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Glycogen Storage Disease Type I

Monika Williams, M.D.

Assistant Professor of Pediatrics, Pediatric Genetics & Metabolism
Muenzer MPS Center
University of North Carolina

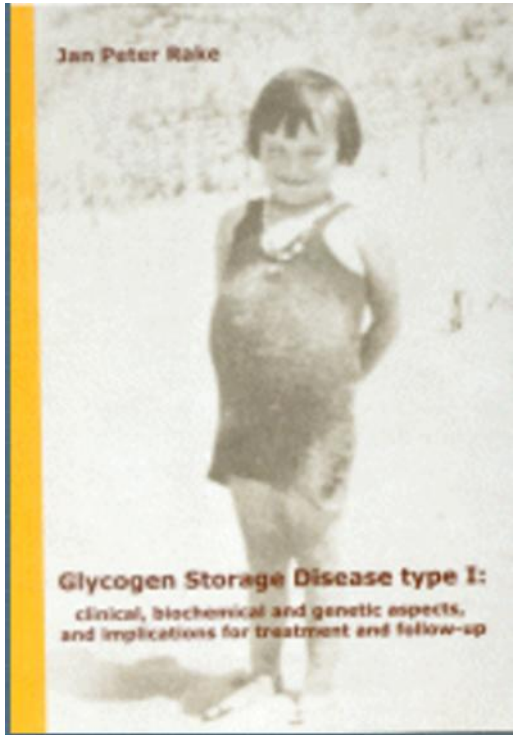
Background

GSD Patients @ UNC

- GSD Ia - 6
- GSD Ib - 2
- GSD III - 3
- GSD IX - 2
- GSD V - 2

Videos:

- https://youtu.be/hfbaoCf-GRE
- https://youtu.be/MExb7gA3Zeo?si=hvmR3wbp7hcJ4u9H



GSD I

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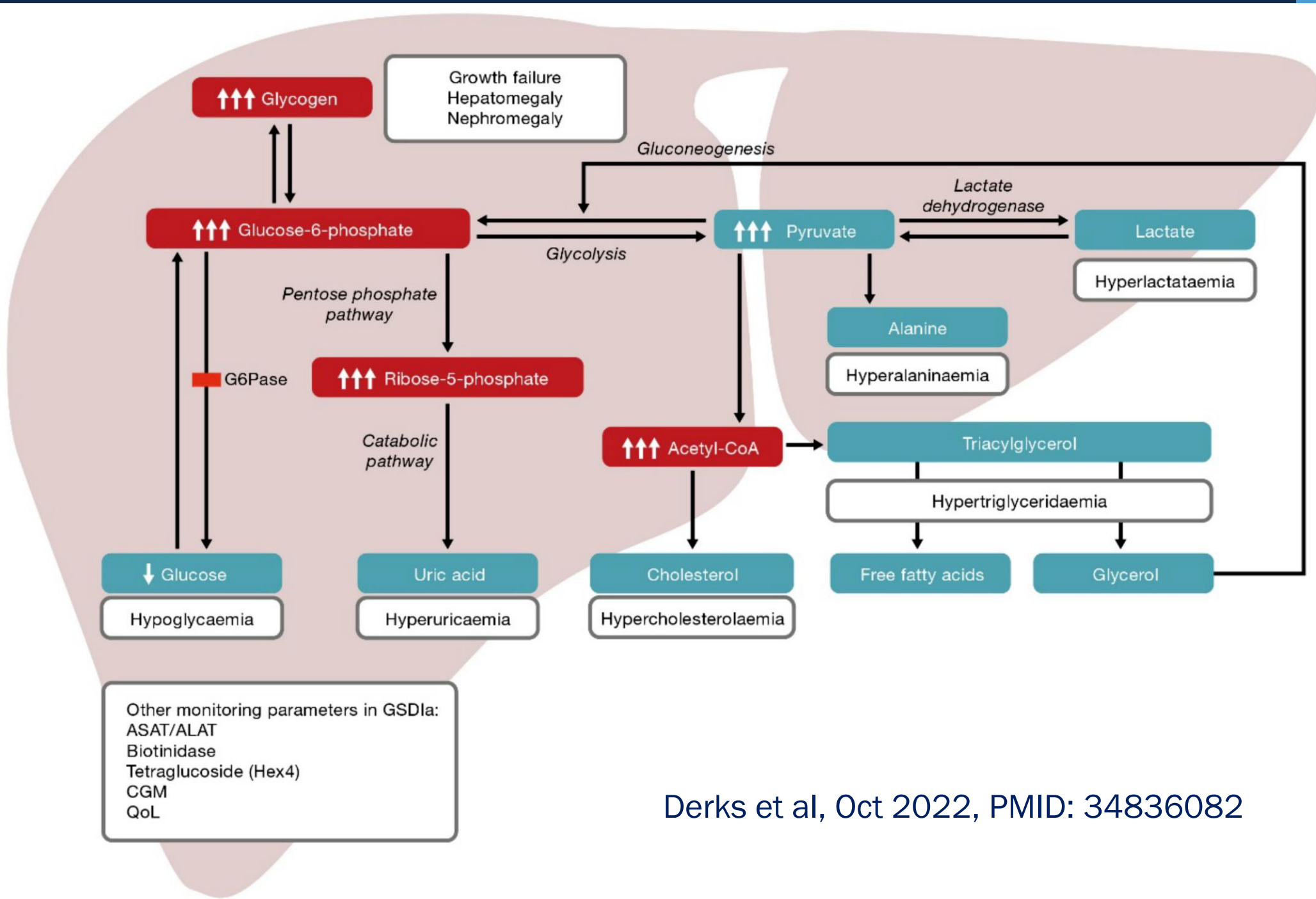
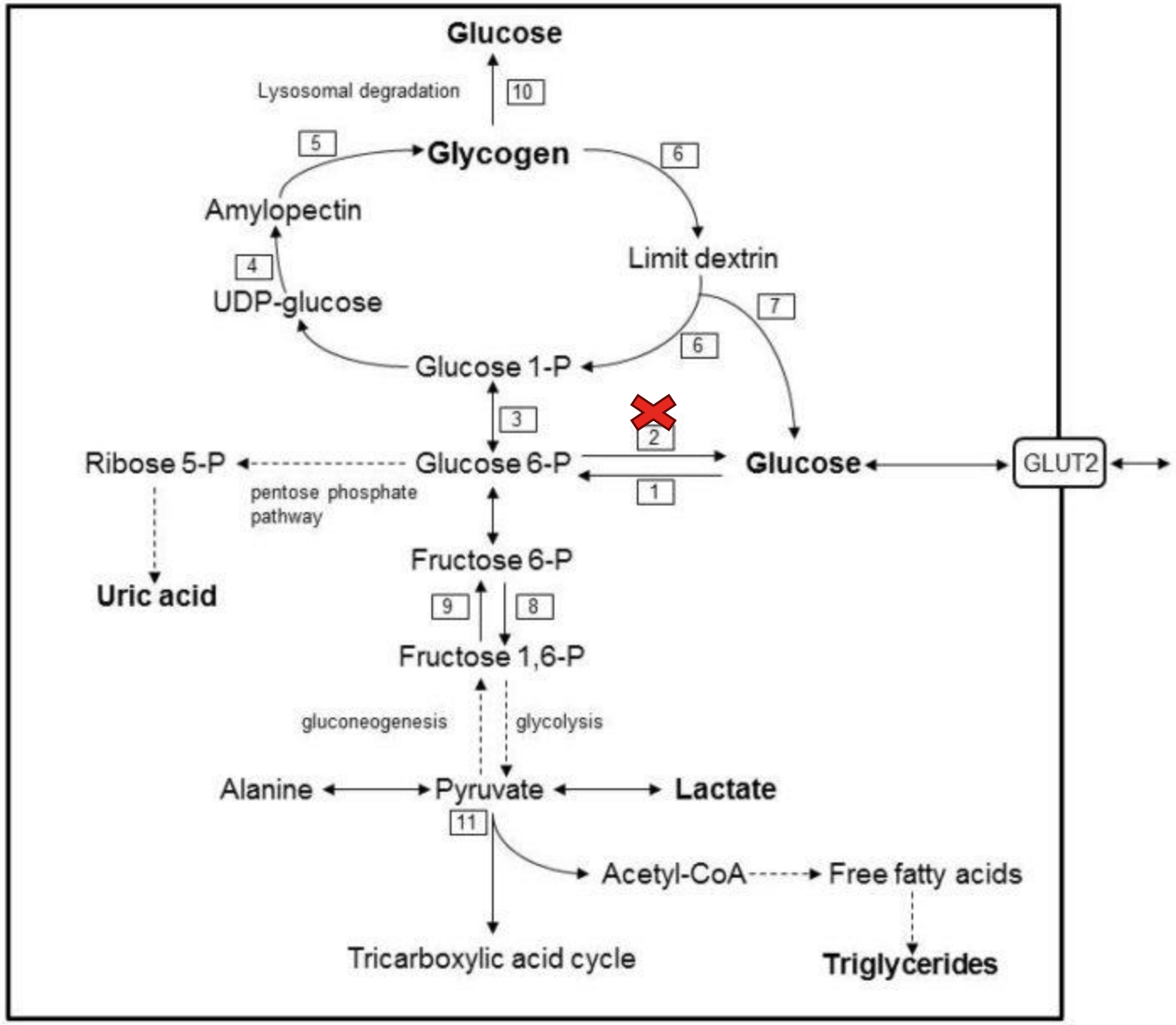
- Pathogenic variants in either *G6PC1* (GSDIa) or *SLC37A4* (GSDIb)
- Most commonly presents at age 3-4 months with hepatomegaly, hypoglycemia, seizures, lactic acidosis, hyperlipidemia

- Complications: short stature, von Willebrand-like disease, delayed puberty, osteoporosis, renal disease, gout, hypertension, hepatic adenomas, pancreatitis
- GSD Ib: chronic neutropenia resulting in recurrent bacterial infections, gingivitis, periodontitis, and genital and intestinal ulcers, IBD



Derks et al, Oct 2022, PMID: 34836082



https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/pediatrics/metabolic-glycogen-disorders/

17 May 2002

	Glucose (mg/dl)	Lactate (mmol/l)
1.00 pm	133	**9,07**
3.00 pm	130	**2,05**
5.00 pm	86	**4,44**
7.00 pm	121	**5,72**
9.00 pm	110	**5,79**
11.00 pm	74	**7,49**
1.00 am	86	**9,61**
3.00 am	103	**6,05**
5.00 am	85	**6,17**
7.00 am	106	**7,34**
10.00 am	155	**5,82**
12.00 am	128	**3,63**

Reference range: 0,5 – 2,2

Labs

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	Aug 2010	Aug 2011	Dec 2011
Hb (g/dL)	10.3	11.5	11.8
TG 62-150 mg/dL)	2717	469	407
Cholesterol (131-201 mg/dL)	619	340	282
Uric acid (2.4-5.3 mg/dL)	7.9	6.2	5.1

GSD I Management

- 1960-1971 Porto-caval shunts
- 1971-1982 Continuous feeds

- 1982: Cornstarch
- 2009: Glycosade

GSD I Complications

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- Cohort 1: born < 1971: era prior to medical therapy (*n* = 6)
- Cohort 2: born 1971 - 1985: continuous feeds era (*n* = 32)
- Cohort 3: born 1986 - 1998: initial era of cornstarch therapy (*n* = 38)
- Cohort 4: born 1999 - 2002: new dosing guidelines (*n* = 25)

101 post-pubertal patients
(57 M and 44 F)

	<1971 vs 1999-2002	1971-1985 vs 1999-2002	1986-1998 vs 1999-2002
HCA	100% vs 4% (p<0.001)	68% vs 4% (p<0.001)	37% vs 4% (p=0.002)
Microalbuminuria	83% vs 4% (p<0.001)	47% vs 4% (p<0.001)	18% vs 4% (p-0.131)
Proteinuria	17% vs 0% (p=0.194)	18% vs 0% (p-0.030)	5% vs 0% (p=0.514)

Dambska et al, 2017, PMID: 28568353

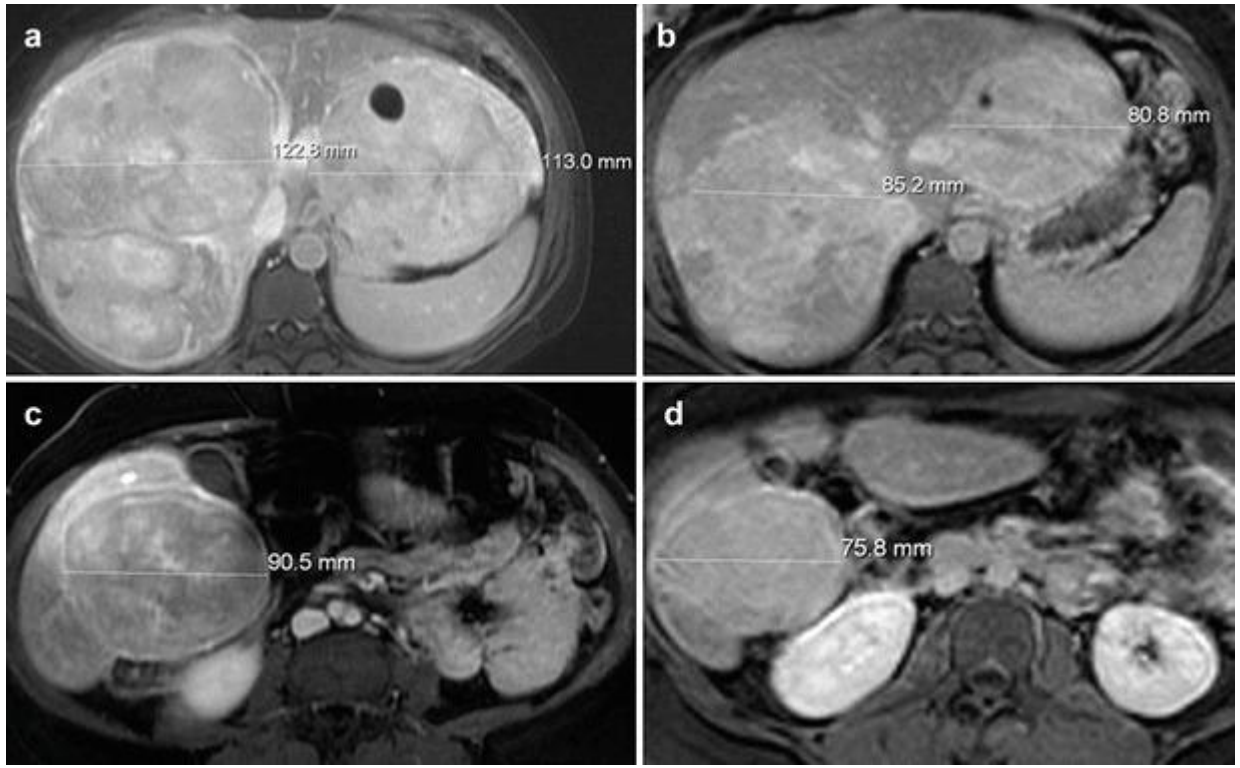
GSD I – Hepatic Adenomas

Adenoma development:

average triglyceride level of 753 mg/dL (SD ± 293)

Adenoma regression:

average triglyceride level of 340 mg/dL (SD ± 164)



Post-contrast MRI of a patient with GSD I with HCAs

Initial (a,c)

4 years later (c,d)

Beegle at al, 2015 PMID: 25308557

GSD I – Hepatic Adenomas

HCA was diagnosed in 5/8 GSD Ia patients

"In all of those patients, it developed it at adolescence, and it was associated with high serum levels of TG (>500 mg/dL)"

Szymańska et al. 2015 PMID: 32414085

Fig. Liver resection in 2 GSD Ia patients

GSD I – Kidney Disease

Glomerular hyperfiltration → Microalbuminuria → Proteinuria

Individuals with GSDIa may also develop hypocitraturia and hypercalciuria, increasing their risk of nephrocalcinosis and nephrolithiasis

Derks et al, Oct 2022, PMID: 34836082

GSD I – Kidney Disease

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Microalbuminuria:

- ✓ GSD Ia: 23/195 (11.7%)
- ✓ GSD Ib: 6/45 (13.3%)

The median age of onset:

- ✓ GSD Ia: 24 years (range 9-56)
- ✓ GSD Ib: 25 years (range 20-38)

11/14 patients had decreased protein excretion when ACE inhibition was associated with improved metabolic control

	TG in patients with decreased microalbuminuria (mg/dL)	TG in patients with increased microalbuminuria (mg/dL)
Initial	667 ± 353	802 ± 119
Final	370 ± 196	800 ± 342
Initial minus final (Δ)	280 ± 337	2.3 ± 224
Δ, p value	0.038	0.99

Tab. Triglyceride vs microalbuminuria status at start and end of treatment

Okechuku et al, 2017, PMID: 28612263

GSD I – Kidney Disease

Investigated the physiological and molecular effects of RAS blockers in 21 GSD I patients

- ACEi/ARB treatment reduced progression of CKD in 57% of patients of this cohort
- Data suggested better renoprotective effect of ACEi vs ARB
- CKD progressed to kidney failure in 20% of patients, requiring kidney transplantation

Monteillet L et al. Mar 2022, PMID: 34617103

GSD I Corn Starch Therapy

Hypoglycemia risk persists if a single dose of UCCS is delayed/missed or in cases of GI intolerance

Uncooked corn starch therapy:

- Is imprecise
- Does not treat the cause of disease
- May not prevent long-term complications
- May trigger secondary metabolic manifestations

Derks et al, Oct 2022, PMID: 34836082

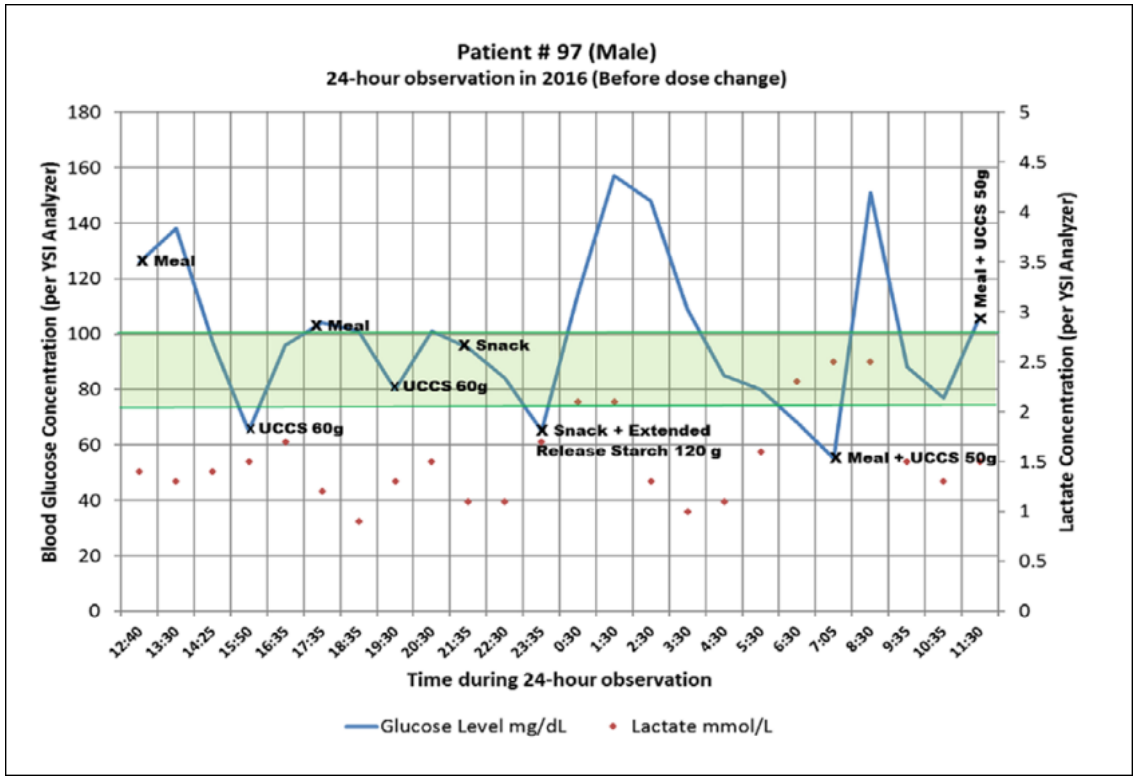
GSD I - Overtreatment

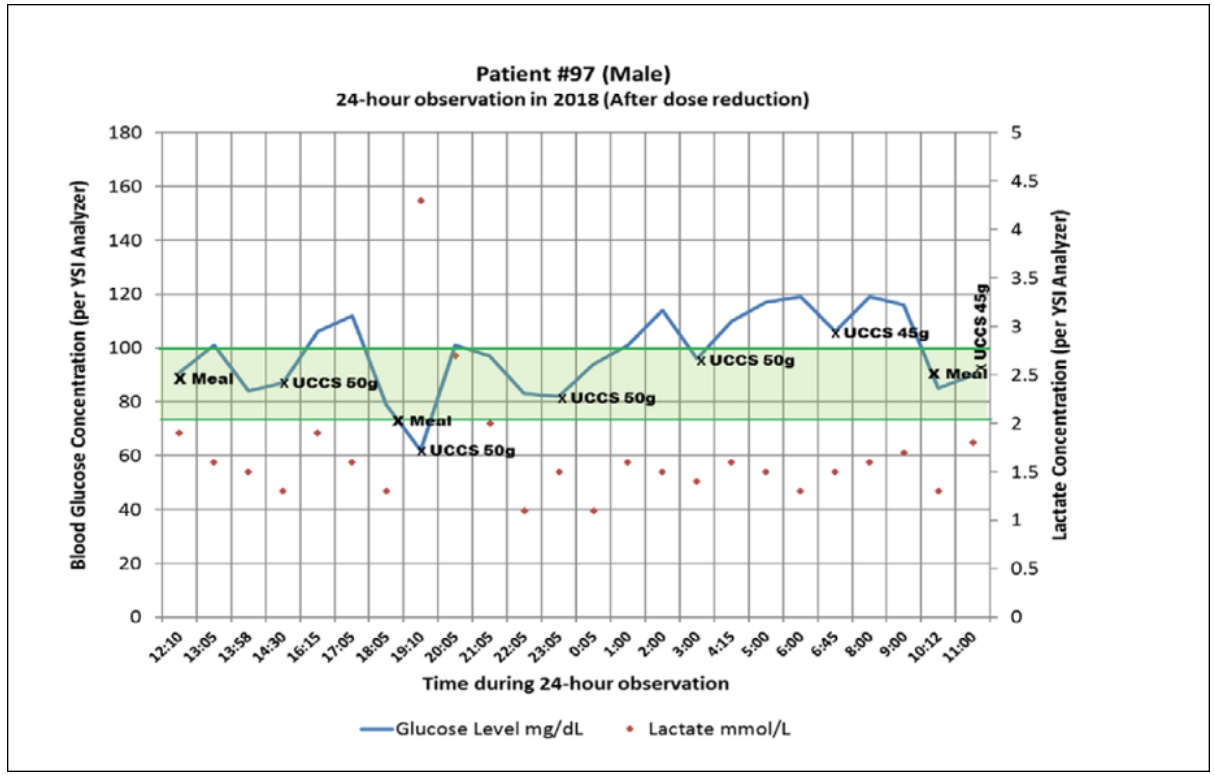
Aging is associated with decreasing metabolic rate

Failure to reduce cornstarch with age leads to:

- Over-treatment; Obesity; Worsening hepatomegaly; Relative hyperinsulinism; Rebound hypoglycemia

Dahlberg et al, 2019, PMID: 31415093





GSD I – Diabetes Mellitus

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- Several case reports
- DM1 or DM2
- Risk factors: obesity, overtreatment, recurrent pancreatitis
- Increased risk of complications
- Symptoms overlap
- Approach: multidisciplinary care, CGMs, metabolic control

Aggarwal et al, Mar 2021, PMID 35114770
Celis et al, Jun 2021 Abstract

Cohn et al, 2017, PMID 29127952
Marcalo et al, Mar 2021, PMID: 33766968

GSD I - IBD

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- Inflammatory bowel disease is well characterized in individuals with GSD Ib
- May be under-recognized in GSD Ia patients
- In contrast to IBD found in the GSD Ib population, the patients with GSD Ia are developing this complication as adults

Derks et al, Oct 2022, PMID: 34836082
Lawrence et al, 2015 and 2017,PMIDs: 26093626; 25304890

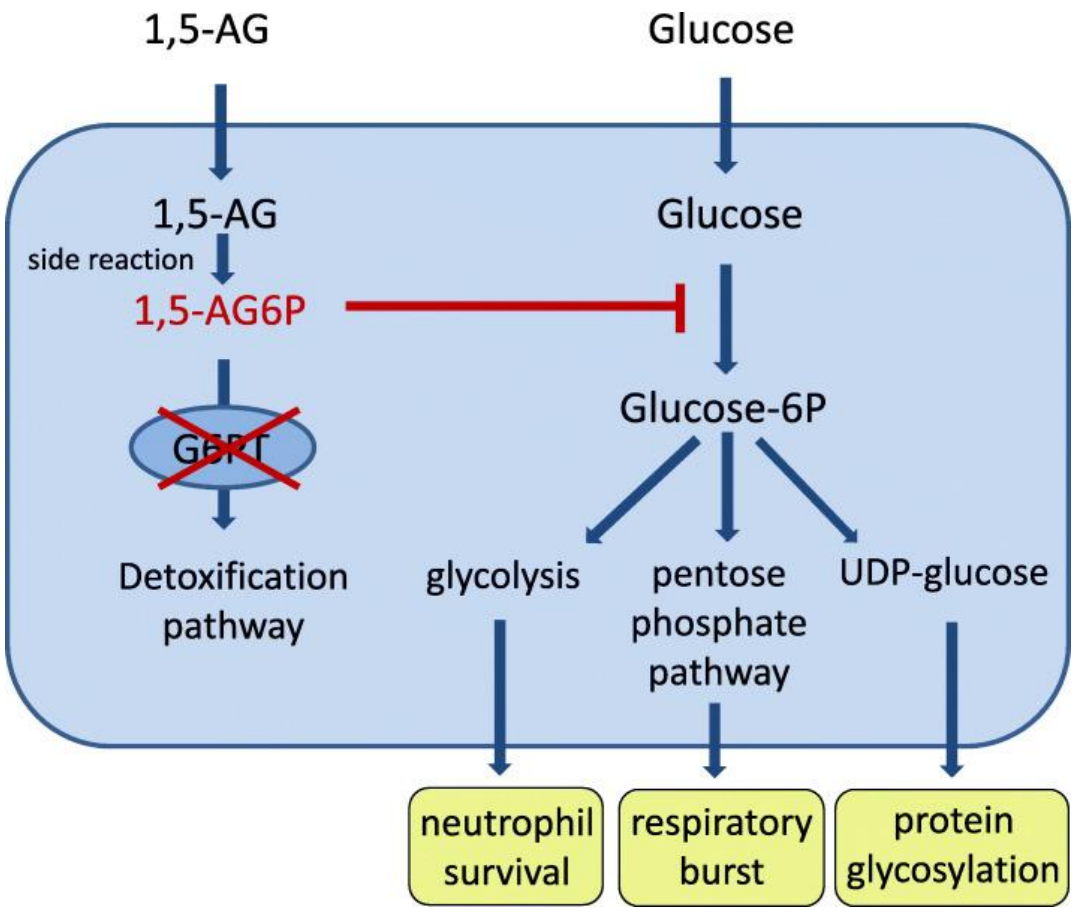
Gene therapy in GSD Ia

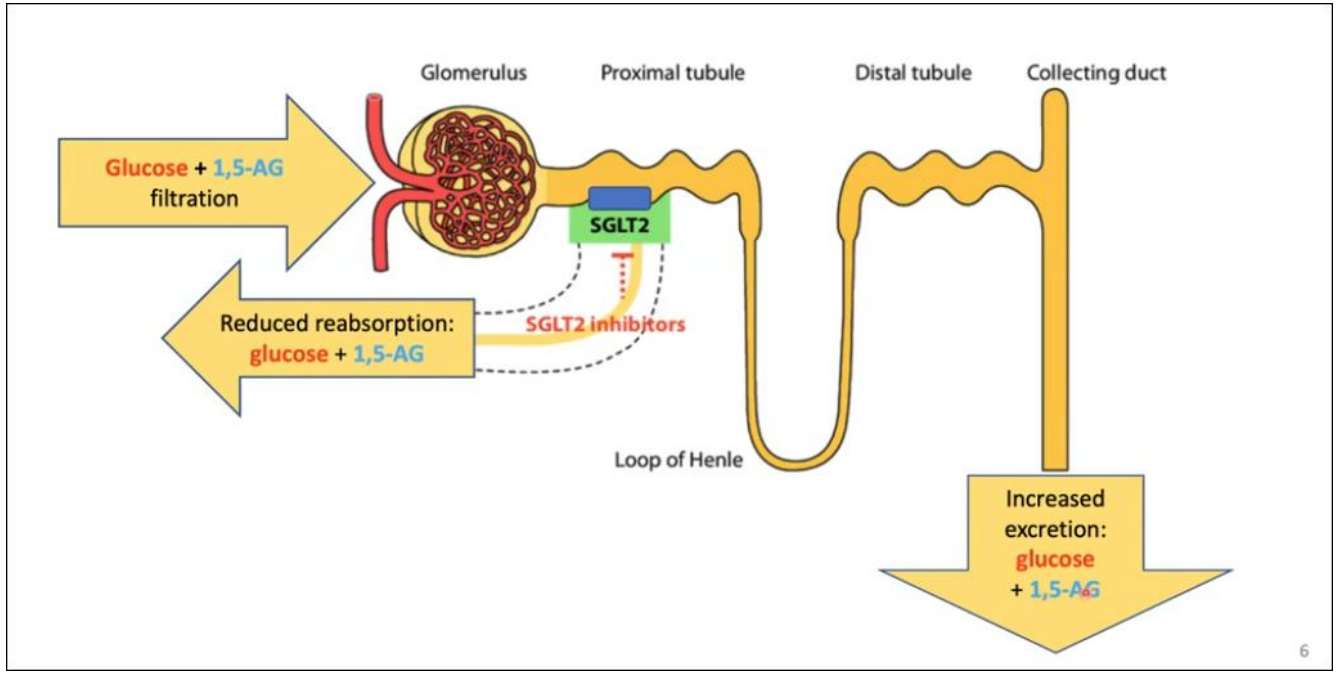
1) AAV8: DTX401

2) mRNA-3745 (trail terminated)

3) BEAM-301

Empagliflozin – GSD Ib





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Monika_Williams@med.unc.edu