AEEg
Asociación Española de Enfermos de Glucogenosis

Hepatic GSDs and Sport

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OUTLINE

Where does the muscle get its energy from?

Why is exercise so important for all of us?

What should those with liver-GSD bear in mind when exercising?

Sources of energy

- Carbohydrates (sugars)

- Fats

- Protein

Major function of different nutrient

- sugar / carbohydrates:

  nutrition of brain, sugar = “fast” fuel
- fat:

  fuel for muscle, transport of vitamins
- protein:

  growth, muscles,

  2nd line energy-source

  (gluconeogenesis = transformation into sugar)

What does the brain live off?

- Sugar!!! (carbohydrates)
- More than 60% (or 6 out of 10 grams) of the sugar in your blood goes to the brain!
- Second line “fuels” for the brain: fat (transformed into ketones in GSD type 0, III, VI and IX), lactate (in GSD I)
- But: the brain does not like ketones and lactate that much; you might get a bad headache

Which fuel for the muscle?

- Sugar
- Fat
- Ketones
- Lactate

- But: you will need different tools for the breakdown of these substrates!
- Watch out: you have to use these tools on a regular basis; otherwise the body will stop to keep them in stock!!!!

“Cash” or energy for muscle

- ATP (= money, “pocket change”): just enough for 2 seconds of a 100 yard sprint

- Glycogen: 400-500 g in muscles, 100 g in liver

- Fat (triglycerides = BIG CASH):
  8 kg (nearly 18 lb.) in fatty tissue
  in a 70 kg (156 lb.) person

More about the muscle‘s cash

- „ATP“ (adenosine triphosphate): pocket money, immediately available, but can’t buy much
- „Glycogen“ is the money in your purse. Can buy more if oxygen is present (you can grow more blood vessels to get more oxygen to the muscle by exercising!)
- „Fat deposits“ are your savings in the bank. You need a messenger to go to the bank and get some of them for you. And it takes some time until this “money” has been brought to the muscle.

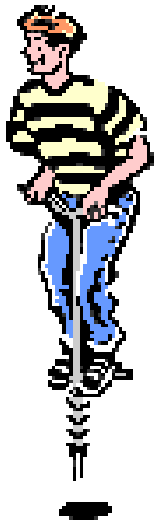
Energy yields of different fuels

	Time to peak output	Sufficient supply for	Substrate	Chemical reaction	Yield
Free ATP anaerobic (without oxygen)	Less than 0.1 seconds	Less than 2 seconds	ATP		1 ATP
Glucose – anaerobic from glycogen (without oxygen)	Less than 10 seconds	Less than 5 minutes	Glycogen	Partial break down into lactate	2 ATP
Glucose – aerobic from glycogen (with oxygen)	2 minutes	1½ hour	Glycogen	Complete breakdown into CO_2 and water	37 ATP
Oxidation of fatty acids palmitic acid (with oxygen)	More than 15 minutes	More than 1 day (!)	Fatty tissue	Complete breakdown into CO_2 and water	129 ATP

Adapted from **Preisler N** et al. *JIMD* 2015

Which fuel does the muscle use?

- Depends on availability of fuels
- Depends on availability of oxygen
- Depends on duration and kind of activity



Which fuel is used when?

Activity	Fat	Glucose
Rest	100%	little
Moderate effort	50%	50%
Maximum effort	0-10%	90-100%

Different muscle fibers

- Type I muscle fibers prefer **fatty acids**
  (number of type I fibers can be increased with endurance training like Nordic walking, jogging and cross country skiing)

- Type II muscle fibers prefer **glucose** (**glycogen**)
  (number of type II fibers increases with very fast exercises or with weight lifting)

Benefits of exercise (1)

- **Exercise is great for your brain:** less depression, better memory, better concentration, less ADHD and quicker learning;
- … is the best way to prevent or delay the onset of Alzheimer's disease!
- **You might get happier.** Exercise triggers the release of chemicals in the brain—serotonin, norepinephrine, endorphins, dopamine—that dull pain, lighten mood and relieve stress.

Benefits of exercise (2)

- **Exercise helps new vessels to develop.** Thus you can get more oxygen to the muscles to burn substrates.
- **Exercise strengthens your heart and lowers blood pressure.**
- **… makes your muscles grow.**
- **… improves the density of your bones.**
- … decreases risk of breast and colon cancer
- **Exercise might make you age slower.** Exercise increases levels of a molecule that protects telomeres, ultimately slowing how quickly they shorten over time. Exercise, then, appears to slow aging at the cellular level and thus increases life expectancy.

Benefits of exercise (3)

- **Your body will get better in burning fat.** Thus you are less dependent on carbs/glycogen and you can lose weight.
- Exercise **regulates appetite** to more closely match caloric needs.
- … improves lipid profile
- … increases insulin sensitivity (lowers risk for type 2 diabetes)
- **Exercise increases energy expenditure** (basic metabolic rate BMR) if you exercise for at least 5-6 hours/week

https://www.merrckmanuals.com/professional/nutritional-disorders/obesity-and-the-metabolic-syndrome/obesity

Fløtum LA et al *Biomed Res Int* 2016; **Mohr M** et al *Eur J Appl Physiol* 2015, **Mohr M** et al *Biomed Res Int* 2014; **Pedersen BK** et al *Scand J Med Sci Sports* 2015

To achieve max. benefits:

how often do you have to practice?

- At least 3 times a week (or 15.000 steps a day*)
- Aerobe practicing: at least 10 minutes at medium to sub-maximum strength (adding up to 150 min/week)

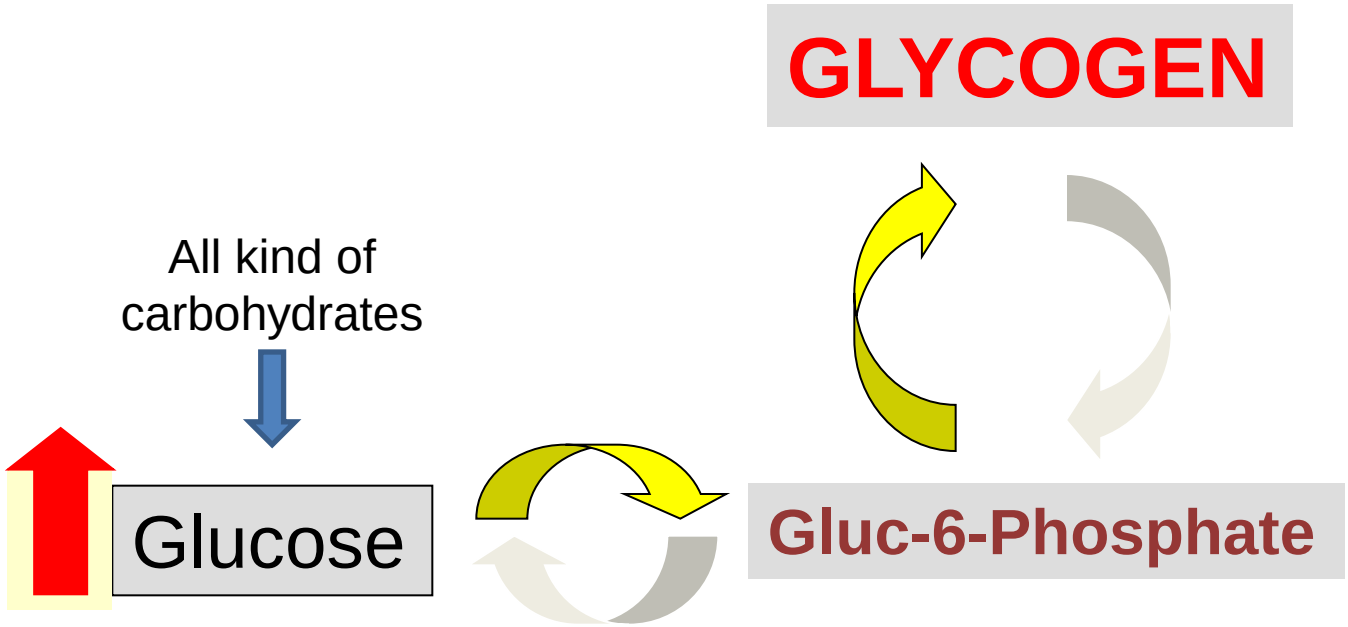
then

- Your muscles will grow and change (more fat burning type 1 fibers)
- Enzyme composition will be adapted to your needs (fat needs other “tools” for breakdown than sugar)
- Strength and stamina will improve

***Tigbe WW** et al *Int J Obes* 2017

Sports and liver GSD

- To understand the special needs in persons with liver- GSD, you have to know WHERE the problem in using glycogen is located.
- Liver GSDs can be sorted in two groups:
  (1) Those where glucose (from glycogen, protein or fat) cannot be RELEASED from the liver cell, these are type GSD Ia and type GSD Ib
  (2) Those GSD-types where glycogen can only partially be broken down (type IIIa /IIIb, type VI and the different types IX) or no glycogen is formed (type 0), but protein and fat can be transformed into glucose (gluconeogenesis). This glucose then can be released into the blood stream. These types of GSD are also called „ketotic GSDs“ as the body forms ketone bodies when breaking down fat.



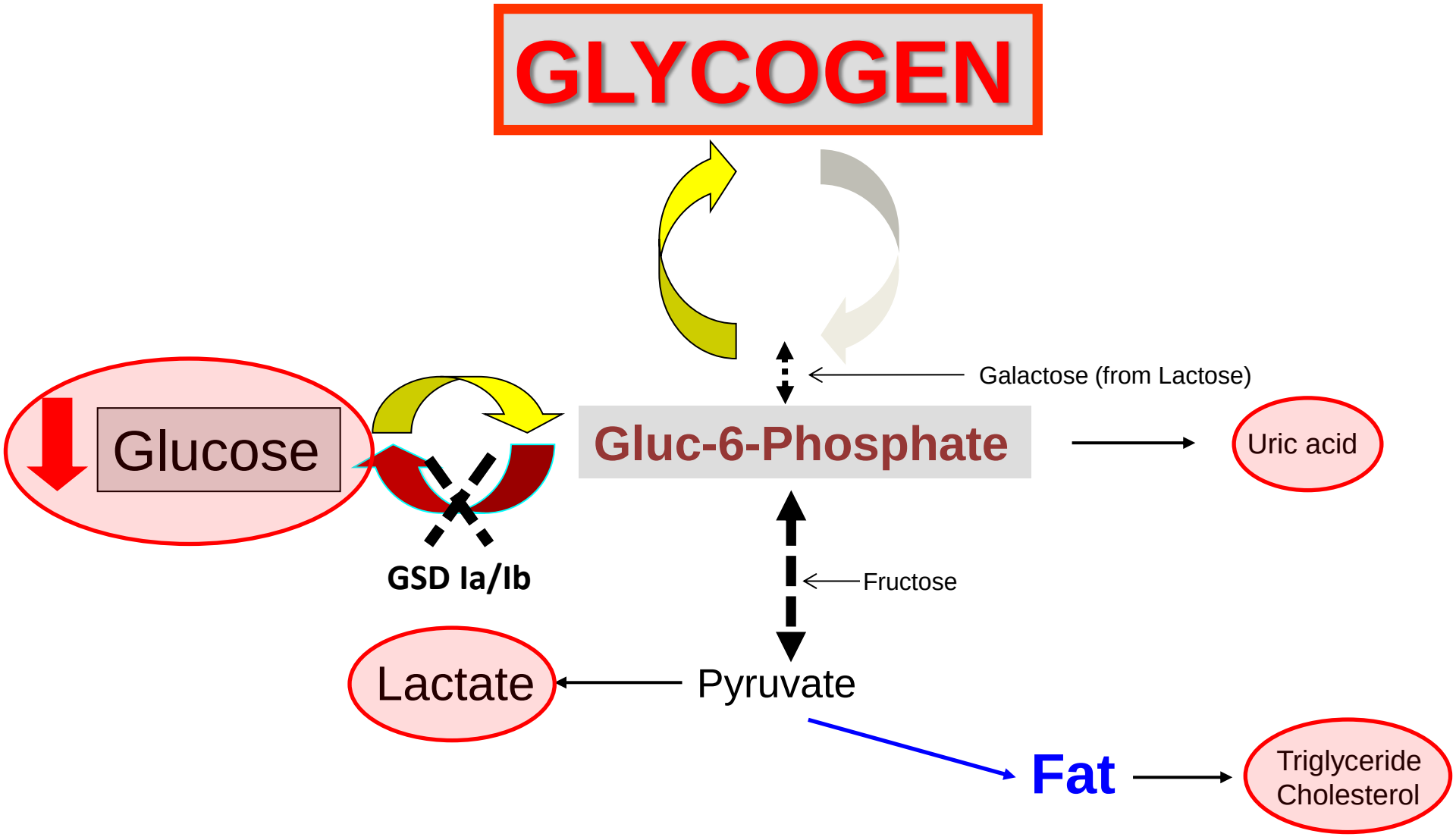
Normal situation:

Part of carbohydrates from food are stored as glycogen, mostly in liver and muscles. If blood sugar falls low, glycogen is split again into glucose. Liver cells are able to release this glucose into blood so blood sugar goes up again.

Adapted from: Fernandes J. & Pikaar NA. Arch Dis Child. 1972 and proposals by David Weinstein and Terry Derks

Metabolic characteristics type Ia and Ib

- In GSD type Ia and type Ib glycogen is formed normally.
- If blood sugar falls low, glycogen is broken down into glucose/sugar. But this sugar cannot be released into the blood.
- Therefore glucose is shunted
  (1) via pyruvate to **lactate** or
  (2) further to triglycerides and cholesterol and/or
  (3) via glucose-6-phosphate into **uric acid** (which will form kidney stones if citrine [from citrons, oranges, grapefruits, lemons] lacks in urine)
- All kinds of carbohydrates can be stored as glycogen, also those from dairy products (lactose, galactose) and fruits (fructose). This leads to enlargement of the liver. Therefore consumption of all of them is restricted in type Ia and Ib.
- During exercise glucose from blood and from muscle glycogen will be burned by the muscles. Blood sugar falls (**hypoglycemia**). Next breakdown of liver glycogen starts. But as the resulting glucose cannot be released into blood, lactate is formed which then leaks into blood (**hyperlactatemia**).



Adapted from: Fernandes J. & Pikaar NA. Arch Dis Child. 1972 and proposals by David Weinstein and Terry Derks

Risks in type Ia and Ib during exercise

- Hypoglycemia
- Hyperlactatemia

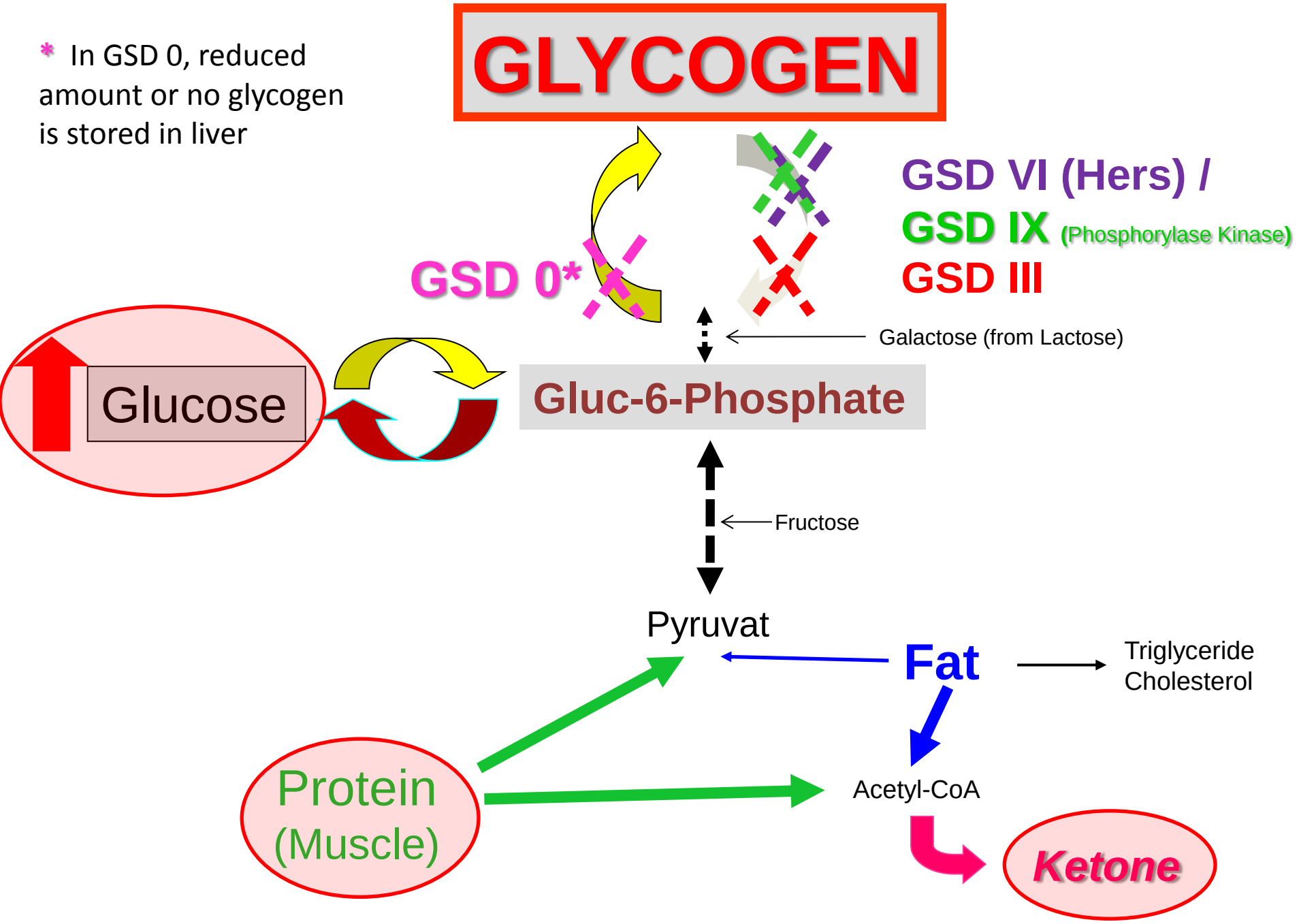
Metabolic characteristics in type IIIa and type 0, IIIb, VI and IX (1)

- In the ketotic forms of GSD (type IIIa, IIIb, VI and IX) glycogen can only partially be broken down into glucose in the liver; in type IIIa breakdown of glycogen is impaired in the muscles, too.
- In GSD type 0 ***NO*** glycogen is formed and therefore no glucose can be retrieved from glycogen.

Metabolic characteristics in type IIIa and type 0, IIIb, VI and IX (2)

- Thus, when no more glucose can be created from glycogen and/or blood sugar is falling low, protein (also from muscles) and fat are used as second line substrates and via gluconeogenesis transformed into glucose.
- Blood sugar will slowly get up again. But as at the same time ketones are formed from fat, you will be able to find these ketones in blood and thus conclude that blood sugar HAD been low before.

* In GSD 0, reduced amount or no glycogen is stored in liver



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Exercise and type IIIa

- Risk of hypoglycemia
- Risk of breakdown of muscles (using protein for gluconeogenesis)
- Further muscle damage is done as lack of lactate formation from glycogen leads to lack of oxygen, thus mostly anaerob breakdown of glycogen (only 2 ATP instead of 37 ATP out of one glucose!!) leading to energy deficiency
- Risk of early exhaustion

Exercise and type 0, IIIb, VI and IX

- The same as above but less severe

Major risks in liver GSD‘s during exercise

GSD Ia / Ib	**Hypoglycemia** as sugar is burned in muscle and no sugar can be set free from liver glycogen
GSD 0, IIIb, VI and IX	**Hypoglycemia** as no (type 0) or only part of liver glycogen can be broken down into sugar and released into blood
GSD IIIa	**Hypoglycemia** (see type 0, IIIb, VI and IX) and **breakdown of muscle tissue** as muscle glycogen only partially can be broken down into sugar and thus muscle protein might be „burned“; early exhaustion

Sports **NOT** suited for those with GSD IIIa

- Everything where you need ***quickly*** lots of energy, thus
  - No weight-lifting
  - No sprinting
  - No extreme sport

Sports to be preferred in liver GSD

rather

- Endurance sports!
  - (Nordic) walking / hiking
  - Moderate bicycling
  - Moderate jogging
  - Moderate soccer/handball
  - Judo (if your liver is not grossly enlarged)

Special benefits of sports in GSD

Sport

- …. (additionally to all the other benefits!)
- Teaches your muscles to use fat
- Helps you saving sugar for brain
- Gets blood sugar levels more stable
- Lowers risk for overweight
- Lowers risk for type 2 diabetes mellitus

Extra energy for exercise

- Many persons with liver-GSD tire easily with exercise.

Why?

- Limited access to muscle glycogen (type IIIa)
- Ineffective (anaerobic) breakdown of muscle glycogen (type IIIa)
- Limited availability of glycogen from liver

What to do?

- Additional carbohydrates and protein

Which kind of carbohydrates for exercise???

- Dextrose?
  - No: getting too “fast” into blood! If blood sugar rises above 80mg/dL (4.4mmol/L), lipolysis (mobilization and use of fat) stops
- Maltodextrin
  - Careful: blood sugar should be kept below 80mg/dL
  - Excess sugar from Maltodextrin will be stored as fat and glycogen
- Cornstarch (UCCS)
  - Might be too “slow” with high intensity exercise

How much extra „fuel“?

- Depends on intensity and duration of activity
- Provide more/repeat “fuel” for longer activities

But be careful:

- High blood sugar (insulin!) suppresses release of fatty acids from fatty tissue
- Check blood sugars! (and lactate and ketones)
- Careful: blood sugar might drop **AFTER** sports!

Extra intake before physical activity

- **(Nordic) walking/jogging at moderate speed:**
  20 min before starting:
  5-10 g cornstarch, type 0/III/VI/IX: add 5-10 g protein
- **Soccer:**
  cornstarch 20 min before starting (+ protein see above), some additional maltodextrin (12-24 g/L fluid) to be sipped during the game
- **Swimming/sprinting at high speed:**
  high energy demands! check sugars!!!

- *Fat/ketone drinks for exercise: under testing*

Extra fuel for exercise: It‘s not only you…

New England Patriots (NFL)
Jim Mahoney via AP

Chicago Blackhawks (NHL)
Alexandre Fortin

Golden State Warriors (NBA)
Stephen Curry

These teams take **cornstarch** and **protein** before the game!

AFTER sports

- Snack (to prevent hypoglycemia)
- Extra protein (10g),

  this helps to build up muscles*

*__Sollie et al__. *J Appl Physiol* 2018

How much exercise?

- 150 min (2½ hours) each week for health benefits
- 5-6 hours per week for weight reduction and maintenance of reduction

Too much, too heavy sport?

- Start at 50% of your maximum
- Do not lift heavy weights or do overly strenuous activity
- If your muscles are sore after activity, then you have exercised too much/too hard

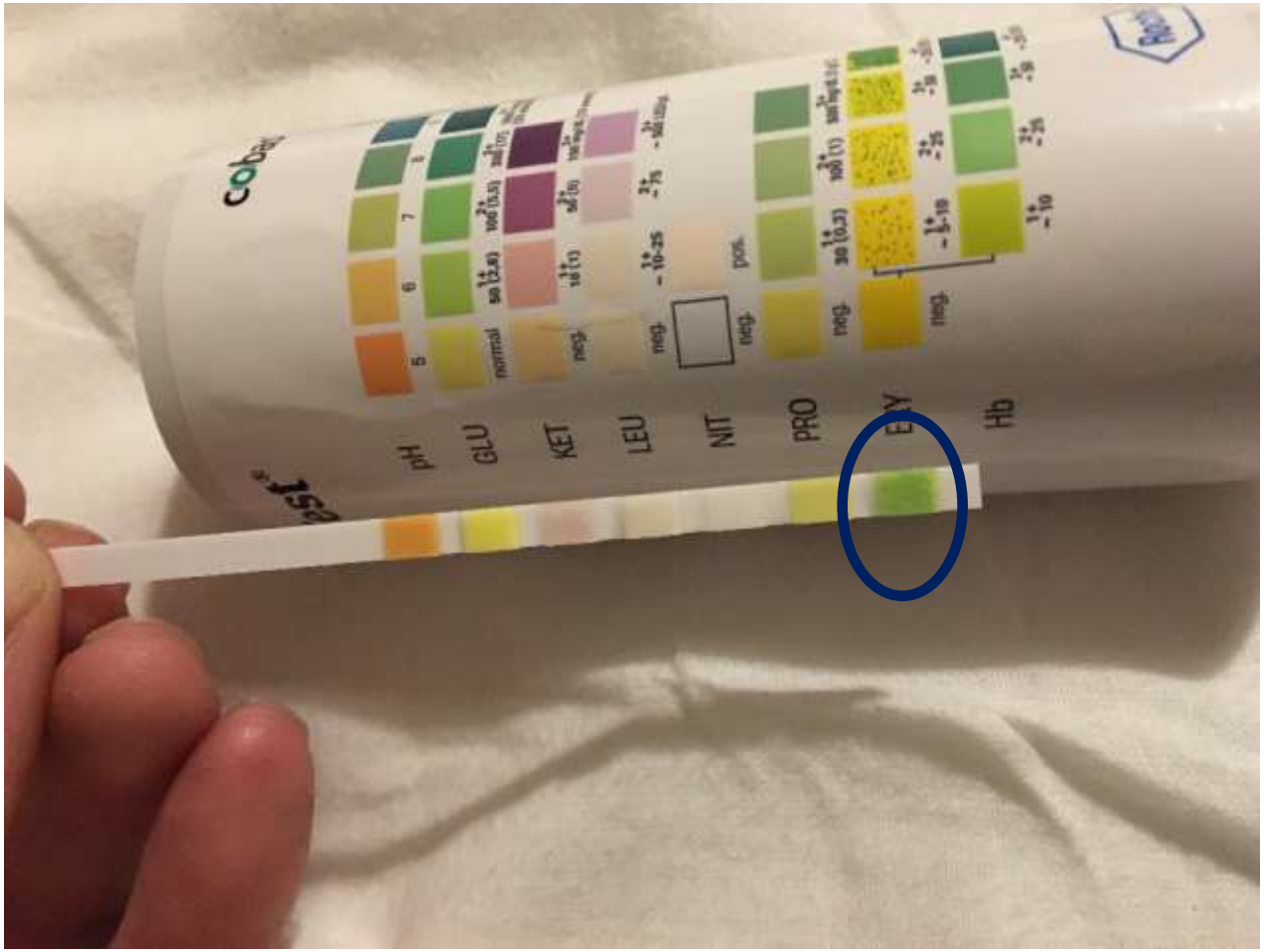
How can you find out?

- Creatinine kinase? Not the best idea as it has to be done in blood; easier accessable:
- Test urine for Myoglobin!!!!

Myoglobin

- Myoglobin = muscle protein
- If muscle cells are damaged, myoglobin can be found in blood and - after about 6 hours - in urine.
- Myoglobin cross-reacts with hemoglobin, thus easy to detect in urine.

Myoglobinuria



How exercise can change your life

Fight for a cure

Jake, type Ia, 16 years old, 2016

https://www.youtube.com/watch?v=MExb7gA3Zeo

Sports and GSD on Facebook

GSD fitness and motivation

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