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Remission in Non-Operated Patients with Diffuse Disease and Long-Term Conservative Treatment.

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Underlying pathomechanisms of Congenital Hyperinsulinism can have many different faces …

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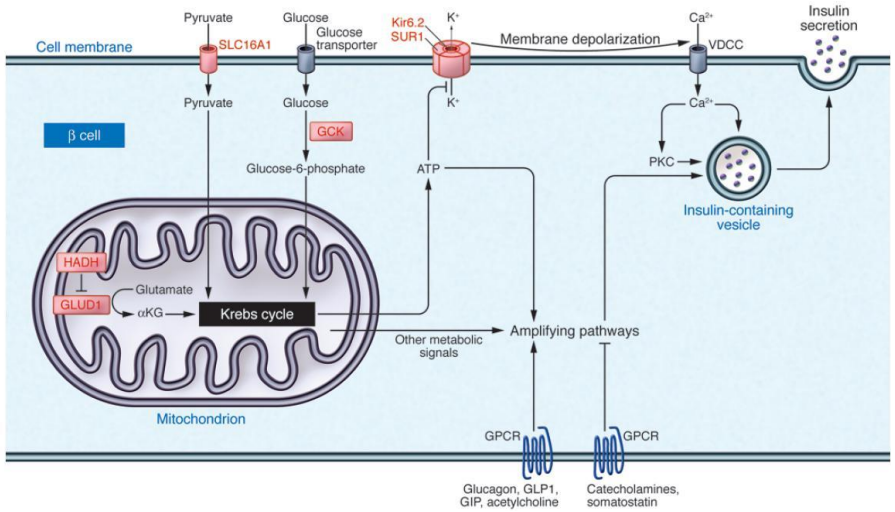

Model of the pancreatic β-cell with identified defects resulting in hyperinsulinemia *

➔ dysregulated insulin secretion mostly uncoupled from the blood glucose concentration

➔ inadequate high insulin concentration in turn:
- ➔ leads to hypoglycemia
- ➔ blocks the generation of alternate energy substrates

➔ threshold for hypoglycemia to cause brain damage is unknown

* Figure from Glaser, Benjamin (2011): Lessons in human biology from a monogenic pancreatic β cell disease. In: *J. Clin. Invest.* 121 (10), S. 3821–3825

Therapeutic options: main strategy according to the underlying histopathology

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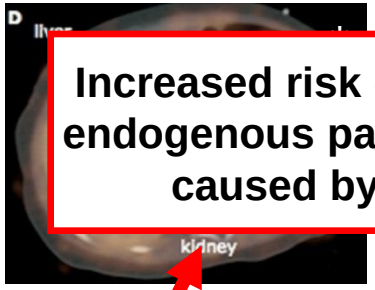
Background: Rapid diagnosis and consequent therapeutic actions are crucial in order to prevent recurrent episodes of hypoglycemia and long-term damages

	Diffuse form	Focal form
		
Former times	Surgical treatment	Surgical treatment
Nowadays	Pharmacological treatment ?	Surgical or pharmacological treatment

Increased risk of diabetes due to an endogenous pancreatic insufficiency caused by pancreatectomy

Serves both the principles of
1) Nonmaleficence
2) Beneficence

* Pictures from: Hardy, Olga T… chi, Mariko; Ruchelli, Eduardo; Zhuang, Hongming et al. (2007): Diagn… m by 18F-fluorodopa PET scan. In: *J. Pediatr.* 150 (2), S. 140-…

Present data elucidating the probability of remission

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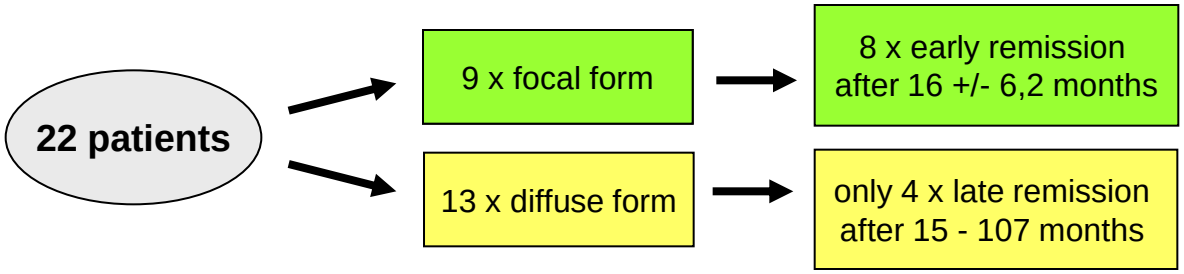
Already in the late 90s, an Israeli team examined the probability of remission in non-operated patients under long-term conservative treatment.
Findings were interpretated in dependence on the presumed underlying histopathology. *



Within the focal lesions, high rates of programmed cell death of β-cells could be detected.
➔ possible explanation for the apparent self-limiting character of focal forms

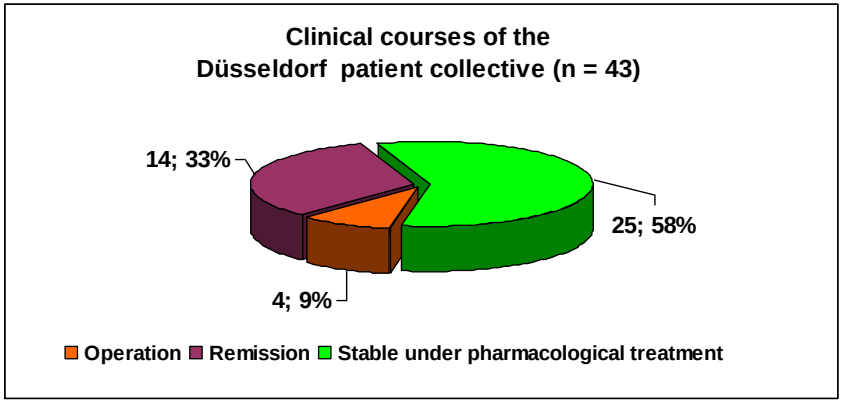
In 2011, Banerjee and colleagues from Manchester tried to identify prognostic factors for the probability of remission:

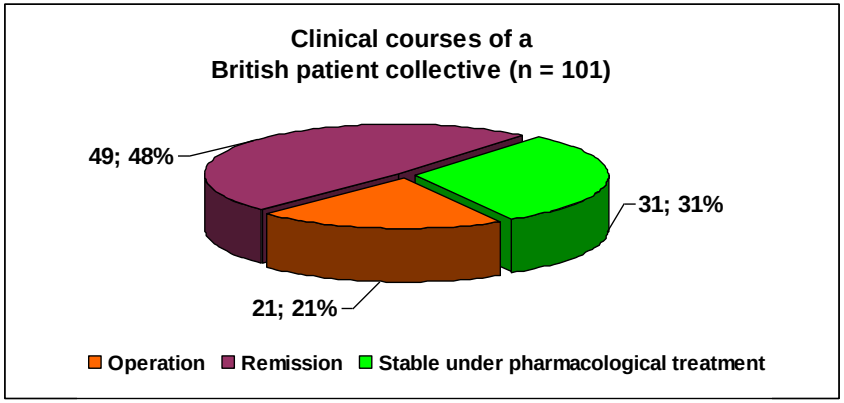
Positive correlation:
- responsiveness to diazoxide
- absence of identified gene mutations

No correlation:
- initial glucose requirement
- birth weight

* Data from Glaser, B.; Ryan, F.; Donath, M.; Landau, H.; Stanley, C. A.; Baker, L. et al. (1999): Hyperinsulinism caused by paternal-specific inheritance of a recessive mutation in the sulfonylurea-receptor gene. In: *Diabetes* 48 (8), S. 1652–1657

Comparison of therapeutic approaches in clinical practice





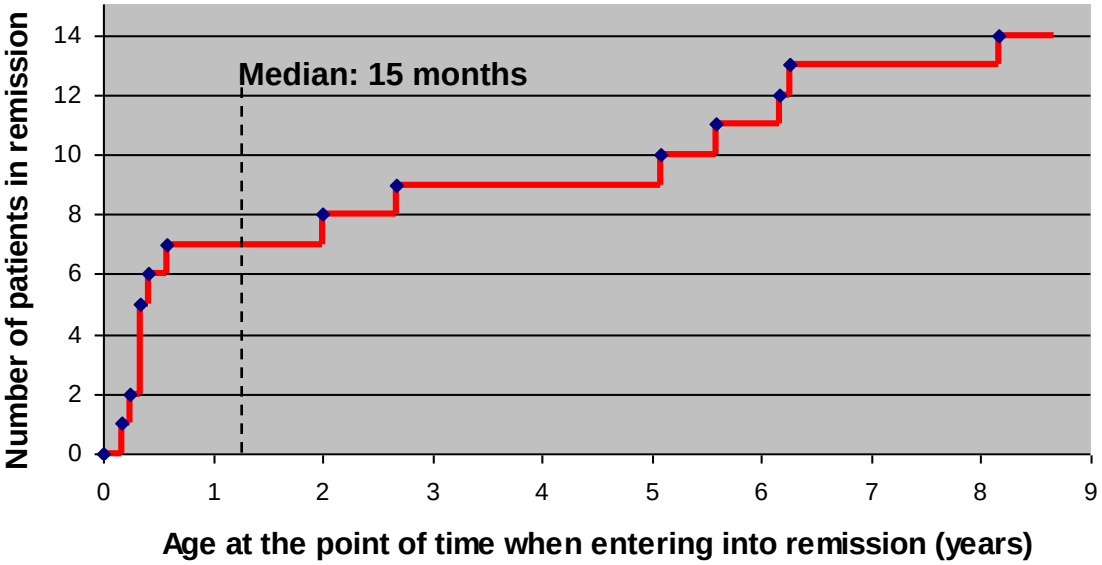
Pharmacological treatment mainly diazoxide as a first step
and, if diazoxide fails: octreotide and its analoga.

Definition of remission: no occurance of symptomatic hypoglycemia
with normal food intake after cessation of all pharmacological treatment.

Surgical intervention, especially a near-total pancreatectomy in case of a diffuse form, must be well considered with regards to long-term effects.
It may be a helpful device if a focal form is confirmed by a PET-Scan of the pancreas.

* Data from: Banerjee, I.; Skae, M.; Flanagan, S. E.; Rigby, L.; Patel, L.; Didi, M. et al. (2011): The contribution of rapid KATP channel gene mutation analysis to the clinical management of children with congenital hyperinsulinism. In: *Eur. J. Endocrinol.* 164 (5), S. 733–740

Some facts and figures from Düsseldorf describing the remission



	Octr.*	Diaz.*	Total
Remission	**5**	**9**	**14**
Therapy	**3**	**19**	**22**
Total	**8**	**28**	**36**

*only monotherapy is compared

p_1 (Octr.) = 5/8 ≈ 0,625

p_2 (Diaz.) = 9/28 ≈ 0,321

Odds-Ratio ≈ 3,519

Banerjee 2011
average: 101 days for remission

range: 6 days to 7,5 years

25th perc. 30 days

75th perc. 300 days

* Data were analysed by means of IBM® SPSS® Statistics for Windows, Version 20.0 (IBM Corporation, Armonk, New York). The p-value of the Odds-Ratio was determined using the Mantel–Haenszel test.

Case report of a non-operated patient with diffuse disease and long-term pharmacological treatment

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Case presentation

- male infant ,,U.K.“ born at 37^{+2} gestational weeks by caesarean sectio
- second child from consanguineous parents
- 5.320 g weight, 54 cm lenght → macrosomic
- first postpartal glucose measurement revealed a very low level of 29 mg/dl
  → glucose infusion started

Investigation

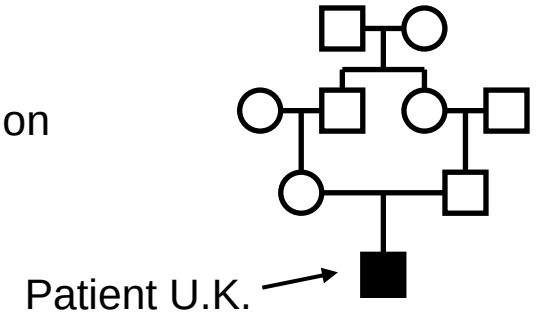
- during hypoglycemic episodes, elevated insulin concentrations were found

Glukose	Insulin
27 mg/dl	107 mU/l
35 mg/dl	61 mU/l

- at the same time, ketone bodies were undetectable
- defect of the β-oxidation was excluded

➔ **characteristic for Congenital Hyperinsulinism**

Genetic analysis: homozygous KCNJ11 mutation
→ K_{ATP}-channelopathy
→ diffuse form



Case report of a non-operated patient with diffuse disease and long-term pharmacological treatment

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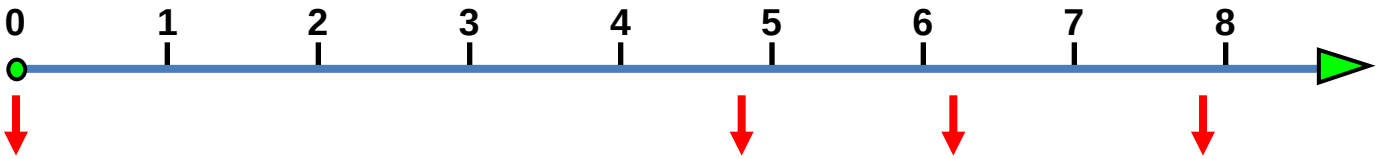
Therapy

- as the patient did not show any satisfactory response to diazoxide, octreotide was given subcutaneously
- under drug therapy combined with frequent feedings every 3 hours, the blood glucose level stabilised progressively



Birth
Start of octreotide therapy

4 years old
Change from octreotide to lanreotide

6 years old
Last injection of lanreotide

7 years old
Evaluation of the fasting tolerance in remission

BMI ≈ 23,4 (> 3 SD)

➔ peripheral insulin resistance may have contributed to the entrance into remission

Structured review on conservative treatment

- We have a good chance for successful longterm treatment
- Lack of clinical studies
- Medline (ab 1947) und Embase (ab1988)
- 1261 patients with congenital hyperinsulinism

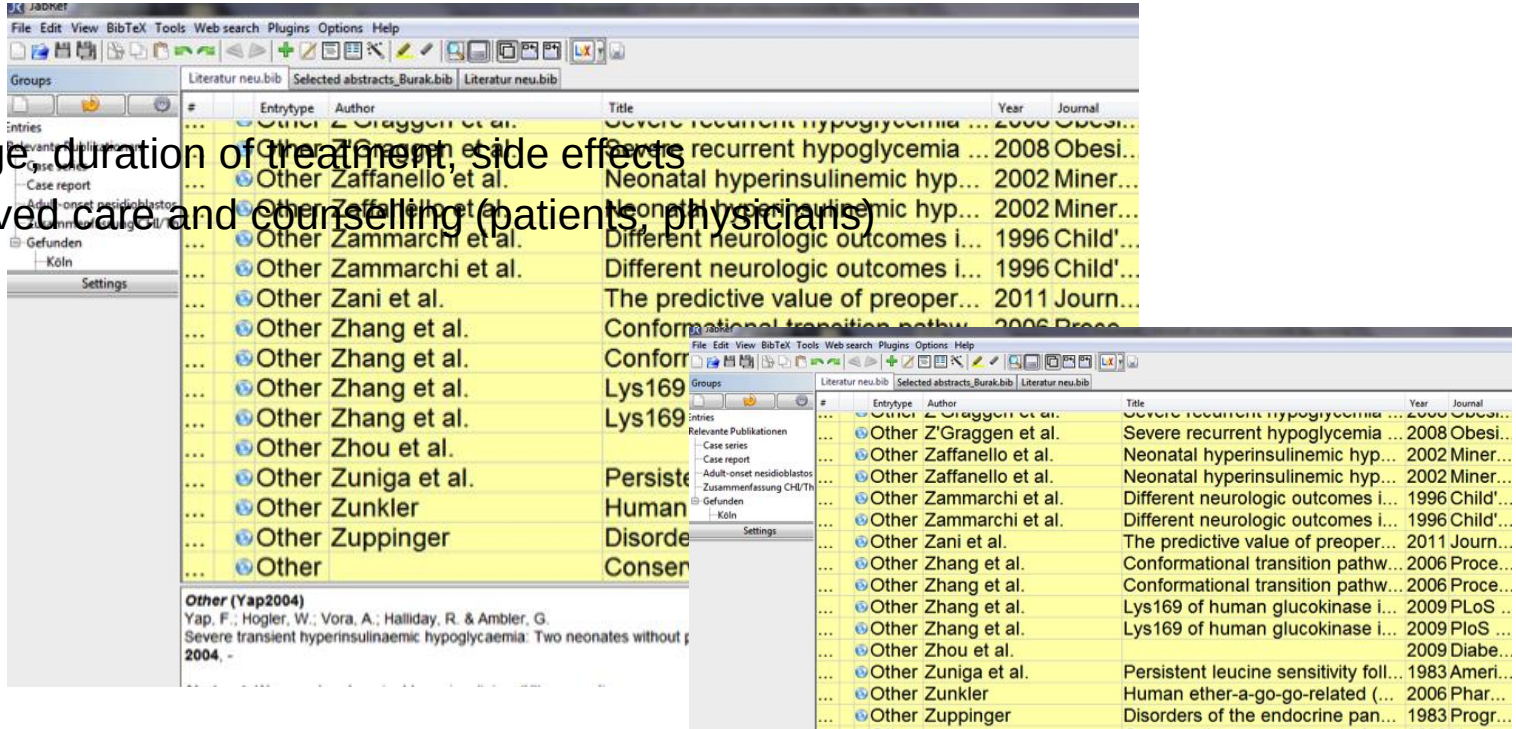
→ 619 patients with longterm treatment

→ Side effects for 1039 treatments reported

Aim

- Dosage, duration of treatment, side effects

→ Improved care and counselling (patients, physicians)



Conclusion

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➔ Data concerning the remission which have been found in an isolated population of Ashkenazi Jews in Isreal can also be relevant for European patient collectives.

➔ Compared with Manchester, the Düsseldorf patient collective enters later into remission which might be a consequence of a different definition of congenital and transient hyperinsulinism.

➔ Reported cases of diffuse diseases entering late into remission are useful arguments for a long-term conservative treatment.

➔ Although based on just a small number of cases, treatment with octreotide is associated with a high probability of remission in our patients and is therefore a resonable alternative to surgical intervention if diazoxide fails to elevate blood glucose concentration sufficiently.

➔ The probability of remission remains difficult to predict. Identification of prognostic factors and causative mechanisms should be objectives of future research projects.

Thanks a lot for your attention.

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