Renal Function in Glycogen Storage Disease Type I, Natural Course, and Renopreservative Effects of ACE Inhibition

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Background and objectives: Renal failure is a major complication in glycogen storage disease type I (GSD I). We studied the natural course of renal function in GSD I patients. We studied differences between patients in optimal and nonoptimal metabolic control and possible renoprotective effects of angiotensin converting enzyme inhibition.

Design, setting, participants, & measurements: Thirty-nine GSD I patients that visited our clinic were studied. GFR and effective renal plasma flow (ERPF) were measured by means of I^{125} iothalamate and I^{131} hippuran clearance and corrected for body surface area. Microalbuminuria was defined as >2.5 mg albumin/mmol creatinine and proteinuria as >0.2 g protein per liter. Optimal metabolic control was present when blood glucoses were >3.5 mmol/L, urine lactate/creatinine ratios <0.06 mmol/mmol, triglycerides <6.0 mmol/L, and uric acid concentrations <450 μmol/L.

Results: Quadratic regression analysis showed a biphasic pattern in the course of GFR and ERPF related to age. Microalbuminuria was observed significantly less frequently in the patients with optimal metabolic control compared with the patients with nonoptimal metabolic control. A significant decrease in GFR was observed after starting ACE inhibition.

Conclusions: This study describes a biphasic pattern of the natural course of GFR and ERPF in GSD I patients, followed by the development of microalbuminuria and proteinuria. Optimal metabolic control has a renoprotective effect on the development of microalbuminuria and proteinuria in GSD I patients. Treatment with ACE inhibitors significantly decreases the GFR, especially in GSD I patients with glomerular hyperfiltration.

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Glycogen storage disease type I (GSD I) is an autosomal recessive inborn error of carbohydrate metabolism caused by a defect in the glucose-6-phosphatase (G6Pase) enzyme complex. It has an estimated incidence of 1 in 100,000 newborns. The G6Pase enzyme complex is needed in both glycogenolysis and gluconeogenesis to hydrolyze glucose-6-phosphate to glucose. The enzyme defect results in severe fasting hypoglycemia, hyperlactacidemia, hyperuricemia, and hyperlipidemia. Untreated patients have a protruding abdomen because of marked hepatomegaly (storage of glycogen and fat), short stature, truncal obesity, rounded doll face, wasted muscles, and bleeding tendency caused by impaired platelet function (1,2).

The disease can be well controlled metabolically by use of a lifelong intensive dietary treatment, aimed at maintaining normoglycemia and suppressing secondary metabolic derangements. The diet consists of frequent meals during the day and gastric drip feeding or uncooked cornstarch at night. The life expectancy of patients with GSD I has considerably improved, although various complications occur with increasing age (3).

In patients with GSD I, several renal complications have been reported. Enlargement of the kidneys is the earliest finding, caused by accumulation of glycogen in the kidneys and often contributing to the diagnosis of GSD I. Because of the hyperuricemia, uric acid nephrolithiasis and gout nephropathy can develop. These complications can, however, be prevented by improvement of the metabolic derangements with dietary treatment and by means of a xanthine oxidase inhibitor. Another cause of nephrolithiasis is the decreased urinary citrate excretion in combination with an increased urinary calcium excretion that occurs in GSD I patients. This condition can be treated with potassium citrate supplementation (4,5). Proximal tubular dysfunction has also been described in patients with GSD I. Hyperphosphaturia and loss of bicarbonate in urine can lead to renal tubular acidosis. These findings often resolve after starting intensive dietary treatment (6).

Both glomerular hyperfiltration and persistent proteinuria have previously been reported (7–10). Renal biopsies performed in three GSD I patients with persistent proteinuria

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showed focal segmental glomerulosclerosis (11). These findings might suggest an etiology of glomerular hyperfiltration and proteinuria similar to diabetic nephropathy (12). With increasing age, the impairment of renal function in GSD I patients might become an important factor in quality of life and life expectancy.

In patients with diabetes, randomized controlled trials have shown that treatment with angiotensin converting enzyme inhibitors (ACEi) significantly reduces the risk for onset of nephropathy, the risk for progression from microalbuminuria to microalbuminuria and increases the rate of regression to normoalbuminuria (13). Even in normotensive diabetic patients, these drugs reduce the intraglomerular pressure by specifically relaxing the efferent glomerular arterioles (14). This effect has not yet been proven in GSD I patients, although Melis *et al.* (15) described a decrease in GFR and a delay in progression from glomerular hyperfiltration to microalbuminuria in patients with GSD I.

In this study, we analyzed the natural course of the GFR, effective renal plasma flow (ERPF), and the incidence of microalbuminuria and proteinuria in 39 patients with GSD I. We studied differences in GFR, microalbuminuria, and proteinuria between GSD I patients classified as having optimal or nonoptimal metabolic control. Finally, we analyzed the effects of ACEi on the severity of microalbuminuria and proteinuria.

Materials and Methods

Patients

A total of 39 patients, 32 GSD Ia and 7 GSD Ib, that visited our clinic were studied. The GSD I diagnosis was confirmed by enzymatic and/or mutation analysis. Of these subjects, 16 were male and 23 were female. Median age at diagnosis was 0.6 yr (range, 0.0 to 9.8 yr). Median age at first investigation was 11.6 yr (range, 0.8 to 23.1 yr). Median body mass index Z-score for age (BMI Z-score) was 0.88 (range, −3.45 to 2.92). None of the patients had used anti-hypertensive drugs before the first renal studies were performed. GFR measurements before and after start of the ACEi were available in 22 patients; the median time between the start of the ACEi and the following GFR measurement was 1.6 yr (range, 0 to 5.1 yr).

Measurement of Laboratory and Clinical Data

GFR, ERPF, and filtration fraction (FF) measurements were performed by means of I^{125} iothalamate and I^{131} hippuran clearance (16). Height and weight were measured in every patient before investigation. GFR and ERPF measurements were corrected for body surface area. Reference values for all age groups beyond 1 yr of age for GFR are between 90 and 145 ml/min per 1.73 m^2 and for ERPF are <625 ml/min per 1.73 m^2 (17). BP (mmHg) was determined before every GFR measurement. Hypertension was considered present when the p95 value for age was exceeded (18). Creatinine and urea concentrations in blood were studied before every GFR measurement.

To distinguish between patients with optimal and nonoptimal metabolic control, blood glucose, triglyceride, and uric acid levels, as well as urine lactate/creatinine ratios, were studied according to standard laboratory procedures in all patients at the time of renal investigations. All patients were in a steady state concerning metabolic control. In 2000, the European Study on Glycogen Storage Disease type I was completed, and biochemical targets were defined for the management of GSD I (19). According to these guidelines, patients are considered to have optimal metabolic control when blood glucoses are >3.5 mmol/L, urine lactate/creatinine ratios are <0.06 mmol/mmol, triglycerides are <6.0 mmol/L, and uric acid concentrations are <450 μmol/L. We studied possible differences in the natural course of renal function between patients with good metabolic control and patients with poor metabolic control by assessment of the above-described biochemical parameters.

Microalbuminuria and proteinuria were assessed in 12- and 24-h urine collections, respectively. Microalbuminuria was defined as >2.5 mg albumin/mmol creatinine and proteinuria as >0.2 g protein/L.

Microalbuminuria assessments (mg/mmol creatinine) before and after the start of the ACEi were studied for the purpose of investigating a possible renopreservative effect of the ACEi on renal function of GSD I patients.

Statistical Analyses

Because the frequency of renal function measurements differed among our patients, we analyzed the first renal function measurement of every patient to prevent over-representation of some of the patients. The age at first investigation varied considerably, because some of the patients were referred to our hospital at a later age and, in some older patients, renal function was not investigated in childhood. In total, 39 GFR, ERPF, and FF values were analyzed. GFR, ERPF, and FF measurements, corrected for body surface area (BSA), were plotted against age at the time of the investigation. The course of the GFR and ERPF in relation to age, gender, and metabolic control was analyzed by linear and quadratic regression (SPSS 14.0). The differences in milligram albumin excretion per millimoles creatinine and protein excretion in grams per liter between patients with optimal and nonoptimal metabolic control were analyzed by a Mann-Whitney test (SPSS 14.0). The incidence of microalbuminuria and proteinuria in relation to metabolic control was analyzed by performing a Pearson χ^2 test (SPSS 14.0). Differences in GFR before and after the start of the ACEi in the entire patient group and in the subset of patients started with the ACEi in the period of glomerular hyperfiltration were analyzed by a Wilcoxon signed rank test (SPSS 14.0). The effects of ACEi on the severity of microalbuminuria and proteinuria in the entire patient group and in the subset of patients started with ACEi before the age of 12 yr was analyzed by a Wilcoxon signed rank test (SPSS 14.0).

Results

All patients showed normal creatinine and urea concentrations in blood. Hypertension was observed in 2 of 39 patients: a 15-yr-old boy and a 23-yr-old woman. The female patient with hypertension also had severe microalbuminuria and proteinuria. According to the above-described parameters, 11 patients met the criteria for optimal metabolic control and 28 patients had nonoptimal metabolic control. The age at investigation did not differ between the patients with optimal and nonoptimal metabolic control (mean, 10.0 and 10.5 yr, respectively).

Of the 39 included patients, 26 showed glomerular hyperfiltration (67%). Figure 1 shows GFR corrected for BSA in relation to age. Quadratic regression analysis showed a clear biphasic pattern in the course of GFR related to age (P = 0.01). Women in our patient group had a significantly lower GFR than men (P = 0.02). ERPF measurements showed a similar biphasic pattern in relation to age (P = 0.00), as shown in Figure 2. Filtration fraction ratios showed normal values for age (range, 0.19 to 0.28). Repeated GFR measurements per patient are shown in Figure 3. The mean slope of the individual GFR

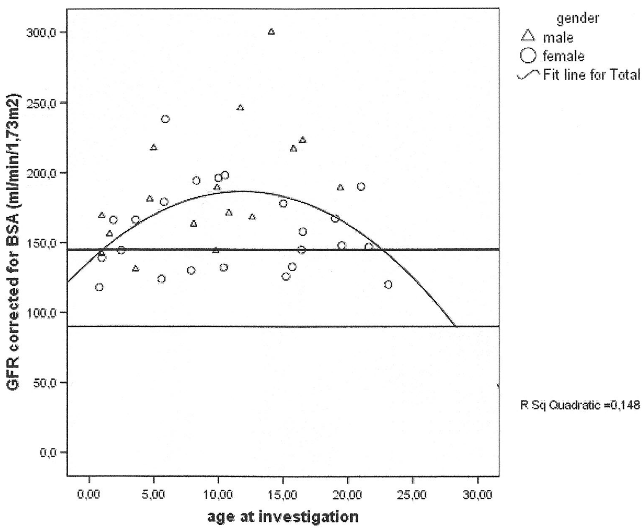

Figure 1. Natural course of GFR in GSD I patients.

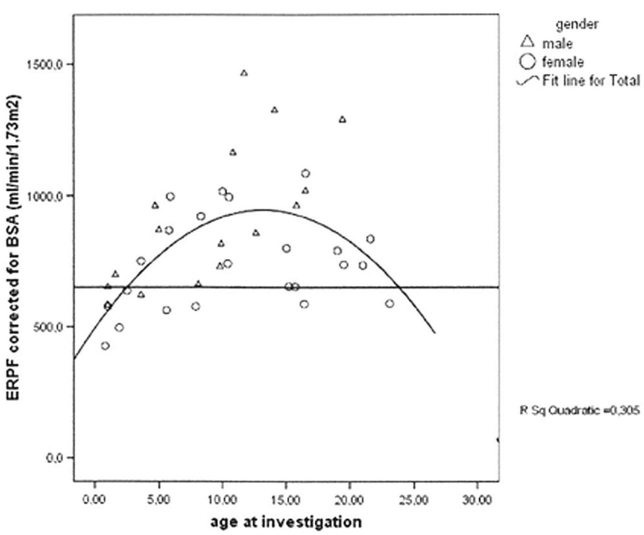

Figure 2. Natural course of ERPF in GSD I patients.

curves is 0.19 ml/min per 1.73 m^2 per year between 0 and 10 yr, 0.38 ml/min per 1.73 m^2 per year between 10 and 15 yr,and −0.43 ml/min per 1.73 m^2 per year over 15 yr of age. This confirms the biphasic pattern shown in Figure 1. The degree of metabolic control did not have any effect on the course of the GFR (P = 0.331).

The incidence of microalbuminuria and proteinuria is shown in Table 1. Beyond the age of 18 yr, microalbuminuria is seen in 67% and proteinuria in 42% of our patients. The patients with nonoptimal metabolic control had a tendency toward a higher urinary albumin excretion per millimole creatinine (median, 2.80) than the patients with optimal metabolic control (median, 1.13; P = 0.09). Also, urinary protein concentrations tended to be higher in patients with nonoptimal metabolic control (mean, 0.33 g/L) in comparison to optimal controlled patients (mean, 0.02 g/L; P = 0.14). Microalbuminuria was observed significantly less frequent in the patients with optimal metabolic control compared with the patients with nonoptimal metabolic control (Table 2; P = 0.02). Proteinuria seemed to be less frequent in the patients with optimal metabolic control compared with patients with nonoptimal metabolic control, although no significant difference could be found (Table 3; P = 0.10).

Treatment with the ACEi started at a mean age of 14.6 yr. Figure 4 shows the GFR values corrected for BSA, in relation to age, before and after starting the ACEi. Regression analyses showed no significant differences in the course of GFR, although GFR in the patients without the ACEi seems to show a higher peak GFR and a tendency toward a steeper decline thereafter. We compared GFR values before and after starting the ACEi in 22 GSD I patients and found a tendency toward a decrease in GFR of 16 ± 8 ml/min per 1.73 m^2 after starting the ACEi (P = 0.06). However, because of the biphasic course of renal function described before, decreases in GFR can be caused by the natural course alone. Therefore, we studied a subgroup of 13 patients that had hyperfiltration before starting the ACEi. In these patients, a significant decrease in GFR of 25 ± 12 ml/min per 1.73 m^2 was observed after starting the ACEi (P = 0.04).

Data on urinary albumin and protein excretion before and after starting the ACEi were available for 23 GSD I patients. The changes in the severity of microalbuminuria (in mg/mmol creatinine) after the start of the ACEi varied considerably between patients. No significant decrease in microalbuminuria after starting the ACEi could be established (P = 0.80). In the small group of patients that started with the ACEi before the age of 12 yr (n = 8), no differences in the degree of microalbuminuria after starting the ACEi could be found (P = 0.21). No decrease in proteinuria was observed after starting the ACEi (P = 0.67). Also, in the patients that started the ACEi before the age of 12 yr, no decrease in proteinuria could be seen (P = 0.65).

Discussion

Our data suggest that the natural course of renal function in GSD I shows a biphasic pattern with a peak GFR in the mid-second decade. The course of the ERPF shows a similar course, indicating that hyperperfusion is the cause of the hyperfiltration in GSD I patients as opposed to an increased intraglomerular pressure, in which a normal ERPF and an increased FF would be expected.

Even in some of our youngest patients, microalbuminuria and proteinuria was detected. In the young adult GSD I patients (18 to 24 yr), microalbuminuria was present in 67% and proteinuria in 42% of patients.

This pattern of hyperfiltration, later accompanied by microalbuminuria and overt proteinuria, followed by a decline in GFR thereafter, resembles the course of diabetic nephropathy (12). This resemblance is confirmed by the fact that histologic studies of renal biopsies in GSD I patients have shown similarities with the histologic findings in diabetic nephropathy(20,21). In diabetic patients, however, hypertension is an important additional risk factor in the development of nephropathy (14). In our group of GSD I patients, hypertension did not seem to play a role in the development of nephropathy, because only two of our patients met the criteria for hyperten-

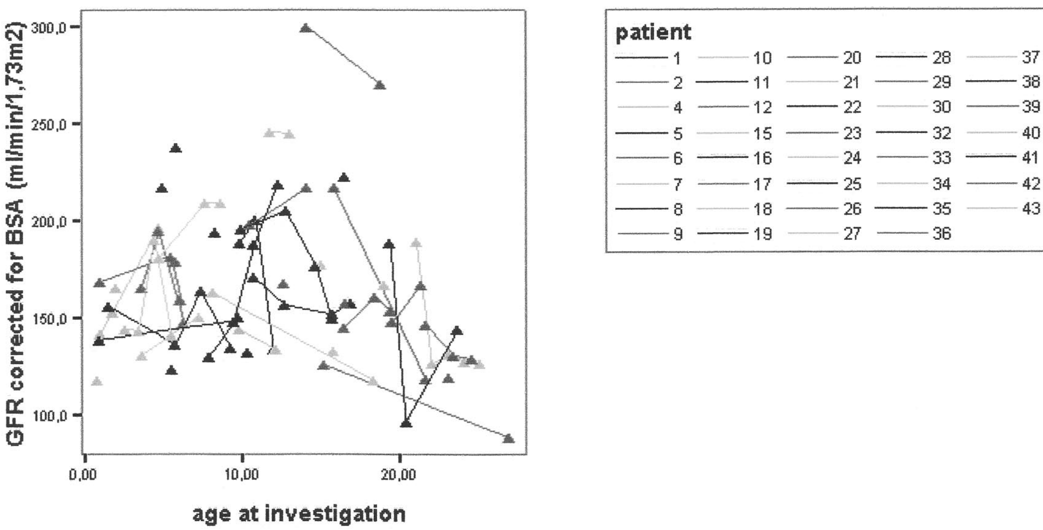

Figure 3. Repeated GFR measurements per patient.

Table 1. Incidence of microalbuminuria and proteinuria per age group

	0–6 yr	6–12 yr	12–18 yr	18–25 yr
Microalbuminuria	5/9 (55%)	2/8 (25%)	0/7 (0%)	8/12 (67%)
Proteinuria	0/9 (0%)	1/8 (13%)	0/7 (0%)	5/12 (42%)

Table 2. Relationship between microalbuminuria and metabolic control

	Metabolic Control		Total
	Nonoptimal	Optimal	
Microalbuminuria			
Present	14	1	15
Not present	12	9	21
Total	26	10	36

Table 3. Relationship between proteinuria and metabolic control

	Metabolic Control		Total
	Nonoptimal	Optimal	
Proteinuria			
Present	6	0	6
Not present	20	10	30
Total	26	10	36

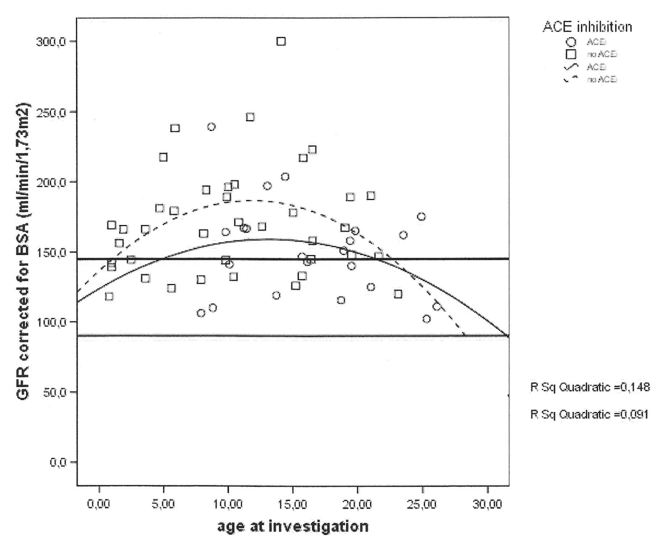

Figure 4. GFR in GSD I patients before and after ACE inhibition.

sion. Moreover, even in GSD I patients with apparent dyslipidemia, no premature atherosclerosis was shown (22).

The degree of metabolic control did not influence the course of the GFR in our patients, but the patients with nonoptimal metabolic control showed a tendency toward higher urinary albumin excretions in comparison to the patients in optimal metabolic control. Moreover, a higher incidence of microalbuminuria and a trend toward a higher incidence of proteinuria was seen in the group with nonoptimal metabolic control compared with the patients with optimal metabolic control. Although the assessment of metabolic control took place at the time of the first renal investigation, it has shown to be a good reflection of the metabolic control of a longer period of time in our patients. Our data therefore indicate that optimal metabolic control has a renoprotective effect on the development of microalbuminuria and a possible renoprotective effect on the development of proteinuria in GSD I patients.

In patients with diabetic nephropathy, a renoprotective effect of the ACEi has been described (13,14). In our patients, a significant decrease in GFR was observed when the ACEi was prescribed to the patients with glomerular hyperfiltration. We could not prove a renoprotective effect of the ACEi on the severity of microalbuminuria and proteinuria in our study group of GSD I patients. This could be because of the relative small number of patients and the fact that, in a large group of these patients, an ACEi was not started until glomerular hyperfiltration or microalbuminuria had been established. However, in diabetic nephropathy, treatment with the ACEi in the presence of microalbuminuria and even the ACEi treatment of overt diabetic nephropathy have been shown to be effective (14). Probably, renal damage in GSD I patients is caused early in life by increased amounts of glucose-6-phosphate, leading to activation of the protein kinase C and upregulation of the renal angiotensinogen (12). This might explain why starting an ACEi later in life does not have an influence on the development of microalbuminuria and proteinuria. In that case, ACEi treatment should be started earlier, as suggested by Melis *et al.* (15), in the stage of hyperfiltration, to prevent renal damage. In diabetic patients, hypertension is an important risk factor in the development of diabetic nephropathy. The majority of our patients did not have hypertension, and therefore, an ACEi might not have such a significant effect as is seen in diabetic patients. However, in the earlier stages of renal disease, diabetic patients with microalbuminuria often are normotensive (14), so hypertension might become apparent later in life in GSD I patients. Long-term follow-up of GSD I patients is necessary to see if hypertension will develop in these patients. Prospective studies, started early in life, are needed to investigate whether an ACEi might be of benefit in GSD I patients.

In conclusion, this study described a biphasic pattern of the natural course of GFR and ERPF in GSD I patients, followed by the development of microalbuminuria and proteinuria. This bears resemblance to the development of nephropathy in patients with diabetes mellitus, although GSD I patients lack the risk factors of hypertension and arteriosclerosis, as is seen in diabetic patients. Optimal metabolic control has a renoprotective effect on the development of microalbuminuria and proteinuria in GSD I patients. Treatment with an ACEi significantly decreases the GFR, especially in GSD I patients with glomerular hyperfiltration. The ACEi did not decrease the severity of microalbuminuria or proteinuria in this group of patients. However, this effect might become more clear in a larger number of patients started with an ACEi early in life. Therefore, prospective trials, studying this possible renoprotective effect of ACEi, are warranted.

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Disclosures

None.

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