	5	110/80	40
10	F	A	17.3	8	Cornstarch[a]	91	50	110/60	100
11	F	A	18.3	6	Cornstarch	108	75	132/92	80
12	M	B	21.6	14	Cornstarch	122	5	126/76	70
13	M	A	27.8	Never	None	107	<5	142/98	130
14	M	A	33.2	Never	None	104	<5	128/72	140

[a] Irregular compliance

maintained on their home dietary and medication regimen. From each patient, timed urine collections were obtained for determination of GFR by creatinine clearance, total protein, albumin, and urea nitrogen. Values from replicate specimens were averaged. Four patients had inulin clearance determinations of GFR, and 11 patients had GFR determined by ^{99m}Tc-DTPA clearance [11]. Thirteen of the subjects had GFR determined by two different methods. Dietary protein intake was evaluated by recall of the home regimen and by measurement of a timed urine collection for urea nitrogen [12]. The results were then expressed as percent of RDA recommendations for age [13]. Thirteen patients had renal ultrasonography [14]. Serum levels of glucose, lactate, triglycerides, uric acid, and cholesterol were monitored preprandially and twice throughout the night during the first 24 hours of the hospital admission.

Laboratory procedures

Inulin clearance studies were performed during water diuresis according to standard protocols. Inulin concentrations in urine and plasma were determined by standard methods [15]. Creatinine clearance, total urinary protein, and albumin excretion were determined from timed urine collections. All values for GFR were normalized to ml/min/1.73 m^2. Control normal data for these assessments of GFR were obtained from the work of our group [16, 17] and the literature [11]. Albumin excretion in the urine was determined by an enzyme-linked immunoassay [18]. Data in children reflect no size- or age-related changes requiring standardization of values in terms of surface area [19]; the normal urinary albumin excretion rate ($U_{alb}V$) is less than 20 μg/min.

Results

Table 1 presents clinical information concerning the study subjects. The patients were almost evenly divided as to sex (8 female, 6 male). Eleven of these patients had GSD Type IA; 3 had type IB. The youngest patient, age 6 months, was studied within days after the initiation of the overnight intragastric feeding program. Seven of the children had started on the overnight feeding regimen before the age of one year, while four of the patients had been somewhat older (ages 4 to 14 years) at the time the program commenced. The two oldest patients in this series (who were brothers) had never been on a dietary regimen designed to avoid fasting.

Two of the patients (6 and 12) were obsese with weights greater than 120% of ideal body weight; the rest (with exception of patient #7) were within 10% of ideal body weight for height and age. The height percentiles of the patients varied from subnormal (<5%) to well within the normal range (50 to 75%). In general, the patients who had been on the program for a longer period of time and who had been compliant in its implementation demonstrated "catch-up" growth which place them within the normal percentiles, as shown by other workers [4]. Blood pressure was elevated in patient 13, intermittently raised in patient 11 and normal in the others. The dietary protein intake at the time of study, as calculated from urinary urea nitrogen excretion, was significantly greater than RDA recommendations in only four young patients (patients 2, 3, 4 and 5). These values were consistent with the protein intake as judged by dietary recall.

Other important clinical chemistry data for the patients are given in Table 2. Normal values are given at the bottom of the Table. The uric acid concentrations were normal in seven individuals, minimally elevated in four and above 7 mg/dl in only three subjects. The observations obtained at the time of the renal studies were consistent with the levels previously noted for these same patients. Eight of the 14 subjects were on treatment with allopurinol, an inhibitor of xanthine oxidase.

As previously reported [20], the pre-prandial lactate concentrations seen in most patients remained elevated (3 to 5 mM) when compared to normal controls (0.5 to 1.5 mM), but clearly lower than in the untreated state (8 to 12 mM). The lactate levels observed after the overnight infusion were generally lower than the pre-prandial specimens. The elevated plasma lactate levels were not accompanied by systemic acidemia (data not shown, but venous pH measurements averaged 7.38).

The serum triglyceride concentrations were elevated in all patients, including those who were conscientiously adhering to the prescribed program. Cholesterol levels were higher than normal in almost all (10 of 13) subjects.

The glucagon level was elevated in only one of the nine patients in whom it was measured. Pre-prandial levels of growth hormone were generally below 10 mg/ml (data not shown).

Table 2. Chemical parameters of control in the GSD-I patients

Pt.	Uric acid *mg/dl*	Lactate *mM/liter* Preprandial	Lactate *mM/liter* After overnight regimen	Triglyceride *mg/dl*	Cholesterol *mg/dl*	Glucagon *pg/ml*
1	5.8	3.4	2.5	2,830	305	ND
2	6.4	3.5	2.1	325	141	102
3	5.1	5.7	3.1	867	222	127
4	6.5	3.4	1.5	833	233	187
5	5.6	4.2	4.3	572	ND	106
6	4.6	3.0	3.0	541	220	113
7	6.2	1.2	0.9	245	193	ND
8	6.0	1.6	1.3	370	441	418
9	3.4	2.0	4.4	754	236	96
10	7.2	4.0	2.2	1,186	233	95
11	5.5	4.2	4.8	464	175	ND
12	8.3	7.8	2.0	576	514	ND
13	7.4	ND	5.2	469	312	ND
14	6.9	3.6	5.0	527	383	ND
Mean	6.1	3.7	2.9	754	278	
SEM	0.3	0.5	0.4	173	30	
Normal values	2.0–6.0	0.5–1.5	0.5–1.5	70–170	40–200	50–150

Table 3. Renal evaluation of the GSD-I patients

Pt.	Creatinine	GFR *ml/min/1.73 m²* *Tc-DTPA*	Inulin	Kidney size *Ultrasound*	Urinary albumin excretion *μg/min*
1	87	129	—	Large	11
2	300	ND	—	Large	5
3	237	153	—	Large	15
4	124	143	—	±[a]	19
5	156	267	—	Large	19
6	113	200	—	ND	7
7	167	146	—	NI	14
8	154	150	—	±	14
9	217	ND	178	±[a]	29
10	152	189	188	±[a]	32
11	156	172	—	Large	113
12	219	180	219	Large	Proteinuria
13	137	132	—	Asymmetrical	Proteinuria
14	163	ND	198	±[a]	Proteinuria
Mean	170	169	195		
SEM	15	12	9		

[a] Top limit of normal

The renal evaluation of these patients is summarized in Table 3. The GFR data are also presented graphically in Figure 1. The degree to which the GFR was increased is quite striking. In order of presumed specificity of measurement, the inulin clearance was increased in all four of the patients in whom it was used, with a mean ± SEM of 195 ± 9 ml/min/1.73 m^2 (normal: 111 ± 6 ml/min/1.73 m^2 [16]). The GFR as assessed by the Tc-DTPA method was 169 ± 12 ml/min/1.73 m^2; 9 of the 11 patients were above the normal range (120 ± 15 [11]). The creatinine clearance was also elevated to the same degree, with a value of 170 ± 15 ml/min/1.73 m^2 (normal: 125 ± 7 [17]).

The three patients in this series who were above 20 years old demonstrated gross proteinuria (range 2 to 8 g/day). Urinary albumin excretion was normal (<20 μg/min) in the youngest patients, but significantly (29 to 113 μg/min) increased in three patients aged 15 to 20 years.

Renal ultrasonography was performed on 13 patients. Using the standards of Rosenbaum, Korngould and Teele [14], one patient (7) had normal kidney size and texture, five had borderline large kidneys (patients 4, 8, 9, 10 and 14) and six demonstrated clear-cut nephromegaly (patients 1, 2, 3, 5, 11 and 12). Patient #13 had asymmetric measurements, with the right kidney being at the top limits of normal, while the left kidney was clearly normal. There appeared to be no correlation between kidney size and the degree of glomerular hyperfiltration. Coarsened texture or increased echogenicity was noted in 11 of 13 subjects (2, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14). Patient 4 was found to have bilateral nephrolithiasis, which was determined to be secondary to hypercalciuria.

Patients 12 and 13 underwent renal biopsies which showed focal and global segmental glomerulosclerosis, interstitial fibrosis, mild to moderate diffuse mesangial proliferation, and

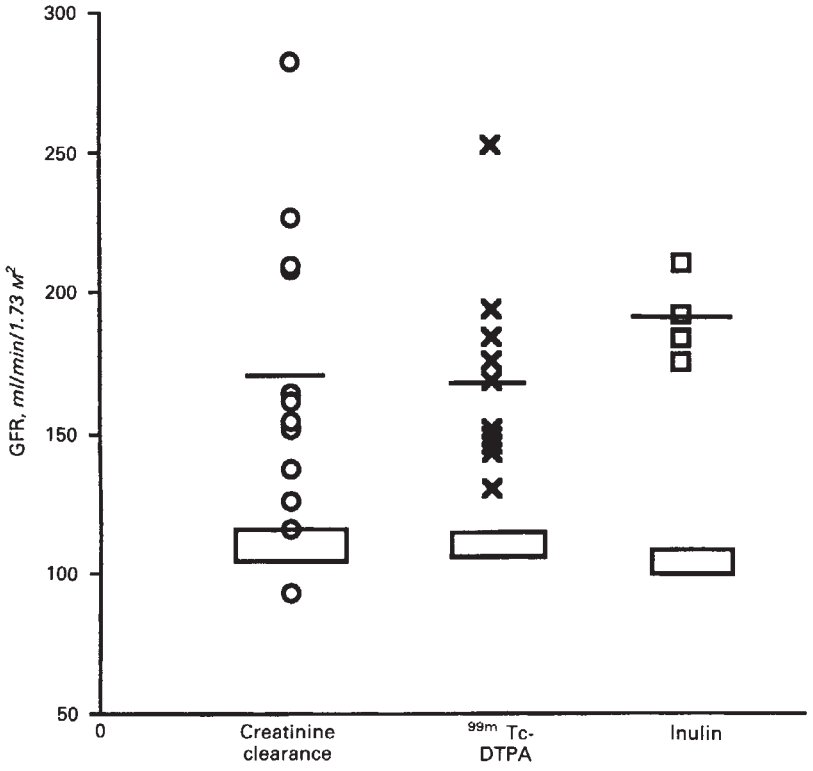

Fig. 1. *Glomerular filtration rate was estimated by three methods in patients with GSD.* In 14 patients, creatinine clearance was measured, in 12 patients plasma disappearance rates of ^{99m}TcDTPA were calculated, and in 4 patients, standard inulin clearances were performed. (□, mean ± SEM.) Normal ranges were determined from previous studies.

focal hyalinosis. Irregular basement membrane widening was found in one of the subjects. No evidence of immune deposits was found by immunofluorescence techniques. No uric acid crystals were noted on specific straining. Excessive glycogen was demonstrated in tubular epithelial nuclei.

Discussion

This study confirms and extends the observations of Chen and colleagues [9] that chronic renal disease is common in older patients with GSD-I. All three individuals in this series above the age of 20 were excreting between 2 and 8 grams of protein per day; in addition, two other patients (ages 22 and 25) who could not participate in our complete study collected 24-hour urine specimens which documented proteinuria in excess of 0.5 g/day. If these five patients are added to those presented by Chen et al [9], 15 of 16 patients with GSD-I who were older than 20 years of age had evidence of nephropathy (the one exception was a patient said to have "partial" glucose-6-phosphatase deficiency [9]).

It would also appear from the pathological evidence that the renal damage is specifically related to GSD-I (or to some aspect of the disturbed physiology found in this disease), and not to an acquired renal insult. The lesions seen on renal biopsy in our two patients included tubular glycogen deposition, interstitial fibrosis, and focal and global segmental sclerosis. These observations are similar to the characteristic abnormalities reported in the three subjects studied by Chen and co-workers [9], the three patients described by Verani and Bernstein [21], and the one young patient reported by Jonas and co-workers [22].

The major new finding in this study is the observation that glomerular hyperfiltration is found in virtually all patients with GSD-I, including those with no other documented renal functional abnormality. The prospective assessment of GFR in our patients with GSD-I documented glomerular filtration rates in the range of 170 ml/min/1.73 m^2. Twelve of the 14 patients had a clear-cut elevation of GFR by at least one of the methods employed. The only exceptions to the elevated GFR were the youngest patient (6 months old) and the individual who demonstrated the most severe degree of proteinuria. It is plausible that the baby had not yet had sufficient time to develop hyperfiltration, while the individual excreting 8 g/day of protein had already suffered sufficient glomerular damage as to cause a decrease to normal from a previously elevated filtration rate.

The pathologic lesions seen in the glomeruli of the GSD-I patients are quite similar to the changes seen in the partially nephrectomized animal model where single nephron glomerular pressure, plasma flow and filtration rate have all been documented to be high [10]. The progressive renal disease seen in GSD is therefore compatible with the role of hemodynamic factors (increased flow and/or pressure) in the initiation and/or progression of glomerular damage as postulated by Brenner [23]. On the other hand, the increased GFR may not be etiologic for the renal damage, but merely associated with other factors more responsible. Structural damage and proteinuria could possibly result from the metabolic abnormalities seen even in treated patients. Among the possibilities would be the prolonged presence of hyperlipidemia, which has been implicated in other instances of progressive renal damage [24].

The specific mechanism responsible for the elevated glomerular filtration rate seen in patients with GSD-I is unclear. The known deficiency of glucose-6-phosphatase in the kidney has been suggested as the explanation for the increased GFR [9].

However, the mechanism whereby an enzyme deficiency apparently restricted to the tubular epithelium causes glomerular hyperfiltration is obscure.

Other possible causes of glomerular hyperfiltration were sought in our patients. No relationship was noted between the GFR and other variables such as: protein intake, deviation from norms of height or weight, blood pressure, or degree of elevation of lipid levels. Increased glomerular filtration has been noted in diabetes mellitus and pregnancy, clinical conditions which were not found in our patients with GSD-I. The administration of glucagon or growth hormone to both normal and diabetic individuals results in an increase in the GFR of approximately 10% [25, 26]. Glucagon and growth hormone levels have been shown to be high in untreated GSD-I patients [27], but our data and those of Slonim et al [28] indicate that these are normalized with the introduction of the frequent feeding regimen.

Modern therapy for GSD-I dictates that patients continuously absorb glucose in order to avoid the abnormalities consequent to a fall in serum glucose concentration, which makes this situation superficially akin to the continuous feeding of hyperalimentation and hyperphagia. Nephromegaly [29] and hyperfiltration [30] have been seen with hyperalimentation therapy. Hyperphagia and obesity in an animal model has been associated with nephromegaly, glomerular hyperfiltration, albuminuria and focal glomerulosclerosis [31, 32]. However, only two of the study patients were obese. More importantly, patients 13 and 14 had never been treated with a continuous feeding regimen, but developed the same renal lesion as seen in the other GSD subjects. This strongly suggests that the nephropathy results from an abnormality associated with the disease itself, and not from the current continuous feeding treatment approach to GSD-I.

Excess protein intake is known to produce glomerular hyperfiltration, and restrictions concerning the type of carbohydrate intake in the patients with GSD-I raise the possibility of an increase in the protein consumed by the individuals. In addition, some groups [27] have advocated the use of Vivonex® as the basic overnight infusion; Vivonex® contains 10% protein. However, the overnight program used in our institution utilizes glucose alone, infused at the rate of 100 to 150% of the hepatic glucose production rate [20]. Moreover, on direct examination of protein intake (dietary history and urinary urea excretion), only 4 of the 14 subjects were found to be consuming protein greatly in excess of the RDA recommendations for age. While increased protein intake cannot account for the elevated GFR, it is possible that a high protein intake may contribute to the hyperfiltration process in GSD-I, similar to what has been noted in diabetes [33]. Reduced protein diets may afford a therapeutic approach for these patients.

It has recently been reported that the administration of lactic acid can increase GFR in both normal and diabetic subjects [34]. The mean level of lactate achieved after infusion was 1.3 mM in the diabetic patients, a concentration not as high as the lactate values often seen in GSD-I individuals. The possibility thus arises that persistently elevated levels of lactate might play a role in the mechanism of hyperfiltration. In line with this reasoning, it is also plausible that the increased levels of alanine, proline and glutamate in patients with GSD-I [27] might be involved in the process leading to hyperfiltration. Administration of these amino acids by stomach tube to dogs increases the GFR by 30 to 40%, similar to the increase in GFR after the ingestion of meat [35].

The evolution of renal disease in patients with GSD-I would appear to be analogous with what has been described for the nephropathy associated with insulin-dependent diabetes mellitus (IDDM) [36]. A long period of "silent" disease exists, with glomerular hyperfiltration as the only demonstrable renal abnormality. After 15 to 20 years, some patients begin to show an increase in the rate of urinary albumin excretion suggestive of early glomerular damage associated with changes in glomerular permeability. In IDDM, this stage has been referred to as "incipient nephropathy" [35]. Overt nephropathy with obvious proteinuria is found after 20 years of disease, with progression to more profound renal damage and ultimate renal failure. A GFR in the normal range during the period of overt nephropathy may signal the start of a progressive fall. Further studies of the renal lesion in GSD-I (including the mechanism underlying the observed hyperfiltration and interventions designed to prevent or delay glomerular damage) are likely to yield insights of importance and relevance to that more common metabolic disease, diabetes.

In summary, we have identified glomerular hyperfiltration as a common finding in patients with GSD-I. Virtually all GSD-I patients beyond the age of one year demonstrate an increase in GFR averaging almost 50%. Glomerular damage is reflected initially by an increased albumin excretion rate, but appears to progress to gross proteinuria. These changes are accompanied by the presence on renal biopsy of focal and global glomerulosclerosis and interstitial fibrosis. Because of this sequence of events, it is possible that the renal damage seen in GSD-I may be an example of glomerular hyperfiltration-hypertension mediated disease, although its specific etiologic role remains to be determined.

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