Management of hypoglycemia

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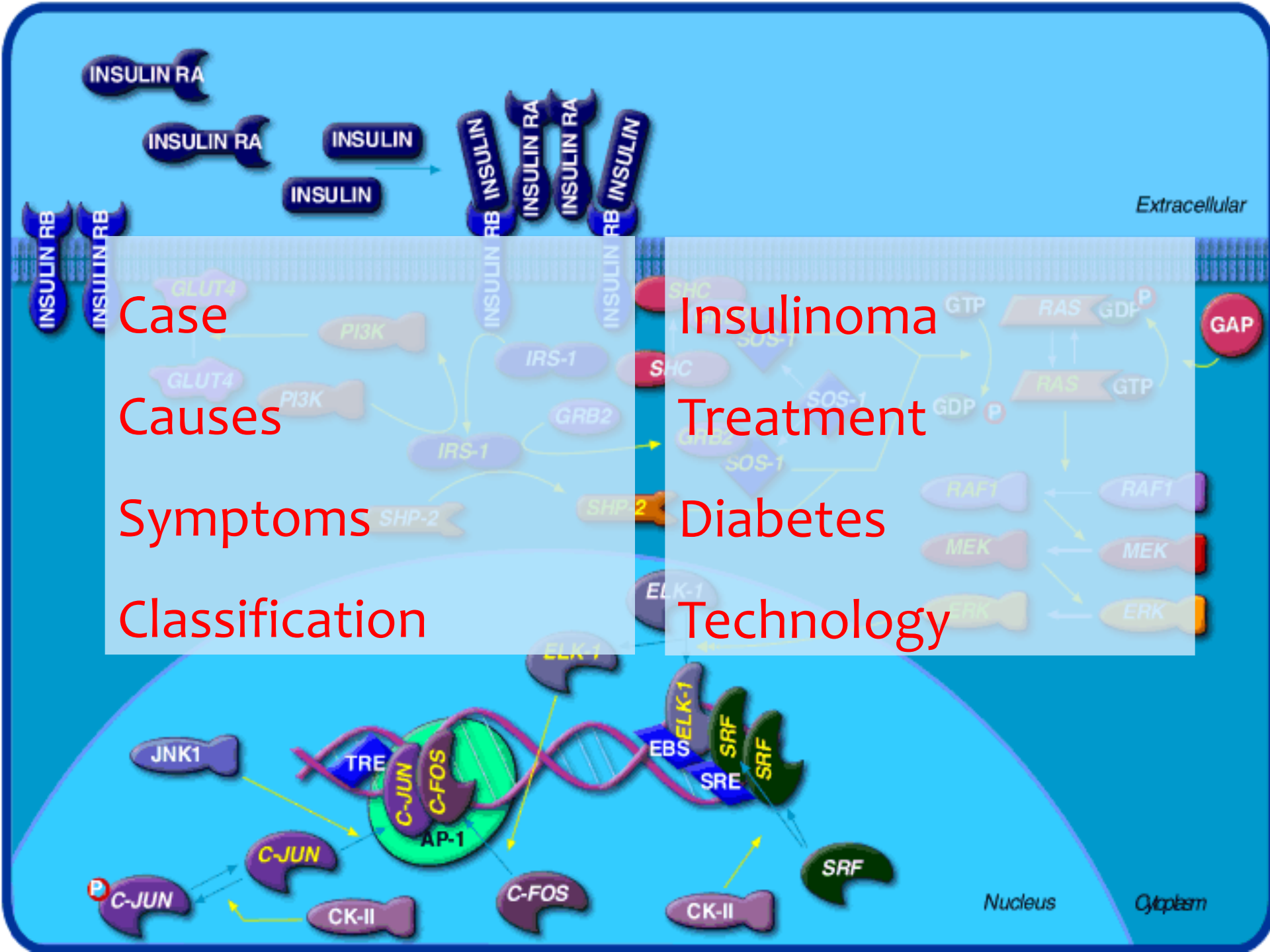

Case
Insulinoma
Causes
Treatment
Symptoms
Diabetes
Classification
Technology
INSULIN RA
INSULIN
INSULIN RB
Extracellular
GLUT4
PI3K
IRS-1
GRB2
SHC
SHP-2
SOS-1
RAS
GTP
GDP
GAP
RAF1
MEK
ERK
ELK-1
JNK1
TRE
C-JUN
C-FOS
AP-1
EBS
SRF
SRE
CK-II
Nucleus
Cytoplasm

Case 1 & 2

- 43-year-old woman
- 4 years Repeated episodes
  - sweating
  - slurred speech
  - confusion
- Two accidents
- Glucose: 1.8 mmol/L
- Insulin High
- C-peptide High
- Proinsulin High
- improved after intravenous

- 27-year-old man
- Episodes
  - sweating
  - slurred speech
  - Confusion
- Glucose: 1.8 mmol/L
- Insulin High
- C-peptide Low
- Proinsulin Low

Possible Diagnosis?

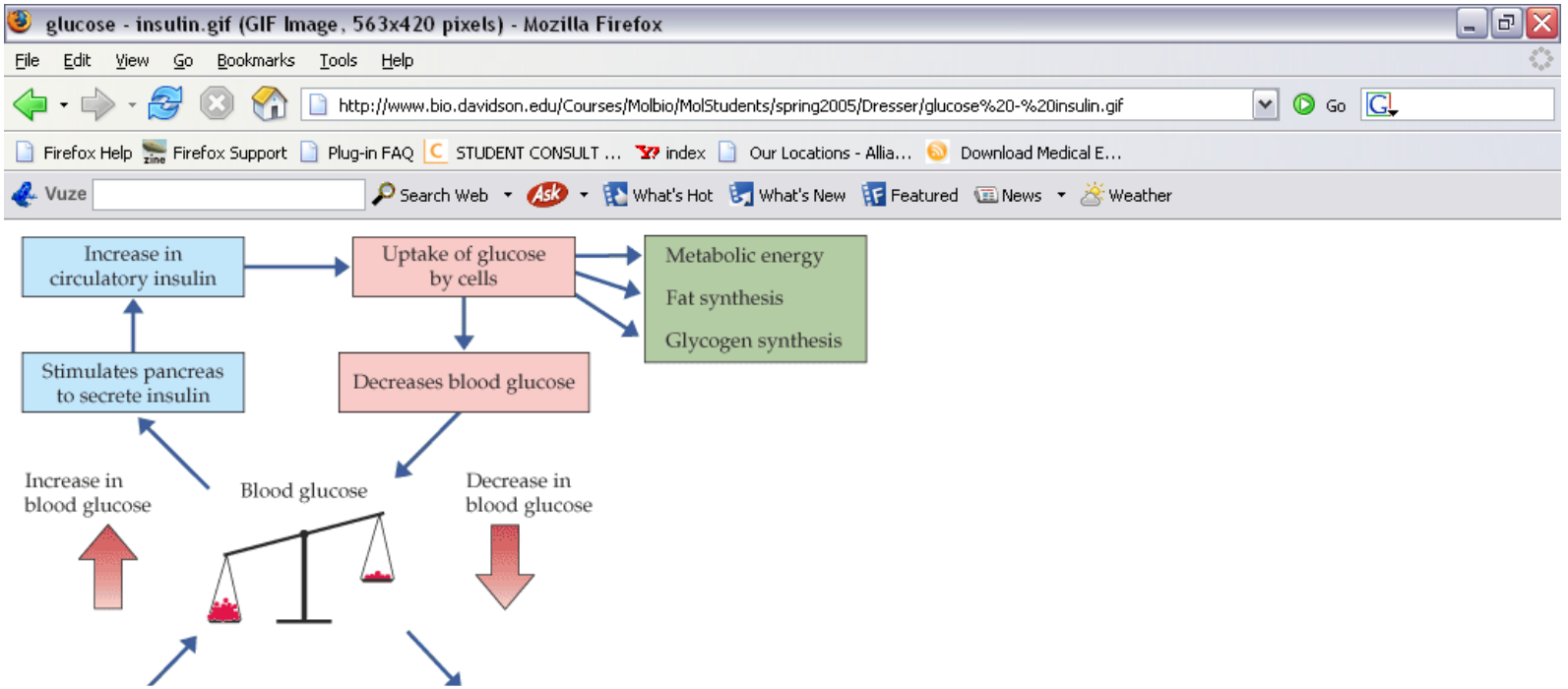
A) Insulin use

B) Insulinoma

C) Antibodies to Insulin receptor

Glucose pathway

Insulin



Glucagon

Causes

Drugs

* **Insulin- most common cause**
* Timing, dose, type
* clearance of insulin (eg, renal failure);
* altered counter regulation

* **Sulfonylurea's**
* Metformin does not cause hypoglycemia
* High dose salicylates, b –blockers, quinine, quinolones

Renal failure

* Chronic kidney disease
* decreased clearance (insulin and Sulfonylurea's)

Hepatic Failure

* Decreased glycogenolysis
* Decreased gluconeogenesis
* Large functional reserve,(20% func required to prevent hypoglycemia)
* Genetic defects in glycometabolic pathways

Endocrinopathies

* Adrenal (glucocorticoid) insufficiency
* Growth hormone deficiency
* Glucagon deficiency
* Pituitary disease (decreased combined corticotropin and GH deficiency)

Poisoning

(ethanol, propanolol, salicylates)

* Ethanol inhibits gluconeogenesis

* Ethanol-induced **hypoglycemia** occurs 12-72 hrs after ingestion

Neoplasm

* Non–islet-cell tumors
* Hepatocellular carcinoma,
* Adrenocortical tumors,
* Carcinoid tumors,
* leukemia, and lymphomas

* Most of these tumors secrete IGF –II molecule
* Some also secrete Glucagon- like peptide(GLP-1) and Somatostatin

Insulinoma

* Pancreatic β-cell tumors that secrete Insulin
* Small,solitary, benign(< 10% malignant)

Inability of insulinoma cells to suppress insulin secretion during low levels of circulating glucose, leading to severe hypoglycemia

Diagnosis and Tumor Localization

* Hunger test
* Very high Insulin levels
* spiral CT, arteriography, ultrasonography (endosono..)

Treatment of Choice

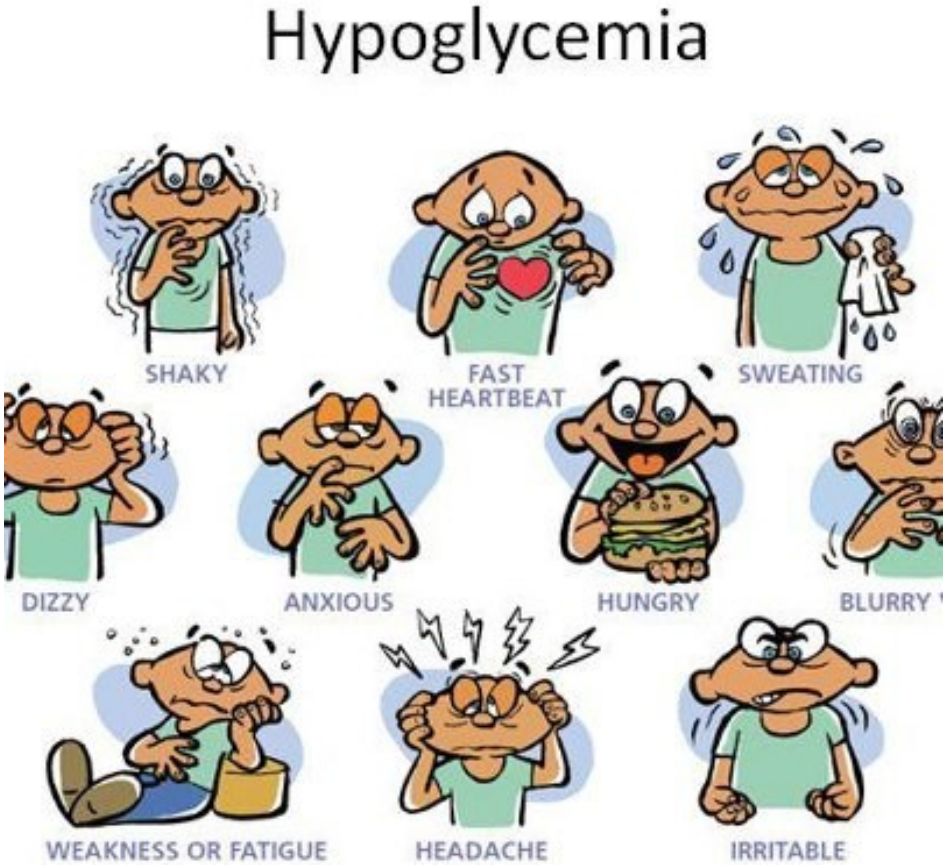
Symptoms

Adrenergic Symptoms

* early with a rapid decline
* tachycardia, tachypnea, vomiting, and diaphoresis

Neuroglycopenic Symptoms

* slower or prolonged
* poor feeding, altered mental status, lethargy and seizures



Classification of Hypoglycemia

Fasting hypoglycemia

* Post-absorptive period (hours after a meal)

Reactive (*postprandial*) hypoglycemia

* Controversial
* Low postprandial glucose - not sufficient
* 10% to 30% OGTT , glucose <2.7 mmol/l, with no symptoms
* Patients with symptoms require further workup

Dumping Syndrome/ Alimentary Hypolycemia

* Alimentary **hypoglycemia** presents 2 hrs after a meal

Dumping Syndrome

Pathophysiology

* disruption of controlled gastric emptying
* decreased transit time
* rapid elevation in plasma glucose that triggers exaggerated insulin response.
* abnormal insulin then causes a precipitous drop in blood glucose

Counter regulatory hormones

Main defense

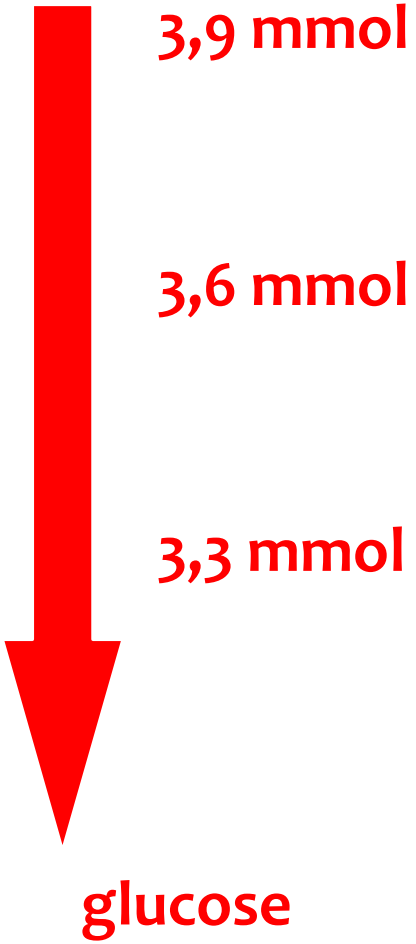
- increased release Glucagon, Epinephrine, Cortisol and GH

- **Glucagon**
  - glycogenolysis and gluconeogenesis

- **Epinephrine**
  - ß-adrenergic receptors
    - glycogenoalysis and gluconeogenesis
  - alpha-2-receptors
    - insulin secretion

Hormones by glucose level

* **Glucagon and epinephrine secretion**
  * Glucose levels: 3.6 to 3.9 mmol/L
* **Growth hormone secretion**
  * Glucose levels: 3.3 to 3.6 mmol/L
* **Cortisol secretion**
  * Glucose levels: < 3.3 mmol/L



Diagnosis

Establishing the cause

* History (liver failure, sepsis, autoimmune disease, neoplasm, alcohol, drugs)

Establishing fasting hypoglycemia

* Supervised 72 hour fast test
* Hospital setting to lower risk to the patient
* Hypoglycemia in first 48 hours (95% of cases)

72h Fast Test

Protocol

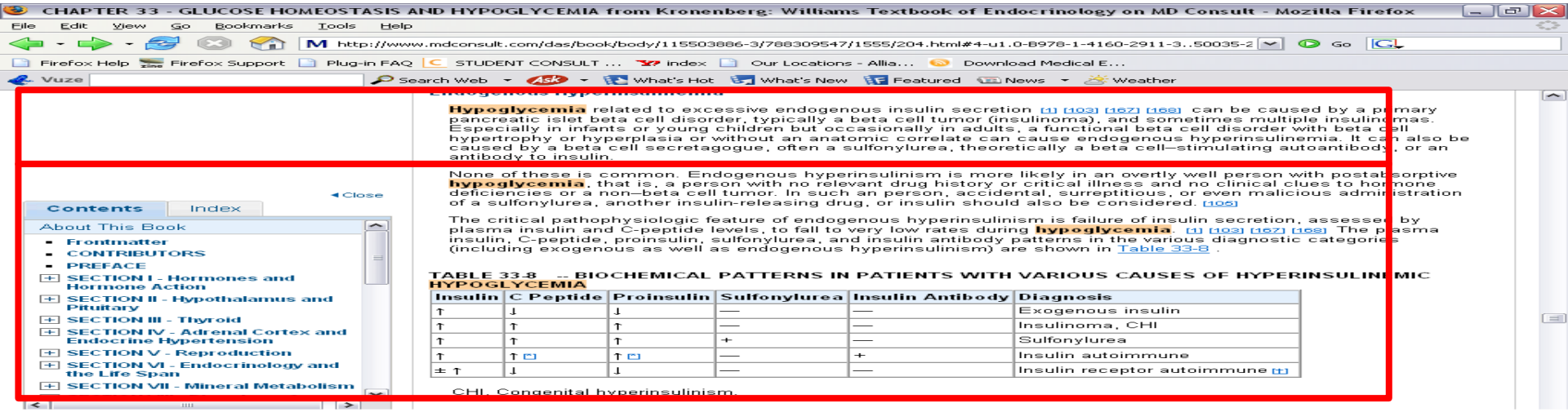
- Date an time on the onset of the fast
  - last intake of calories
- Discontinue all non essential medications
- Calorie-free and caffeine-free beverages
- Blood specimens 3-6 hours
  - plasma glucose
  - Insulin
  - C-peptide
  - Proinsulin

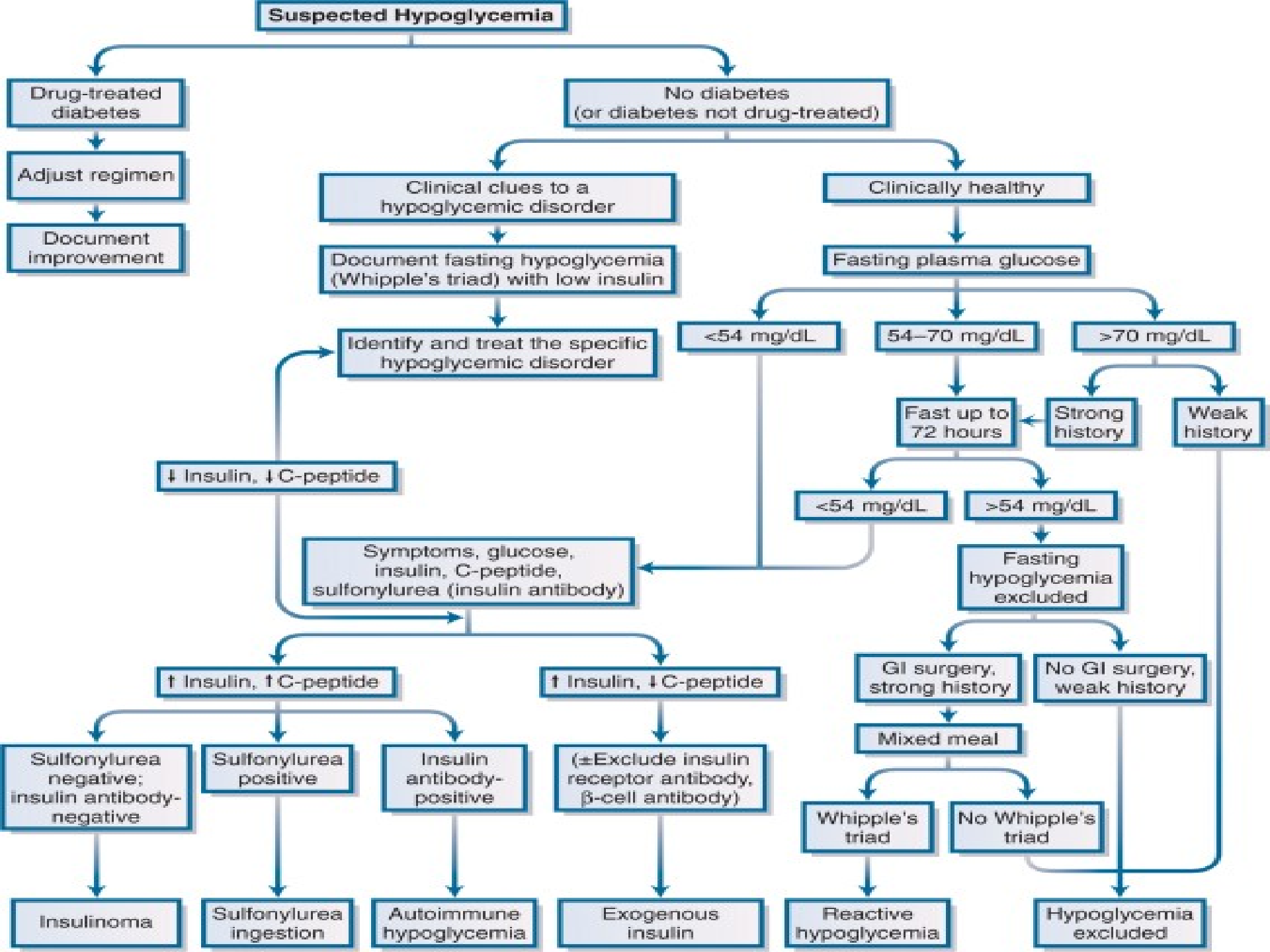
* The patient has symptoms or signs of hypoglycemia

* <3.0 mmol/L if Whipple's triad
  * sulfonylurea levels

* 1 mg of glucagon
  * plasma glucose measured 10, 20, and 30 minutes later.

Interpretation 72 h test




Suspected Hypoglycemia
Drug-treated diabetes
Adjust regimen
Document improvement
No diabetes (or diabetes not drug-treated)
Clinical clues to a hypoglycemic disorder
Document fasting hypoglycemia (Whipple's triad) with low insulin
Identify and treat the specific hypoglycemic disorder
Clinically healthy
Fasting plasma glucose
<54 mg/dL
54–70 mg/dL
>70 mg/dL
Strong history
Weak history
Fast up to 72 hours
<54 mg/dL
>54 mg/dL
Fasting hypoglycemia excluded
GI surgery, strong history
No GI surgery, weak history
Mixed meal
Whipple's triad
No Whipple's triad
Reactive hypoglycemia
Hypoglycemia excluded
↓ Insulin, ↓ C-peptide
Symptoms, glucose, insulin, C-peptide, sulfonylurea (insulin antibody)
↑ Insulin, ↑ C-peptide
↑ Insulin, ↓ C-peptide
Sulfonylurea negative; insulin antibody-negative
Sulfonylurea positive
Insulin antibody-positive
(±Exclude insulin receptor antibody, β-cell antibody)
Insulinoma
Sulfonylurea ingestion
Autoimmune hypoglycemia
Exogenous insulin

Principles of Treatment

* Priority in treating hypoglycemia
  * maintain plasma glucose > 2,9 mmol/l
* Underlying cause
* **Patients with Ab to insulin receptor**
  * high-dose glucocorticoid (prednisone, 60 mg/d)
* **Insulinoma**
  * Diazoxide 100-800 mg/day
  * suppressing insulin secretion
  * Surgical
* **Do not overload**
  * Hyperglycemia (sugars and counter-regulatory hormones)

Simple Sugars (oral) vs Dextrose (i.v.) vs Glucagone (i.v. s.c.)

Hypoglycemic Coma

* Unconsciousness
* Very dangerous
* Brain defects
* Delayed recovery from hypoglycemia
* IV mannitol (40 g as a 20% solution over 20 minutes)
* Glucocorticoids (e.g., dexamethasone, 10 mg),
* both can be used

Diabetes Hypoglycemia

By severity

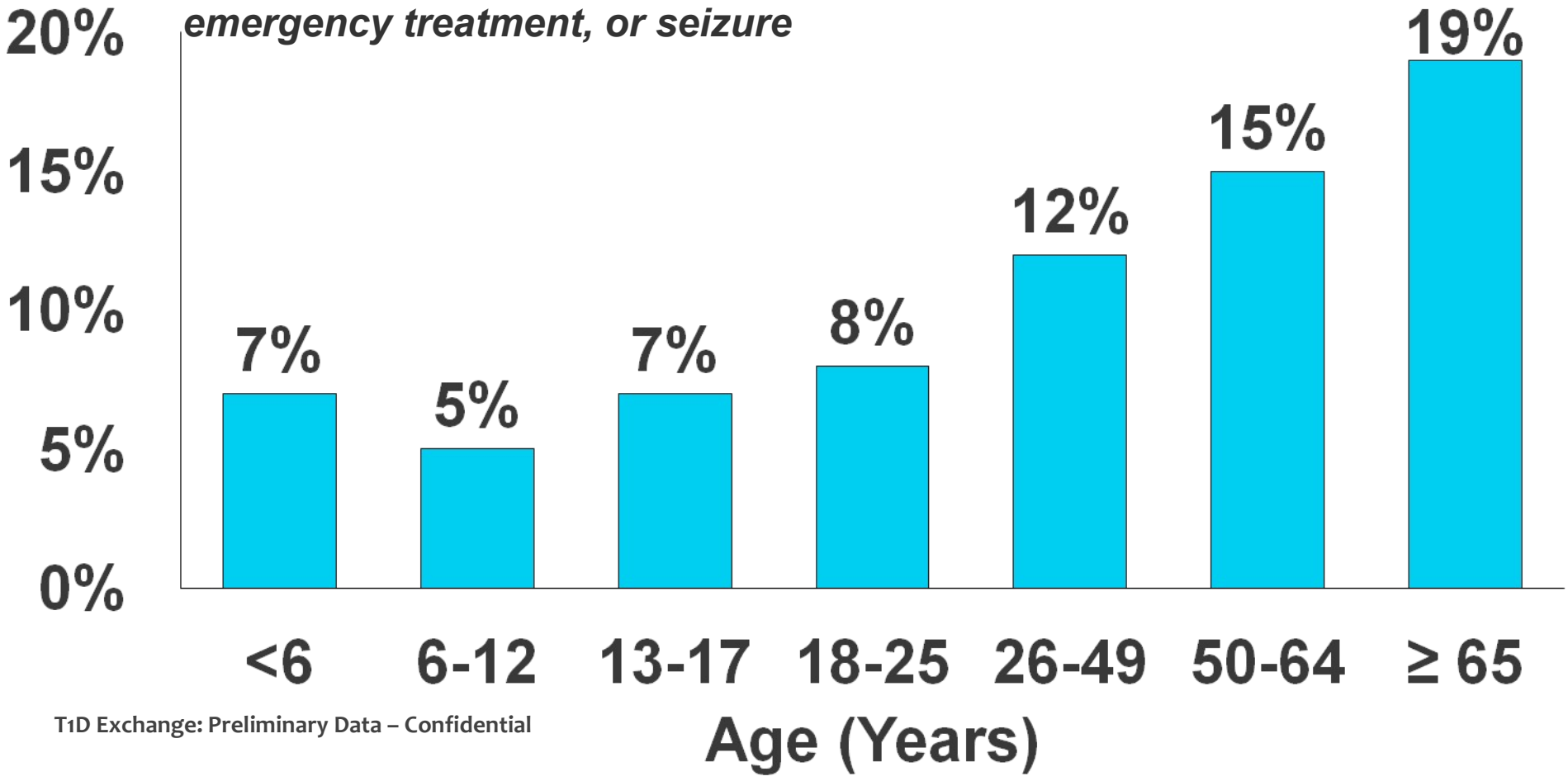
* **Asymptomatic** Hypoglycemia
  * low blood sugar, no symptoms
  * Self treated: glucose tablets, gel or sugary foods
* **Mild** Hypoglycemia
  * symptoms
  * Self treated: glucose tablets, gel or sugary foods
* **Severe/profound** Hypoglycemia
  * Urgent assistance Medical emergency
  * intravenous glucose or glucagon administration
  * Reduced consciousness

Hypoglycemia Unawareness

* 50% of type 1 patients
  * diminution in their epinephrine response to hypoglycemia
* Patients lose
  * autonomic warning symptoms
  * somatic neurologic function
* Usually
  * duration of diabetes and autonomic neuropathy

12-month Frequency of Severe Hypoglycemia*

**1 or more events: Includes events that required glucagon injection, emergency treatment, or seizure*



T1D Exchange: Preliminary Data – Confidential

Type 1 exchange Macedonia

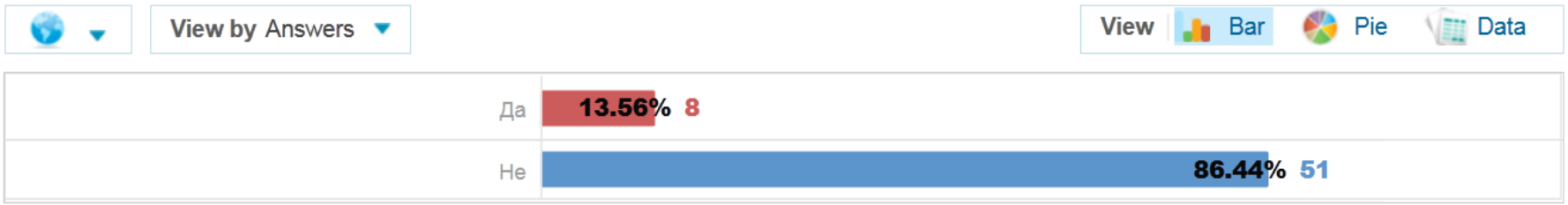
Q23 Колку епизоди на умерена хипогликемија (шеќер во крвта <3.8mmol/L) сте имале во последниот месец? (доколку сте немале внесете 0) 58 Respondents

0,3 дневно

Q24 Колку епизоди на тешка хипогликемија (со губење на свест) сте имале во последната година? (доколку сте немале внесете 0) 56 Respondents

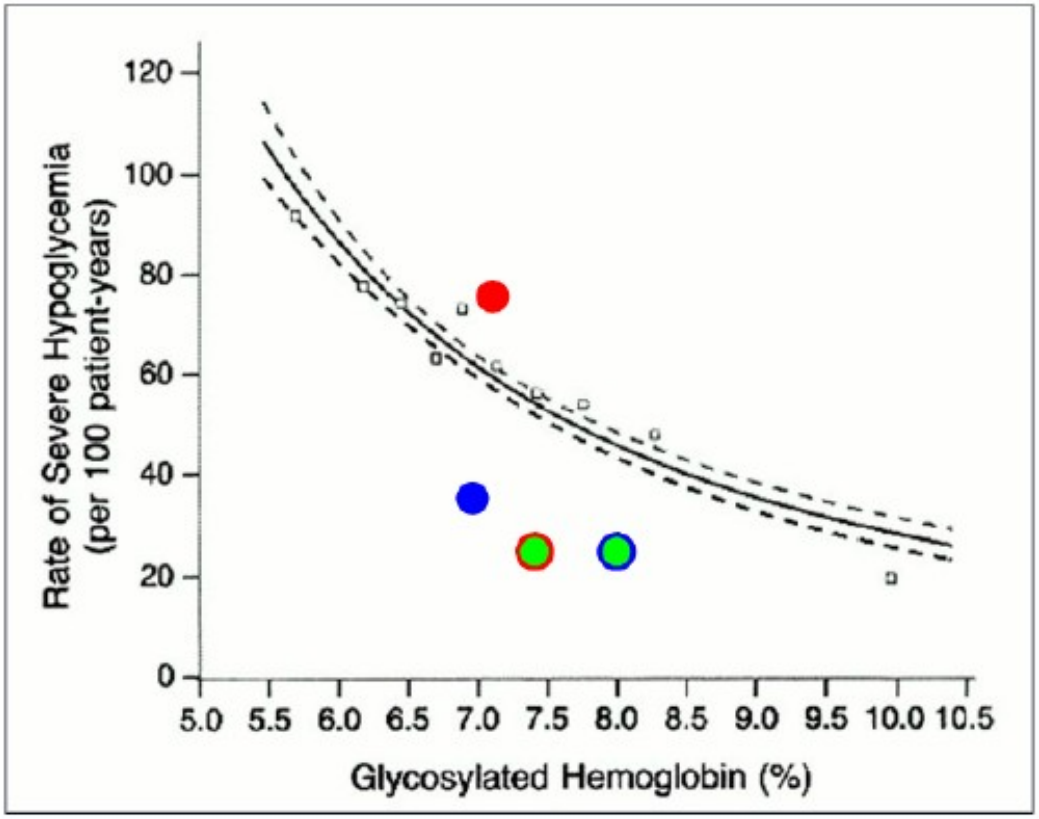
7%

Q20 Дали во последните 12 месеци сте биле хоспитализирани поради хипогликемија? 58 Respondents



Preliminary data on file: April 2013

Comparison of Severe Hypoglycemia and A1C: DCCT[12] (1993), JDRF[1] (2008), and STAR 3[11] (2010) Studies



DCCT (intensive therapy):
62 per 100 pt-yrs,
A1C(6.5 yr): 9.0% → 7.2%

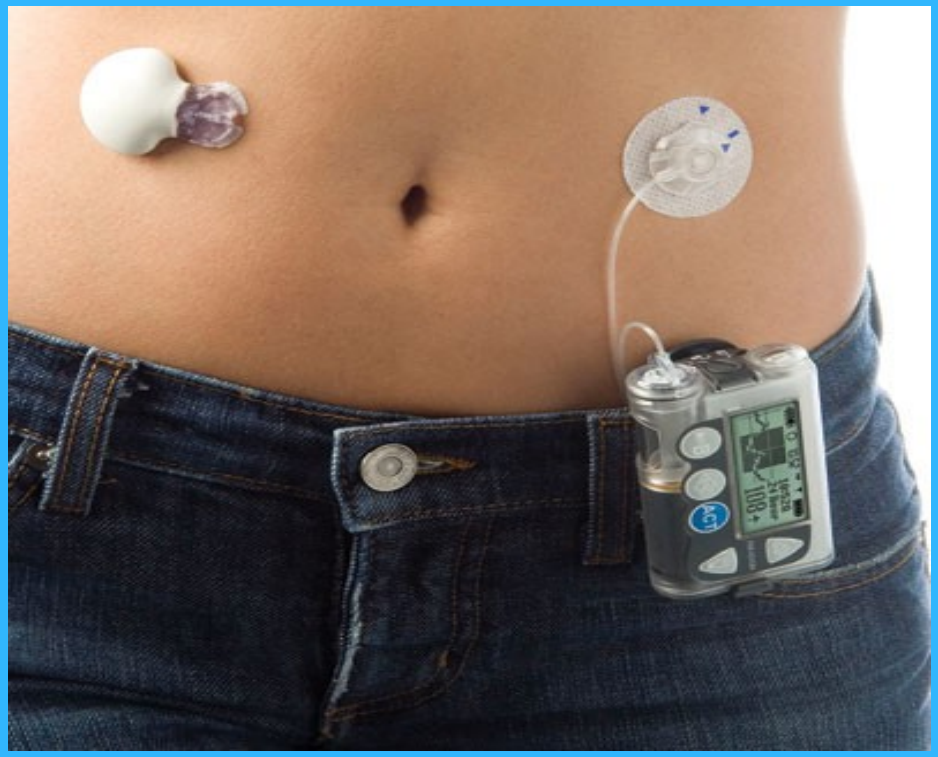
JDRF CGM (adults, 1 subject excluded):
20.0 per 100 pt-yrs;
A1C (6 mo): 7.5% → 7.1%

STAR 3 MDI (all ages):
13.5 per 100 pt-yrs;
A1C (1 yr): 8.3% → 8.1%

STAR 3 SAP (all ages):
13.3 per 100 pt-yrs;
A1C (1 yr): 8.3% → 7.5%

12. Adapted from Figure 5B of: DCCT. *N Engl J Med*. 1993;329:977-986.
1. JDRF data from: JDRF CGM Study Group. *N Engl J Med*. 2008;359:1465-1476.
11. Bergenstal RM, Tamborlane WV, Ahmann A, et al. [published online ahead of print June 29, 2010]. *N Engl J Med*. doi: [X].

Technology and diabetes in hypoglycemic patients (A case study)



Meet Ana

* 32 year's old
* Type 1 diabetes for 28 years
* Micro albuminuria positive
* Mild retinopathy
* Always hypoglycemia-prone
* Glucose control A1c: 5,5-7,0%

2006

* Miscarriage no.1

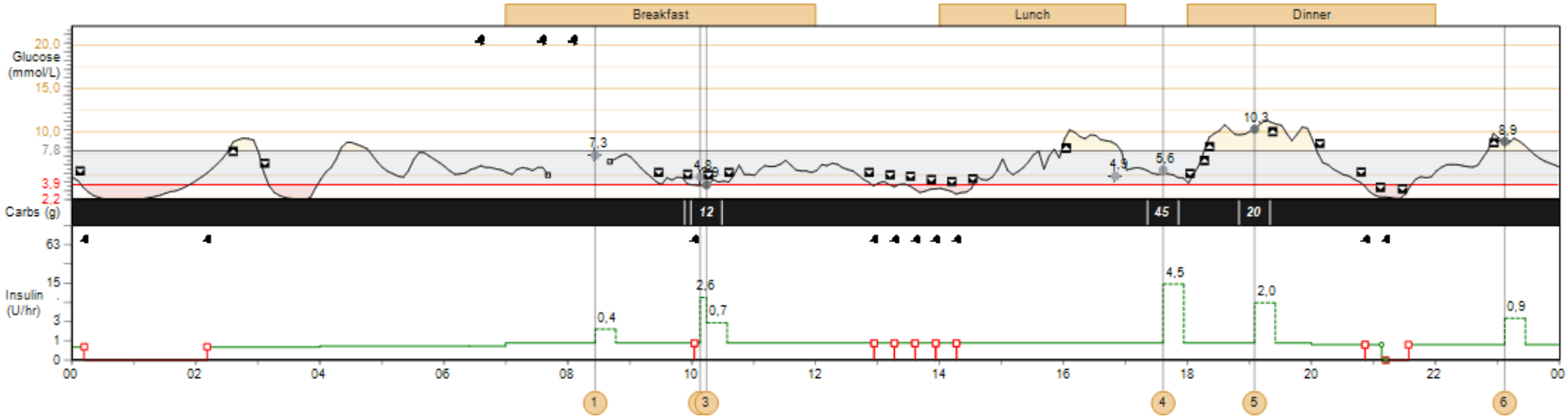
2011

* started on SAP pump (CSII&CGM)
* A1c: 5,2-6,1%
* Pregnancy

2012

* Boy
* 54 cm length
* 3600 gr weight

SAP during pregnancy



Bolus Events										
Bolus Event	1	2	3	4	5	6				
Time	08:26	10:08	10:14	17:36	19:04	23:07				
Bolus Type	Normal	Normal	Normal	Normal	Normal	Normal				
Delivered Bolus Norm (U)	0,400	2,55	0,650	4,50	2,00	0,925				
+ Square Portion (U, h:mm)	–	–	–	–	–	–				
Recommended Bolus (U)	0,400	2,55	0,650	4,50	2,00	0,925				
Difference (U)	–	–	–	–	–	–				
Carbs (g)	–	*28*	*12*	*45*	*20*	–				
Carb Ratio Setting (g/U)	10,0	10,0	10,0	10,0	10,0	10,0				
Food Bolus (U)	–	2,80	1,20	4,50	2,00	–				
BG (mmol/L)	**7,3**	**4,8**	**3,9**	**5,6**	**10,3**	**8,9**				
BG Target Setting (mmol/L)	5,6 - 6,1	5,6 - 6,1	5,6 - 6,1	5,6 - 6,1	5,6 - 6,1	5,6 - 6,1				
Insulin Sensitivity Setting (mmol/L per U)	3,0	3,0	3,0	3,0	3,0	3,0				
Correction Bolus (U)	0,400	-0,250	-0,550	–	1,40	0,925				
Active Insulin (U)	–	0,200	2,75	–	2,85	–				

Statistics	21.11		12.10 - 28.11	
Avg BG (mmol/L)	6,5		10,3 ± 3,7	
BG Readings	7		135	4,9/day
Readings Above Target	2	29%	97	72%
Readings Below Target	–	0%	1	1%
Sensor Avg (mmol/L)	5,8 ± 2,3		9,0 ± 3,4	
Avg AUC > 7,8 (mmol/L)	0,31	0d 23h	2,02	22d 16h
Avg AUC < 3,9 (mmol/L)	0,21	0d 23h	0,03	22d 16h
Daily Carbs (g)	*105*		*154 ± 52*	
Carbs/Bolus Insulin (g/U)	9,5		7,1	
Total Daily Insulin (U)	27,9		39,2 ± 7,3	
Daily Basal (U)	16,9	60%	17,3	44%
Daily Bolus (U)	11,0	40%	21,9	56%
Fills	–	–	9	16,2U

Fear of hypoglycemia

Hypo symptoms

	Standard pump	Sensor augmented pump
Clark score	7 (unaware)	3 (aware)
Hypo symptoms	None	Always (alarms)
Severe hypo	4 (in last 2 year)	None

Her comments

* Prevents or largely prevents night-time hypos
* I can sleep freely
* I am confident enough to drive again
* It has revolutionized my life
  * I have child

Hypoglycemic perspective on Skopje Tour

Thank you for your