Type 1 diabetes

agnieszka.zubkiewicz-kucharska@umed.wroc.pl

1

Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

OR

Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

OR

2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT

OR

A random plasma glucose ≥200 mg/dL (11.1 mmol/L)

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 2.

2

Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay*

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 2.

3

Criteria for the Diagnosis of Diabetes

Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

Fasting is defined as no caloric intake for at least 8 h*

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 2.

4

Criteria for the Diagnosis of Diabetes

2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT

The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water*

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 2.

5

Criteria for the Diagnosis of Diabetes

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L)

6

Prediabetes: IFG, IGT, Increased A1C

Categories of increased risk for diabetes (prediabetes)*

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose in the 75-g OGTT 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 3.

7

Classification of Diabetes

- Type 1 diabetes
  - β-cell destruction
- Type 2 diabetes
  - Progressive insulin secretory defect
- Other specific types of diabetes
  - Genetic defects in β-cell function, insulin action
  - Diseases of the exocrine pancreas
  - Drug- or chemical-induced
- Gestational diabetes mellitus (GDM)

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S11.

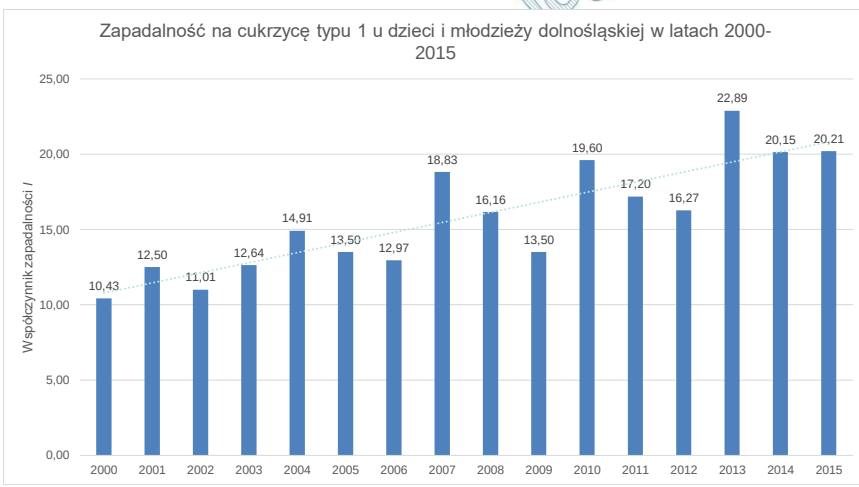
8

Type 1 diabetes

- Type 1 diabetes is a chronic autoimmune disease associated with selective islet β-cell destruction that leads to insulin-dependency.

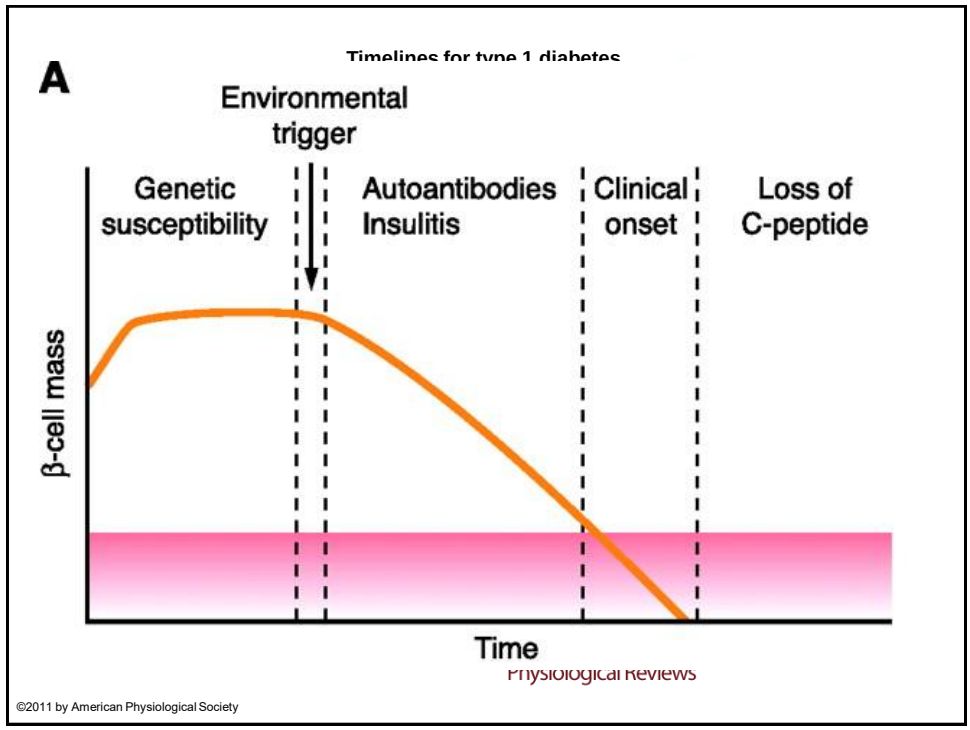
9

Lower Silesia - IR=20,21

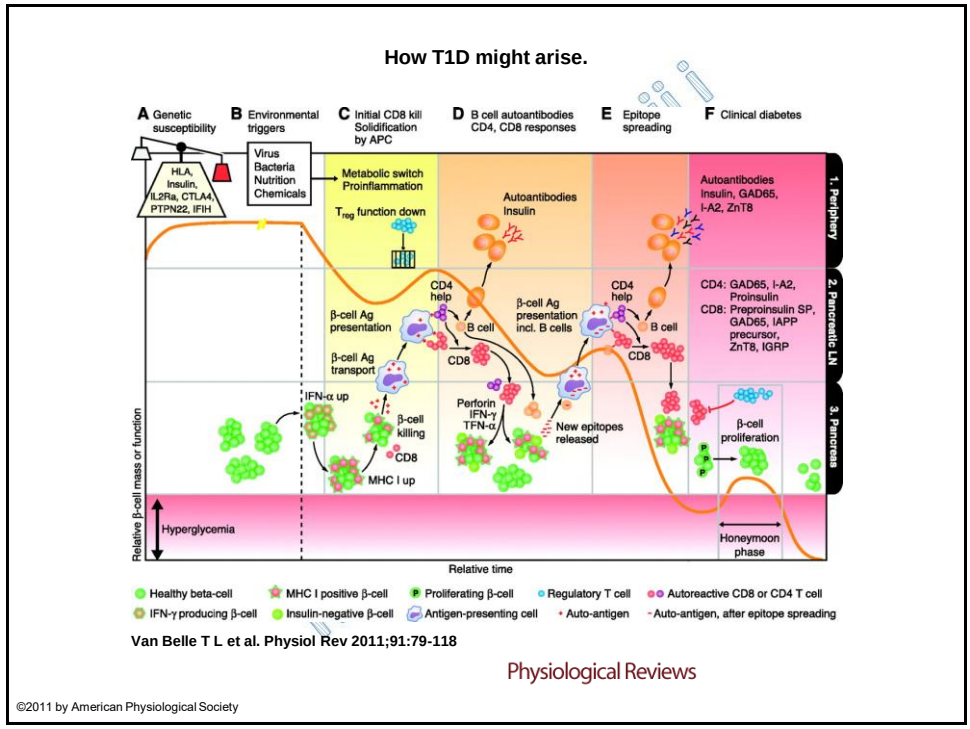


Zubkiewicz, Seifert 2016

10


Timelines for type 1 diabetes
A
Environmental trigger
Genetic susceptibility
Autoantibodies Insulitis
Clinical onset
Loss of C-peptide
β-cell mass
Time
Physiological Reviews
©2011 by American Physiological Society

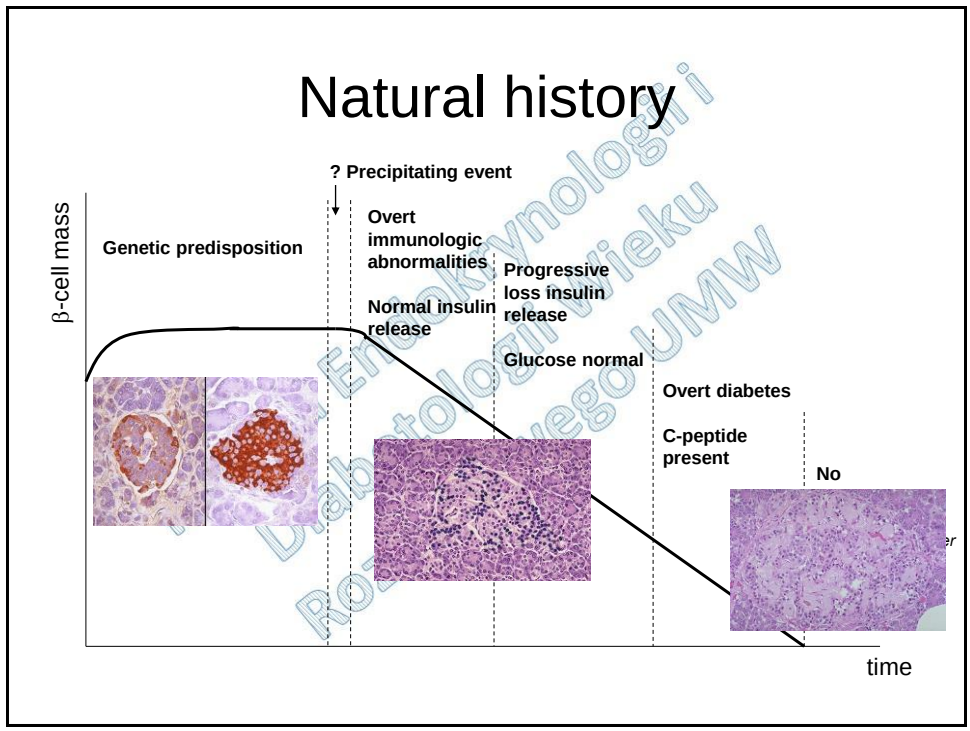
11


How T1D might arise.
A Genetic susceptibility
B Environmental triggers
C Initial CD8 kill Solidification by APC
D B cell autoantibodies CD4, CD8 responses
E Epitope spreading
F Clinical diabetes
HLA, Insulin, IL2Ra, CTLA4, PTPN22, IFIH
Virus Bacteria Nutrition Chemicals
Metabolic switch Proinflammation
Treg function down
Autoantibodies Insulin
Autoantibodies Insulin, GAD65, I-A2, ZnT8
1. Periphery
CD4 help
B cell
CD8
β-cell Ag presentation
β-cell Ag transport
β-cell Ag presentation incl. B cells
CD4: GAD65, I-A2, Proinsulin
CD8: Preproinsulin SP, GAD65, IAPP precursor, ZnT8, IGRP
2. Pancreatic LN
IFN-α up
β-cell killing
MHC I up
Perforin IFN-γ TFN-α
New epitopes released
β-cell proliferation
3. Pancreas
Relative β-cell mass or function
Hyperglycemia
Honeymoon phase
Relative time
Healthy beta-cell
MHC I positive β-cell
Proliferating β-cell
Regulatory T cell
Autoreactive CD8 or CD4 T cell
IFN-γ producing β-cell
Insulin-negative β-cell
Antigen-presenting cell
Auto-antigen
Auto-antigen, after epitope spreading
Van Belle T L et al. Physiol Rev 2011;91:79-118
Physiological Reviews
©2011 by American Physiological Society

12

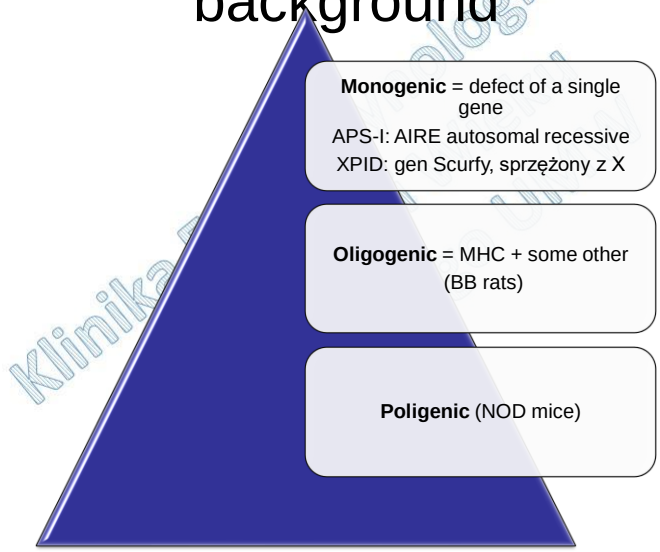

EASD - online lectures - Windows Internet Explorer
EASD
European Association for the Study of Diabetes
ROMA 2008
online lectures
CLOSE
Seasonal pattern at diagnosis in 2176 T1DM patients aged 0-39 years
Observed and fitted numbers
Month
Weets I et al, Diabetologia, 2004
Home

13


Natural history
? Precipitating event
β-cell mass
Genetic predisposition
Overt immunologic abnormalities
Normal insulin release
Progressive loss insulin release
Glucose normal
Overt diabetes
C-peptide present
No
time

14

Diabetes type 1A – genetic background



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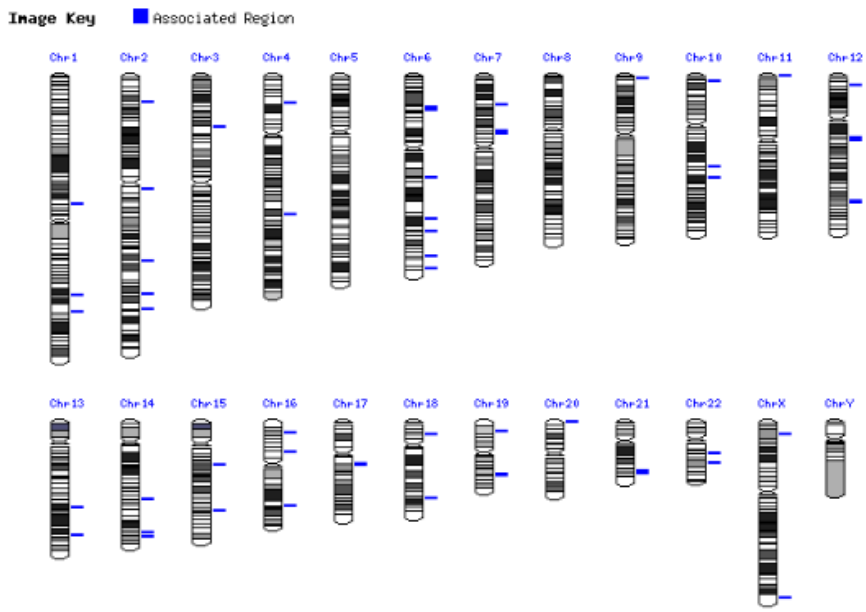
Human Type 1 diabetes susceptibility regions



http://www.t1dbase.org/

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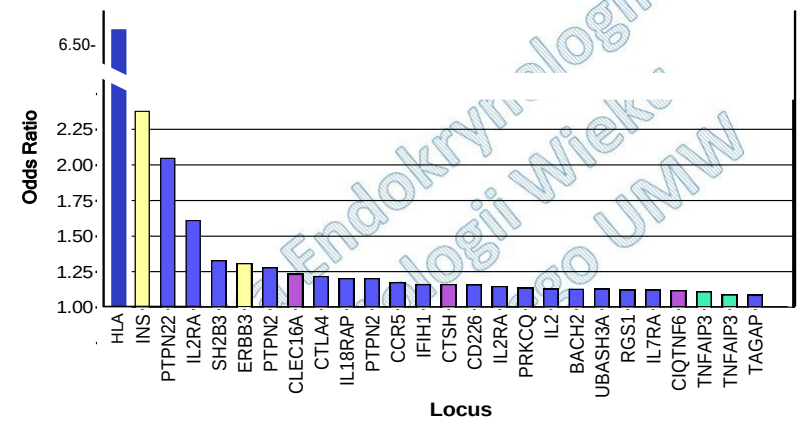
Genome-wide Associations (GWAS) in T1DM

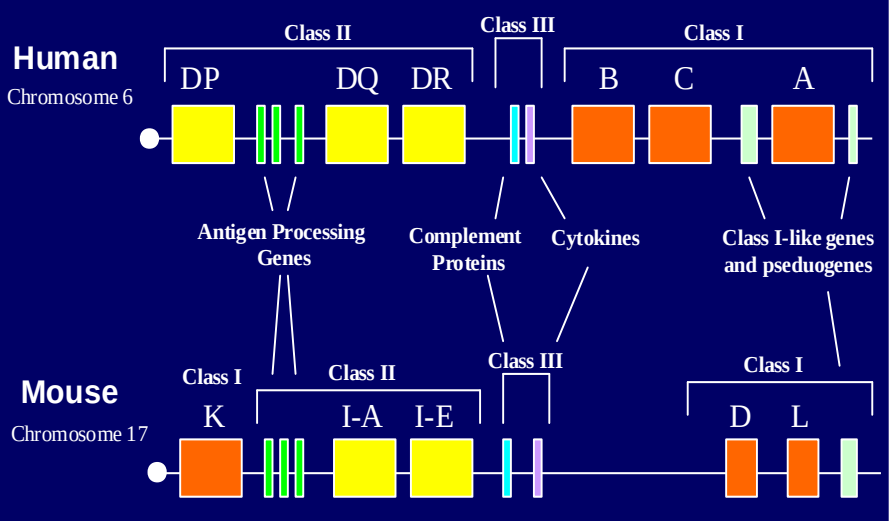


Insulin production and metabolism | Immunity | β cell apoptosis protection | Unknown function

Concannon, Rich, Nepom NEJM 360:1646 2009

17

The Major Histocompatibility Complex



The strongest *locus* IDDM1: HLA in MHC on chromosome 6

18

Genetic predisposition

- Type I diabetes develops in genetically predisposed individuals.
- Diabetes associated HLA alleles are:
- **DR 3**
- **DR 4**
- **DQ 8**

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Genetic predisposition in <u>Polish</u> population

- **HLA DQB1*0302,**
- **HLA DQB1*02-DQA1*0301**
- **HLA DQB1*0302-DQA1*0301**
- **HLA DRB1*03-DRB1-04.**

- Other haplotypes: **HLA-DQB1*0602 i *0603, DQA1*0102, DRB1*0403 i DRB1*1501** are protective

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There are three prerequisites for development of the autoimmune disease type 1 diabetes (T1D).

- First, β cell-reactive T cells need to be activated;
- Second, the response needs to be proinflammatory;
- And finally, immune regulation of autoreactive responses must fail.

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Precipitating event

- Infection: **viral, Coxackie B, rubella, epidemic parotitis, herpes**
- Infection: **bacterial, parasites, fungi**
- Food: **soya bean, gluten, wheat, milk**
- Other: heavy metals, nitrates, other **chemical impurities** …

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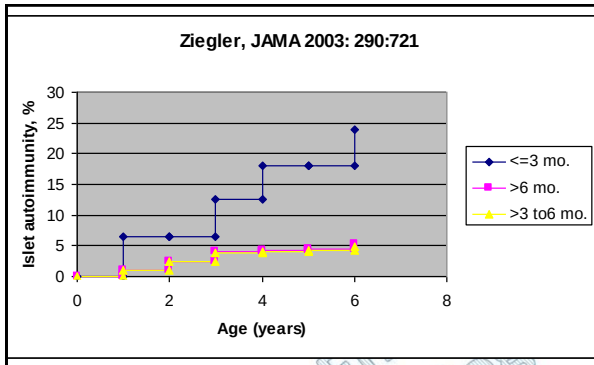

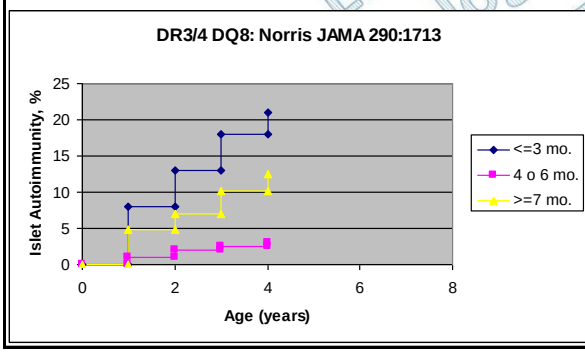

BabyDiab & DAISY trials

Age at gluten administration is strongly related to anti islet antibodies occurence in infants.

25

TEDDY Study

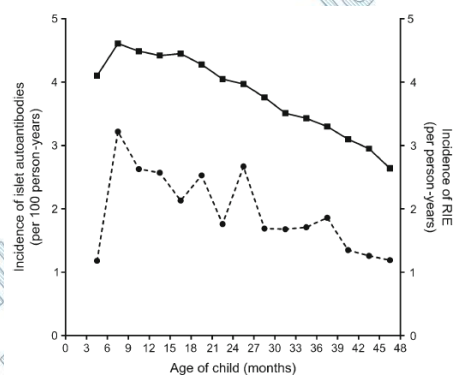

Fig. 1 Incidence of islet autoimmunity per 100 person-years (dashed line) peaked between 6 and 9 months of age, and declined thereafter. Incidence of RIE per person-years (solid line) also peaked between 6 and 9 months and declined thereafter. Age-specific RIE rates were strongly correlated with the decline in islet autoimmunity incidence

Diabetologia (2017) 60:1931–1940

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TEDDY Study

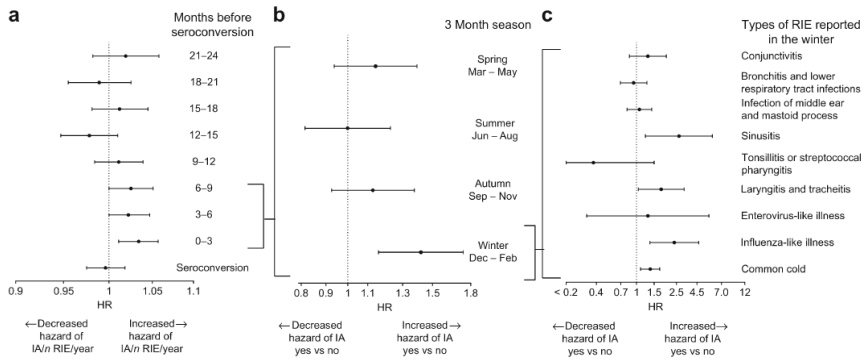

Fig. 2 (**a**) RIEs occurring between 0 and 3 months, 3 and 6 months, and 6 and 9 months before the autoantibody seroconversion period were associated with increased risk of islet autoimmunity ($p \leq 0.05$ for all), whereas RIE rates in the other 3 month periods were not ($p > 0.10$). (**b**) In a multivariate analysis, the presence of a winter but not a spring, summer or autumn RIE, occurring in the 9 month period before seroconversion, was associated with islet autoimmunity. (**c**) In a multivariate analysis, the specific infections in the winter with significant association with islet autoimmunity were sinusitis, laryngitis and tracheitis, influenza-like illness and common cold

Diabetologia (2017) 60:1931–1940

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TEDDY Study

Conclusions The present prospective study consisting of almost 8000 participants has confirmed the findings of two smaller prospective studies (the Norwegian MIDIA study with 885 participants and German BABYDIET study with 148 participants [4, 5]) of the risk association between respiratory infection and islet autoimmunity. The observed temporal pattern suggests an islet autoimmunity-triggering effect by respiratory infections. Next, effort will be made to identify the specific microbes, probably viruses, by analysing biological samples taken from TEDDY participants during the 0–9 month time window prior to the development of islet autoimmunity.

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Type 1 Diabetes Prediction and Prevention Study (Finlandia)

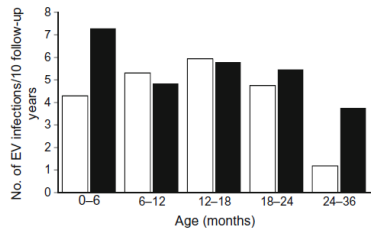

Fig. 2 Infections per 10 follow-up years in different age groups in case and control children. Number of samples in each age group: 0–6 months, 848; 6–12 months, 1579; 12–18 months, 1211; 18–24 months, 862; 24–36 months, 279. The number of enterovirus infections in these age groups did not differ statistically. Black bars, case children; white bars, control children. EV, enterovirus

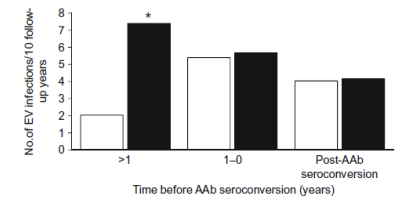

Fig. 3 Number of enterovirus infections per 10 follow-up years in children who turned islet autoantibody-positive before the age of 3 years and their controls. Black bars, case children; white bars, control children. *$p = 0.035$. AAb, autoantibody; EV, enterovirus

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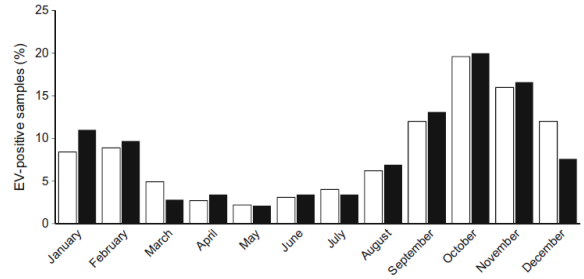
DIPP

Fig. 1 Percentage of enterovirus-positive samples according to the month of sample collection. Black bars, case children; white bars, control children. EV, enterovirus



30

Table 4

Combined odds ratios for pre-diabetes studies stratified by study type

Type of study	No of studies	Combined OR (95% CI)	P value	χ^2/df*
All	9	3.7 (2.1 to 6.8)	<0.001	1.34
Nested case-control studies	6	3.0 (1.5 to 6.0)	0.002	1.57
Studies in Europe	5	5.2 (2.8 to 9.6)	<0.001	0.17

*Cochrane χ^2 divided by degrees of freedom. Values >1 indicate heterogeneity.

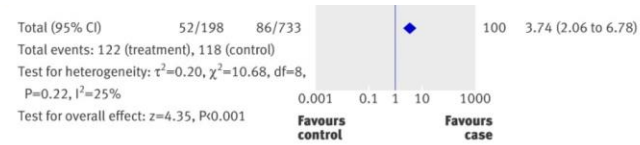


Fig 1 Odds ratios for enterovirus positivity in patients with pre-diabetes versus no diabetes

BMJ. 2011; 342: d35.

31

BABYDIET

Table 2. Description of the BABYDIET Study Population[a]

Variable	Median (Range) Seroconversion	No Seroconversion	*P* Value[b]
Male, No. (%)	12 (46)	54 (44)	.86
Mother smoking during pregnancy, No. (%)[c]	0	13 (9)	.13
Follow-up, y	5.76 (0.75-9.18)	5.09 (0.26-10.01)	.38
No. of dd/child	484 (145-1098)	535 (95-1110)	.89
First year of life	309.5 (123-366)	357.5 (94-366)	.86
Any infections/100 dd	2.20 (1.30-5.15)	1.70 (0.00-5.42)	.02
First year of life	1.94 (0.82-4.88)	1.37 (0.00-3.84)	.002
Respiratory infections/100 dd	1.55 (0.64-4.64)	1.30 (0.00-4.90)	.02
First year of life	1.66 (0.00-4.88)	1.04 (0.00-3.62)	.002
Gastrointestinal infections/100 dd	0.38 (0.00-1.03)	0.13 (0.00-2.29)	.01
First year of life	0.30 (0.00-1.63)	0.00 (0.00-1.79)	.006
Other infections/100 dd	0.33 (0.00-1.64)	0.27 (0.00-1.84)	.22
First year of life	0.00 (0.00-1.31)	0.27 (0.00-1.84)	>.99
Fever events/100 dd	1.00 (0.27-3.51)	0.60 (0.00-2.53)	.001
First year of life	0.83 (0.00-3.51)	0.55 (0.00-2.47)	.04

Abbreviation: dd, documented days.
[a] Infections and fever were documented up to age 3 years.
[b] Determined by χ^2 test and Mann-Whitney *U* test as appropriate.
[c] Three missing values in each group.

JAMA Pediatr. 2013;167(9):800-807. doi:10.1001/jamapediatrics.2013.158

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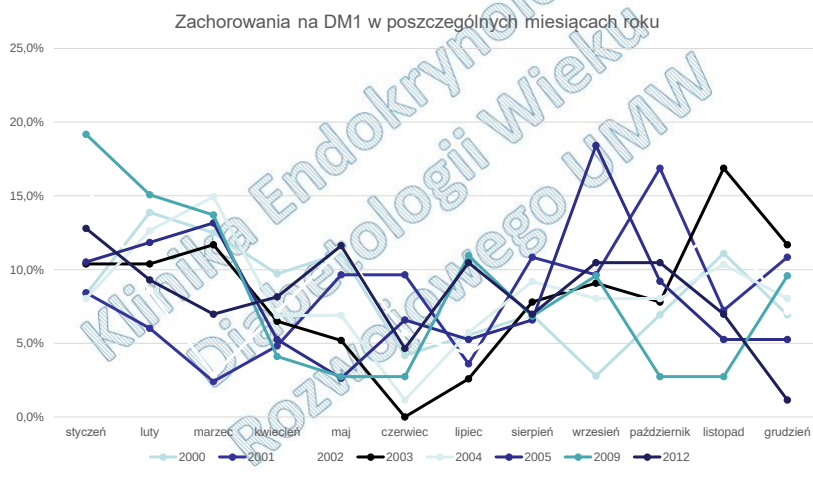
Epidemiologia:



Analiza wyników badań genetycznych w kierunku celiakii u dzieci i młodzieży z cukrzycą typu 1 – doniesienie wstępne.
Monika Seifert, Agnieszka Zubkiewicz-Kucharska, Anna Noczyńska
XIV Konferencja PolPeDiab 24-26.04.2014

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Immunology of diabetes

- Approximately 90% of new-onset type I diabetes are diabetes associated autoantibodies positive.
- The main autoantibodies in T1D are reactive to four islet autoantigens (islet cell autoantibodies or **ICA**):
  - insulinoma-associated antigen-2 (**I-A2**, ICA512, tyrosine phosphatase related IA2 molecule),
  - insulin (micro IAA or m**IAA**),
  - glutamic acid decarboxylase 65 (**GAD65**),
  - zinc transporter 8 (**ZnT8**)

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Islets

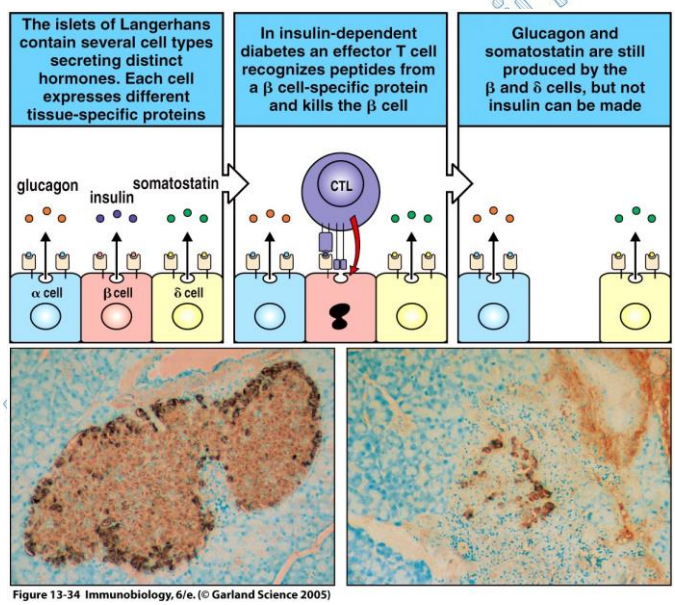

Figure 13-34 Immunobiology, 6/e. (© Garland Science 2005)

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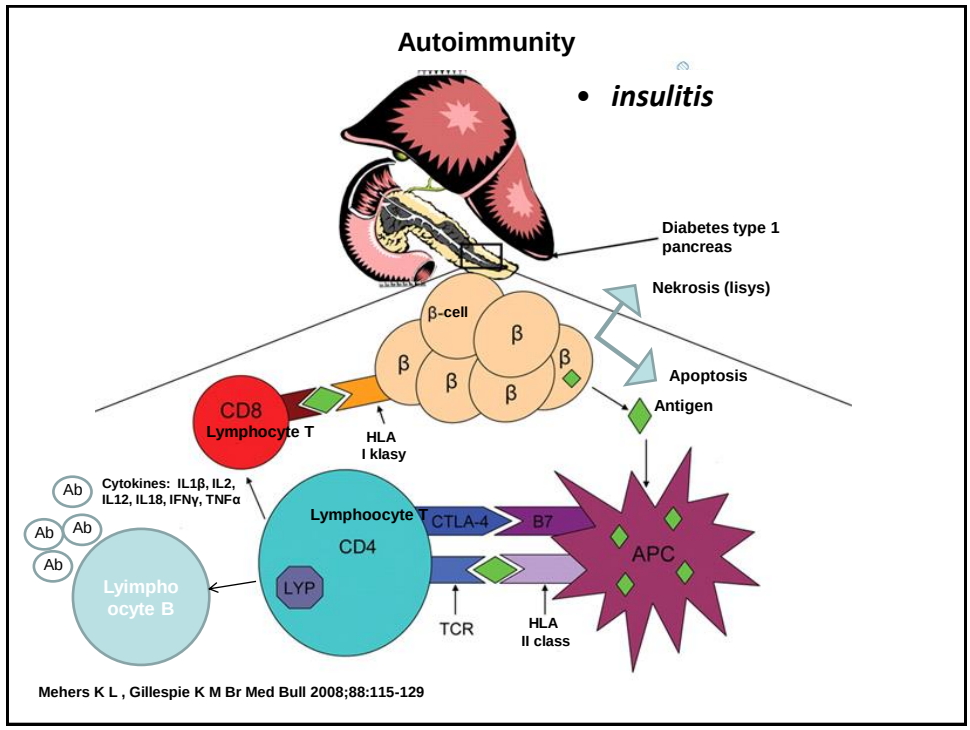
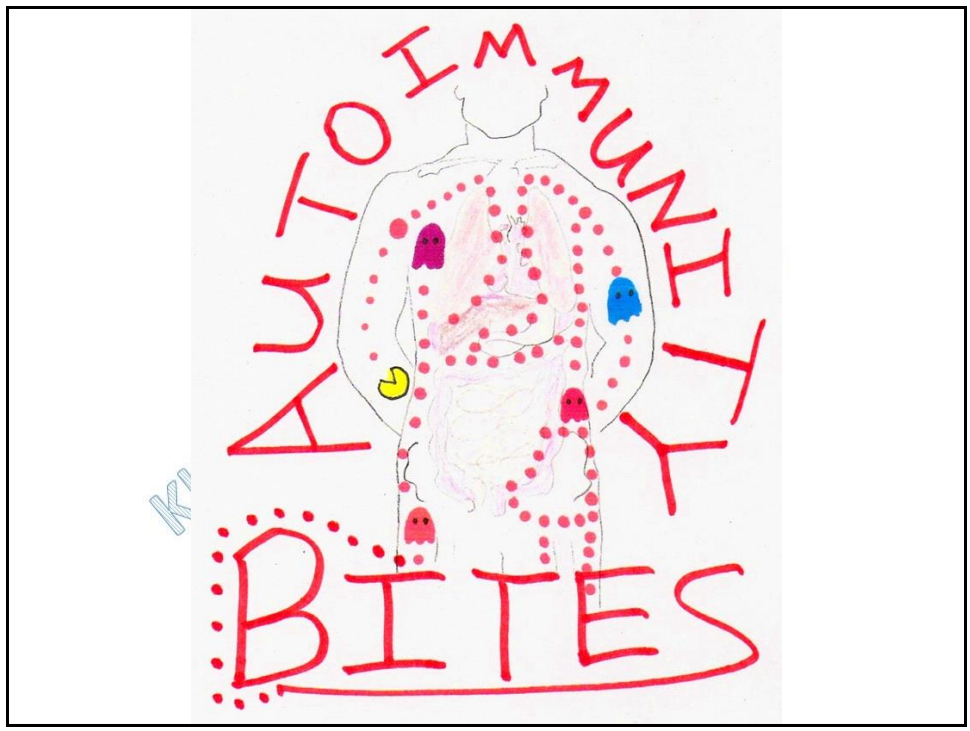

Autoimmunity
• insulitis
Diabetes type 1
pancreas
Nekrosis (lisys)
β-cell
Apoptosis
Antigen
CD8
Lymphocyte T
HLA
I klasy
Ab
Cytokines: IL1β, IL2,
IL12, IL18, IFNγ, TNFα
Lymphoocyte T
CD4
CTLA-4
B7
APC
Lyimpho
ocyte B
LYP
TCR
HLA
II class
Mehers K L , Gillespie K M Br Med Bull 2008;88:115-129

37


AUTOIMMUNITY
BITES

38

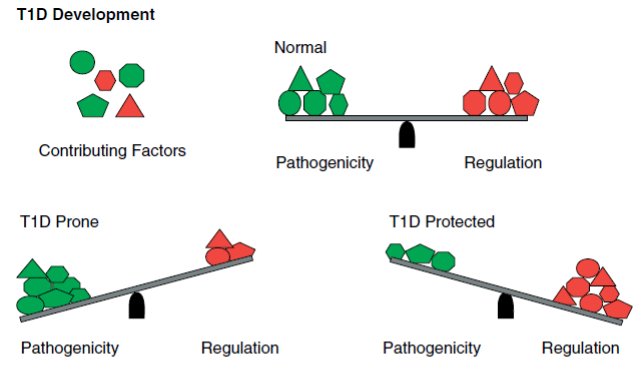


Fig 1. T1D development. A discrete balancing act is performed by the immune system in order to attack foreign pathogens while protecting against the promotion of autoimmunity. Multiple contributing factors influence the development of T1D, including genetics, the environment, and cellular signals. In a normal individual the immune system is balanced, possessing the ability to both promote and suppress cellular responses to pathogens. When an immune system is unbalanced and favors inflammation or excessive cellular responses, the system is unbalanced and favors excesive regulation of cellular responses, the system is protected against the development of T1D and autoimmunity. **Abbreviations:** T1D, type 1 diabetes. Adapted from *Annual Review of Immunology*.[102] [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.].

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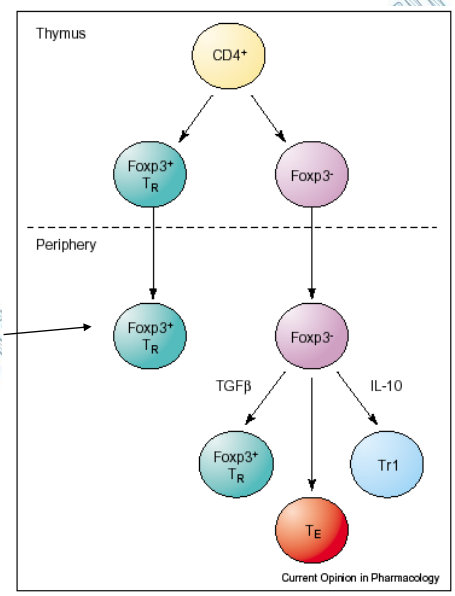
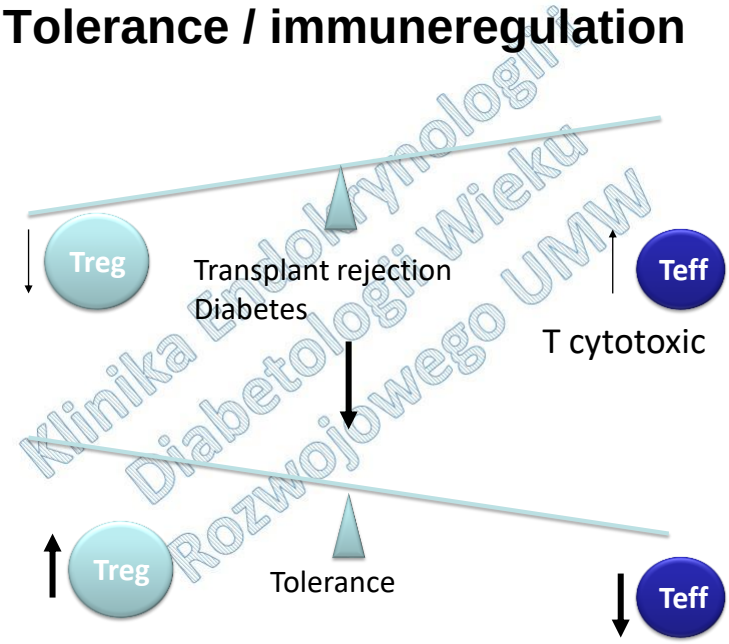
Tregs



CD4CD25
= 10% CD4

41

Tolerance / immuneregulation



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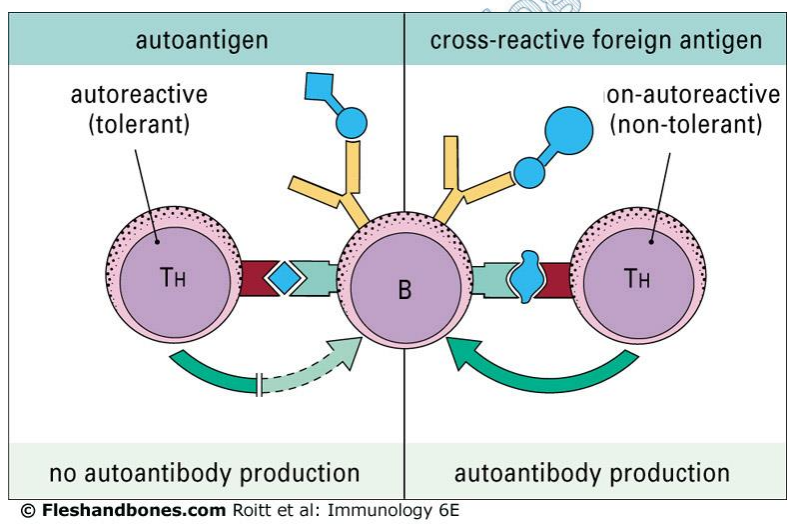
Molecular mimicry



© **Fleshandbones.com** Roitt et al: Immunology 6E

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TABLE 20-3 Molecular mimicry between proteins of infectious organisms and human host proteins

Protein*	Residue†	Sequence‡
Human cytomegalovirus IE2	79	P D P L G R P D E D
HLA-DR molecule	60	V T E L G R P D A E
Poliovirus VP2	70	S T T K E S R G T T
Acetylcholine receptor	176	T V I K E S R G T K
Papilloma virus E2	76	S L H L E S L K D S
Insulin receptor	66	V Y G L E S L K D L
Rabies virus glycoprotein	147	T K E S L V I I S
Insulin receptor	764	N K E S L V I S E
Klebsiella pneumoniae nitrogenase	186	S R Q T D R E D E
HLA-B27 molecule	70	K A Q T D R E D L
Adenovirus 12 E1B	384	L R R G M F R P S Q C N
α-Gliadin	206	L G Q G S F R P S Q Q N
Human immunodeficiency virus p24	160	G V E T T T P S
Human IgG constant region	466	G V E T T T P S
Measles virus P3	13	L E C I R A L K
Corticotropin	18	L E C I R A C K
Measles virus P3	31	E I S D N L G Q E
Myelin basic protein	61	E I S F K L G Q E

*In each pair, the human protein is listed second. The proteins in each pair have been shown to exhibit immunologic cross-reactivity.

†Each number indicates the position on the intact protein of the amino-terminal amino acid in the listed sequence.

‡Amino acid residues are indicated by single-letter code. Identical residues are shown in blue.

SOURCE: Adapted from M. B. A. Oldstone, 1987, *Cell* **50**:819.

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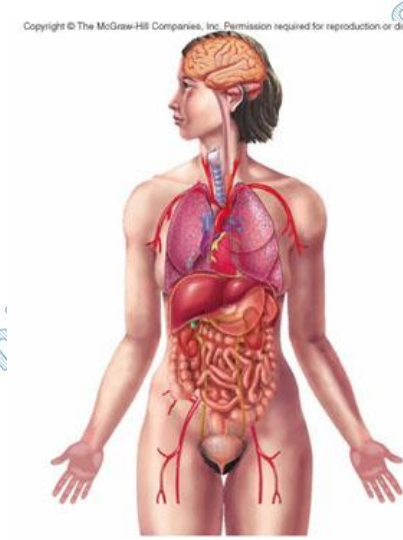
Choose whatever organ. . .



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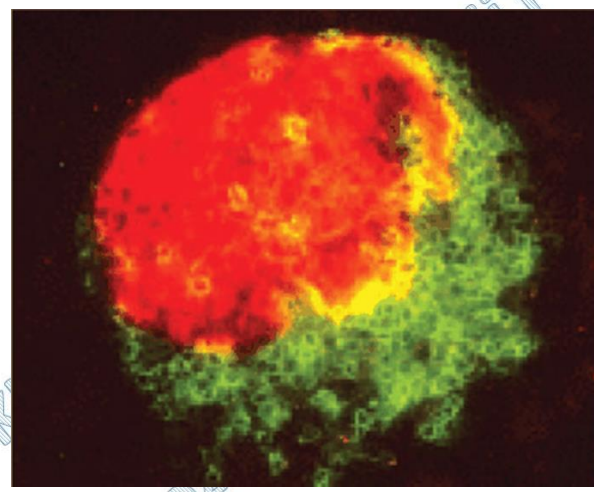
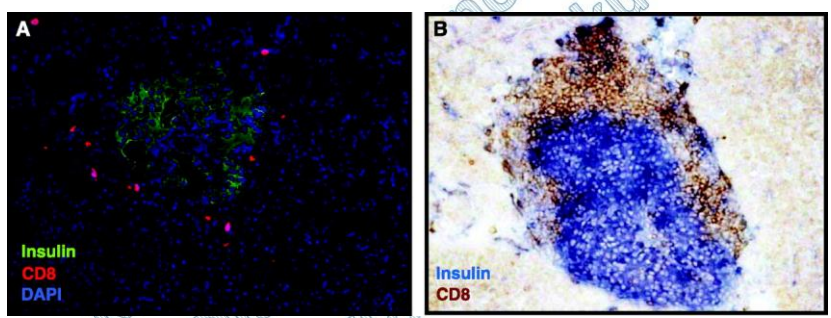
Insulitis



Insulitis.
Fot.Anne Cooke, University of Cambridge.

49

The degree of pancreatic infiltration in T1D patients is limited compared with the insulitis in NOD mice around diabetes onset.



Van Belle T L et al. Physiol Rev 2011;91:79-118

Physiological Reviews

50

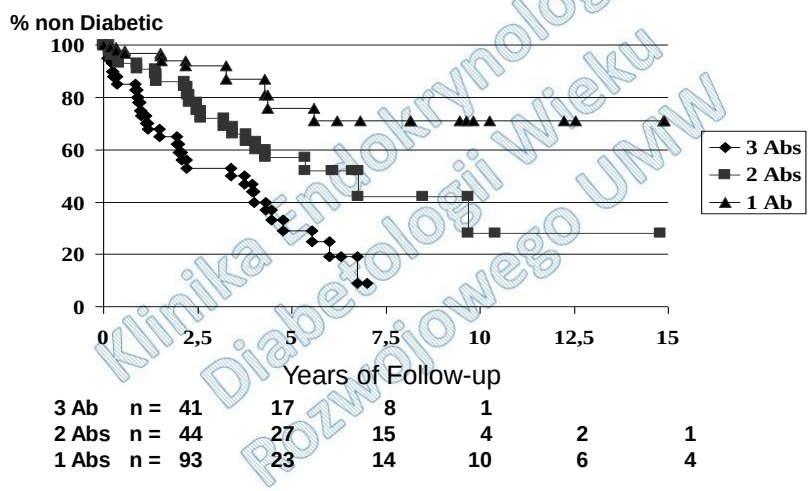
Autoimmunity

- **ICA islet cell antibodies:**
- Anti insulin antibodies (**IAA**)
- **anty-GAD** glutamic acid decarboxylase antibodies
- Tyrosin phosphatase antibodies (**IA2**)
- B-chain antibodies (**ZnP8**)

- **Antibodies are markers of the reaction, they are not the effectors!**

51

Progression o DM1 acc. to Ab load (GAD, ICA512, Insulin)



DAISY

52

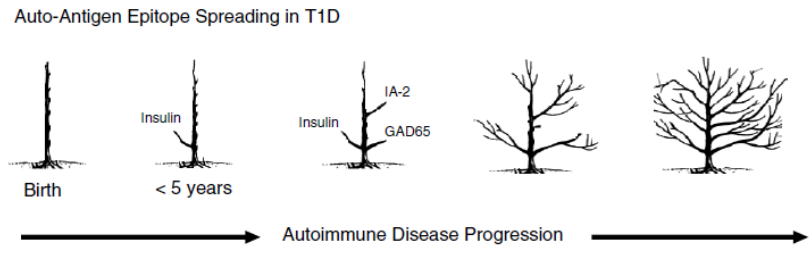
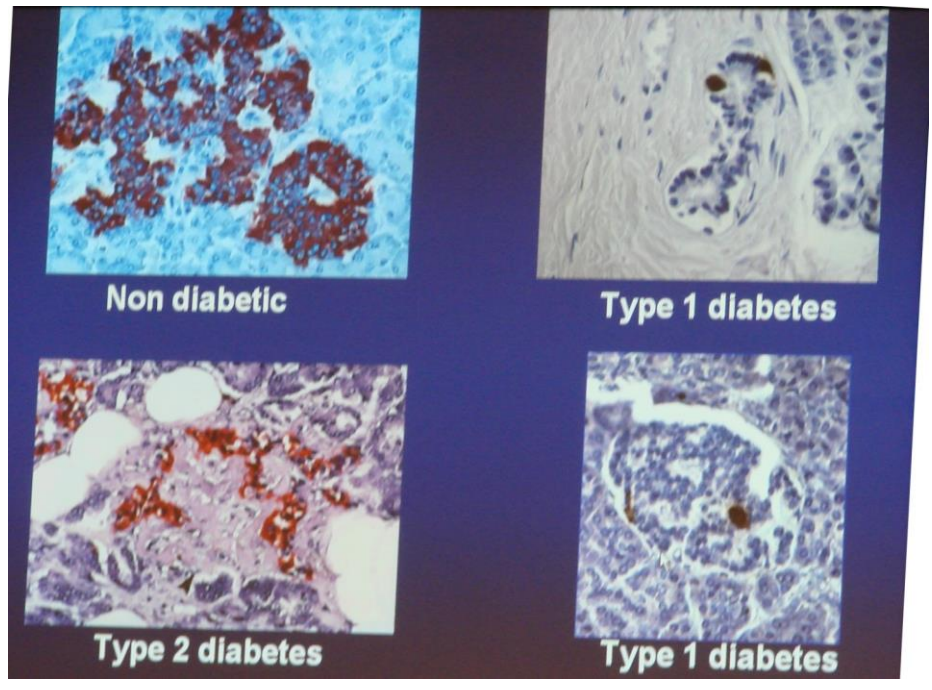


Fig 2. Autoantigen epitope spreading in T1D. As the severity of symptoms associated with T1D increases over time, so does the number of autoantigens recognized by the immune system. Epitope spreading begins once the immune system is triggered within the pancreas, leading to the processing and presentation of self antigens. As β-cell destruction takes place, multiple self antigens become targets of the immune system. During this process, insulin is the first antigenic target,[22] and it is followed by other β-cell–associated components, such as GAD65 and IA–2.[20] Over time, autoantigens are processed differently, creating various recognition epitopes for a given antigen. In Figure 1, the tree symbolizes an immune system at birth that lacks autoimmunity. As the tree grows toward autoimmune T1D, its limbs represent targeted self antigens that develop. As T1D progresses, multiple limbs grow off the tree, each from a different antigen. These growing limbs next branch off, representing the unique epitopes recognized from differential processing of similar self peptides. As T1D develops, the tree grows toward autoimmunity by increasing both the number of limbs and the number of branches on a given limb, representing the process of epitope spreading observed in T1D disease development. **Abbreviations:** GAD65, glutamic acid decarboxylase 65; IA-2, islet-cell antigen-2; T1D, type 1 diabetes.

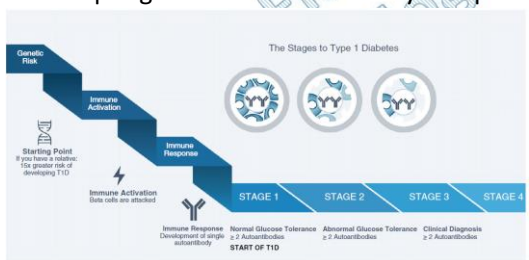
53



54

Prediction, identification and treatment of early stage type 1 diabetes
Anette-Gabriele Ziegler

- Children with multiple beta-cel autoantibodies progres to symptomatic T1D (Ziegler, JAMA 2013)
- Accepting beta-cel autoimmunity as a pathologic entity



C-Path Consortium

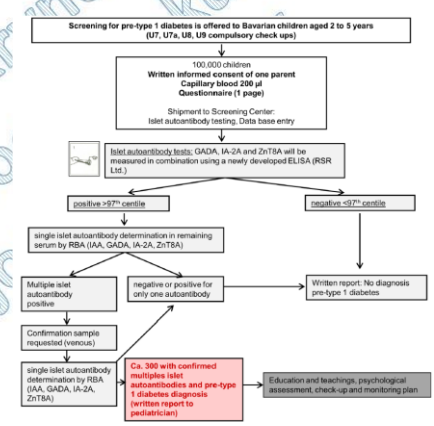
DOI: 10.1111/pedi.12734

ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

55

Aiming for early diagnosis of beta cel autoimmunity on a public health level

Fr1da



56

Fr1da

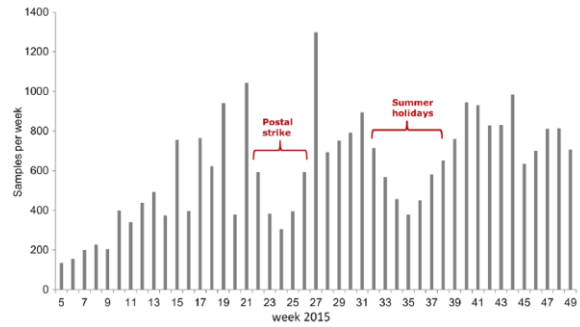


Figure 2 Numbers of children who underwent the islet autoantibody screening per week between February and November 2015.

57

Fr1da

Table 1 Characteristics of the study participants as of 30 November 2015

	Number (%) of children/samples
Screened children	26 760 (13 713 males (51.2%))
Screened children with a first degree relative with type 1 diabetes	962 (3.6%)
Samples with a sufficient volume to perform the 3-screen ELISA	25 868 (96.7%)
Samples with insufficient volume for the 3-screen ELISA but sufficient for the RBA	748 (2.8%)
Samples with insufficient volume for the 3-screen ELISA or the RBA prompting a request for a new sample	144 (0.54%)
Sample obtained again and sent to the centre	48
Children with multiple islet autoantibodies detected in the first sample	105 (0.39%)
Children with confirmed multiple islet autoantibodies (ie, pre-type 1 diabetes)	63
Children diagnosed with asymptomatic type 1 diabetes between the first and second sample	4
Children without confirmation of multiple islet autoantibodies	14
Children pending confirmation	24

RBA, radiobinding assay.

58

Fr1da Update

- **249 (0.31%)** Ab + children:
  - 16 – „spontaneous" T1D (BG >200 mg/dl)
  - 205 – education and OGTT
    - 181 (88.3%) normoglycemic
    - 16 (7.8%) dysglycemic (+22 w follow-up)
    - 8 (3.9%) hyperglycemia/T1D (+18 in the follow-up)

73/249 (29.3%) – dysglycemia/T1D

127 – in the interventional study

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Fr1da Conclusions

- The study in population with non-symtomatic autoimmunization is possible, with high response rate
- DKA reduction
- Stress level in participants did not change due to the study
- High rate of participation in the observational study

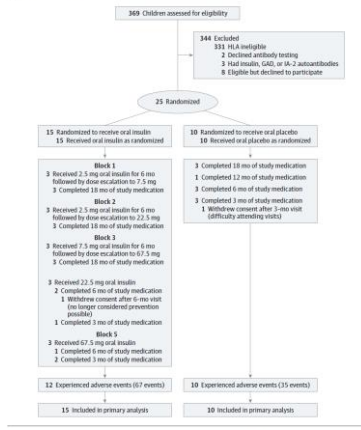
60

Effects of High-Dose Oral Insulin on Immune Responses in Children at High Risk for Type 1 Diabetes

The Pre-POINT Randomized Clinical Trial

JAMA. 2015;313(15):1541-1549. doi:10.1001/jama.2015.2928

Figure 1. Flow of Pre-POINT Randomized Clinical Trial



Conclusions

In this pilot study of children at high risk for type 1 diabetes, daily oral administration of 67.5 mg of insulin, compared with placebo, resulted in an immune response without hypoglycemia. These findings support the need for a phase 3 trial to determine whether oral insulin can prevent islet autoimmunity and diabetes in such children.

T-cells show regulatory phenotype after treatment with oral insulin

61

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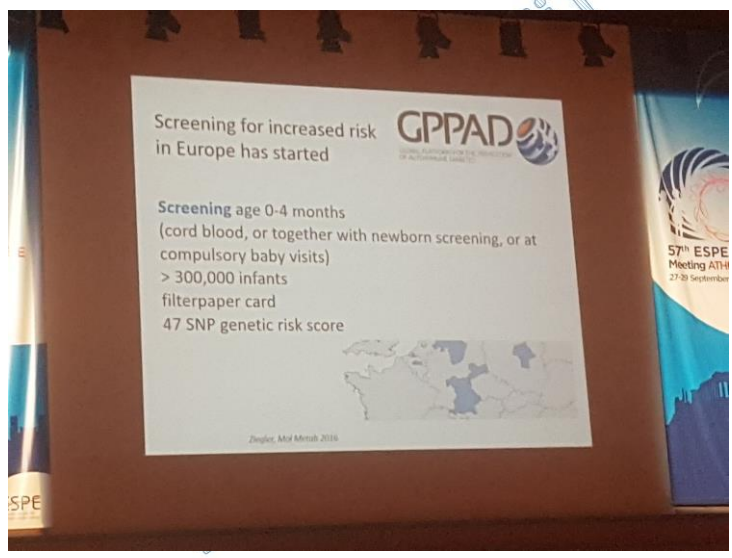
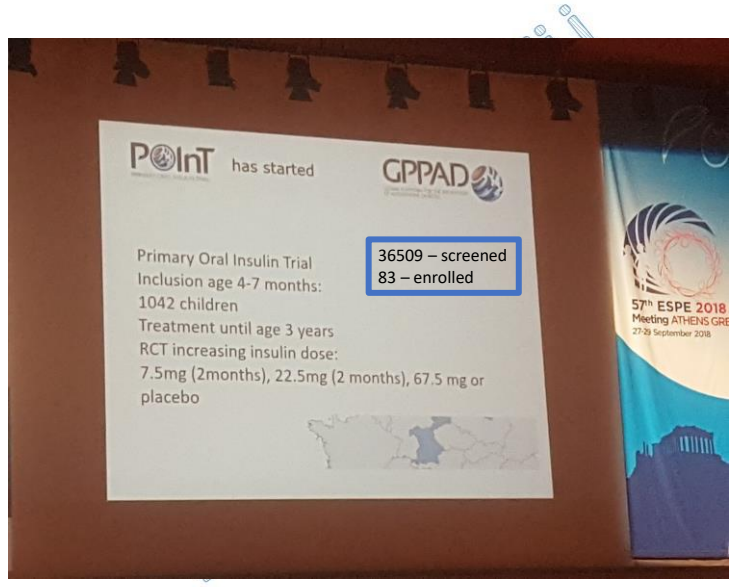

Screening for increased risk in Europe has started
GPPAD
Screening age 0-4 months
(cord blood, or together with newborn screening, or at compulsory baby visits)
> 300,000 infants
filterpaper card
47 SNP genetic risk score
Ziegler, Mol Metab 2016
57th ESPE
Meeting ATH

63


PInT has started
GPPAD
Primary Oral Insulin Trial
Inclusion age 4-7 months:
1042 children
Treatment until age 3 years
RCT increasing insulin dose:
7.5mg (2months), 22.5mg (2 months), 67.5 mg or placebo
36509 – screened
83 – enrolled
57th ESPE 2018
Meeting ATHENS GRE
27-29 September 2018

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RESEARCH LETTER

Association of Rotavirus Vaccination With the Incidence of Type 1 Diabetes in Children

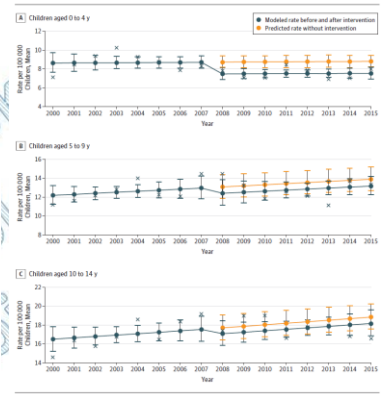
Kirsten P. Perrett, MBBS, FRACP, PhD
Kim Jachno, BSc, MBiostat
Terry M. Nolan, MBBS, PhD, FRACP, FAFPHM, FAHMS
Leonard C. Harrison, MBBS, MD, DSc, FRACP, FRCPA, FAHMS

Published Online: January 22, 2019. doi:10.1001/jamapediatrics.2018.4578

Table. Age Group–Based Modeling of Type 1 Diabetes Incidence Rate Ratios Before and After Introduction of Oral Rotavirus Vaccine

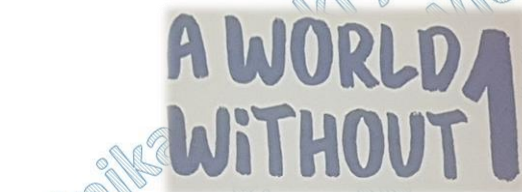
Age Group, y	Average Rate per 100 000 Children (95% CI)		Modeled Incident Rate Ratio (95% CI)	*P* Value
	Observed	Modeled		
0-4				
Pre-2008	8.7 (7.1-10.2)	8.6 (7.7-9.7)	0.85 (0.74-0.99)	.04
Post-2008	7.5 (6.9-8.4)	7.4 (5.9-9.2)		
5-9				
Pre-2008	12.6 (11.2-14.5)	12.2 (11.3-13.2)	0.95 (0.77-1.17)	.61
Post-2008	12.8 (11.1-14.5)	11.6 (8.9-15.0)		
10-14				
Pre-2008	17.0 (14.6-19.2)	16.5 (15.2-17.9)	0.97 (0.83-1.12)	.64
Post-2008	17.6 (16.6-19.0)	15.9 (13.0-19.5)		
0-14				
Pre-2008	12.8 (7.1-19.2)	12.6 (10.6-14.8)	0.93 (0.63-1.37)	.71
Post-2008	12.7 (6.9-19.0)	11.6 (7.1-19.0)		

Figure. Age Group–Based Modeling of Type 1 Diabetes Incidence Rate Ratios Before and After Introduction of Oral Rotavirus Vaccine



Crosses are the observed yearly rates used to fit the modeled rates.

65



66

Type I diabetes: symptoms

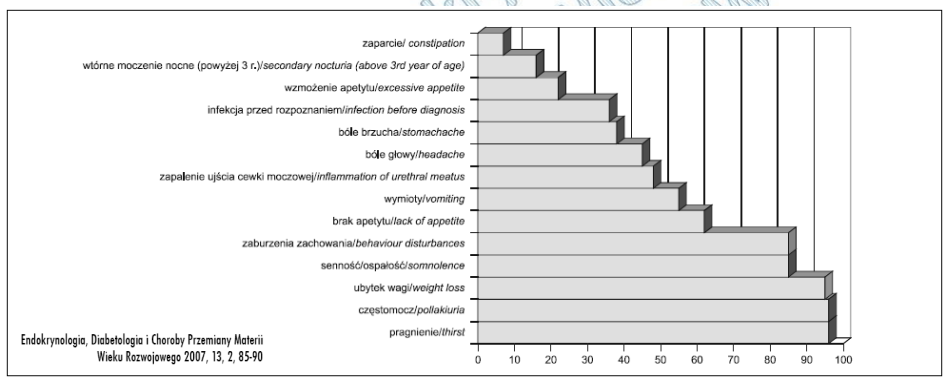
- Weight loss
- Pollakiuria, polyuria, nycturia
- Polydipsia
- Dehydratation
- Fatigue
- Abdominal pain
- Hyperventilation, breathlessness
- Vulvovaginitis, balanoposthitis
- Consciousness disturbances
- COMA

67

Ocena występowania i analiza wybranych czynników ryzyka kwasicy ketonowej w momencie ujawnienia cukrzycy typu 1

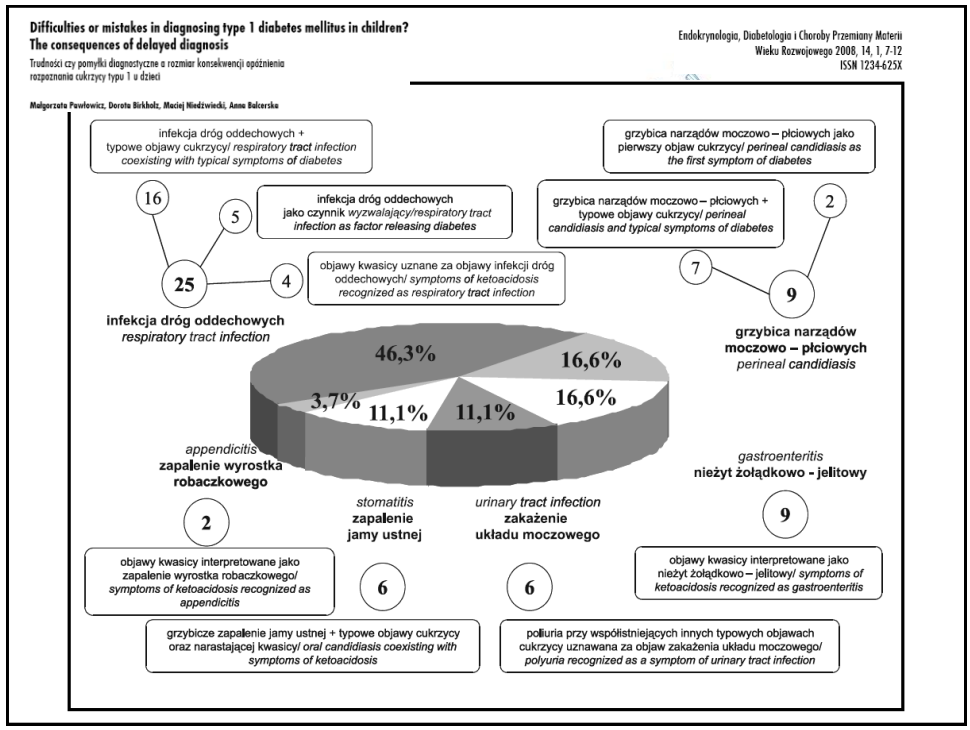
The occurrence and analysis of chosen risk factors of DKA among children with new onset of DMT1

Bogusława Olak-Białoń, Grażyna Deja, Przemysława Jarosz-Chobot, Ewa Otto Buczkowska



Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego 2007, 13, 2, 85-90

68



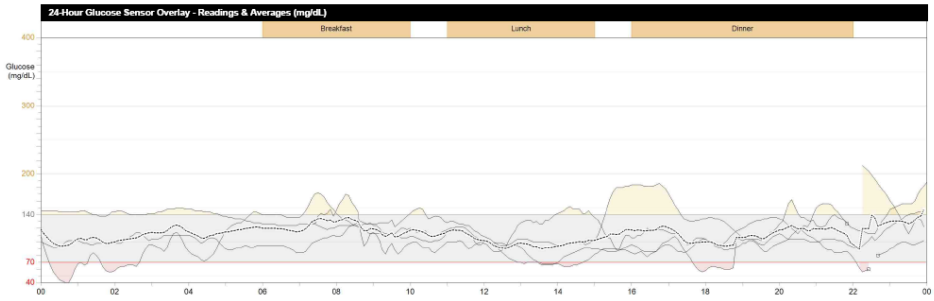
69

Treatment:

- Insulin therapy – individually planned
- Diet – including proteins, fat, carbohydrates, fiber, minerals, vitamins
- Exercises

70

Goals



– Near-normoglycemia
– As few hypos as possible

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Goals of T1DM Management

- Utilize intensive therapy aimed at near-normal BG and A1C levels
- Prevent diabetic ketoacidosis and severe hypoglycemia
- Achieve the highest quality of life compatible with the daily demands of diabetes management
- In children, achieve normal growth and physical development and psychological maturation
- Establish realistic goals adapted to each individual's circumstances

72

Insulin action:

- Stimulation of glucose transport into appropriate cells
- Increase of glycogen synthesis in liver and muscle, decrease glycogen breakdown
- Decrease of cAMP concentrations in tissues
- Decrease of adipose tissue lipolysis
- Activation of fatty acids synthetic pathway, triglycerides production
- Decrease of hepatic gluconeogenesis
- Induction of proto-oncogenes e.g. c-fos
- Activation of proteins synthesis

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Insulin:

- Rapid-acting analogs
- Short-acting (regular) human insulin.
- Intermediate-acting (NPH) human insulin
- Long-acting analogs
- Premixed insulin, containing short-acting insulin and NPH in different proportions
- Premixed insulin, containing rapid-acting analog and NPH in different proportions

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Intensive insulin therapy

- Using different injection devices (Insulin PENs)
- NPH or long acting analog as a basal insulin (once/twice a day) + regular/rapid-acting insulin for a meal-time regimen

75

Intensive insulin therapy

- Using personal insulin pump (PIP)
- Regular/rapid-acting insulin only

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Conventional insulin therapy

- Basal insulin (NPH or long-acting analog) + Regular insulin for breakfast, lunch and dinner

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Indications for intensive treatment:

- Children
- Professionally active
- With frequent hypoglycemia
- Practicing sport
- With poor metabolic control
- Overweight
- To correct hyperglycemia
- In small children

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Goals of insulin therapy in children:

- Appropriate growth and psychomotor development
- Appropriate social development
- Appropriate personal development
- To lower the risk of complications

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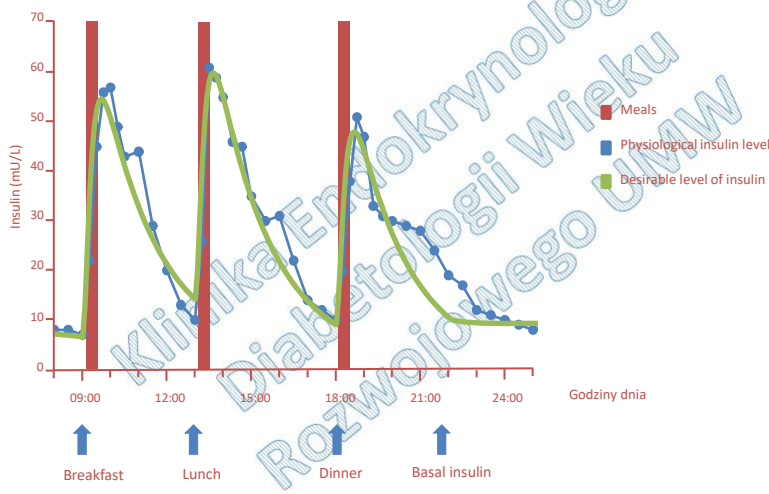
Physiologic Multiple Injection Regimens: The Basal-Bolus Insulin Concept

- Basal insulin
  - Controls glucose production between meals and overnight
  - Near-constant levels
  - Usually ~50% of daily needs
- Bolus insulin (mealtime or prandial)
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1 hour post-meal
  - 10% to 20% of total daily insulin requirement at each meal
- For ideal insulin replacement therapy, each component should come from a different insulin with a specific profile or via an insulin pump (with 1 insulin)

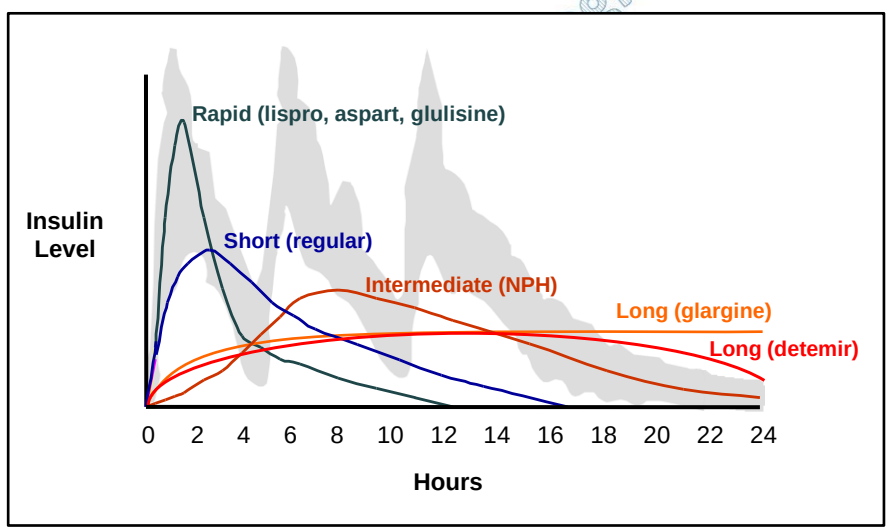
80

FIIT – Functional Intensive Insulin Therapy



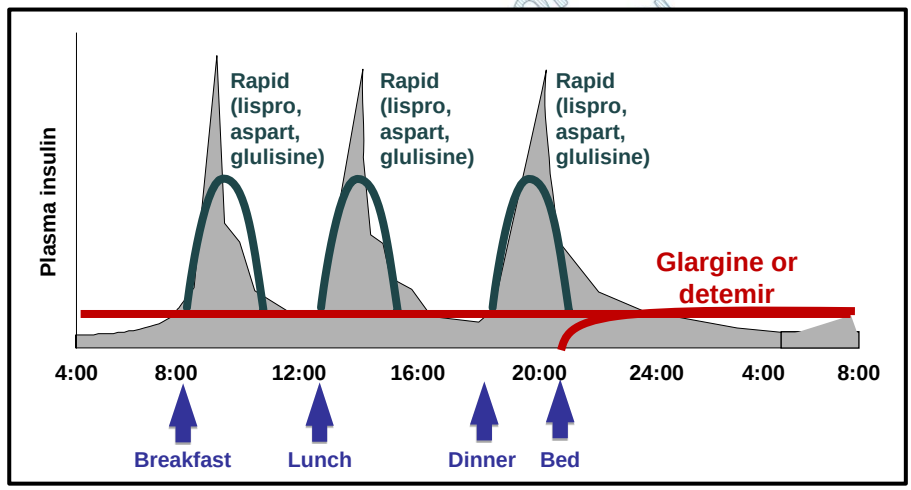
81

Pharmacokinetics of Insulin Products



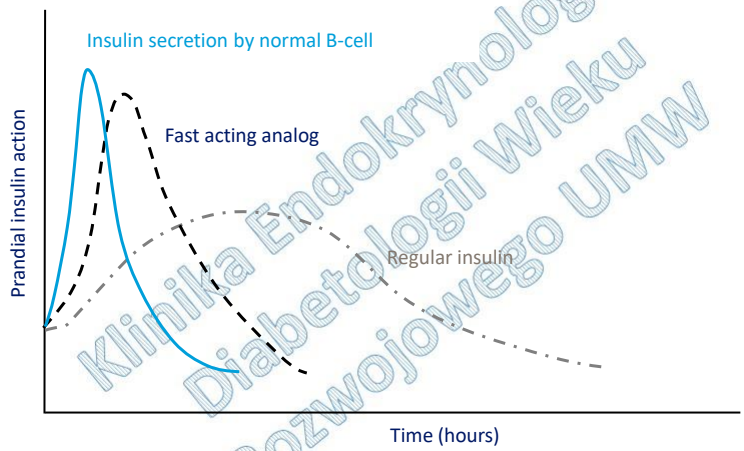
82

Basal/Bolus Treatment Program With Rapid-Acting and Long-Acting Analogs



83

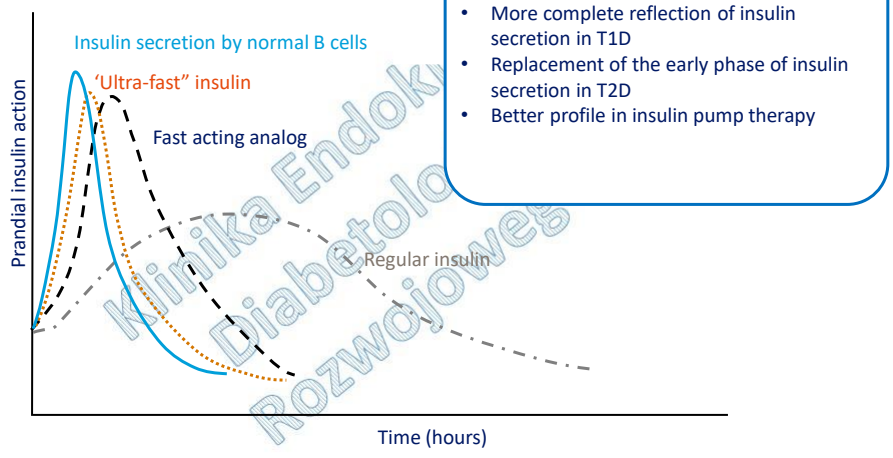
Fast acting insulin analogues vs regular insulin



Home. Diabetes Obes Metab 2015;17:1011–20

84

Ultra-fast acting prandial insulin



Ultra-fast insulin:
- More complete reflection of insulin secretion in T1D
- Replacement of the early phase of insulin secretion in T2D
- Better profile in insulin pump therapy

Home. Diabetes Obes Metab 2015;17:1011–20

85

Insulin Replacement Not Always Sufficient for Glucose Control in T1DM

- Normal glucose regulation involves multiple hormones (eg, insulin, glucagon, amylin, incretins) and multiple organ systems (eg, pancreas, liver, stomach, brain)
- Insulin replacement therapy does not fully mimic the actions of insulin secreted by the pancreas in a healthy individual
  - Insulin exposure in the liver is lower with replacement therapy than with natural production, resulting in inadequate suppression of endogenous glucose production
  - Higher doses of insulin are required to achieve sufficient suppression of endogenous glucose production, but these are associated with hypoglycemia and weight gain

Aronoff SL, et al. *Diabetes Spectrum*. 2004;17:183-190;
Brown L, et al. *Sci Transl Med*. 2010;2:27ps18; Lebovitz HE. *Nat Rev Endocrinol*. 2010;6:326-334.

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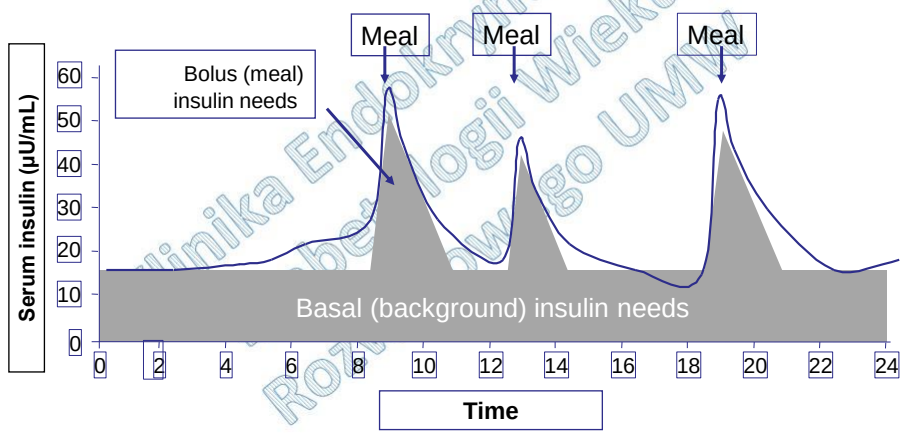
Continuous Subcutaneous Insulin Infusion

94

Normal Insulin Secretion



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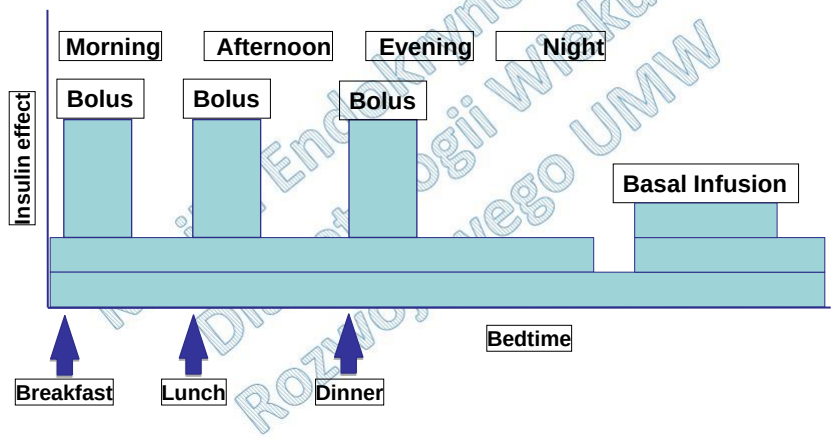
CSII With Rapid-Acting Analog



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Features of Modern Insulin Pumps Not Shared by MDI

- Variable basal and prandial infusion rates
  - Meal profiles (eg, square/extended/dual wave), preset basal rate changes, etc
- Onboard calculators for meal insulin boluses
- Alarms/reminders (eg, missed bolus)
- Ability to download pump data to computer
- Integration with CGM for automatic feedback control (“semi-closed loop”)

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Technological Features of Insulin Pumps*

Insulin delivery	• Small bolus increments: 0.05-0.10 units • Extended boluses for delayed digestion or grazing • Multiple insulin-to-carbohydrate ratios, sensitivity factors, BG targets • Bolus calculators (based on BG level and carbohydrate quantity) • Low basal rates: 0.025-0.05 units/h • Multiple basal rates • Temporary basal rates and suspension mode
Safety features	• Alarms for occlusion and low insulin reservoir • Active insulin to prevent insulin stacking • Keypad lock • Waterproof or watertight
Miscellaneous	• Electronic logbook software (insulin doses, BG levels, carbohydrates) • Integrated food databases with customization • Reminder alarms for BG checks, bolus doses • Wireless communication with remote glucose meter • Integration with continuous glucose monitoring technology

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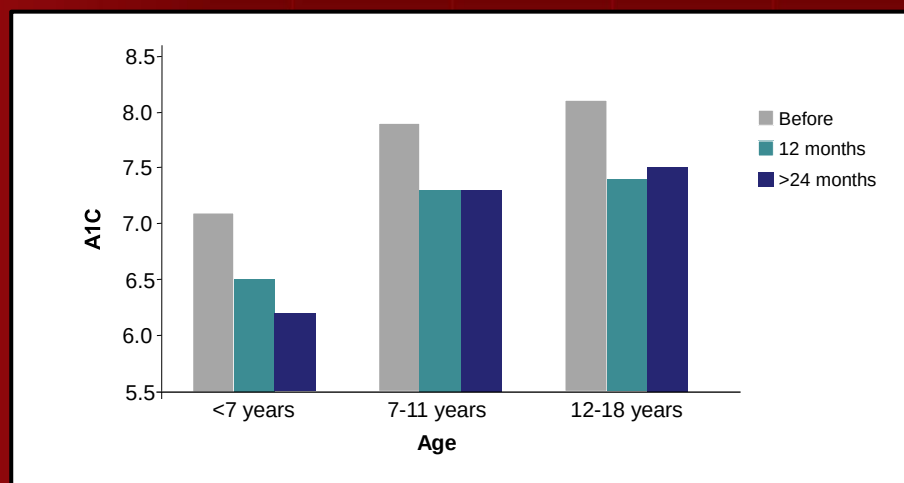
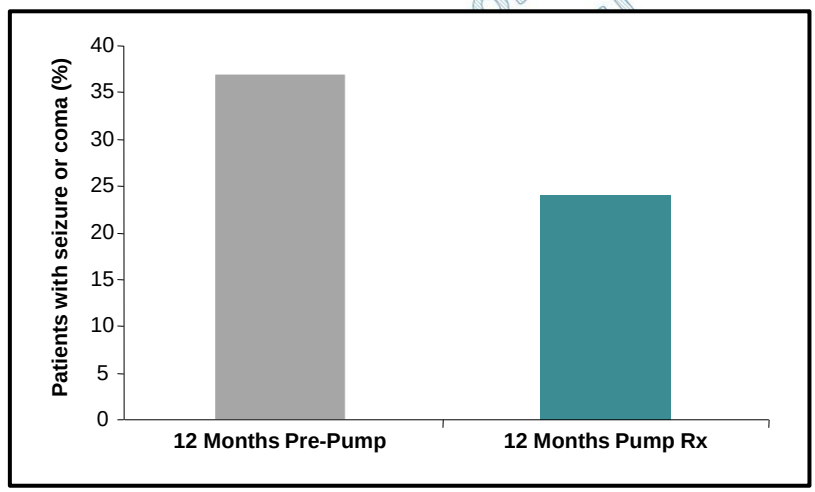
Improved Control With CSII



99
AACE Diabetes Resource Center
Ahern JA, et al. *Pediatr Diabetes.* 2002;3:10-15.

99

Reduced Risk of Severe Hypoglycemia (Seizure/Coma)



100

2006 Berlin Consensus Conference on Pumps in Pediatrics

Almost all pediatric patients with T1DM are candidates for CSII

- CSII strongly recommended for children with
  - Recurrent severe hypoglycemia
  - A1C above target range for age
  - Unacceptable fluctuations in blood glucose
  - Microvascular complications
  - Lifestyle compromised by insulin regimen
- CSII may also be beneficial in
  - Very young children
  - Dawn phenomenon
  - Competitive athletes

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Insulin Pump Use in Children

Advantages

- Improved blood sugar control
- Insulin availability and convenience
- Use of multiple basal rates, temporary basal rates
- Ease of administering multiple boluses
- Reduction of hypoglycemia
- Flexibility and freedom
- Control of post-meal blood sugar/CGM values
- Ease of adjusting insulin doses with exercise and travel

Disadvantages

- Remembering to give insulin boluses with food intake
- Ketonuria or ketoacidosis
- Psychological factors
- Expense
- Weight gain
- Skin infections
- Insulin unavailability and instability
- Infusion site locations and set changes
- Physical/logistical considerations

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Characteristics of Successful CSII Patients

- Access to diabetes team knowledgeable in CSII, with 24/7 HCP access (physician or RN/CDE)
- Insurance
- Adequate intellectual ability to
  - Understand glycemic trending, even without CGM
  - Master carbohydrate counting or similar system for estimation of prandial insulin dosing (frequent SMBG can make up for poor carb estimation)
  - Understand basics of insulin therapy, including how to correct hyperglycemia before and after meals

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Characteristics of Successful CSII Physicians

- Time to spend with the patient
- Consistent philosophy of insulin use among all members of diabetes healthcare team
- Electronic infrastructure in the office or clinic to faciliate downloads and utilize the technology most effectively
- Basic understanding of principles of insulin use (MDI or CSII)

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Definitions in the Context of Insulin Pumps

- Pharmacodynamics vs pharmacokinetics
  - Insulin-on-board (IOB)
    - Amount of insulin from the last bolus that has not yet been absorbed based on pharmacodynamic (not pharmacokinetic) data
  - Insulin stacking
    - Correction dose of insulin, used to treat before-meal or between-meal hyperglycemia in a situation when there is still significant IOB
- Insulin sensitivity factor
  - Correction factor based on amount of glucose reduction (mg/dL) expected from 1 unit of insulin for the individual patient

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CSII: “Smart Pump” Limitations

- All modern pumps include a “bolus calculator” with goal of preventing insulin stacking, but patient must still
  - Check blood glucose
  - Understand “glycemic trends”
  - Estimate carbohydrate content with reasonable accuracy
  - Account for lag time
  - Assume no variability of food or insulin absorption
  - Use appropriate IOB

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Continuous Glucose Monitoring

113

Definitions

- Professional CGM
  - Equipment owned by the provider
  - Patient “masked” (not blinded) to CGM data
- Personal CGM
  - Device owned by patient
  - Blood glucose data visible, able to be seen continuously

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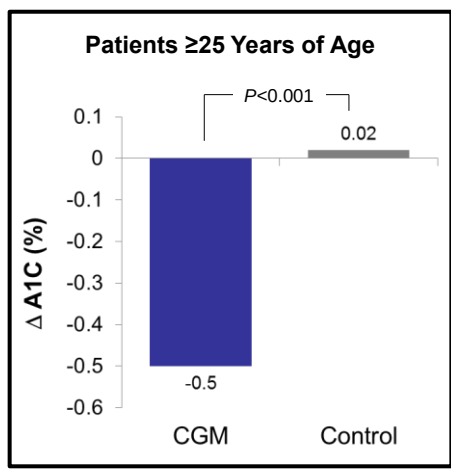
CGM in T1DM: JDRF Sensor Trial



- Patients
  - Baseline A1C >7.0%
  - Age cohorts
    - 8-14 years (n=114)
    - 15-24 years (n=110)
    - ≥25 years (n=98)
- Improvement sustained for 12 months in patients aged ≥25 years
- No significant difference between CGM and control group among patients <25 years of age

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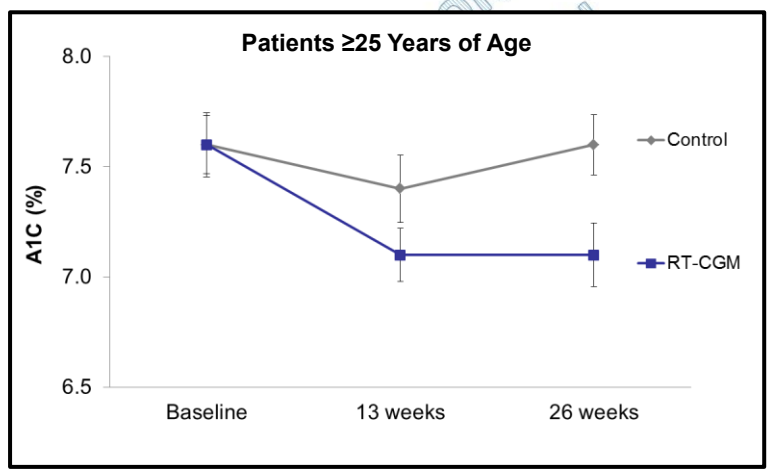
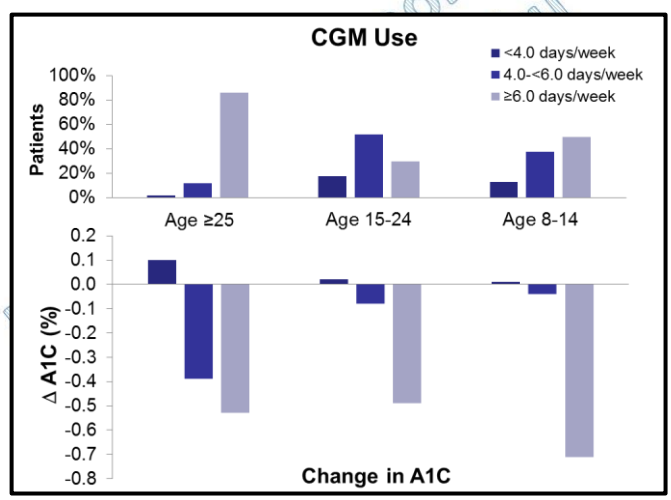
Change in A1C Over Time: JDRF Sensor Trial



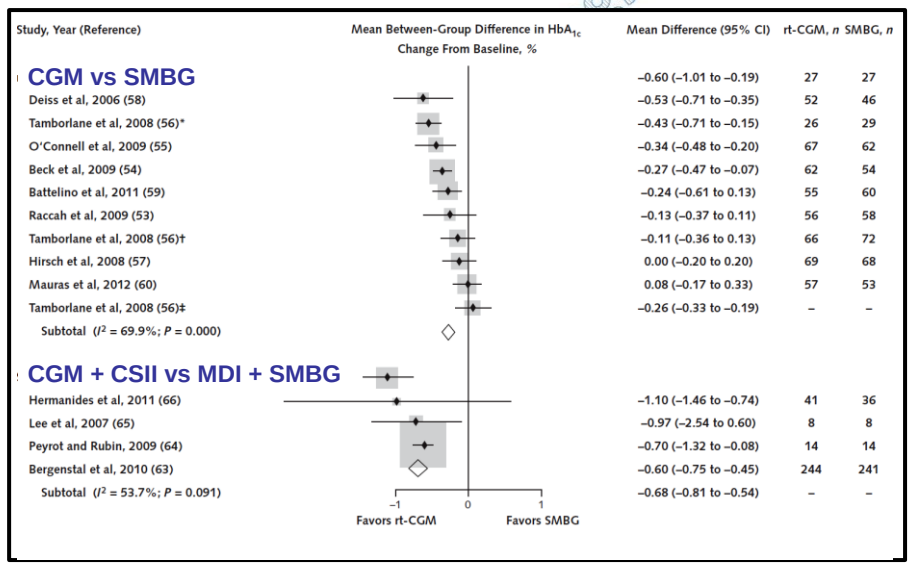
116

Relationship Between Frequency of CGM Use and Change in A1C: JDRF Sensor Trial



117

CGM vs SMBG: 2012 Meta-analysis



123

Pediatric Diabetes Consensus Conference: Use of CGM

- Frequent, nearly daily use of CGM:
  - Can lower A1C levels in children and adolescents who are not well-controlled, irrespective of the treatment regimen
  - Can reduce exposure to hypoglycemia and maintain target A1C levels in well-controlled patients
- Intermittent use of CGM:
  - May be of use to detect post-meal hyperglycemia, nocturnal hypoglycemia, and the dawn phenomenon

128

AACE Recommendations for Personal CGM

"Good" Candidates

- A1C levels >7% and able to use the device near-continuously
- Type 1 diabetes with hypoglycemia unawareness or frequent hypoglycemia
- Hyperglycemia over target or with excessive glycemic variability
- Requiring A1C lowering without excessive hypoglycemia (eg, potentially disabling or life-threatening)
- Preconception and pregnancy

Other Candidates

- Youth who frequently monitor their BG levels
- Committed families of young children (<8 years of age), especially if there are problems with hypoglycemia

2- to 4-week trial recommended

129

AACE Recommendations for Professional CGM for Youth

- May be useful if major changes in diabetes regimen
- Nocturnal hypoglycemia/dawn phenomenon
- Hypoglycemia unawareness
- Postprandial hyperglycemia

130

Closed Loop Systems

"Artifical Pancreas"

131

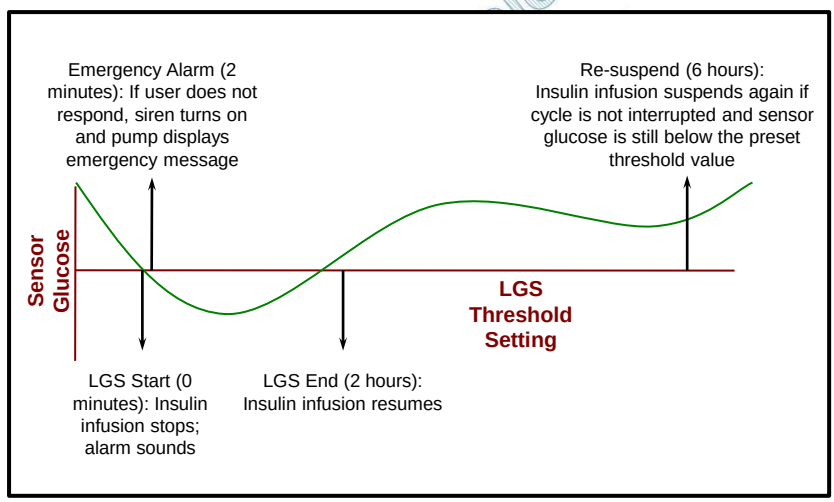
Effectiveness and Safety of an Artificial Pancreas

- Study comparing 2 systems in patients with type 1 diabetes aged 5-18 years (N=17)
  - Closed loop "artificial pancreas" linking CSII insulin delivery with CGM (33 nights)
  - Standard CSII (21 nights)
- No significant difference in glycemic outcomes in primary analysis
- Secondary analysis of pooled data:

	Closed loop	CSII	*P* value
Time in target BG range (%)	**60** (51-88)	40 (18-61)	0.0022
Time BG ≤70 mg/dL (%)	2.1 (0.0-10.0)	4.1 (0.0-42.0)	0.0304
BG <54 mg/dL (no. events)	0	9	

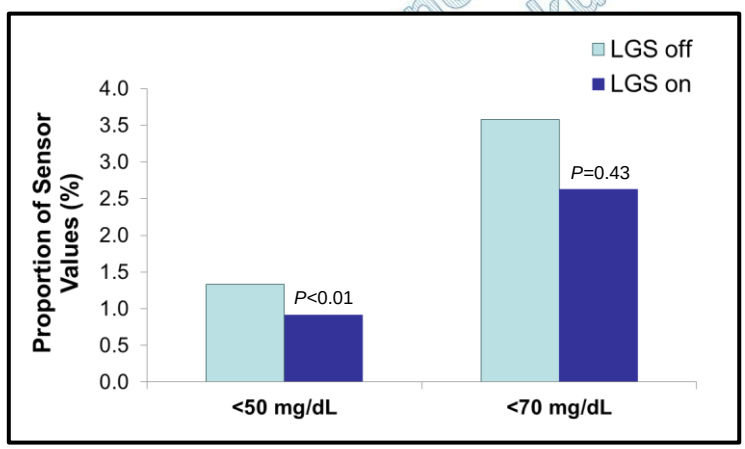
132

Emerging Options: CSII with "Low Glucose Suspend" Feature



133

Low Glucose Suspend Feature Reduces Hypoglycemic Exposure

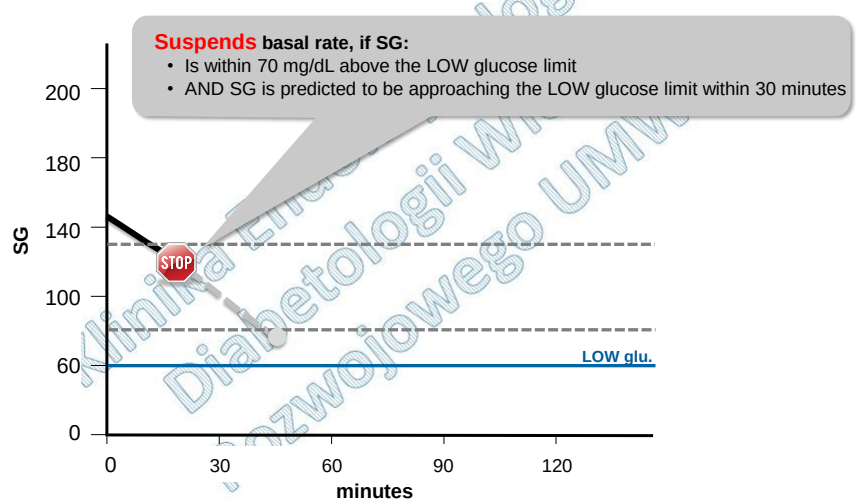


134

Minimed 640G with Smart Guard

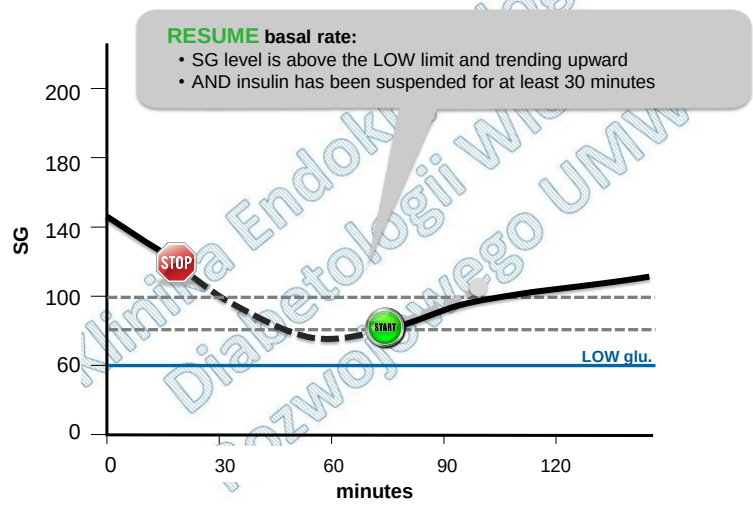
135

Suspend BEFORE low



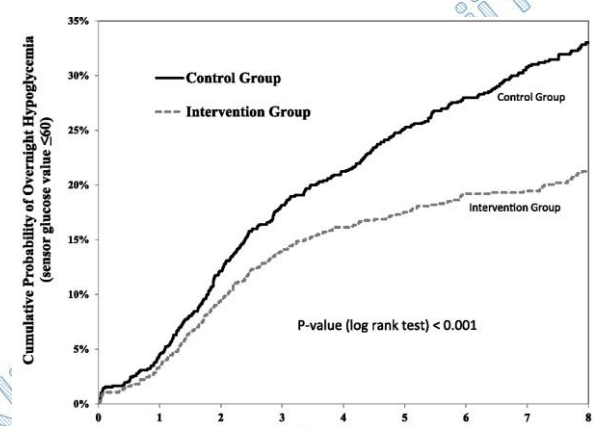
136

Automatically RESUME basal rate based on the SG value



137

Cumulative probability of first overnight hypoglycemia event.



Control									
# at Risk:	970	928	852	794	764	713	645	528	338
# Outcomes:	0	42	76	58	30	38	26	23	14
# Censored:	0	0	0	0	0	13	42	94	176
Intervention									
# at Risk:	942	909	853	811	790	762	706	595	386
# Outcomes:	0	33	56	42	21	13	15	2	11
# Censored:	0	0	0	0	0	15	41	109	198

David M. Maahs et al. Dia Care 2014;37:1885-1891

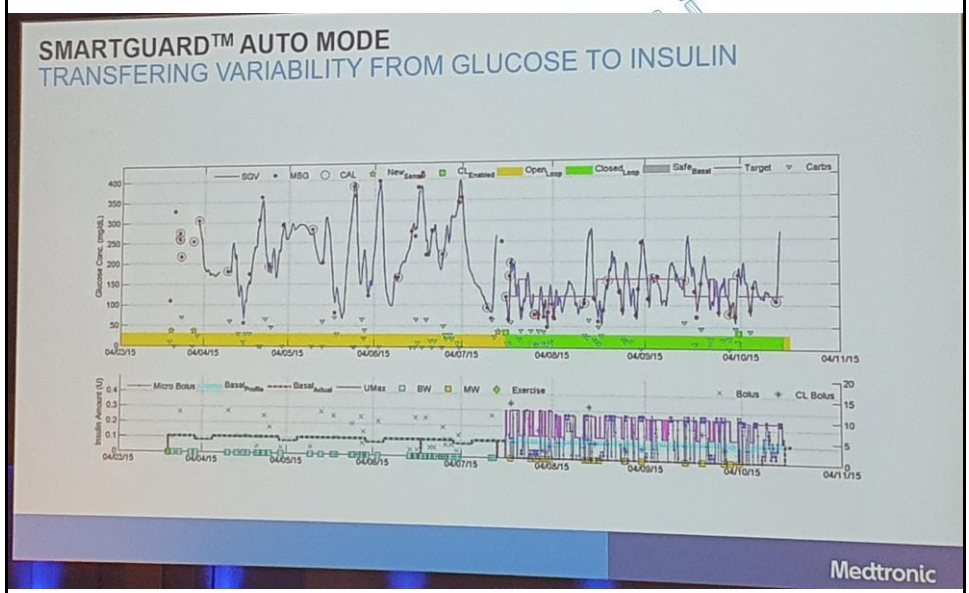
American Diabetes Association.

138

MiniMed 670G – hybrid closed loop

https://diatribe.org/drugdevice-name/medtronic-minimed-670g#sthash.FpnjZ4pj.dpuf

139



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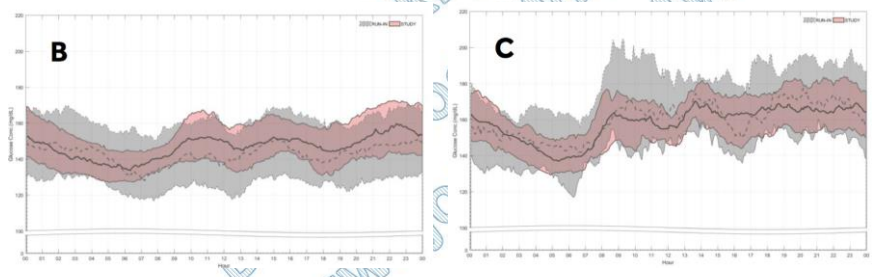
MiniMed 670G – pivotal study

HbA1c 7,4% → 6,9%



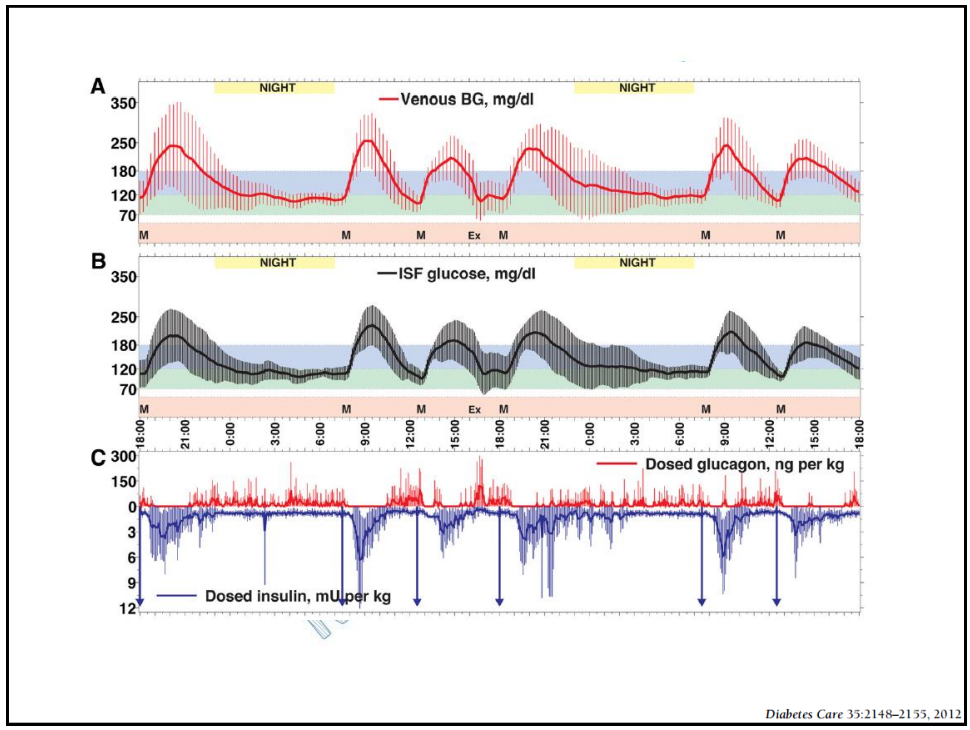
DIABETES TECHNOLOGY & THERAPEUTICS
Volume 19, Number 3, 2017
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2016.0421

141

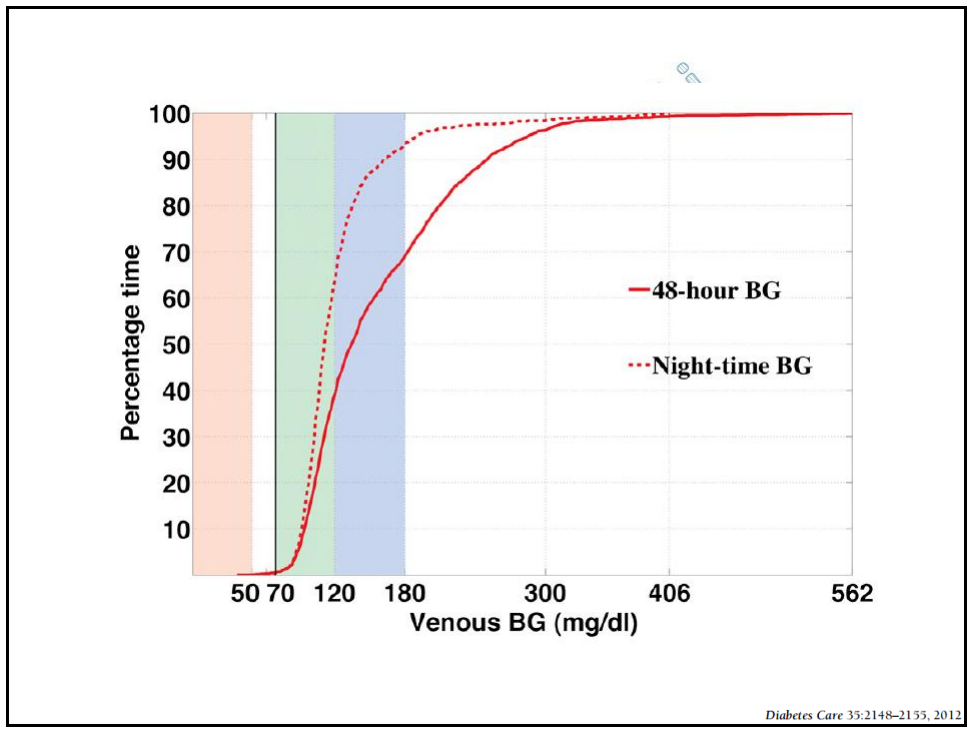
Closed loop – bihormonal

Professor Ed Damiano
Revolutionizing Treatment for Diabetes Control

142


A
NIGHT
Venous BG, mg/dl
NIGHT
350
250
180
120
70
M
M
M
Ex
M
M
M
B
NIGHT
ISF glucose, mg/dl
NIGHT
350
250
180
120
70
M
M
M
Ex
M
M
M
18:00
21:00
0:00
3:00
6:00
9:00
12:00
15:00
18:00
21:00
0:00
3:00
6:00
9:00
12:00
15:00
18:00
C
300
150
0
3
6
9
12
Dosed glucagon, ng per kg
Dosed insulin, mU per kg
Diabetes Care 35:2148–2155, 2012

143


100
90
80
70
60
50
40
30
20
10
Percentage time
48-hour BG
Night-time BG
50 70
120
180
300
406
562
Venous BG (mg/dl)
Diabetes Care 35:2148–2155, 2012

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βeta βionics
A Massachusetts Public Benefit Corporation

introducing the iLet™

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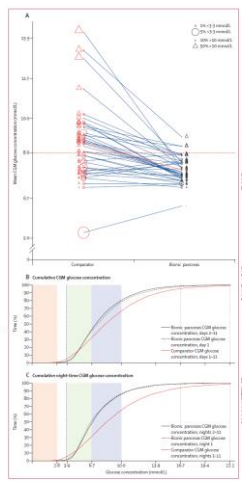
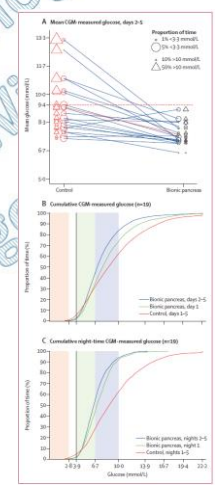
Bihormonal closed loop



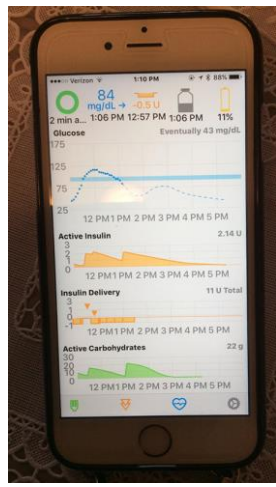
Published Online
December 19, 2016
http://dx.doi.org/10.1016/
S0140-6736(16)32567-3



Lancet Diabetes Endocrinol 2016
Published Online
February 2, 2016
http://dx.doi.org/10.1016/
S2213-8587(15)00439-1

146

#WeAreNotWaiting



- While using OpenAPS, self-reported outcome measures (by 18 of the first 40 users) showed:
  - median HbA1c dropped from 7.1% to 6.2%
  - median percent time in range (80-180 mg/dL) increased from 58% to 81%
  - All but one respondent reported some improvement in sleep quality, and 56% reported a large improvement.

147

Artificial Pancreas/Closed Loop Systems Summary

- Hypoglycemia minimizer: LGS
- Hyperglycemia minimizer: better algorithms, faster insulin into system (Halozyme, amylin/insulin co-formulation, heated insulin, GLP-1 analogues?)
- Better sensors

148

Diabetes complications:

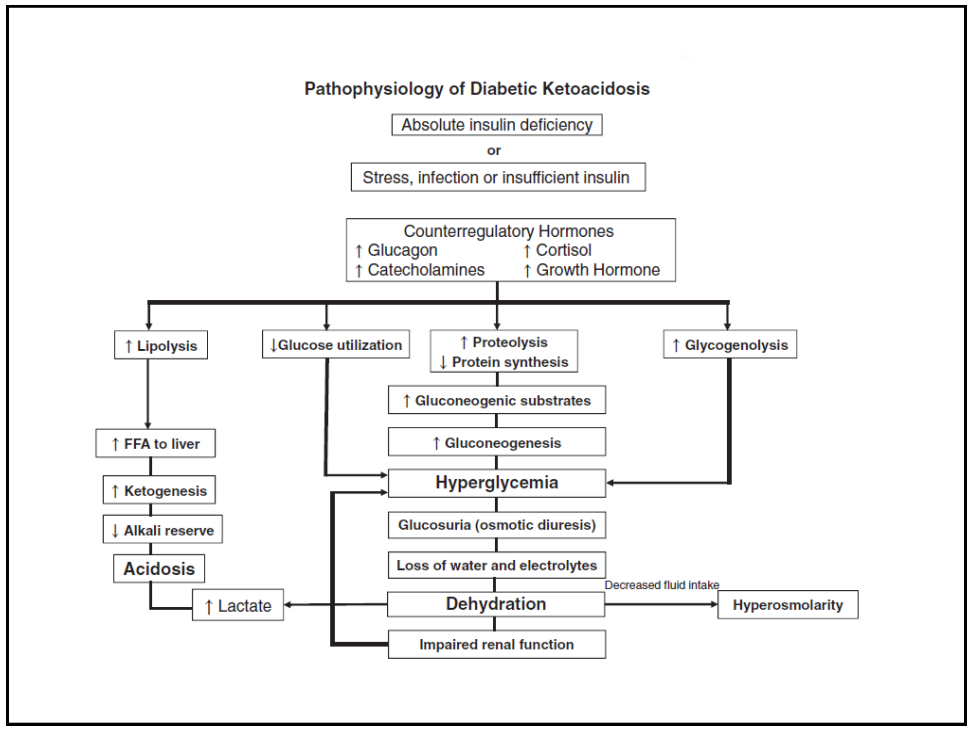
- Acute:
- Ketoacidosis
- Hypoglycemia
- Chronic:
- Nephropathy
- Retinopathy
- Neuropathy (symmeric, autonomic)

149

Ketoacidosis:

- Acute insulin deficiency leads to diabetic ketoacidosis
- Causes:
  - Infections (especially with diarrhea and vomiting)
  - Diet non-compliance
  - Inappropriate insulin supply (not adequate dose, omitting the dose, injection device's failure)

150



151

If this vicious circle will not be interrupted with insulin and electrolytes administration and rehydration of the patient, the DKA and dehydration will lead to one's death.

152

Definition of diabetic ketoacidosis (DKA)

The **biochemical criteria** for the diagnosis of DKA are (5):

- Hyperglycemia (blood glucose >11 mmol/L [≈200 mg/dL])
- Venous pH <7.3 or bicarbonate <15 mmol/L
- Ketonemia and ketonuria.

The **severity of DKA** is categorized by the degree of acidosis (18):

- Mild: venous pH <7.3 or bicarbonate <15 mmol/L
- Moderate: pH <7.2, bicarbonate <10 mmol/L
- Severe: pH <7.1, bicarbonate <5 mmol/L

Pediatric Diabetes 2009: **10** (Suppl. 12): 118–133

153

Clinical manifestations of diabetic ketoacidosis

- Dehydration
- Tachypnea; deep, sighing (Kussmaul) respiration
- Nausea, vomiting, and abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness, progressive obtundation, and loss of consciousness

154

Goals of therapy

- Correct dehydration
- Correct acidosis and reverse ketosis
- Restore blood glucose to near normal
- Avoid complications of therapy
- Identify and treat any precipitating event

Pediatric Diabetes 2009: **10** (Suppl. 12): 118–133

155

Received: 11 April 2018 | Accepted: 31 May 2018
DOI: 10.1111/pedi.12701

WILEY

ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state

Joseph I. Wolfsdorf[1] | Nicole Glaser[2] | Michael Agus[1,3] | Maria Fritsch[4] | Ragnar Hanas[5] | Arleta Rewers[6] | Mark A. Sperling[7] | Ethel Codner[8]

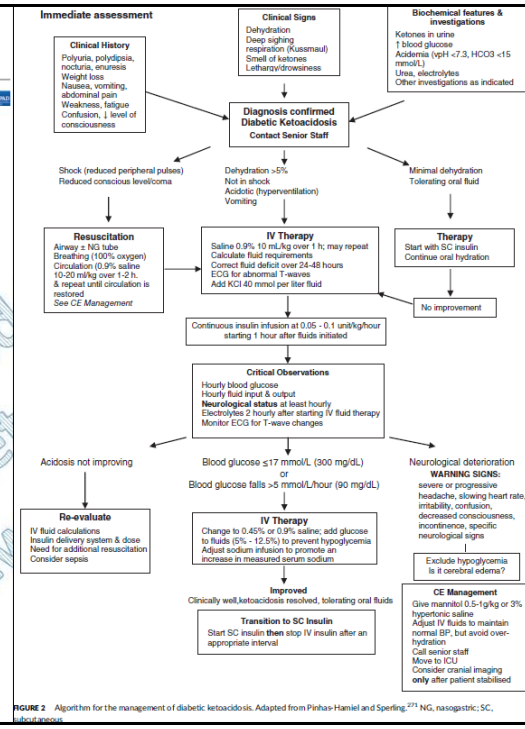
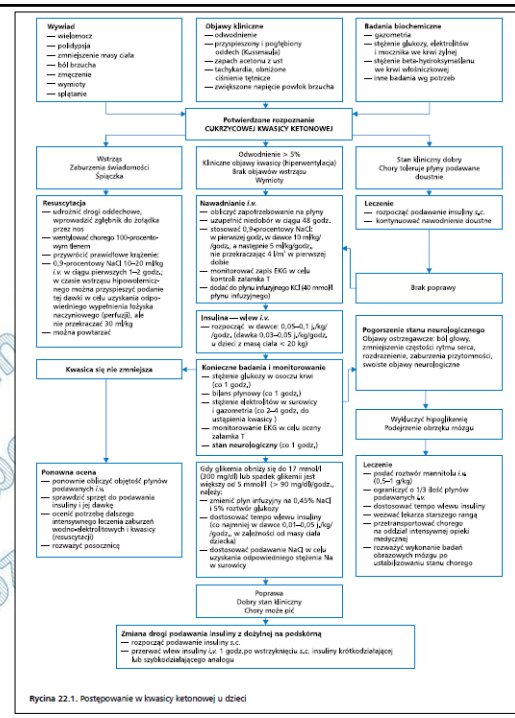


FIGURE 2 Algorithm for the management of diabetic ketoacidosis. Adapted from Pinhas-Hamiel and Sperling.[271] NG, nasogastric; SC, subcutaneous

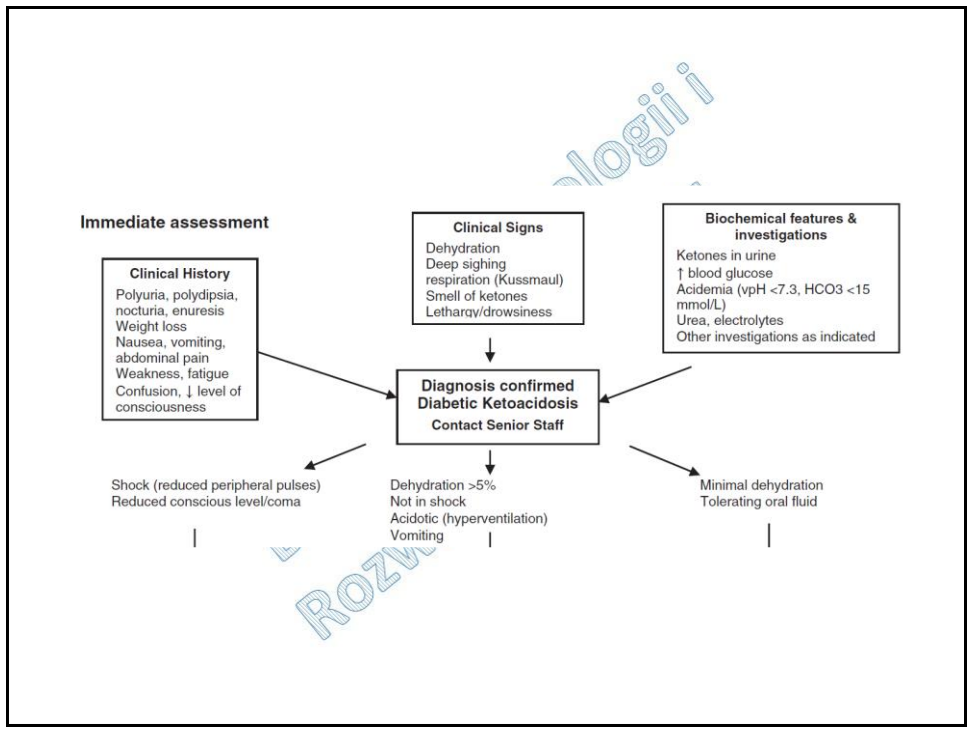
156

Algoritm of DKA therapy
Polish Diabetes
www.cukrzyca.info.pl

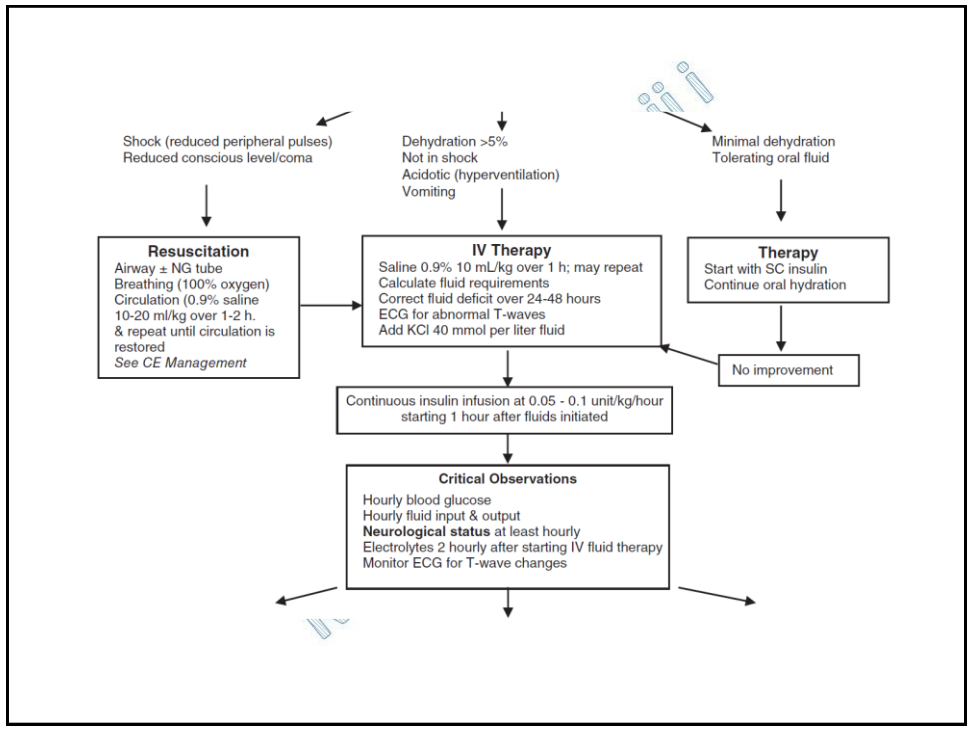


Rycina 22.1. Postępowanie w kwasicy ketonowej u dzieci

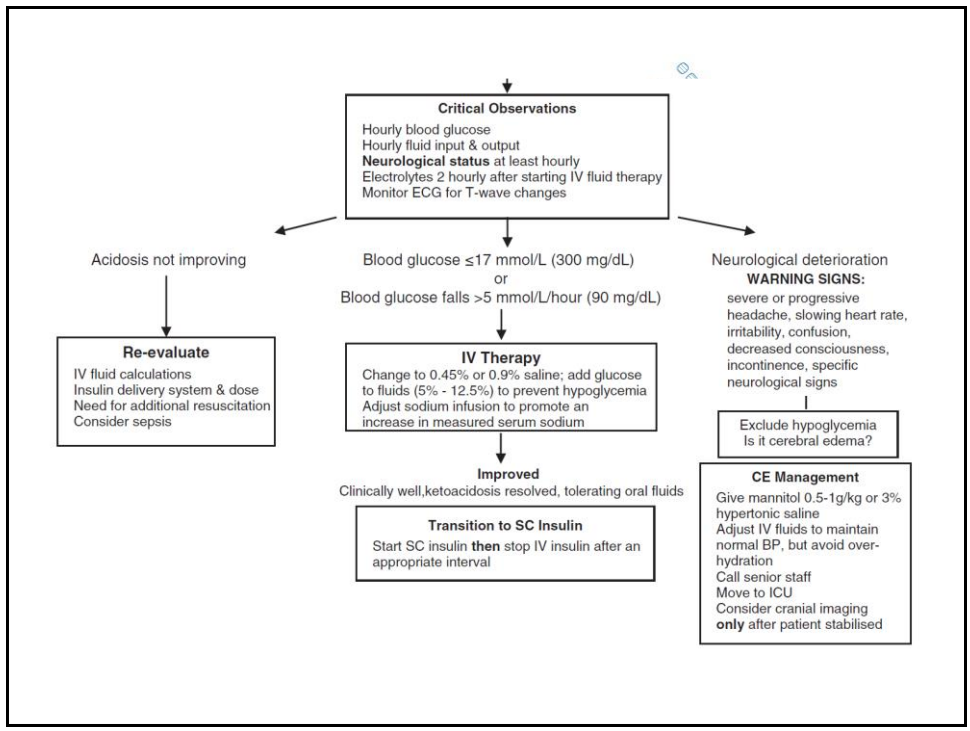
157



158


Shock (reduced peripheral pulses)
Reduced conscious level/coma
Dehydration >5%
Not in shock
Acidotic (hyperventilation)
Vomiting
Minimal dehydration
Tolerating oral fluid
Resuscitation
Airway ± NG tube
Breathing (100% oxygen)
Circulation (0.9% saline
10-20 ml/kg over 1-2 h.
& repeat until circulation is restored
See CE Management
IV Therapy
Saline 0.9% 10 mL/kg over 1 h; may repeat
Calculate fluid requirements
Correct fluid deficit over 24-48 hours
ECG for abnormal T-waves
Add KCl 40 mmol per liter fluid
Therapy
Start with SC insulin
Continue oral hydration
No improvement
Continuous insulin infusion at 0.05 - 0.1 unit/kg/hour starting 1 hour after fluids initiated
Critical Observations
Hourly blood glucose
Hourly fluid input & output
Neurological status at least hourly
Electrolytes 2 hourly after starting IV fluid therapy
Monitor ECG for T-wave changes

159


Critical Observations
Hourly blood glucose
Hourly fluid input & output
Neurological status at least hourly
Electrolytes 2 hourly after starting IV fluid therapy
Monitor ECG for T-wave changes
Acidosis not improving
Re-evaluate
IV fluid calculations
Insulin delivery system & dose
Need for additional resuscitation
Consider sepsis
Blood glucose ≤17 mmol/L (300 mg/dL)
or
Blood glucose falls >5 mmol/L/hour (90 mg/dL)
IV Therapy
Change to 0.45% or 0.9% saline; add glucose to fluids (5% - 12.5%) to prevent hypoglycemia
Adjust sodium infusion to promote an increase in measured serum sodium
Improved
Clinically well,ketoacidosis resolved, tolerating oral fluids
Transition to SC Insulin
Start SC insulin then stop IV insulin after an appropriate interval
Neurological deterioration
WARNING SIGNS:
severe or progressive headache, slowing heart rate, irritability, confusion, decreased consciousness, incontinence, specific neurological signs
Exclude hypoglycemia
Is it cerebral edema?
CE Management
Give mannitol 0.5-1g/kg or 3% hypertonic saline
Adjust IV fluids to maintain normal BP, but avoid over-hydration
Call senior staff
Move to ICU
Consider cranial imaging
only after patient stabilised

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AVOID bicarbonate

Severe acidosis is reversible by fluid and insulin replacement; insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate. Treatment of hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids.

Controlled trials have shown no clinical benefit from bicarbonate administration.[183–186] Bicarbonate therapy may cause paradoxical CNS acidosis[187,188] and rapid correction of acidosis with bicarbonate causes hypokalemia.[187,189,190] Bicarbonate administration may be beneficial in the rare patient with life-threatening hyperkalemia or unusually severe acidosis (vpH <6.9) that has compromised cardiac contractility.[191]

161

Hypoglycemia:

- Over exercise
- Omitting meal
- Over dosage of insulin (e.g. due to infusion device failure or by mistake)

162

Hypoglycemia:

- **Asymptomatic**: blood glucose <55 mg/dl (3mmol/l)
- **Intermediate**: presence of autonomic symptoms
- **Unaware**: **neuroglycopenia**: unusual behavior
- **Severe**: with hypoglycemic coma and central nervous system injury

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Hypoglycemia symptoms:

CNS (neurological)
- Fatigue
- Dysmnesia
- Concentration difficulties
- Hot flush
- Balance disturbances
- Headache
- Blurred vision, double vision, color blindness
- Loss of consciousness
- Seizures
- Unusual behavior

Autonomic (1)
- Convulsion
- Anxiety
- Palpitation
- Pulsation in thorax
- Numbness of mouth, fingers, tongue
- Excitation
- Starvation
- Nausea
- Pallor
- Sweat

164

Hypoglycemia symptoms

- Occurrence of these symptoms depends on: central nervous system reaction on glucose deficiency and its damage (polyneuropathy), rate of glucose level reduction, age and level of counterregulatory response.
- Children are more sensitive for hypoglycemia - counterregulatory hormones secretion start at glycemia 68 mg/dl (3,8 mmol/l), whereas in adults at 56 mg/dl (3,1mmol/l).

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Counterregulatory response hormones:

- **Glucagon** (increase glycemia by releasing glucose from hepatic glycogen)
- **Catecholamines** (glycogen, adipose tissue and proteins breakdown)
- **Cortisol** (inhibiting glucose uptake, stimulating adipose tissue and proteins breakdown)
- **Growth hormone** (inhibiting glucose utilization and stimulating adipose tissue metabolism)

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Hypoglycemia

1. Early (warning) symptoms: trembling, sweat, starvation, tingling sensation, headache.
2. Light neuroglycopenia: double vision, indistinct speech, concentration difficulties
3. Severe neuroglycopenia: violent/unusual behavior, disorientation
4. Loss of consciousness: hemiparesis, seizures

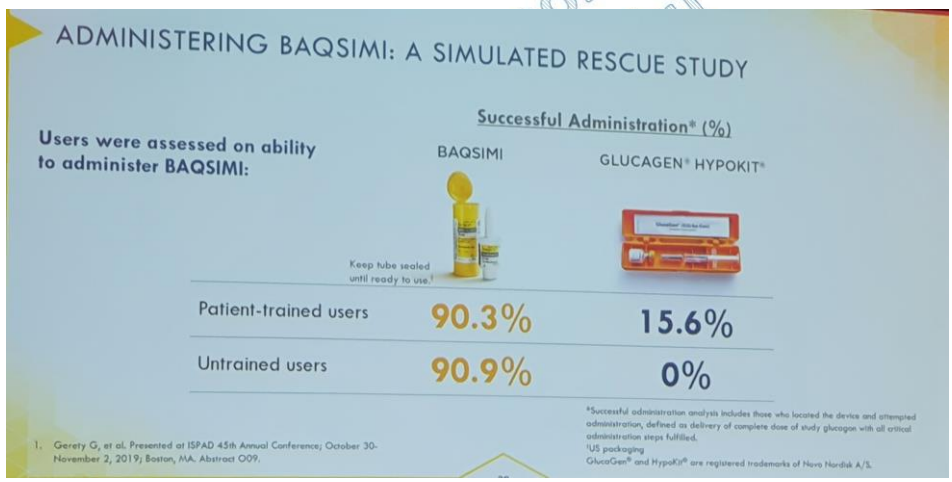
167

Treatment of hypoglycemia

- Light and intermediate, if the patient is conscious: glucose, juice, jelly, a sandwich afterwards
- Severe: the patient is unconscious: **glucagon 0,01mg/kg** body mass. Action profile – onset 10 -15', duration 30-60'
- When the patient become conscious: glucose, juice, jelly, a sandwich.
- Adverse effect of glucagon – nausea, vomiting
- No effect of glucagone if: glycogen reserve is low (exercises, frequent hypoglycemias, starvation), alcohol intake, over dosage of insulin.

168

BAQSIMI – glucagon nasal powder



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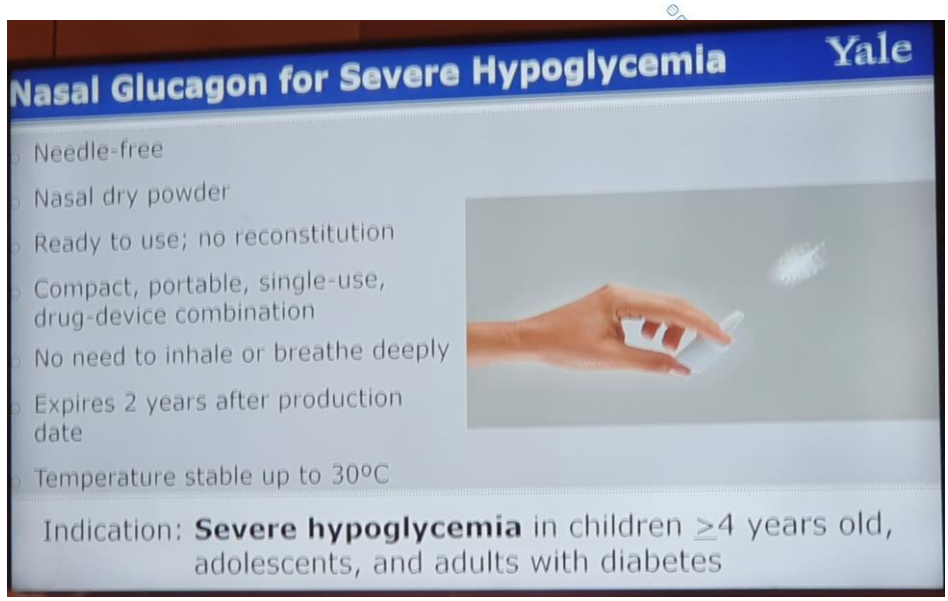

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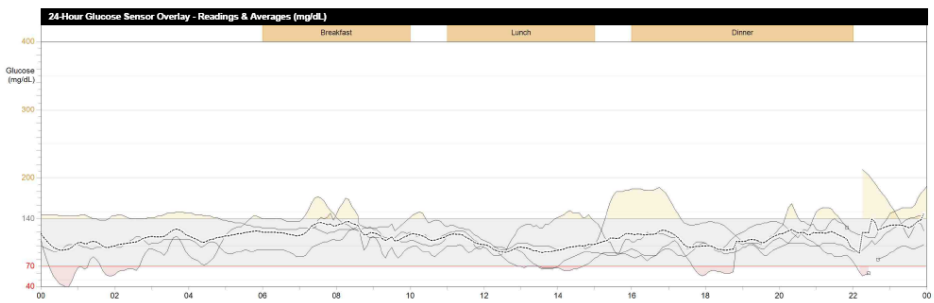
Goals of insulin therapy in children:

- Appropriate growth and psychomotor development
- Appropriate social development
- Appropriate personal development
- To lower the risk of complications

171

Goals

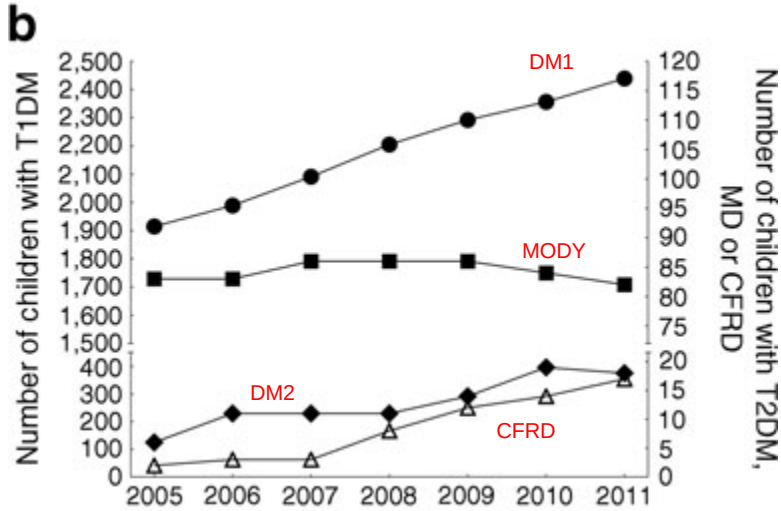


- Near-normoglycemia
- As few hypos as possible

172

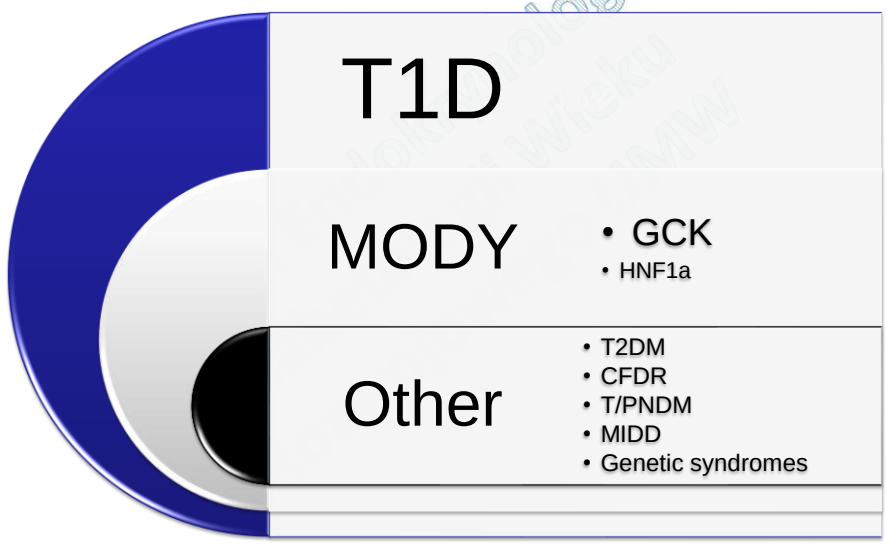
DM EPIDEMIOLOGY IN POLAND

W. Fendler i wsp. Diabetologia (2012) 55:2631–2635



173

Diabetes differentials in youths



To be discussed during the lecture in May (hopefully) ;-)

174