CME Series on Lysosomal Disorders

Kidney Involvement in Lysosomal Disorders

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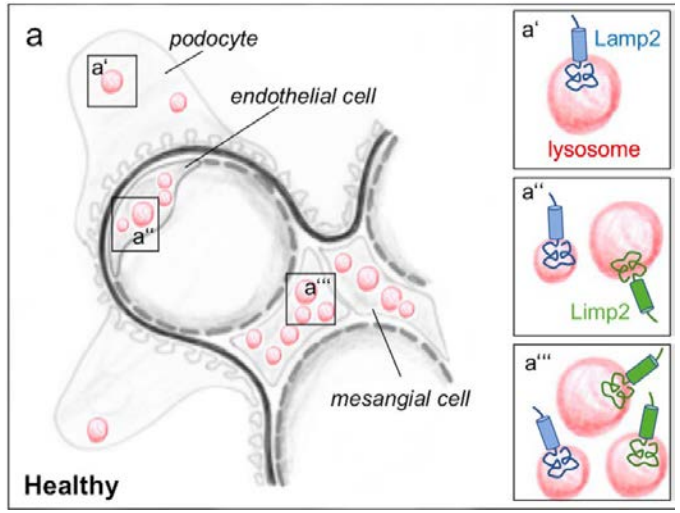
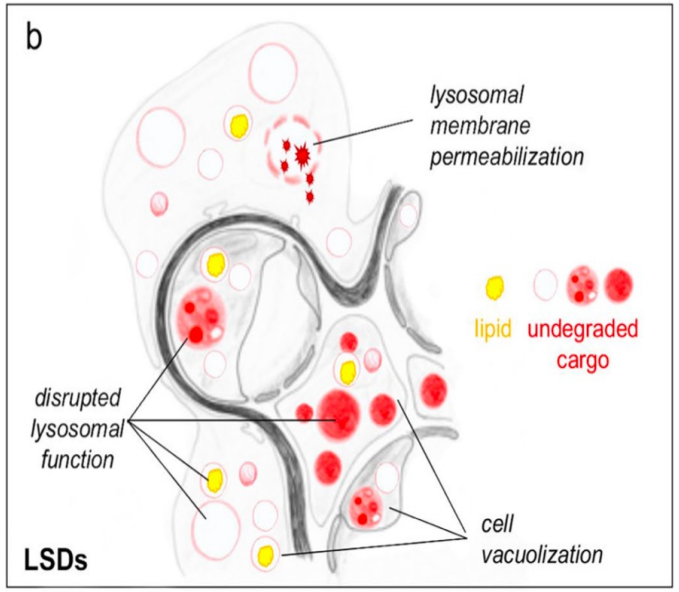
The functions of lysosomes in renal health and disease

- **Recycling of low molecular weight proteins that cross the glomerular filter**
- **Regulation of water reabsorption by the principal cells and electrolyte homeostasis**
- **Lysosomes in healthy glomerular cells:** Dissection of the expression of lysosomal membrane pro- teins among glomerular cell types suggests the existence of different subsets of endocytic/lysosomal vesicles within podocytes, mesangial and glomerular endothelial cells. Limp2-positive vesicles are predominantly found in mesangial and glomerular endothelial cells. Lysosomal disorders primarily affect glomerular cell types differentially due to a potentially differing capacity in lysophagy,

Surendran et al Pediatr Nephrol. (2014)
Meyer-Schwesinger Cell and Tissue Research (2021)





Lysosomal disorders (LSDs) in with renal involvement

Disease (#OMIM)	Gene	Protein	Protein function	Renal findings
Cystinosis #219750 #219800	*CTNS*	Lysosomal membrane protein cystinosin	Cystine transport across the lysosomal membrane	Renal tubular Fanconi syndrome, renal failure, renal calculi
Fabry disease #301500	*GLA*	Lysosomal enzyme α-Galactosidase A	Hydrolysis of the terminal alpha-galactosyl moieties from glycolipids and glycoproteins	Glomerular endothelial cells, hypertrophic foamy podocytes with zebra bodies, mesangial expansion
Sialidosis #256150	*NEUI*	Lysosomal enzyme α-(2-6) neuraminidase	Cleavage of glycosidic linkages of neuraminic acids	Frequently observed glomerulopathy that develops early and causes death. Diffuse and severe vacuolization of glomerular and tubular cells
Mucopolysaccharidosis I #607016	*IDUA*	Lysosomal enzyme α-L-iduronidase	Degradation of glycosaminoglycans	A rare case of nephrotic syndrome
Mucolipidosis II/III #252500 #252605	*GNPTAB* *GNPTG*	Golgi-resident GlcNAc-1-phosphotransferase	M6P modification of mannose residues on lysosomal enzymes	Rare cases of foamy podocytes
Mucolipidosis type IV #252650	*TRPML1*	Lysosomal Ca^{2+} channel	Mediates Ca^{2+} release from the lysosomal lumen to the cytosol, can be activated by starvation, reactive oxygen species, Phosphatidylinositol 3,5 bisphosphate	Accumulation of all phospholipid species, of several glycolipids, and of gangliosides
Niemann-Pick A/B #257200 NPC #607616 #257220	*SMPDI* *NPC1* *NPC2*	Lysosomal enzyme acid sphingomyelinase (ASM) NPC1 and NPC2: lysosomal cholesterol binding proteins	ASM: breakdown of sphingomyelin to ceramide and phosphoryl- choline NPC1 and NPC2: regulation of intracellular cholesterol trafficking	Rare cases of sphingolipid accumulation in kidney
Myoclonus –Nephropathy AMRF (action myoclonus renal failure) #254900	*SCARB2*	LIMP2	Mannose independent targeting of beta GCase	Nephrotic syndrome with vacuolization in distal and collecting tubules (Balreira et al. , 2008)

Adapted from Meyer-Schwesinger
Cell and Tissue Research (2021) 385:371–392

Role of Nephrologists in Diagnosing and Monitoring Lysosomal Disorders

Early Detection and Screening:

Nephrologists are often among the first to identify potential signs of LSDs during routine evaluation of unexplained renal symptoms such as proteinuria, hematuria, or decreased kidney function.

Kidney Biopsy : In cases where the diagnosis is unclear, a kidney biopsy may be performed. Nephrologists analyze biopsy results for characteristic findings of LSDs, such as lysosomal inclusions within renal cells

Interpreting Laboratory Findings:

Nephrologists work closely with geneticists and laboratories to interpret these results in the context of the patient's clinical presentation.

Differential Diagnosis:

They play a key role in differentiating LSDs from other causes of renal pathology through comprehensive clinical evaluation and understanding of the unique manifestations of these disorders.

Consultation and Referral:

Nephrologists often collaborate with or refer patients to geneticists, metabolic specialists, or multidisciplinary teams experienced in managing LSDs for further evaluation and management.

Patient Education and Counseling:

They provide patients and their families with information about the diagnosis, potential renal implications, and the importance of specialized care for managing their condition.

Role of Nephrologists for Comprehensive Care and Treatment Approaches

- **Managing Kidney-Related Symptoms and Complications:**
  - Treatment strategies for hypertension, electrolyte imbalances, and progression to chronic kidney disease.
  - Role in the administration of ERT and SRT, considering renal function.
- **Advanced Renal Support and Patient Education:**
  - Dialysis and kidney transplantation for patients with end-stage renal disease (ESRD).
  - Educating patients on lifestyle modifications and the importance of regular monitoring.
- **Collaboration and Research:**
  - Collaborative efforts with a multidisciplinary team for holistic patient care.
  - Engagement in research for better understanding and treatment innovations.

Fabry Disease: Optimizing the Efficacy and Safety of Enzyme Replacement Therapy

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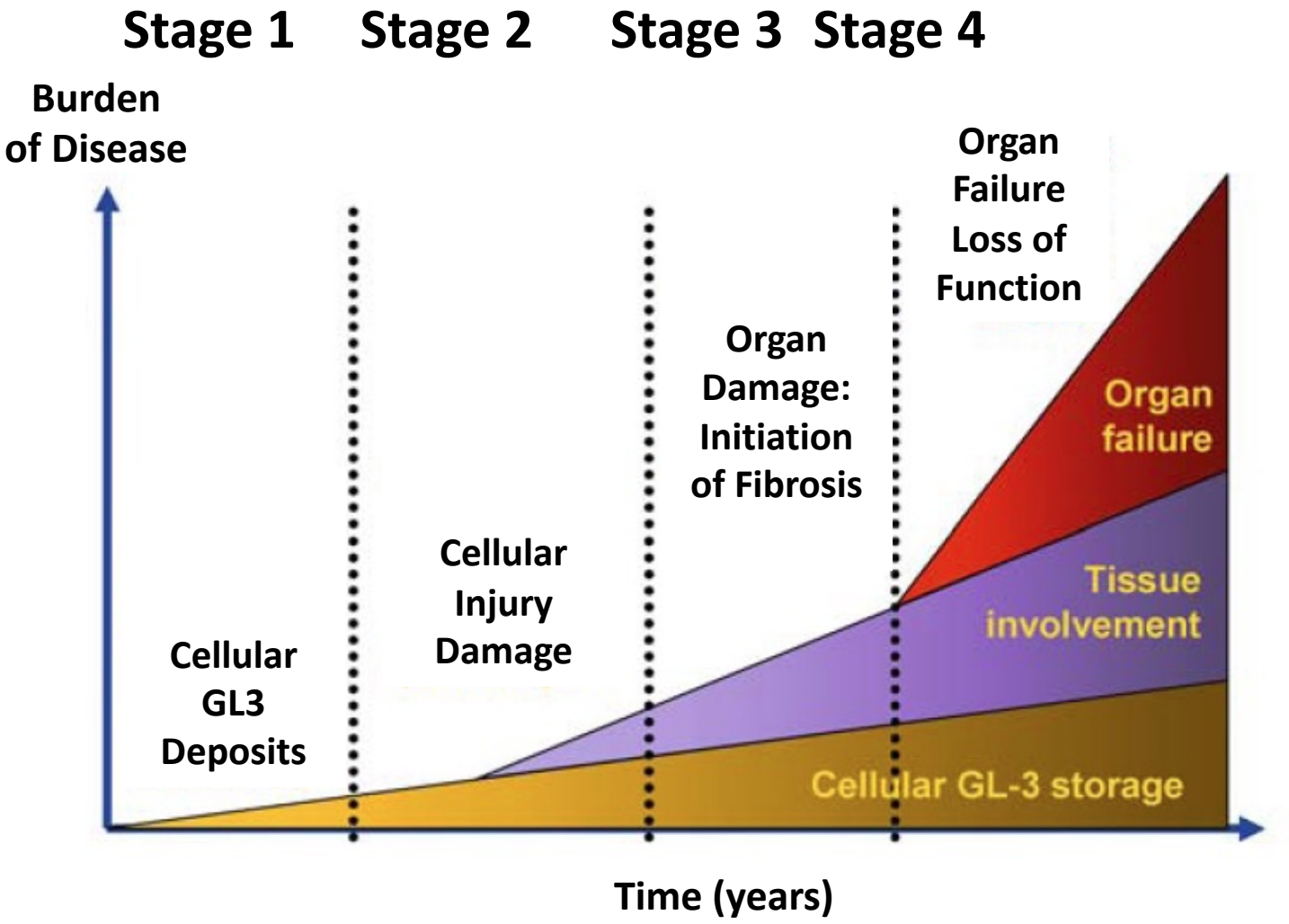
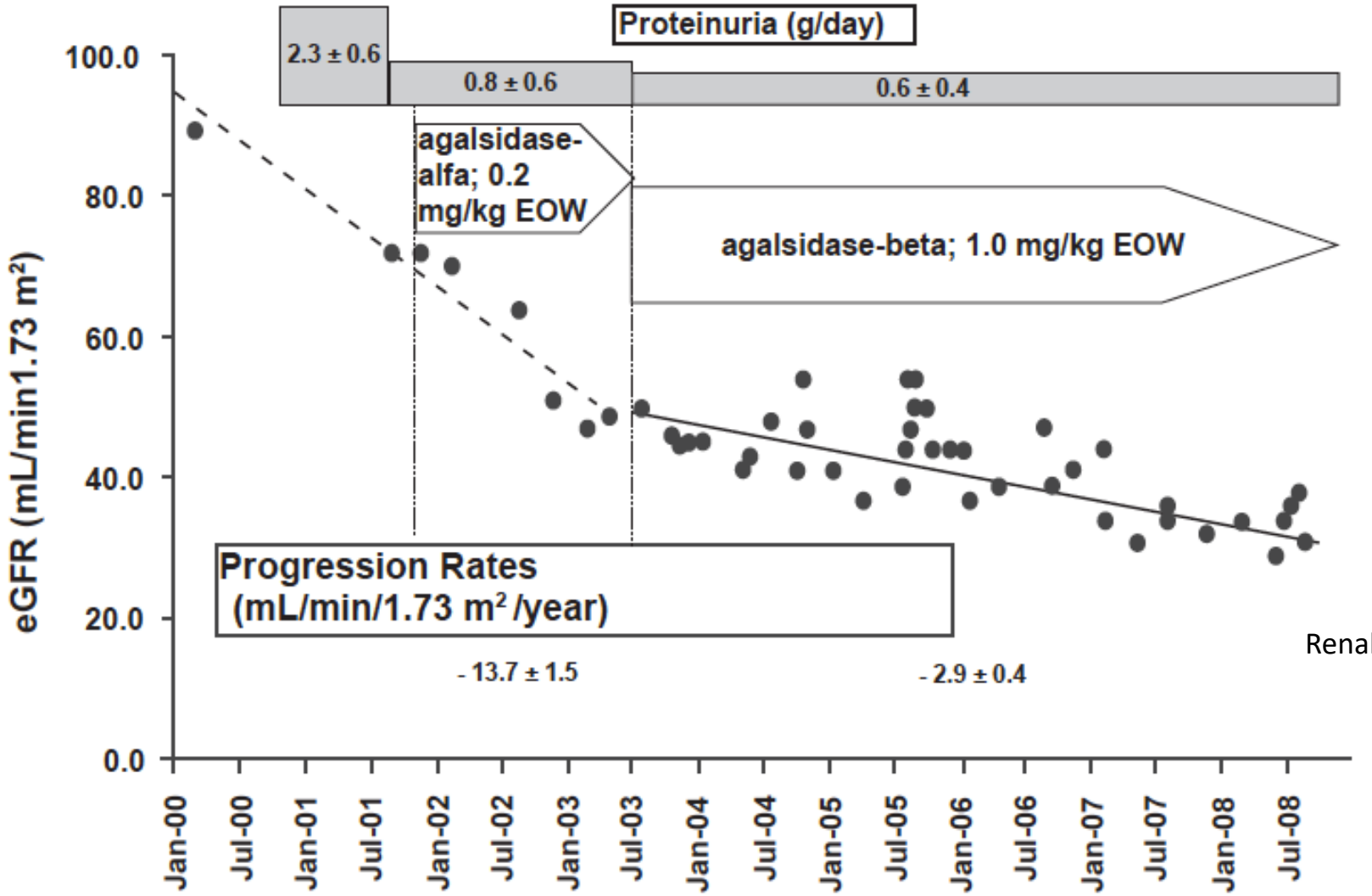
Fabry Disease: Accumulation, Cellular Injury, Compromised Function, Organ Failure



Tondel et al. *Nephron* 2015 129:16-21

ERT at 0.2 mg/kg versus 1.0 mg/kg



Renal Transplant: 2022

Fervenza et al. *Biologics.* 2008; 2: 823-843.