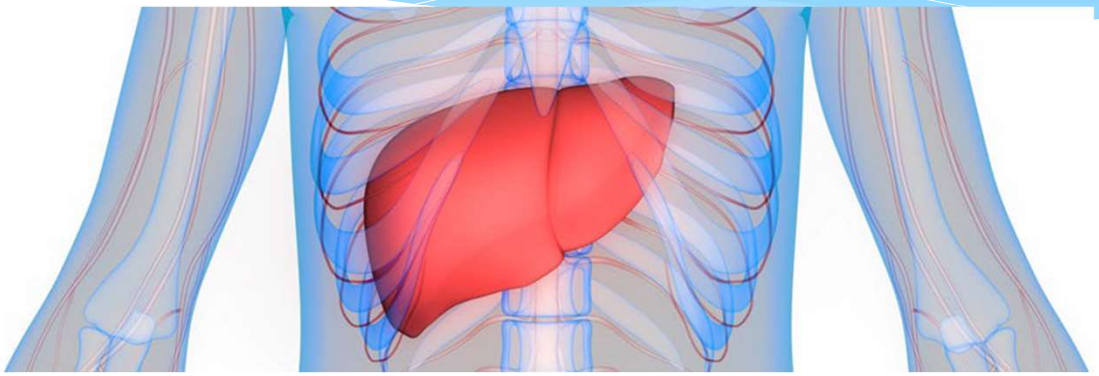
# Dieetbehandeling bij levergebonden Glycogeen stapelingsziekten



Diëtist Metabole Ziekten
Beatrix Kinderziekenhuis | UMCG
Foekje de Boer

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# Disclosures

* NCT02318966 - Glycosade v UCCS in the Dietary Management of Hepatic GSD (Glyde) sponsored by Vitaflo International, Ltd.

* NCT03517085 - Safety and Dose-Finding Study of DTX401 (AAV8G6PC) in Adults With Glycogen Storage Disease Type Ia (GSDIa) sponsored by Ultragenyx Pharmaceutical Inc.

* All contracts are via the UMCG Contract Research Desk and all payments are to the UMCG.

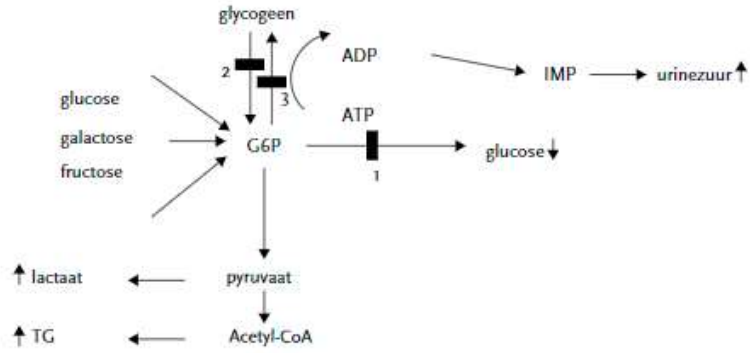
# Inhoud

- Glycogeen stapelingsziekten
- Wat werkt er niet goed
- Dieetbehandeling
- Hulpmiddelen zoals sensor en ketonenmeter
- Opnames GSD-patienten
- Casus

# Typen GSD

* 11 typen GSD bekend
* Levergebonden GSD's, onderscheid:
  - niet-ketotische
  - ketotische
  - afwijking in de opslag
* Dieetbehandeling bij type I, III, VI, IX

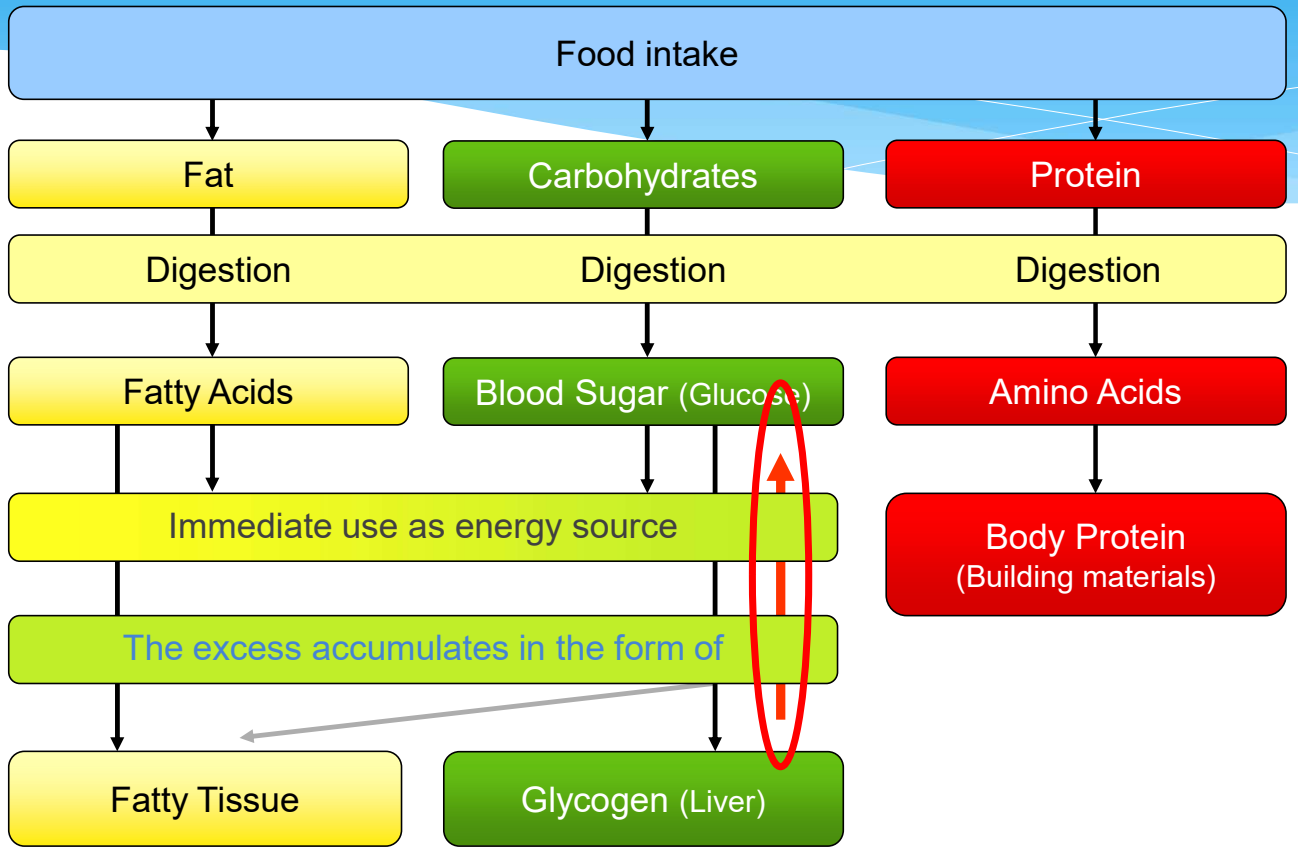
# Schematische weergave van GSD



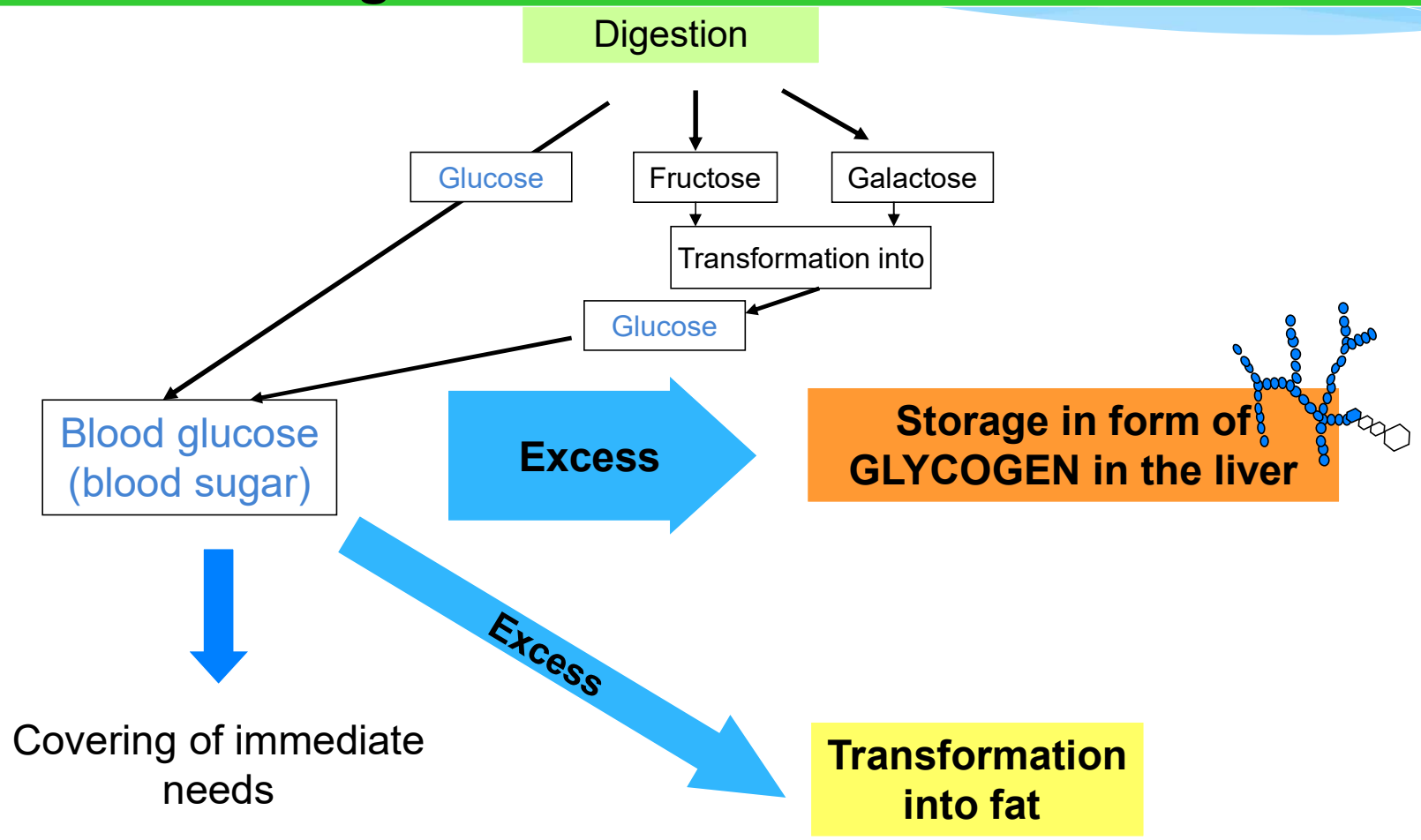

**Figuur 1**
Schematische weergave glycogeen stapelingsziekten

1. Glycogeenstapelingsziekte type 1
2. type III, VI, IX
3. type IV

# Usage of food types and nutrients



# Absorption of carbohydrates from food
# Normal glucose metabolism after a meal



# Normal glucose metabolism between meals

No food consumption

Digestion

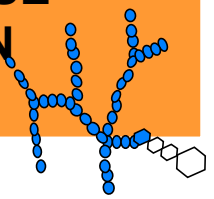
Glucose | Fructose | Galactose

Blood glucose (blood sugar)

G6Pase

Release early

**GLUCOSE RELEASE from GLYCOGEN in the liver**



Production late

**GLUCOSE PRODUCTION from other substances (e.g. protein) in the liver**

Covering of immediate needs

# Glucose metabolism between meals in case of GSD I

No food consumption

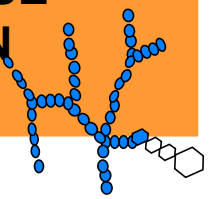
Digestion

Glucose | Fructose | Galactose

Blood glucose (blood sugar)

Release early

**GLUCOSE RELEASE from GLYCOGEN in the liver**



Production late

**GLUCOSE PRODUCTION from other substances (e.g. protein) in the liver**

Immediate needs are not covered

⇨ **too low blood sugar = hypoglycemia**

# Treatment of GSD I

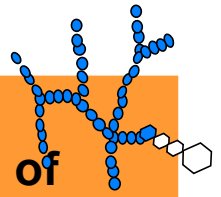
**Continuous supply of carbohydrates containing low amounts of fructose or galactose: glucose (grape sugar), maltose, maltodextrin, starch**

**Glucose** | Fructose | Galactose

Blood glucose (blood sugar)

Avoiding of the excess

**Minimizing of storage in a form of GLYCOGEN in the liver**



**<u>Continuous covering</u>**
of immediate needs
⇨ **normal blood sugar**
**= normoglycemia**

**GLUCOSE PRODUCTION in the liver not necessary**

# Doel dieetbehandeling

* Voorkomen hypoglycemie, maar ook hyperglycemie
* Voorkomen, beperken, uitstellen van  complicaties
* Verkrijgen goede metabole instelling,  conditie en QoL
* Goede groei (kinderen), acceptabele BMI

# Exogeen glucose afhankelijk

Glucoseaanvoer uit de voeding:

* frequente koolhydraatrijke maaltijden (iedere 2,5-4 uur)
* (nachtelijke) continue sondevoeding
* gebruik van complexe koolhydraten om de maaltijdfrequentie te verlagen

# Bepalen glucosebehoefte

* mg glucose/kg/minuut
* Vertalen naar koolhydraten per uur of per voeding
* Hierna individualiseren
* Voedingsdagboek/huidige inname inventariseren

# Carbohydrates

* Calculation/Estimation of hourly EGPFormula

$$Y = 0{,}0014x^3 - 0{,}214x^2 + 10{,}411x - 9{,}084$$

$[Y]$ = mg/min; $[x]$ = kg

- Carbohydrates per hour

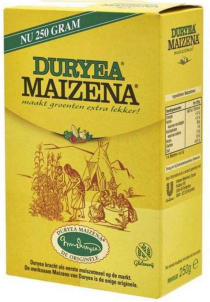
| (kg) | EGP (mg/kg/min) | EGP ch/gram/hour | starch gram/hour |
|---|---|---|---|
| 10 | 7,5 | 4,5 | 5,3 |
| 11 | 7,4 | 4,9 | 5,7 |
| 12 | 7,3 | 5,2 | 6,2 |
| 13 | 7,2 | 5,6 | 6,6 |
| 14 | 7,0 | 5,9 | 7,0 |
| 15 | 6,9 | 6,2 | 7,3 |
| 16 | 6,8 | 6,5 | 7,7 |
| 17 | 6,6 | 6,8 | 8,0 |
| 18 | 6,5 | 7,0 | 8,3 |
| 19 | 6,4 | 7,3 | 8,5 |
| 20 | 6,2 | 7,5 | 8,8 |
| 21 | 6,1 | 7,7 | 9,0 |
| 22 | 6,0 | 7,9 | 9,3 |
| 23 | 5,8 | 8,1 | 9,5 |
| 24 | 5,7 | 8,2 | 9,7 |
| 25 | 5,6 | 8,4 | 9,8 |
| 26 | 5,4 | 8,5 | 10,0 |
| 27 | 5,3 | 8,6 | 10,1 |
| 28 | 5,2 | 8,7 | 10,3 |
| 29 | 5,1 | 8,8 | 10,4 |
| 30 | 4,9 | 8,9 | 10,5 |
| 31 | 4,8 | 9,0 | 10,6 |
| 32 | 4,7 | 9,0 | 10,6 |
| 33 | 4,6 | 9,1 | 10,7 |
| 34 | 4,5 | 9,2 | 10,8 |
| 35 | 4,4 | 9,2 | 10,8 |
| 36 | 4,3 | 9,2 | 10,8 |
| 37 | 4,2 | 9,2 | 10,9 |
| 38 | 4,1 | 9,3 | 10,9 |
| 39 | 4,0 | 9,3 | 10,9 |
| 40 | 3,9 | 9,3 | 10,9 |

# Specifieke dieetkenmerken GSD-I

* 65-70en% KH
* Beperkt in fructose, lactose en sacharose
* Eiwit: volgens aanbevolen hoeveelheden. Bij onvoldoende lengtegroei ophogen.
* Vetbeperkt (relatief)
* Aanvullend calcium/vitamine D-preparaat, multivitamine-preparaat

# Carbohydrates

* Starch:
    * Cornstarch, raw (different brands)
        dosing 2-6 hours
        mixed with water or a sugarfree drink
    * Glycosade (extended release cornstarch)
        before going to sleep





# Carbohydrates

* Carbohydrates from food:
    * normal complex carbohydrates
      bread, potato, rice, pasta
    * simple sugars (mono-/disaccharides)
    * sweetners

* Carbohydrates per meal

# Nieuwe behandelingen GSD Ia en Ib met invloed op dieet

* Gentherapie
* mRNA therapie
* Empaglifozine

# GSD la-muis

# Normal glucose metabolism between meals

No food consumption

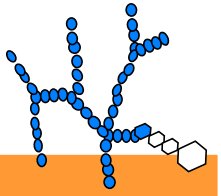
Digestion of carbohydrates

Blood glucose (blood sugar)

Covering of immediate needs

Release early

Production late



**GLUCOSE RELEASE from GLYCOGEN in the liver**

**GLUCOSE PRODUCTION from other substances in the liver**

# Glucose metabolism between meals in case of GSD III, VI and IX

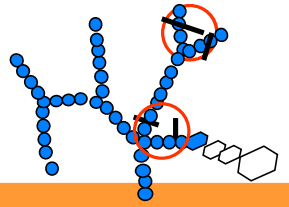
No food consumption

Digestion of carbohydrates

Blood glucose (blood sugar)

Release early

**GLUCOSE RELEASE from GLYCOGEN in the liver**



Production late

**GLUCOSE PRODUCTION from other substances in the liver**

Immediate needs are <u>not</u> covered

⇨

⇨ **too low blood sugar**

**= hypoglycemia**

# Doel dieetbehandeling

* Voorkomen hypoglycemie en hyperglycemie
* Voorkomen dat er ketonen worden gemaakt
* Voorkomen, beperken van  complicaties
* Verkrijgen goede metabole instelling,  conditie en QoL
* Goede groei (kinderen), acceptabele BMI

# GSD III, VI en IX

* Minder exogeen glucose afhankelijk dan GSD I
* Dieet eiwitrijk als compensatie voor de gluconeogenese
* Naast glucose meten, ook meten van ketonen heel belangrijk

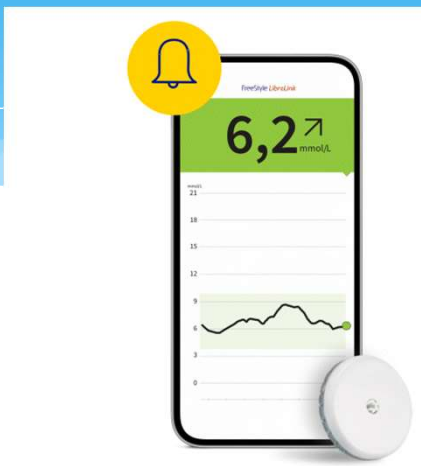
# Dietary guidelines

* Carbohydrate 40-50% of kcals, complex sources preferred
* Limit simple sugars (no rigid restriction lactose/fructose)
* Corn starch to prolong fasting periods
* Protein;
  - 3-4 g per kg body weight in GSD III
  - 2-3 g per kg body weight in GSD VI/IX
* Protein for the late night feed: 1 g / kg bodyweight
* Fat < 30% of kcals, limit saturated fat, sufficient EFA intake
* Vitamin/mineral supplementation, if necessary



# Hulpmiddelen bij behandeling van GSD

* Sensoren:
  - dexcom G6
  - freestyle libre


* Glucosemeter of glucose/ketonenmeter

# Overzicht

**Gemiddelde Glucose**

**6,8** mmol/l

Standaardafwijking **1,9** mmol/l

GMI **6,2**%

**Tijd binnen bereik**

7% Erg Hoog
17% Hoog
**74% Binnen Bereik**
2% Laag
0% Erg Laag

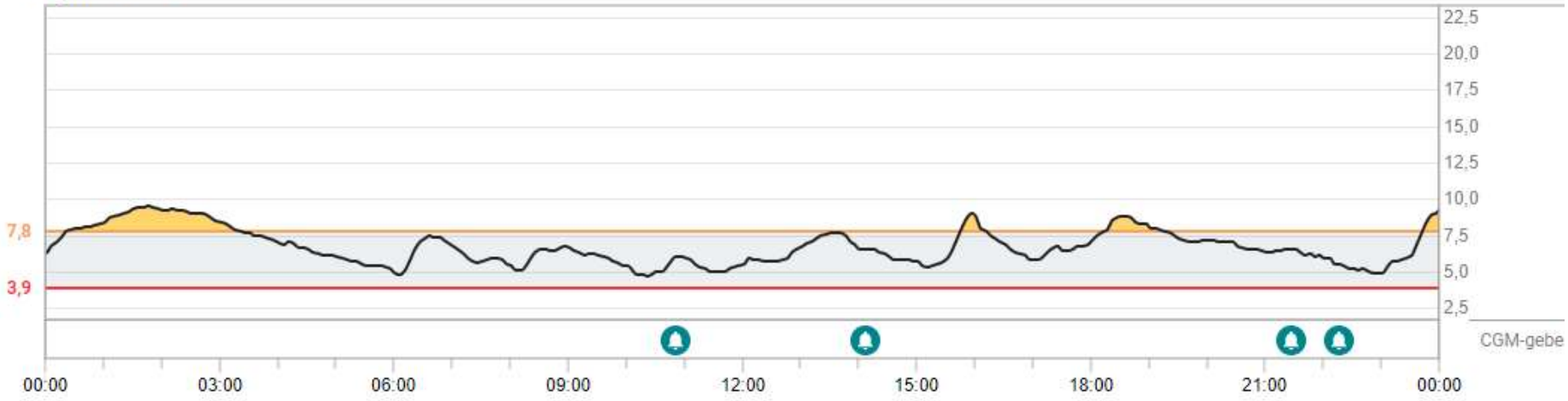
**Streefbereik:**
3,9-7,8 mmol/l

**Sensorgebruik**

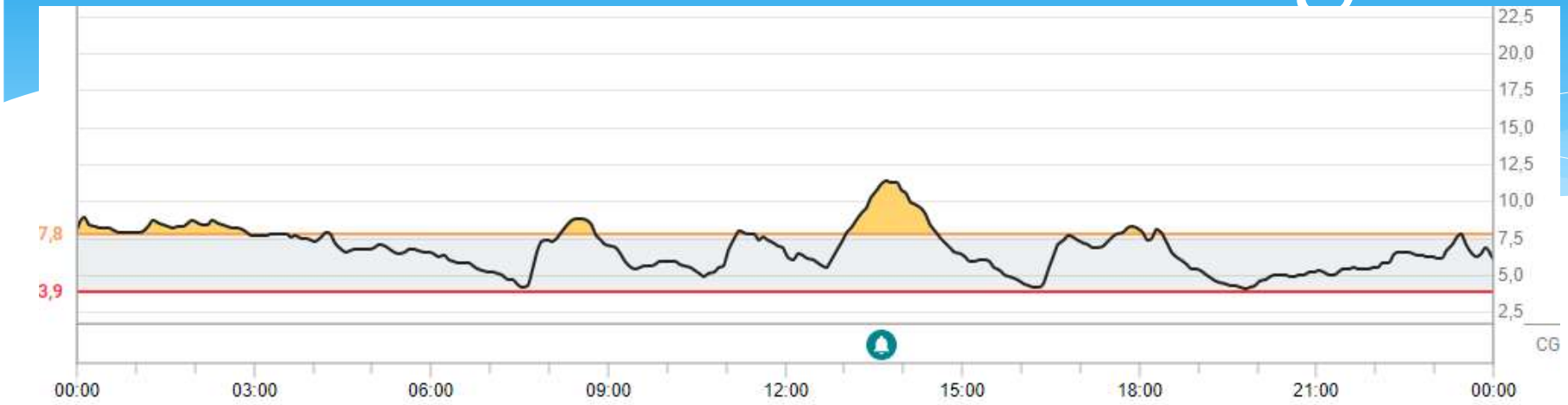
Dagen met CGM-gegevens
**100**%
14/14

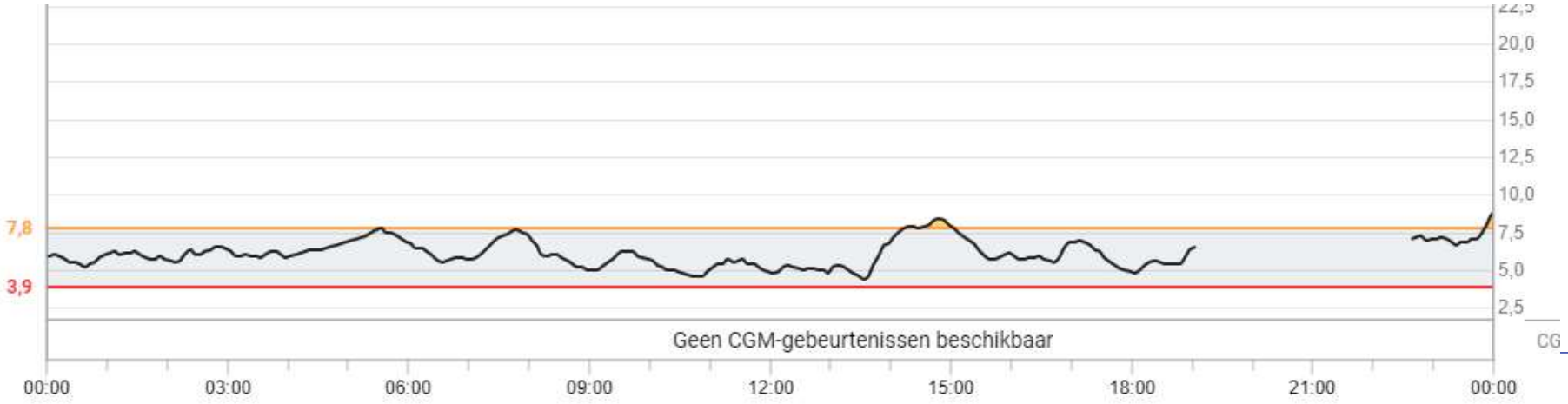
Gemiddeld aantal kalibraties per dag
**0,1**

**do. 26 jan. 2023**



# Overbehandeling

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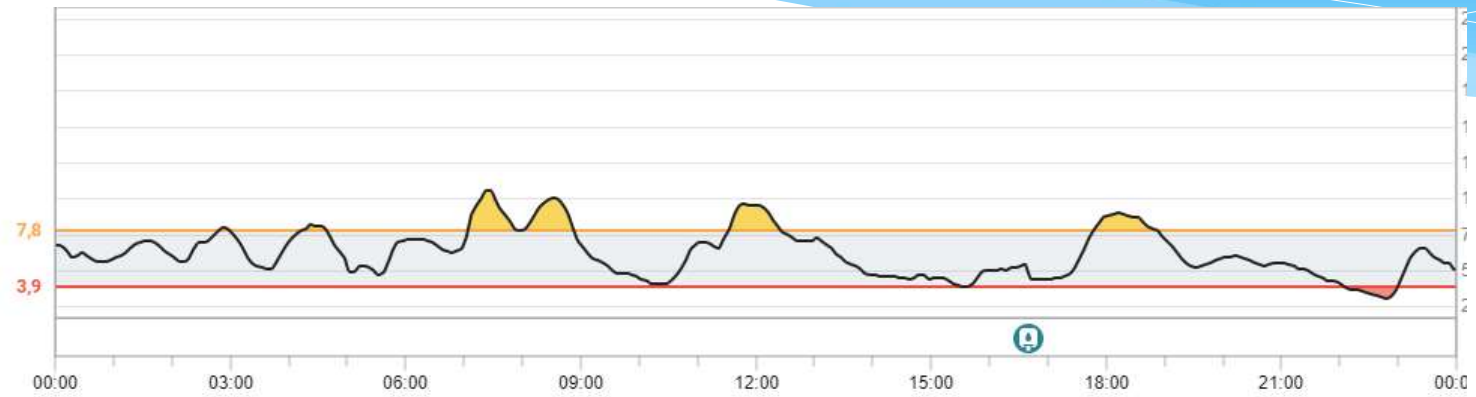
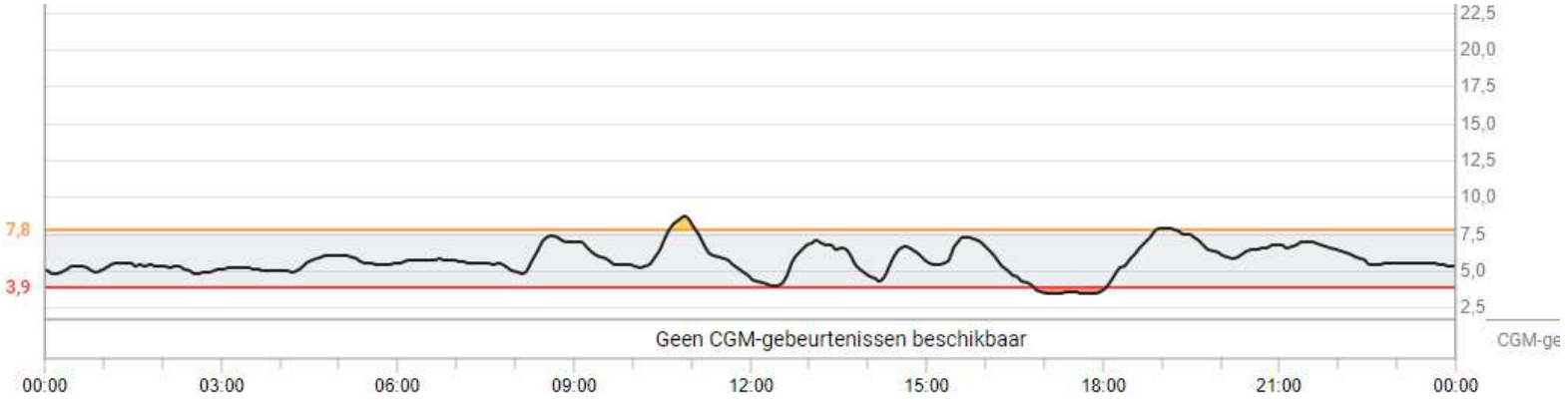
# Van nachtelijke sondevoeding naar maizena om de 4 uren



# Opnames GSD

* Evaluatie
* Bij grote veranderingen in het dieet
* Voorbereiding ingreep/na ingreep
* Metabole ontregeling, infectie, verminderde intake

# Geplande opnames

* Duidelijke afspraken over prikken bloedsuikers en ketonen
* Dieetlijst volgen qua tijd en hoeveelheid
* Wanneer voor onderzoek, altijd maaltijden of maizena mee (voor als het uitloopt)
* Altijd iets bij de hand voor laag bloedsuiker
* Bij dieetaanpassing, dagelijks veranderingen
* Bij OK, afspraken over nuchter zijn/infuus

# Niet geplande opnames

* Bij opname met metabole ontsporing is er geen tijd om te wachten
* Luister naar ouders. Zij weten vaak heel goed wat er moet gebeuren
* Let op bij wisselingen van infuus naar voeding en van druppelsondevoeding naar bolus/eten
* Communicatie essentieel, wie doet wat

# Metabole ontsporing

* Aanvoer van KH blijven voortzetten
* Starten sondevoeding overdag
* Noodoplossing/Noodprotocol
  https://www.emergencyprotocol.net/

# Case: boy 3y6m

- Failure to thrive:
  - Height 84.2 cm (-4.2 SD) and weight 11.5 kg (-0.5 SD)
- Breastfed up to 2 years of age
- Decreased stamina, muscle pain
- Parents from Sudan
- Sister died of liver disease at the age of 2
- Hepatomegaly

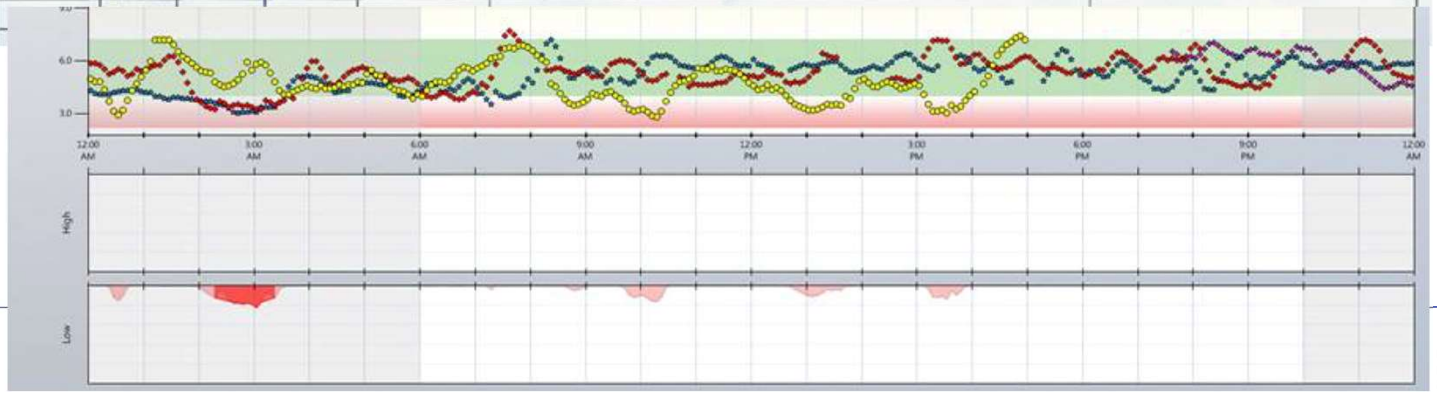
| | |
|---|---|
| Neutrophils | $2.6x10^9$/L |
| Glucose | 5.6 mmol/L |
| Lactate* | 4.2 mmol/L |
| ASAT* | 236 U/L |
| ALAT* | 217 U/L |
| Uric acid | 0.30 mmol/L |
| CK | 62 U/L |
| Triglycerides* | 9.10 mmol/L |
| Total cholesterol* | 6.8 mmol/L |

# Dietary history

* Difficult because of a language problem and no interpreter available at that moment
* Good appetite, eats all foods, likes sweets/fruits
* Normal day-schedule with 3 main meals and 2-3 snacks
* Drinks a lot of juice, also during the night
* Has a lot of caries
* No symptoms of low bloodglucose, but low bloodglucose in measurements

# Asses (1)

| datum | tijd | Bloedsuiker Dexcom | Bloedsuiker contour | ketonen | Eten/drinken (zie instructie) | Bijzonderheden bv sporten, lichamelijke klachten |
|---|---|---|---|---|---|---|
| 30/10 | 02:10 | | | | milk | |
| | 05:50 | | | | milk | |
| | 07:11 | | 5.3 | 0.4 | | |
| | 07:30 | | | | slice of bread + egg + orange juice | |
| | 09:00 | | | | Yoghurt + cake | |
| | 12:10 | | 6.8 | 0.3 | | |
| | 12:45 | | | | fish + rice, orange, + water | |
| | 15:00 | | | | boiled egg + peer + apple + peach | |
| | 16:00 | | | | juice (mixed) | |
| | 19:00 | | | | soup + bread + water | |
| | 20:05 | | 5.4 | 0.3 | | |
| | 20:20 | | | | milk | |
| | 23:30 | | | | milk | |
| 31/10 | | | | | | |
| | 07:17 | | 3.7 | 1.8 | | |
| | 08:10 | | | | milk + slice of bread + cheese + chips | |
| | 14:31 | | 3.7 | 1.8 | bread + cheese + orange juice | |
| | 15:31 | | | | chips + juice + pineapple juice | |

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# Assesment of fasting tolerance

| Breakfast at 6.30 | | |
|---|---|---|
| | | |
| | Blood at 9.00 | Blood at 14.15 |
| Glucose | 4.0 | 3.3 |
| Lactate | 1.4 | 1.3 |
| AcA | - | 0.7 |
| BOHB (ketones) | - | 1.5 |
| Triglycerides | 9.1 | 4.0 |
| Total Cholesterol | 6.6 | 6.7 |

# Dietary calculations

* Fasting period: max. 7 hours based upon assesment of fasting tolerance
* EGP at 12 kg = 7.3 mg gluc/min/kg BW (this means 5.2 g carbohydrate per hour)
* Protein 3-4 g /kg BW = 36-48 grams, for late night feed: 1 g protein/kg BW
* Energy: 80 kcal /kg BW = 960 kcal / day. For catch-up growth factor 1.1-1.2 = 1050-1150 kcal

# Dietplan

During the day 3x shake of dairy (no added sugar) with maizena

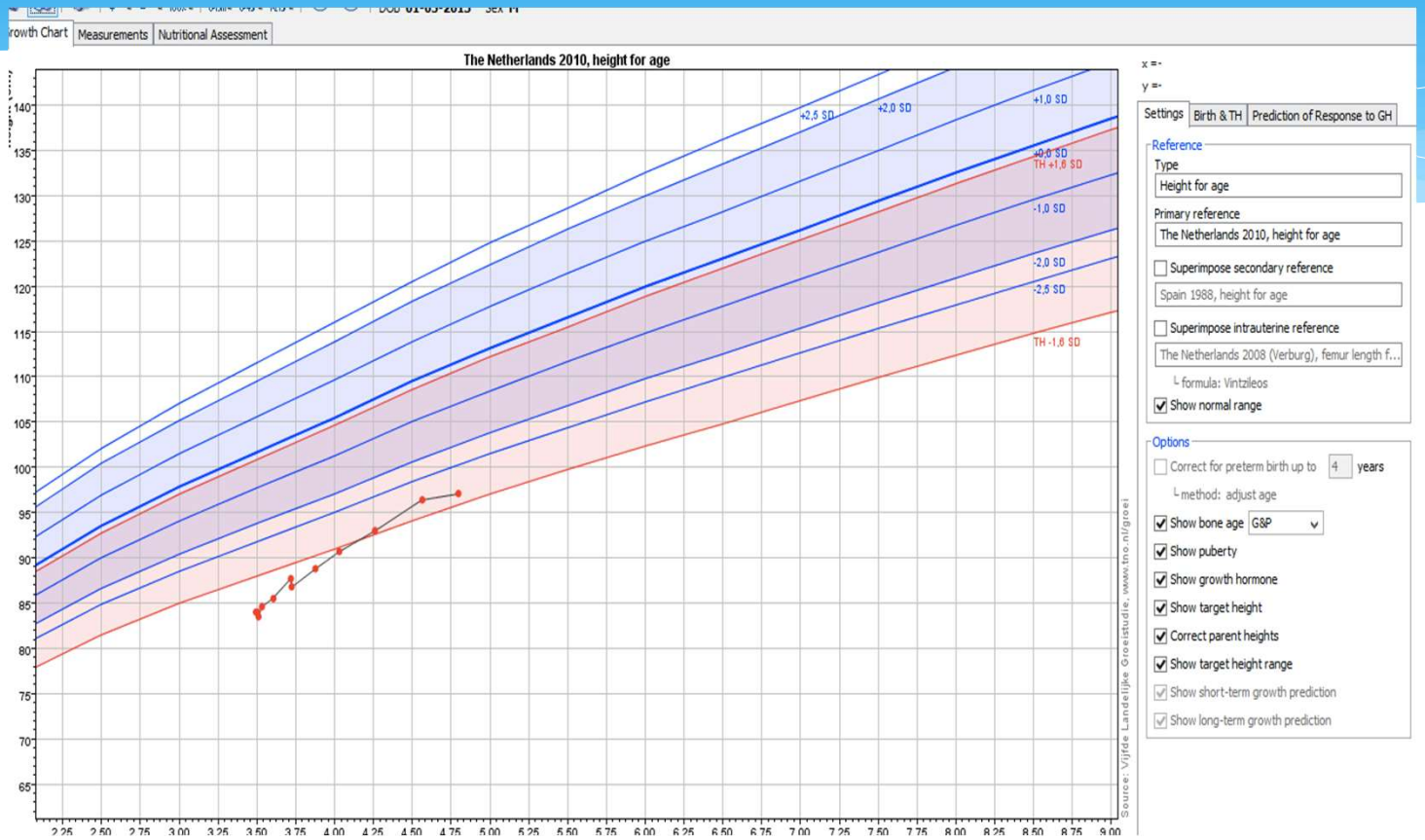
6uur/12uur/18uur

<u>Composition for the day-shake:</u>
75 ml dairy no added sugar
15 g maizena

At 23.00uur: 1 shake of dairy (no added sugar) with maizena and Prosource no carb:

<u>Composition of the late-evening-shake:</u>
100 ml dairy no added sugar
30 ml Pro Source No Carb (= 15 g of protein)
30 g maizena

Meals: no more than 15-20 carbohydrates per meal, max. 5-10 for snacks
Energy: 1100 kcal


Growth Chart
Measurements
Nutritional Assessment
The Netherlands 2010, height for age
+2,5 SD
+2,0 SD
+1,0 SD
+0,0 SD
TH +1,6 SD
-1,0 SD
-2,0 SD
-2,5 SD
TH -1,6 SD
Source: Vijfde Landelijke Groeistudie, www.tno.nl/groei
x =-
y =-
Settings
Birth & TH
Prediction of Response to GH
Reference
Type
Height for age
Primary reference
The Netherlands 2010, height for age
Superimpose secondary reference
Spain 1988, height for age
Superimpose intrauterine reference
The Netherlands 2008 (Verburg), femur length f...
formula: Vintzileos
Show normal range
Options
Correct for preterm birth up to 4 years
method: adjust age
Show bone age G&P
Show puberty
Show growth hormone
Show target height
Correct parent heights
Show target height range
Show short-term growth prediction
Show long-term growth prediction

JIMD
JOURNAL OF INHERITED METABOLIC DISEASE
SSIEM

**retrospective in-depth analysis of continuous glucose monitoring datasets for patients with hepatic glycogen storage disease: Recommended outcome parameters for glucose management**

Fabian Peeks,Irene J. Hoogeveen,R. Lude Feldbrugge,Rob Burghard,Foekje de Boer,Marieke J. Fokkert-Wilts,Melanie M. van der Klauw,Maaike H. Oosterveer,Terry G. J. Derks,

**A generic emergency protocol for patients with inborn errors of metabolism causing fasting intolerance: A retrospective, single-center study and the generation of www.emergencyprotocol.net**

Alessandro Rossi,Irene J. Hoogeveen,Charlotte M. A. Lubout,Foekje de Boer,Marieke J. Fokkert-Wilts,Iris L. Rodenburg,Esther van Dam,Sarah C. Grünert,Diego Martinelli,Maurizio Scarpa, **... See all authors**

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