GSD and the Kidneys

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INTRODUCTION

- Glycogen storage diseases (GSD) are inborn errors of metabolism with abnormal storage or utilization of glycogen

- Development of renal dysfunction in GSD-I cases was first reported by Chen et al. in 1988

- GSD nephropathy is a frequently reported complication, probably primary due to:

  -enzyme deficiency in the kidneys

  -secondary to the abnormal metabolic environment resulting from enzyme deficiency in the liver

GSDs with renal dysfunction

Table 1. Diverse renal findings in various types of glycogen storage disease

Type I	glycogen storage disease (Von Gierke's disease)
	Focal segmental glomerulosclerosis and interstitial fibrosis
	Amyloidosis
	Fanconi-like syndrome
	Renal stones/nephrocalcinosis
Type III	glycogen storage disease (Cori's disease)
	Renal tubular acidosis
Type V	glycogen storage disease (McArdle's disease)
	Myoglobinuria
	Acute renal failure
Other	Hepatic glycogenosis and Fanconi syndrome

GSD1 and renal manifestation

- Renal manifestations of GSD I appear early in childhood and often go undetected
- Glycogen deposition occurs in the kidneys, which typically are large on renal imaging
- Nephromegaly is not sufficient to be readily detected on physical examination
- Renal involvement includes : proximal and distal renal tubular dysfunction and progressive glomerular injury

Proximal and distal tubular dysfunction

- The proximal tubule is the site of a great deal of energy expenditure and G6Pase activity is normally highest

- Proximal tubular dysfunction has been ascribed to glycogen accumulation in proximal tubular cells or inability to produce glucose for metabolic needs

- With proximal tubular dysfunction, wasting of bicarbonate, phosphate, glucose, and amino acids can be seen

- Along the proximal tubule, there is also defective sodium-linked reabsorption of calcium and the organic acids such as citrate

- Glycogen deposition in the proximal tubule does reduce proximal tubular calcium reabsorption and is the likely mechanism for hypercalciuria in GSD I.

- The citrate in the urine plays an important role in chelating urinary calcium and helping to prevent nephrolithiasis or nephrocalcinosis

- In GSD I, instead of the usual increasing urinary excretion of citrate with ongoing maturity, there is an actual decrease in citrate excretion that accelerates during adolescence and early adulthood.

- Even in metabolically well controlled GSD I with normal acid–base status or compensated mild metabolic acidosis without systemic pH change, there is widespread hypocitraturia

- Over time, GSD I patients develop an incomplete distal renal tubular acidosis that may also contribute to the low urinary citrate levels and hypercalciuria

- The combination of hypercalciuria and hypocitraturia enhances the likelihood for urinary calcium precipitation and readily accounts for the high rates of urinary tract calcifications

Therapeutic strategies for renal tubular dysfunction

- Oral citrate supplementation will augment citrate excretion and is likely very beneficial in GSD I patients with low urinary citrate levels
- With citrate supplementation, the aim is to achieve at least 300 mg/g creatinine on spot urine
- Potassium citrate is preferred over sodium citrate because higher sodium intake is linked to greater urinary calcium excretion.
- Liquid potassium citrate preparations are well tolerated at an initial dose of 1 mEq/kg/day TID and / older children and adults, potassium citrate tablet at a dose of 10 mEq TID

- Citrate use should be monitored because it can cause hypertension and life threatening hyperkalemia in the setting of renal impairment

- With hypercalciuria, thiazide diuretics can also be provided as a way to enhance renal reabsorption of filtered calcium and decrease urinary calcium excretion

- The efficacy of therapy can be gauged by interval urinary calcium-to-creatinine ratios.

- Other nonspecific measures to reduce urinary calcium deposition,

  -optimizing hydration

  -maintaining a no-added salt diet

  - supplementing magnesium intake

Glomerular injury

- GSD I mediates hemodynamic and structural changes in the kidney that can lead to the development of glomerular injury

- The mechanisms:

  -activation of the renin–angiotensin system,

  -prolonged oxidative stress,

  - and profibrotic cytokines such as transforming growth factor-β

- These renal changes occur early, and many children with GSD I will have evidence of glomerular hyperfiltration or elevation in the glomerular filtration rate (GFR) to more than 140 ml/min/1.73 m2 within a few years of life.

- These changes in GFR may not be readily detected because they result in serum creatinine levels that are often reported as normal.

- Actually GSD I patients are CKD stage 1 according to DOQI guideline classification (GFR>90)

Glomerular injury

With hyperfiltration, enhanced glomerular blood flow and intraglomerular pressure

accelerate the normal rate of glomerular obsolescence

As glomeruli become obsolete, fibrosis replaces surface area that previously allowed filtration

Histologically it appears as focal and segmental sclerosis

Glomerular injury

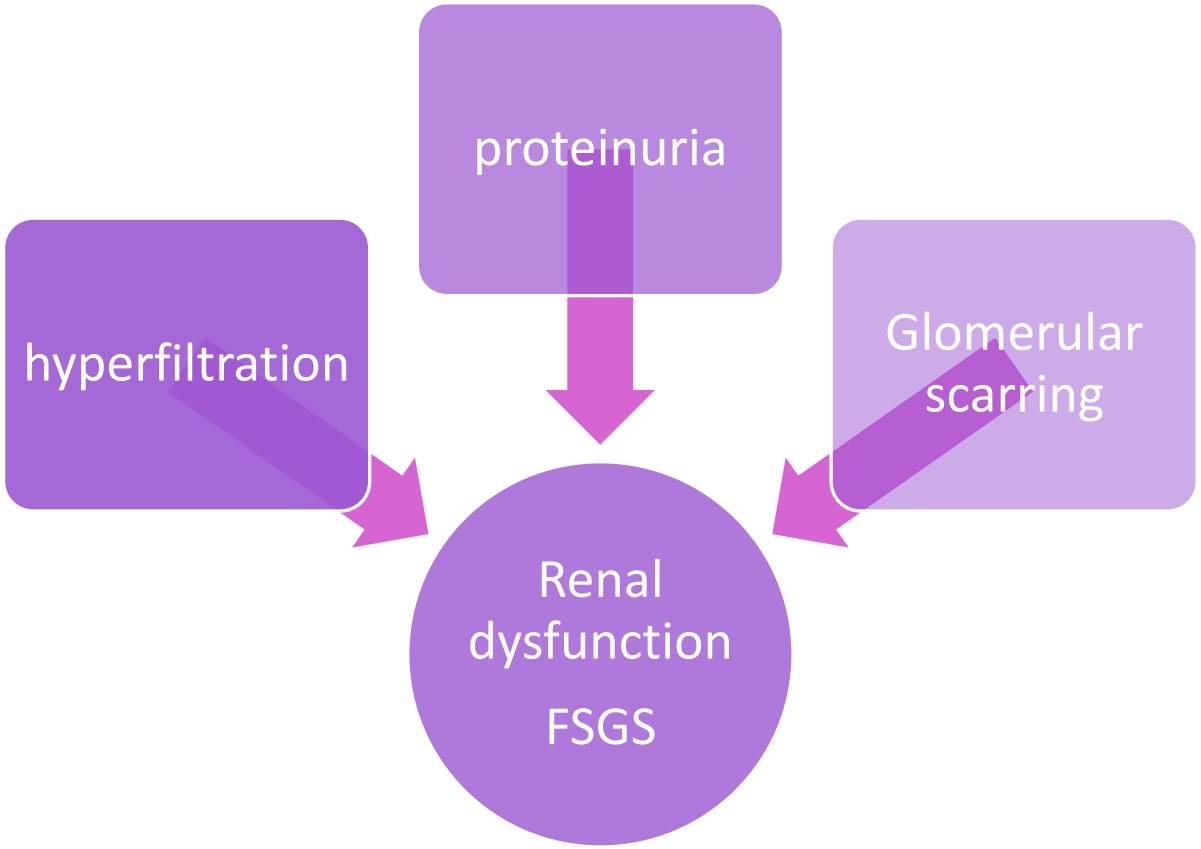
scarring progresses and encompasses entire glomeruli

resulting loss of viability of the tubular segments and areas of interstitial fibrosis

As more and more glomeruli are lost to scarring, the overall GFR decreases

Result is ESRD

- Because there is early glomerular scarring, there is the development of microalbuminuria
- Over time, microalbuminuria has a tendency to progress to frank proteinuria
- Chronic proteinuria is thought to exacerbate glomerular injury through induction of chemokines and inflammatory pathways
- In GSD I, the development of pathologic proteinuria may be inevitable


proteinuria
hyperfiltration
Glomerular scarring
Renal dysfunction
FSGS

Attenuating hyperfiltration injury

- Optimal metabolic control of serum glucose, triglyceride, and uric acid concentrations and urine lactate/creatinine ratios cause less proteinuria

- Once proteinuria has occurred and there is established renal injury in GSD I, it becomes less clear if metabolic control alone alters the loss of GFR over time

- GSD I patients treated with angiotensin blockade show improvement in their degree of glomerular hyperfiltration and can demonstrate restored normal rates of GFR

- Either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) medication by itself can be efficacious

Routine evaluation and management

- GSD metabolic control are beneficial to general renal health because they help prevent acidosis , hyperuricemia and hyperlipidemia
- Chronic acidosis: hypercalciuria and hypocitraturia
- Hyperuricemia and hyperlipidemia : causing or accelerating renal injury
- Effective dietary therapy for their GSD I : unlikely diffuse proximal tubular dysfunction.

- Periodic assessment of serum electrolytes, calcium, and phosphate , blood urea nitrogen and creatinine levels

- GFR should be estimated from the serum creatinine using Bedside Schwartz Equation in children or the MDRD Equation for adults

- Hyperfiltration is present if estimated GFR exceeds 140 ml/min/1.73 m2, and angiotensin blockade should be considered

- Screening urinalysis should be performed at intervals on all GSD I patients.

- Hematuria : assessment of urinary calcium excretion and ultrasound imaging of the urinary tract for calcifications.

- Renal ultrasound should be performed at intervals to assess kidney size and to assess for evolving nephrocalcinosis or nephrolithiasis

- Despite good metabolic control, hypocitraturia and hypercalciuria may be common in GSD I and, as a result, urine should be assessed at regular intervals for calcium and citrate excretion even if urinalysis is benign

- Urine should also be assessed for microalbuminuria and proteinuria

- Positive results should be confirmed using a first morning void sample to rule out any orthostatic component.

- Persistent microalbuminuria or frank proteinuria : initiation of angiotensin blockade despite patients being normotensive.

- Medications should be adjusted to try to blunt the proteinuria to levels that are normal or as near normal without causing hyperkalemia and hypotension

- Hypertension accelerates renal injury : blood pressure should be maintained in a normal range for adults and at less than the 90th percentile for age, gender, and height for children.

- Long-term exposure to nephrotoxic medications should also be avoided : nonsteroidal anti-inflammatory drugs such as ibuprofen and is especially if there is any reduction in GFR

- Metabolic derangement from ongoing chronic renal insufficiency may exacerbate some of the issues that arise from GSD

- In this case the option of both liver and kidney transplant may be considered

Renal function in pediatric GSD-I patients after Liver transplantation

- post-LT renal function was well preserved in most GSD-I patients
- LT cannot reverse the preoperative renal dysfunction but may prevent or slow the progression of albuminuria and CKD
- The timepoint of starting cornstarch therapy in GSD-I patients of pre-school age may be critical for long-term renal function

CONCLUSION

- Chronic renal disease is a serious risk for patients with GSD I.
- Glomerular hyperfiltration is seen in the early stage of the renal dysfunction and can occur before proteinuria
- The predominant underlying renal pathology is focal segmental glomerulosclerosis
- The risk factors for developing the glomerulosclerosis in GSD-I include hyperfiltration, hypertension, hyperlipidemia and hyperuricemia
- Renal stones and/or nephrocalcinosis are also common findings
- Corn starch and strict metabolic control has significantly improved the prognosis of patients with GSDIa