Sykursýki hjá börnum og unglingum

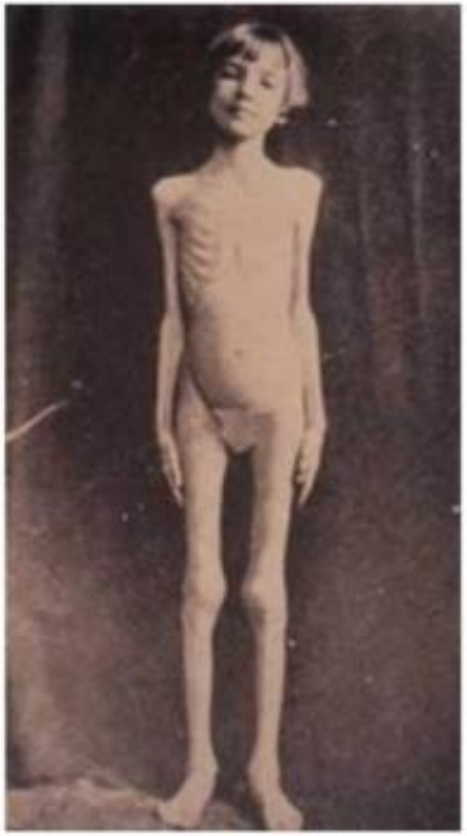
Soffía Jónasdóttir innkirtlasérfræðingur barna
Barnaspítala Hringsins
2023

Yfirlit fyrirlestrar

- Sagan
- Tilfelli
- Einkenni
- Meðferð
- Orsök og greining
- Lækning -
- Tæki og tól
- Hvert stefnir
- Tíðni


3000 ára gamall sjúkdómur
1552 B.C., when Hesy-Ra, an Egyptian physician, documented frequent urination as a symptom of a mysterious disease that also caused emaciation. Also around this time, ancient healers noted that ants seemed to be attracted to the urine of people who had this disease.
In 150 AD, the Greek physician Arateus described what we now call diabetes as "the melting down of flesh and limbs into urine.
The term "diabetes"(to siphon or pass through) was first coined by Araetus of Cappodocia (81-133AD). Later, the word mellitus (honey sweet) was added by Thomas Willis (Britain) in 1675 after rediscovering the sweetness of urine and blood of patients (first noticed by the ancient Indians
Diabetes mellitus is called Madhumeha in ancient Indian Ayurvedic medicine
In 1889, Joseph von Mering and Oskar Minkowski found that removing the pancreas from dogs led them to develop diabetes and die shortly afterward.
In 1910, Sir Edward Albert Sharpey-Schafer proposed that diabetes developed when there was a lack of a particular chemical that the pancreas produced. He called it insulin, meaning island, because the cells in the islets of Langerhans in the pancreas produce it
In 1921, Frederick Banting and Charles Best introduced an extract of pancreatic islet cells from healthy dogs into dogs with diabetes. Doing this reversed diabetes and marked the discovery of the hormone insulin.
In January 1922, 14-year-old Leonard Thompson was the first person to receive an injection of insulin to treat diabetes. Thompson lived another 13 years with the condition

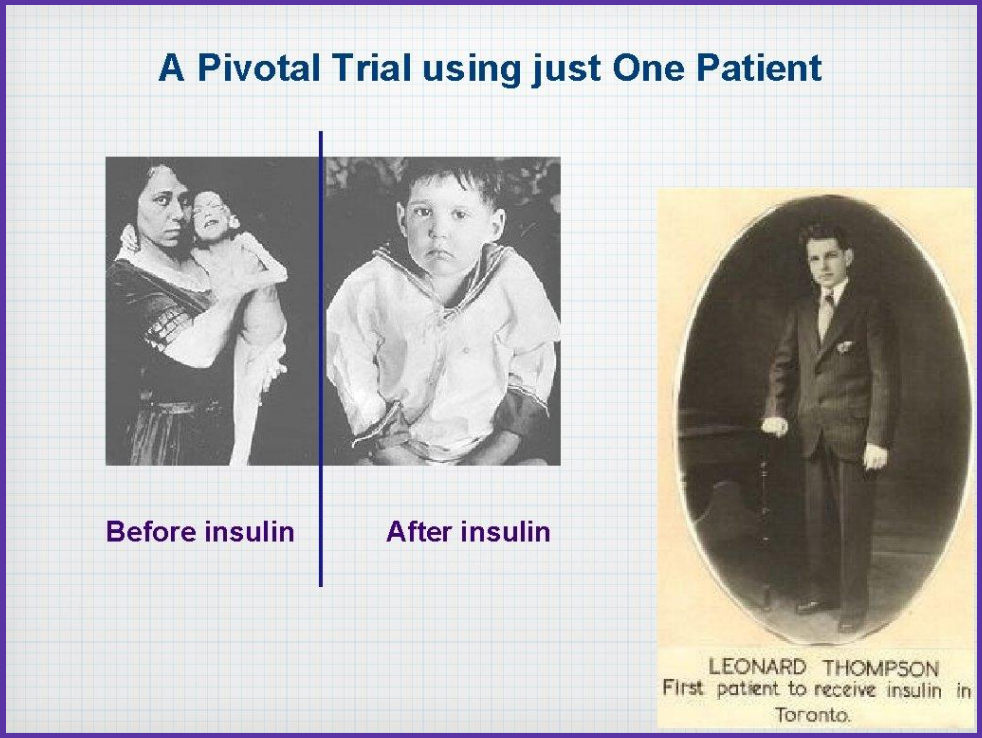
Before the discovery of insulin



Diabetes . . . is a melting down of the flesh and limbs into urine. The nature of the disease is chronic, but the patient is short-lived if the constitution of the disease be completely established, for the melting is rapid, the death speedy. Thirst unquenchable; and one cannot stop them from either drinking or making water.

Aretaeus A.D. 81-136

Banting og Best uppgötvuðu insúlín 1921



Leonard Thomson
from Toronto 1.1.1921

100 ára afmæli


TORONTO
C.C. VIAL
per C.C.
JAN 2 1 '25
LABORATORIES
TS—10 C.C. VIAL
Units per C.C.
JAN 2
10 Units per C.
10 Units per C.
UNITS—10 C.C.
10 Units per C.

Saga 21. aldarinnar

While the discovery of insulin 100 years ago transformed type 1 diabetes from a fatal illness to a chronic illness, it is not a cure. Quality of life challenges and long-term complications remain a constant reality for patients with type 1 diabetes no matter how carefully they manage the disease

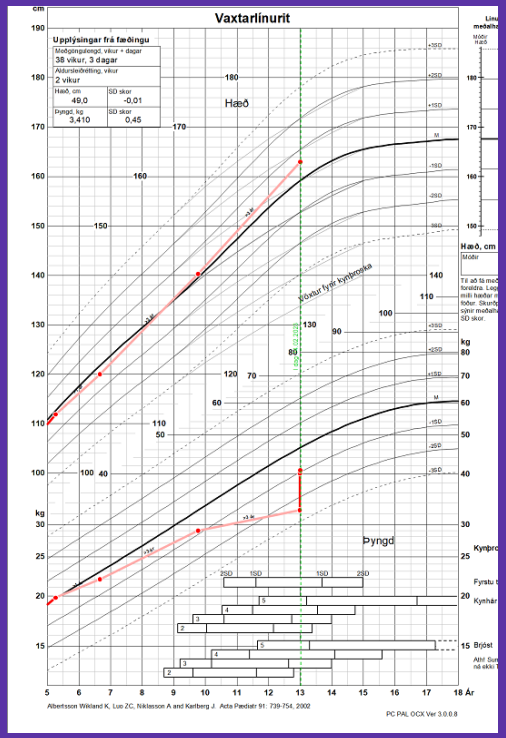
Markmið framtíðarinnar er að ‘’lækna’’ sykursýki

- Theoretical
  - disappearance without a trace
- Practical
  - removes risk of complications
    - short term
    - long term
  - small impact on lifestyle
  - safe

–Lækning í formi þess að

- Viðkomandi hafi algjörlega losnað við sykursýki
- Tæki til að sjá um meðferð sykursýki sé á ‘’autopilot

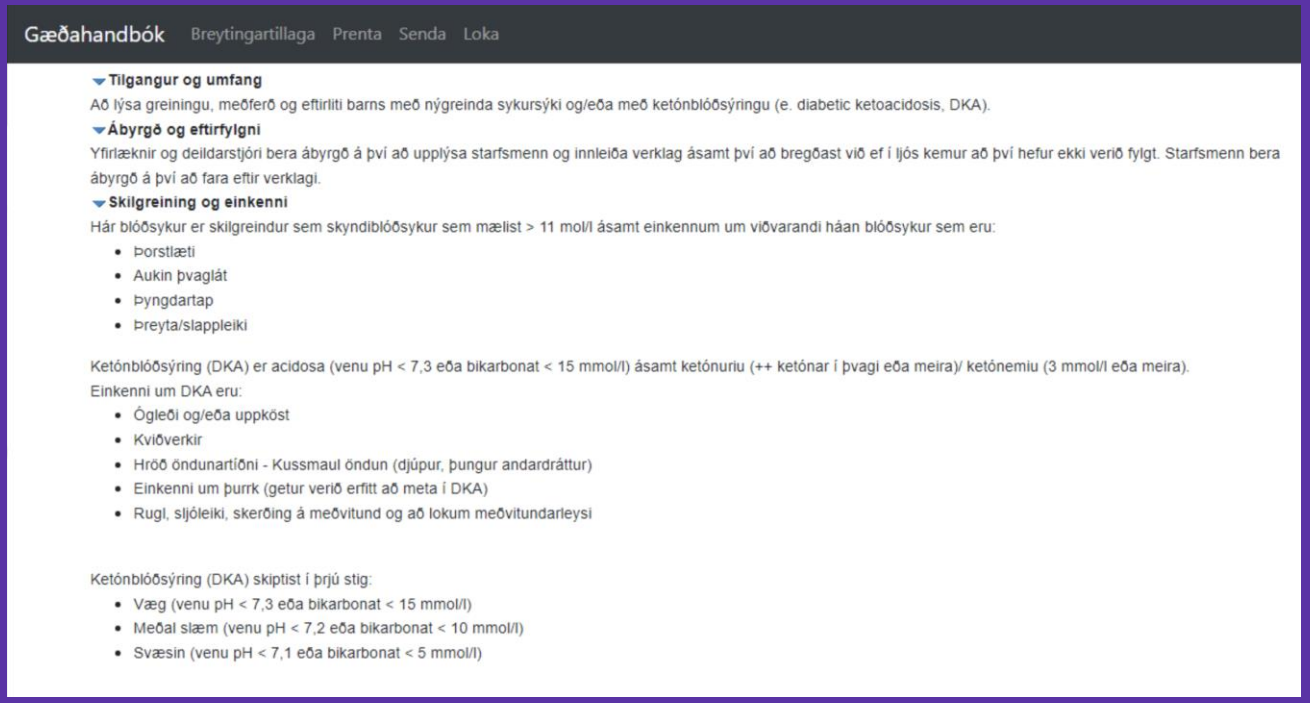
- 12 ára stelpa
- Uppköst í marga daga
- 4 x haft samband við heilsugæslu og Læknavaktina
- Ph 6,9, bicarbonat 2
- 21% dehydreruð



Upphafsmeðferð ketónblóðsýringu:

Til að leiðrétta acidosu, dehydration og blóðsykur

Gæðahandbók LSH – meðferðarplan 4.07.01.01.01 Nýgreind sykursýki og/eða ketónblóðsýring hjá barni



Gæðahandbók Breytingartillaga Prenta Senda Loka

Tilgangur og umfang

Að lýsa greiningu, meðferð og eftirliti barns með nýgreinda sykursýki og/eða með ketónblóðsýringu (e. diabetic ketoacidosis, DKA).

Ábyrgð og eftirfylgni

Yfirlæknir og deildarstjóri bera ábyrgð á því að upplýsa starfsmenn og innleiða verklag ásamt því að bregðast við ef í ljós kemur að því hefur ekki verið fylgt. Starfsmenn bera ábyrgð á því að fara eftir verklagi.

Skilgreining og einkenni

Hár blóðsykur er skilgreindur sem skyndiblóðsykur sem mælist > 11 mol/l ásamt einkennum um viðvarandi háan blóðsykur sem eru:

- Þorstlæti
- Aukin þvaglát
- Þyngdartap
- Þreyta/slappleiki

Ketónblóðsýring (DKA) er acidosa (venu pH < 7,3 eða bikarbonat < 15 mmol/l) ásamt ketónuriu (++ ketónar í þvagi eða meira)/ ketónemiu (3 mmol/l eða meira).
Einkenni um DKA eru:

- Ógleði og/eða uppköst
- Kviðverkir
- Hröð öndunartíðni - Kussmaul öndun (djúpur, þungur andardráttur)
- Einkenni um þurrk (getur verið erfitt að meta í DKA)
- Rugl, sljóleiki, skerðing á meðvitund og að lokum meðvitundarleysi

Ketónblóðsýring (DKA) skiptist í þrjú stig:

- Væg (venu pH < 7,3 eða bikarbonat < 15 mmol/l)
- Meðal slæm (venu pH < 7,2 eða bikarbonat < 10 mmol/l)
- Svæsin (venu pH < 7,1 eða bikarbonat < 5 mmol/l)

- ***Markmið að leiðrétta acidósu , hækka glucósa en ekki lækka dreypi***

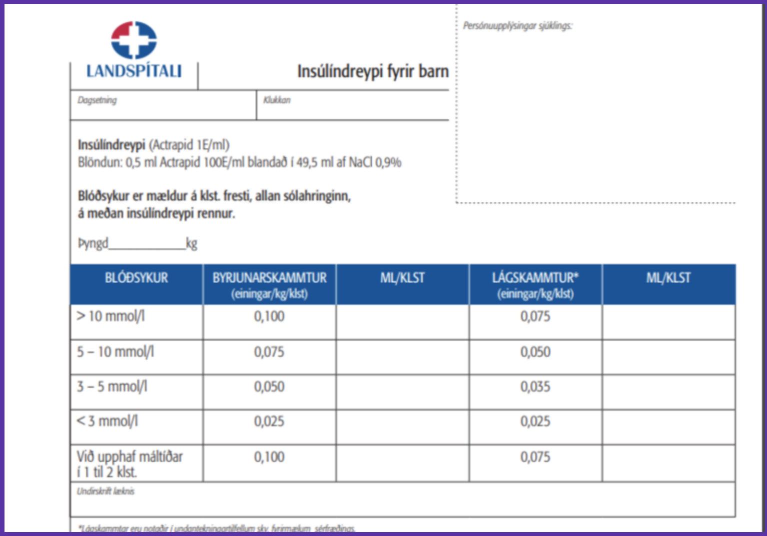
Drop in Na^+ for a given rise in glucose

- For every 5,6 mmol/L of glucose, there is 1.6 mmol/L decrease in sodium

Þegar PH > 7,30 og bicarb um 20 skipt yfir s.c insulin

Innlögn og kennsla

Öll börn fara í innlögð á barnadeild við greiningu



LANDSPÍTALI

Insúlíndreypi fyrir barn

Persónuupplýsingar sjúklings:

Dagsetning

Klukkan

Insúlíndreypi (Actrapid 1E/ml)
Blöndun: 0,5 ml Actrapid 100E/ml blandað í 49,5 ml af NaCl 0,9%

**Blóðsykur er mældur á klst. fresti, allan sólahringinn,
á meðan insúlíndreypi rennur.**

Þyngd____________kg

BLÓÐSYKUR	BYRJUNARSKAMMTUR (einingar/kg/klst)	ML/KLST	LÁGSKAMMTUR* (einingar/kg/klst)	ML/KLST
> 10 mmol/l	0,100		0,075	
5 – 10 mmol/l	0,075		0,050	
3 – 5 mmol/l	0,050		0,035	
< 3 mmol/l	0,025		0,025	
Við upphaf máltíðar í 1 til 2 klst.	0,100		0,075	

Undirskrift læknis

**Lágskammtar eru notaðir í undantekningartilfellum skv. fyrirmælum sérfræðings.*

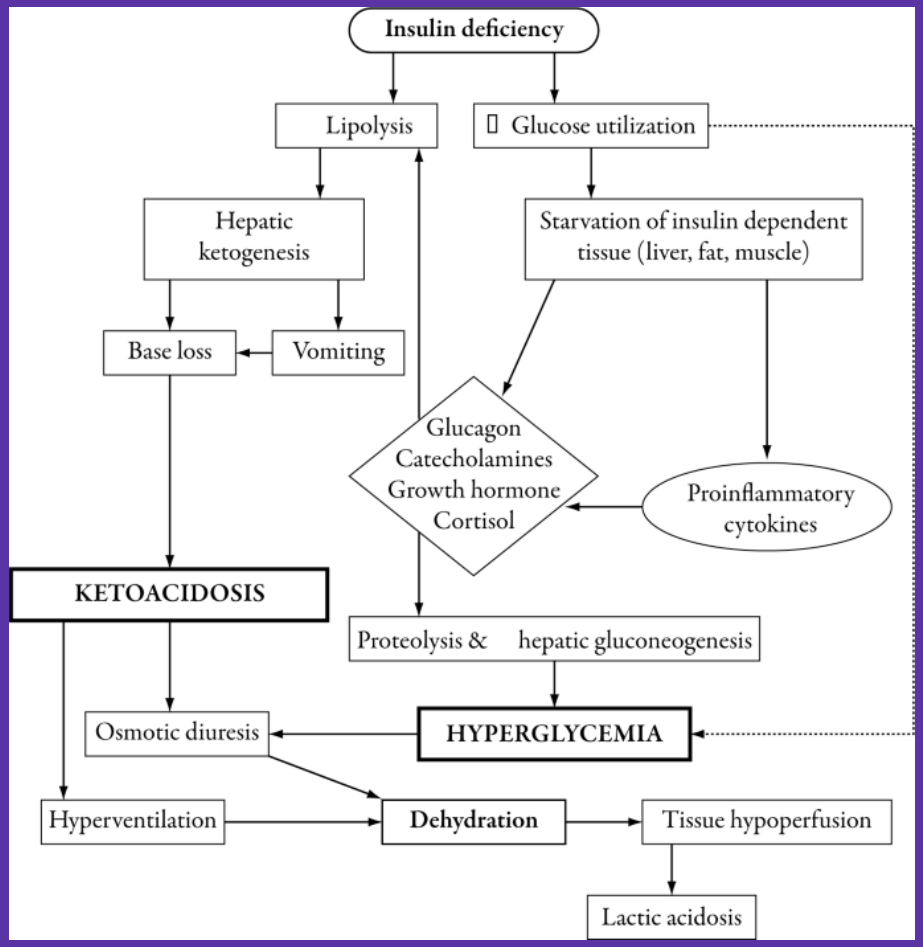
Hver eru einkenni sykursýki og afhverju

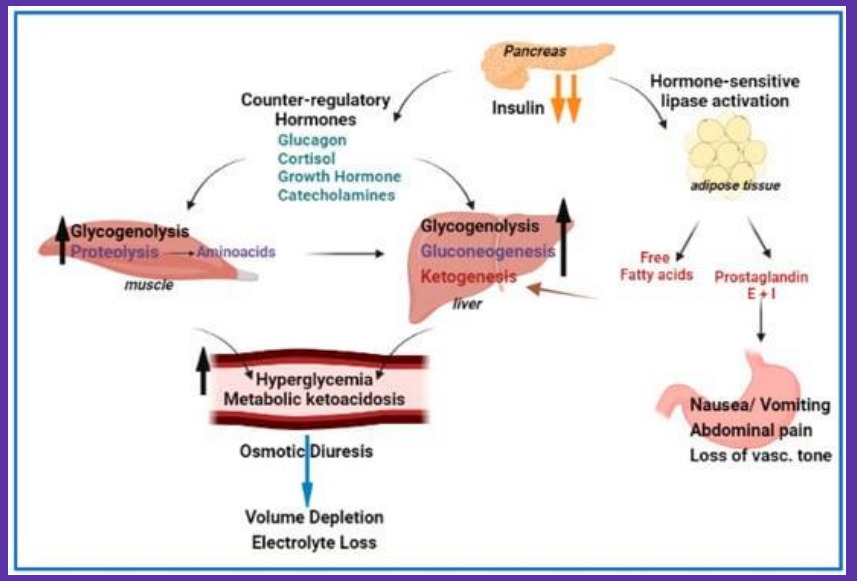
- Destruction of B cells ->
  - > lack of insulin production
    - -> Hyperglycemia
      - >Polyuria, polyphagia, polydypsia, Weight loss, low energy
    - - >>>> Diabetes

- Fastandi blóðsykur > 7,1
- Random blóðsykur > 11,1 – með eink.
- Gerum yfirleitt ekki sykurþolspróf á börnum

- Brain swelling – 24hr – rehydration fasa, yngri,mortality

Pathogenesis of DKA





Hvernig greinist

- Incidental hyperglycemia
- Incidentally discovered diabetes
  - routine sports PE
  - relative with diabetes
- The polys, No DKA
- Diabetic ketoacidosis

meðferðarmarkmið

Fyrsta lagi
- replace missing insulin

Öðru lagi
- do it correctly
  - avoid high blood glucose
  - avoid low blood glucose
  - continue to have a life

Markmið að halda blóðsykri stabílum 4 - 8

Insúlínmeðferð dæla versus pennar

Reglulegar blóðsykurmælingar með sensor eða mæli

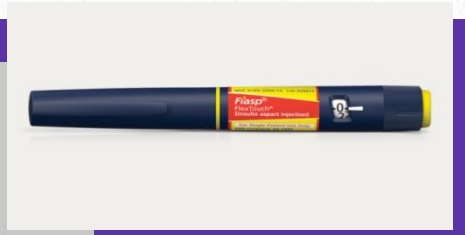
Huga þarf að mataræði og kolvetnatalningu

Regluleg hreyfing

Langtímameðalgildi HgA1c ~ 53 mmol

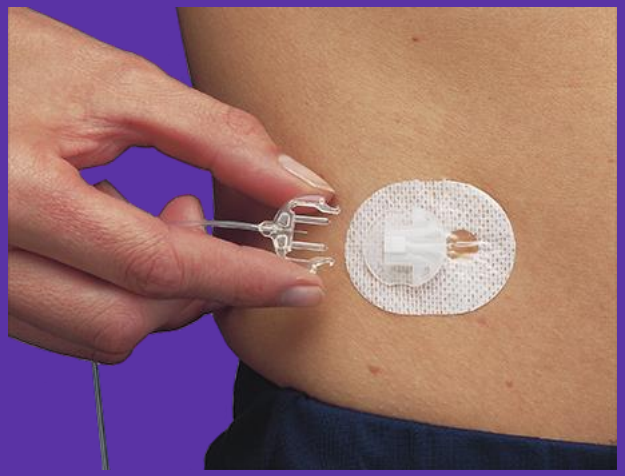
meðhöndluð með stutt og langvirkum insúlínafbrigðum (analogs)

eða insúlíndælu



Dælur

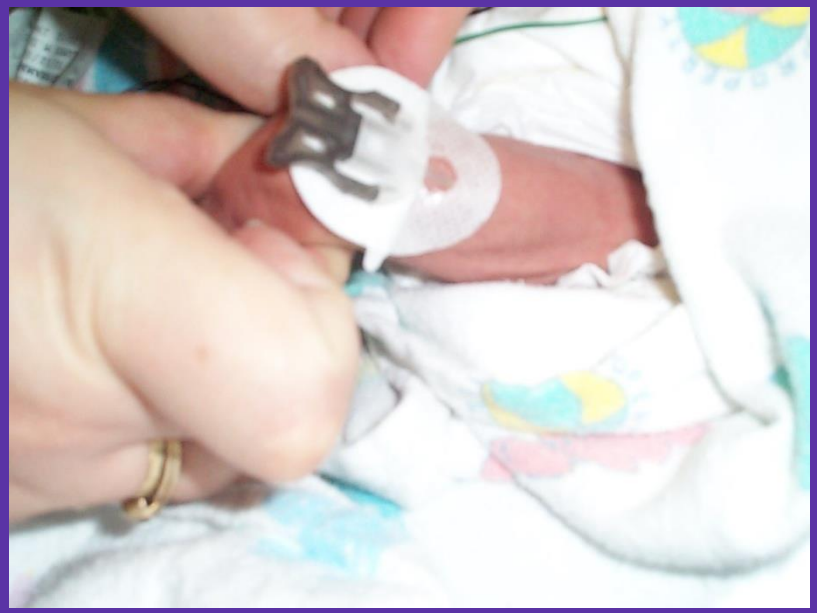
- Insulin gefið sem
  1. Basal
  2. Bolus , sem ræðst að blóðsykursgildi og magni kolvetnis sem er borðað í hvert sinn




10:20 AM
March 5, 2017
149
mg/dL
24
HRS
INSULIN ON BOARD:
1.1 u | 1:09 hrs
OPTIONS
BOLUS


9:38
5.5
mmol/L
0.5 U
Active Insulin
7
7:30
8
8:30
9
9:30
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5

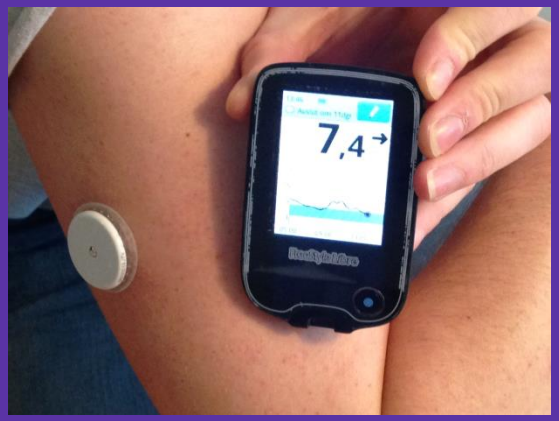
3 week old DM

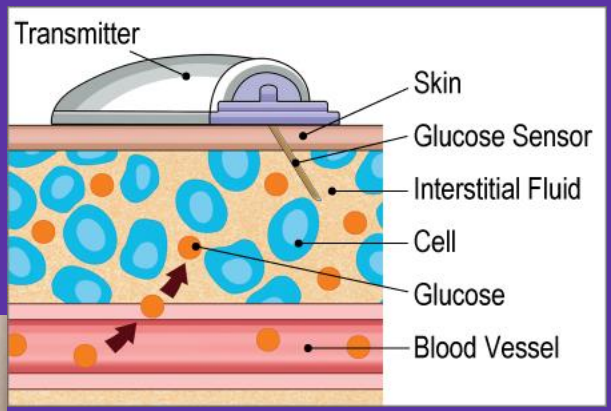


Sensor

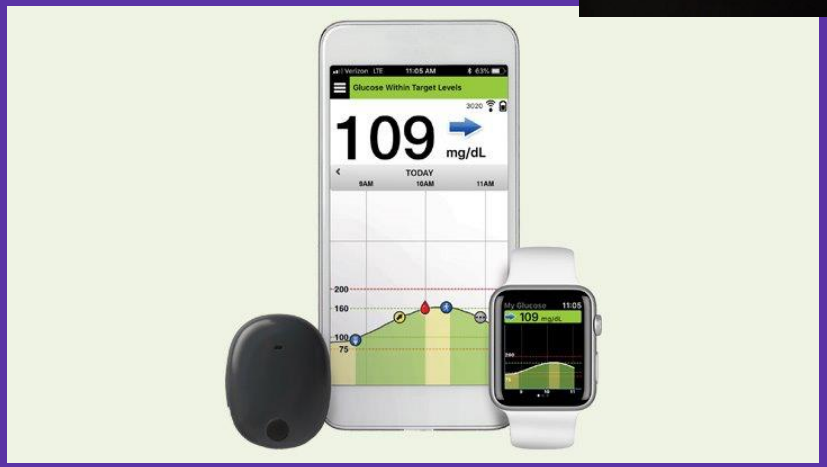
A mobile version of a continuous glucose sensor, 1985

Sensor


7,4

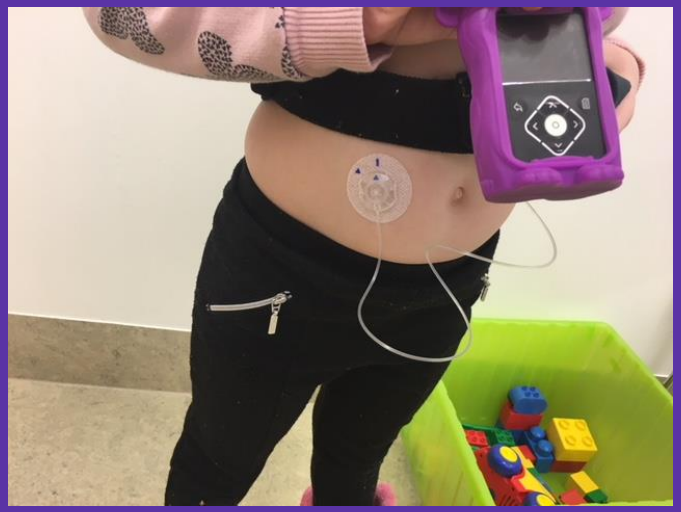

Transmitter
Skin
Glucose Sensor
Interstitial Fluid
Cell
Glucose
Blood Vessel


137
mg/dL
Medtronic

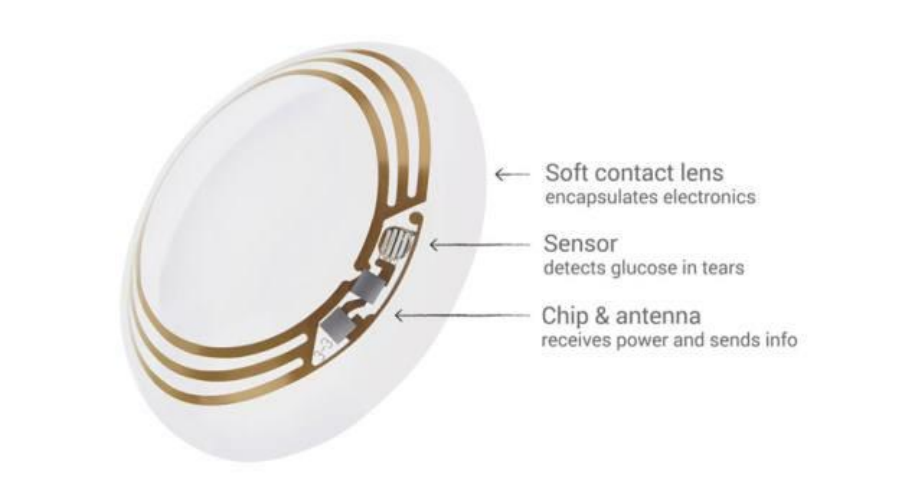

Glucose Within Target Levels
109
mg/dL
TODAY

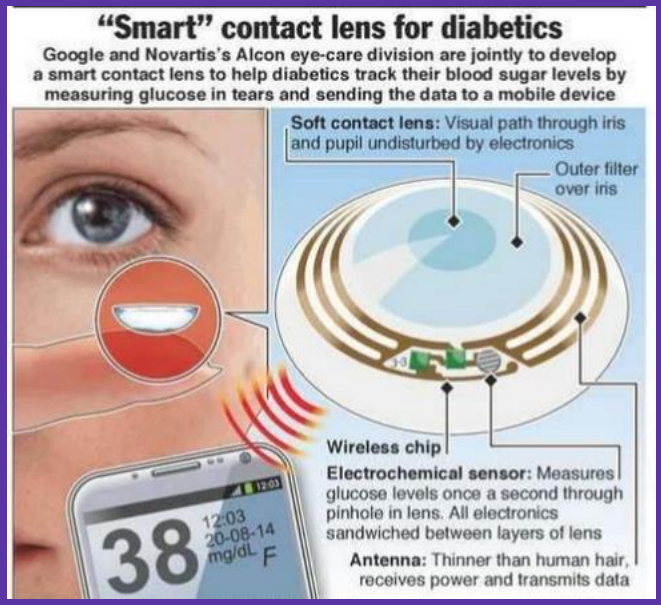
Where to Sense?

- Blood
- Extracellular fluid
- Intracellular fluid
- Transcutaneous
- Other fluids
  - CSF
  - eye



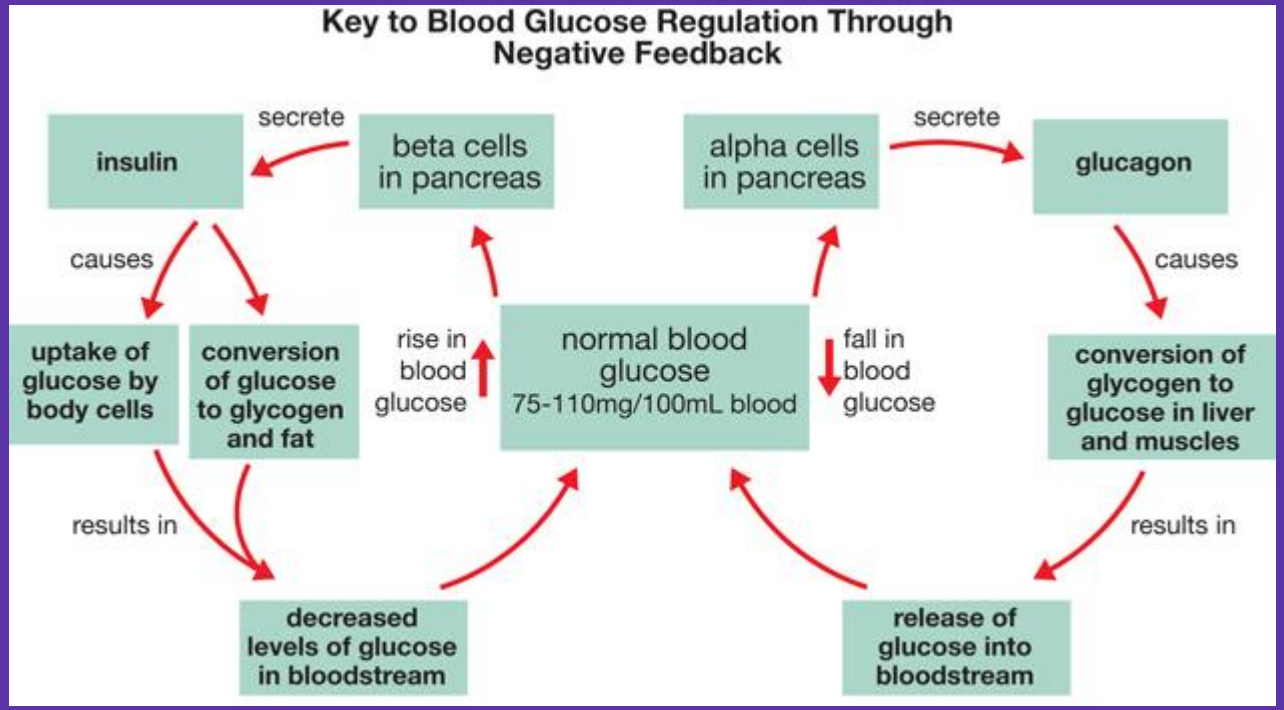
The Google lens





- Google and Novartis
- '' problem glucose can´t be reliable measured in tears ''

Blóðsykurstjórnun



Artificial pancreas

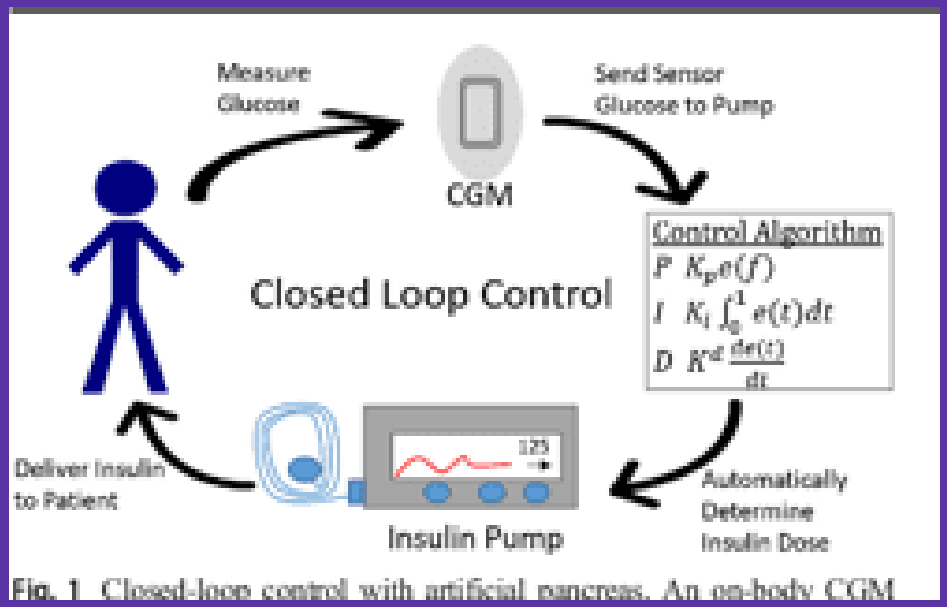
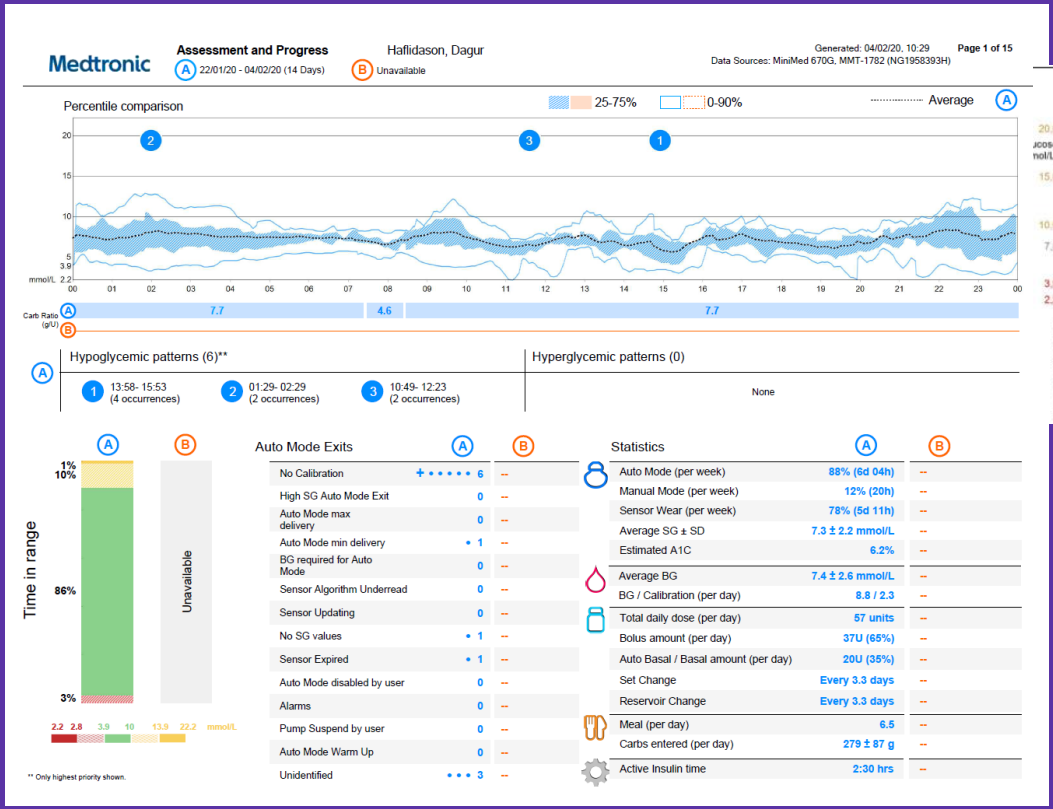


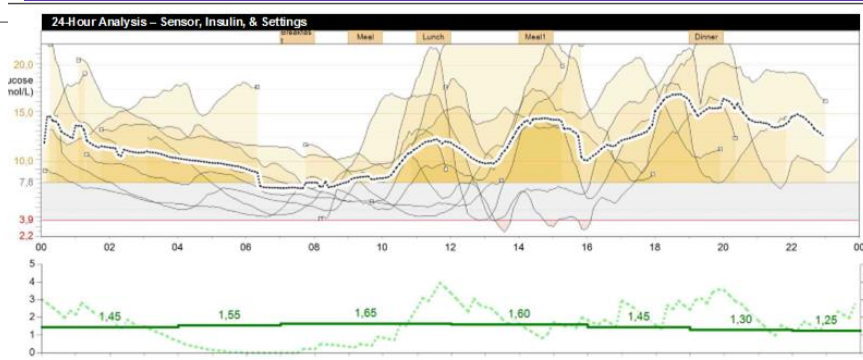
Fig. 1. Closed-loop control with artificial pancreas. An on-body CGM

- The control algorithm
  - biggest challenge
  - using artificial intelligence

- Meðal BG 7,3

Meðal BG 14,6

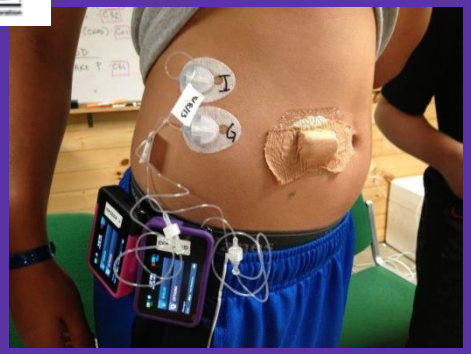





Medtronic
Przegląd dzienny (4 z 6)
27.10.2021, 28.10.2021
Wygenerowano: 02.11.2021, 10:01
Strona 12 z 14
Źródła danych: MiniMed 780G, MMT-1885 (NG2688362H)
Środa 27.10
DDI 16.3 j
Całkowita baza 64% | 10.4 j
Całkowity bolus 36% | 5.9 j
Bolus 51% | 3 j
Korekta automatyczna 49% | 2.9 j
Czas w zakresie
9%
81%
10%
Glukoza (mmol/l)
Bolus (j)
Bolus pos.
Korekta*
Ignorowanie
Węgl. (g)

Beta Bionics

A Massachusetts Public Benefit Corporation



- Bihormonal
- Insulín og Glucagon

- Trials have gone well

iLet Bionic Pancreas system

Göngudeild

- Öll íslensk börn með sykursýki eru í eftirliti á göngudeild sykursjúkra barna – LSH /SAK

Hitta þar

- sérfræðilækna í sykursýki barna,
- Hjúkrunarfræðinga
- Næringarfræðinga
- sálfræðinga
- Félagsráðgjafa

- Göngudeildarheimsókn á 3 mánaða fresti
- HgA1c
- Download af mælum
- Skimun – skjaldkirtilspróf, gluten óþol, microalbumin, blóðfitur, augnbotnaskimun

Blóðsykur stjórnun

er ekki auðveld hjá börnum

Lífstíðarsjúkdómur

- Af hverju er erfitt að stjórna sykursýki
- hjá börnum og unglingum ?

- Smábörn geta ekki tjáð sig um einkenni sykurfalls
- Matarlyst misjöfn
- Hreyfing misjöfn
- Börn eru að vaxa
- Tilfinningaólga unglingsáranna
- Afneitun
- Nenna ekki að vera með þennan sjúkdóm
- Sprauta sig bara stundum / gefa bolus bara stundum
- Átröskun
- Félagsleg vandamál

What Kills Diabetics?

- Acute
  - DKA
    - brain swelling
    - metabolic
    - others
  - Hypoglycemia
- Chronic Complications
  - macrovascular
    - heart
    - lower extremities
  - microvascular
    - retinopathy
    - nephropathy
    - neuropathy

- **Ofvöxtur á stungustað** (lipohypertrophy**)**
  Autoimme-sjúkdómar
  - 4 - 19 % hypothryoidism
  - 6 % Gluten óþol

Einkenni blóðsykurfalls

Væg eða meðalmikil einkenni;

Blóðsykur 2-4mmol/l

- Skjálfti
- Hjartsláttur
- Sviti
- Hungurtilfinning
- Fölvi
- Óróleiki

Svæsin einkenni: Frá miðtaugakerfi

Blóðsykur <2mmol/l

- Rökhugsun ábótavant
- Hegðunarbreytingar
- Pirringur
- Sljóleiki/rugl
- Skert meðvitund
- Meðvitundarleysi
- Krampar

Hvað veldur blóðsykurfalli?

- Hár insúlínskammtur
  - mistök við insúlíngjöf, breyting á upptöku insúlíns, máltíð sleppt, mikil orkubrennsla
- Ung börn
- Góð blóðsykurstjórnun (↓HbA1c)
- Ómeðvituð, endurtekin blóðsykurföll
- Alcohólneysla
- O.fl.

Ef væg eða meðalmikil einkenni:

Gefa fljótvirk kolvetni:

- 3 töflur af þrúgusykri eða
- Hreinan ávaxtasafa, ca.100 ml eða
- Hypostop gel, (1/2 úr túbu)
- mæla blóðsykur eftir 10 mín., ef hækkandi gefa seinvirk kolvetni s.s.banana, mjólk, brauð, ost

Ef rétt f. mat borða strax, fylgja eftir

Aldrei láta barn með lágan blóðsykur vera eitt, ástandið getur versnað hratt

Viðbrögð við krampa vegna blóðsykurfalls utan spítala

- Ráð til foreldra

- Halda ró sinni, vinna fumlaust
- **Ekki** gefa að drekka eða borða
- Setja barn í hliðarlegu
- Undirbúa glucagon gjöf og sprauta í vöðva
- Hringja í 112
- Vera hjá barni

- Þegar barn er komið til meðvitundar, gefið strax sætan djús og síðan að borða

Meðferð við blóðsykursfalli innan spítala

- Lágur blóðsykur (hypoglycemia) er skilgreindur sem P-glúkósi ≤2,8 mmól/L

- Ef sjúklingur er með meðvitund: gefið þrúgusykurtöflur, 1 tafla/10kg eða sykraðan drykk 10-20ml/kg. Ef blóðsykur leiðréttist ekki á 10-15 mín skal íhuga IV meðferð.
- ● Þegar komið hefur verið upp æðaaðgengi gefið bólus af 10% glúkósa (100mg/ml), 2ml/kg IV/IO og í kjölfar þess innrennsli af 10% glúkósa (100mg/ml) með 140mmólNa/L og 5-20mmól K/
- Ef illa gengur að koma upp æðaaðgengi skal gefa glucagon 1mg SC/IM og mæla blóðsykur aftur eftir 10 mínútur. Ath. þó að ef glycogenbirgðir eru tæmdar fæst ekki virkni af glucagon

Hypostop – glucose gel

- Gefið ef viðkomandi er með meðvitund en ekki fær um að drekka
- Gefið í smáskömmtum í munn
- Glucose töflur

Glucagon

- Gefið í vöðva í læri eða mjöðm
- Við alvarlegu blóðsykurfalli, slæfð meðvitund eða meðvitundarleysi og / eða krampar
- Börn <10 ára:0,5mg. Börn > 10 ára: 1 mg.
- Virkar á nokkrum mínútum

Diabetes

Ævilangur sjúkdómur - 24/7

Erfitt að stjórna blóðsykri hjá börnum

- Margar breytur

Dýr sjúkdómur í peningum og mannárum

Mikil áheyrsla á rannsóknir

- Prevention
- Cure

Cure - ” Lækning “

Theoretical

- disappearance without a trace

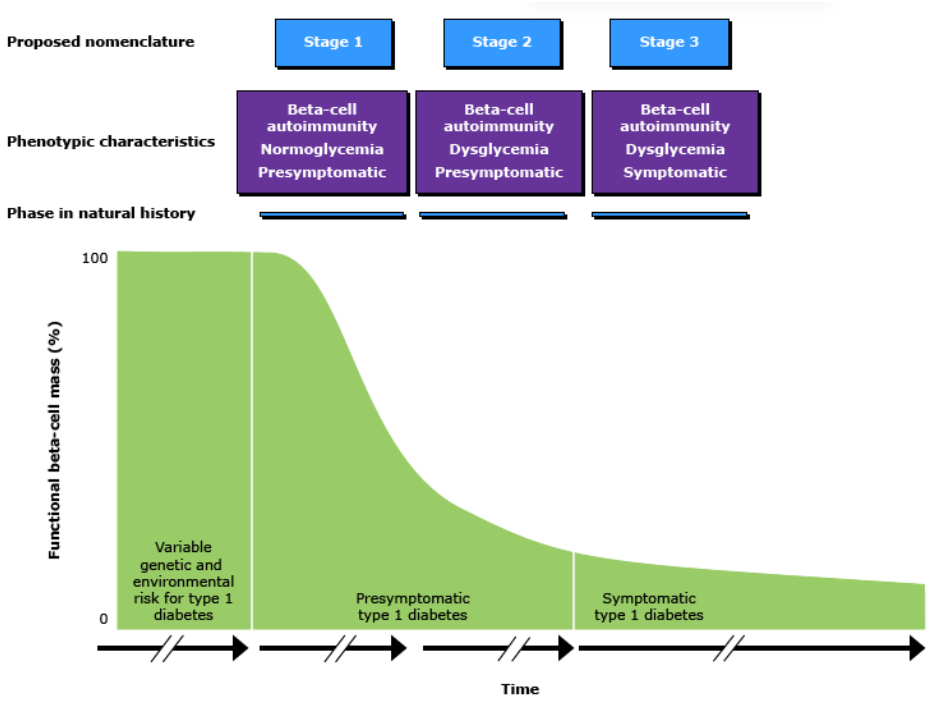
Practical

- removes risk of complications
  - short term
  - long term
- small impact on lifestyle
- safe

Diabetes Research

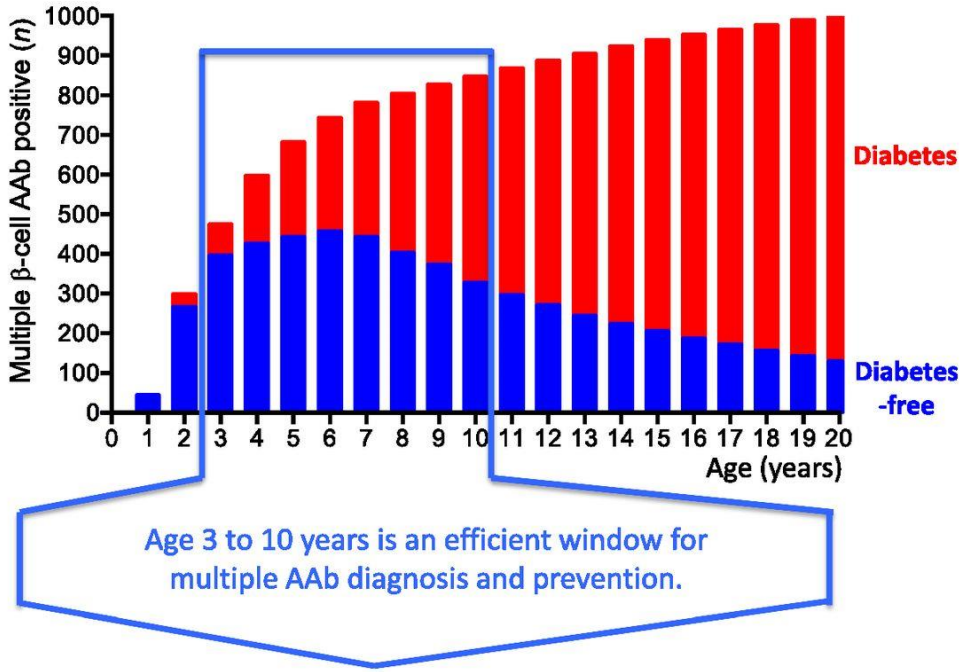
- Prevention
- Cure - Insulin replacement
  - Feedback controlled, closed – loop autopilot
    - transplants
    - glucose sensor controlled pumps
      - artificial pancreas

Phases in natural history of diabetes



The Road to Type 1 Diabetes Prevention

Facts: Multiple β-cell AAb are diagnositc of early type 1 diabetes
Most multiple β-cell AAb cases appear before age 5
Progression rate to diabetes is 10% (older) to 15% (younger) per year



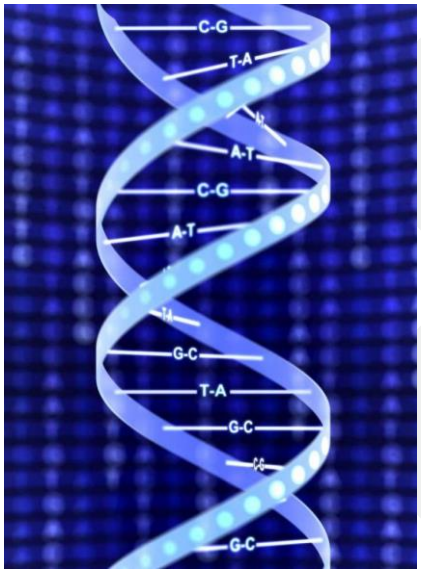
Requirements:
Cost-effective efficient diagnostic test and strategy
Staging of glycemia (normal through diabetic)
Stage-appropriate therapies for trials in 3- to 10-year-olds
Biomarkers of progression and response to therapy
Alternative therapy for failures

Screening

- **Using two different screening approaches**
- The first is using ***genetic risk assessments***, and the second is
- ***islet autoantibody screening***.
- So, if we think about future directions for screening from today, stepping forward, one approach can be
- genetic risk assessments, which will be incorporated into universal newborn screening programs.
- a second would be islet autoantibody testing in primary care offices, or through home-based testing as part of preventative care.

Genetics

- **Polymorphisms of multiple genes are reported to influence the risk of type 1A diabetes**
- including HLA-DQalpha, HLA-DQbeta, HLA-DR, preproinsulin, the *PTPN22* gene, CTLA-4, interferon-induced helicase, IL2 receptor (CD25), a lectin-like gene (KIAA0035), ERBB3e, and undefined gene at 12q)
- **The major susceptibility genes for type 1 diabetes are in the HLA region on chromosome 6p**



- Over 90 percent of patients with type 1 diabetes carry DR4, DQB*0302, and/or DR3, DQB*0201 the risk for islet autoimmunity drastically increased in DR3/4-DQ2/DQ8 siblings who shared both HLA haplotypes identical by descent with their diabetic proband sibling
- - suggesting that **HLA genotyping at birth may identify individuals** at very high risk of developing type 1 diabetes before the occurrence of clear signs of islet autoimmunity and type 1 diabetes onset

- **The lifelong risk of type 1 diabetes is markedly increased in close relatives of a patient with type 1 diabetes**,
- approximately 6 % in offspring, 5 % in siblings, and 50 % in identical twins

Prediction -Time to progression

- There is a variability in progression of B cell injury causes a major therapeutic dilemma with respect to intervention during the preclinical period. Early therapy is likely to preserve more beta cells but may also result in some patients being treated unnecessarily
- The titer of IAA has been used to predict the time to onset of type 1 diabetes, particularly in children younger than five years of age
    - In a study of 4505 healthy schoolchildren, measurement of autoantibodies (GAD, IAA, and IA2/ICA512) prospectively identified all children who developed diabetes within eight years
- TEDDY is an international multi-center trial researching the potential causes T1D in children
- September 2004 – September 2025
- Children up to 4 months of age with specified HLA HLA-DR-DQ genotypes in the general population or having a first-degree relative affected with T1DM are enrolled and followed longitudinally for 15 years approximately 420,000 infants were screened to identify people at risk

PREVENTION AND REVERSAL STRATEGIES

- **Several *immunosuppressive* and *immunomodulatory* agents and other drugs have been given either alone or in combination to decrease the immune-mediated destruction of beta cells that occurs in type 1 diabetes**
- **Azathioprine**
- **Mycophenolate mofetil**
- **Cyclosporine**
- **Anti-CD3 antibodies**
- **Teplizumab** A monoclonal antibody, termed hOKT3gl (Ala-Ala) (teplizumab, is the first disease-modifying immunotherapy for type 1 diabetes to receive regulatory approval in the United States

- **Recently diagnosed type 1 diabetes**

FDA NEWS RELEASE

FDA Approves First Drug That Can Delay Onset of Type 1 Diabetes

More Press Announcements

For Immediate Release: November 17, 2022

Español

Today, the U.S. Food and Drug Administration approved Tzield (teplizumab-mzwv) injection to delay the onset of stage 3 type 1 diabetes in adults and pediatric patients 8 years and older who currently have stage 2 type 1 diabetes.

PROTECT: Randomized, multicenter, 78-week, double-blind, Phase 3, placebo-controlled study

✓ Eligible patients

- Children and adolescents (8–17 yrs)
- ≤6 weeks of diagnosis with Stage 3 T1D*
- ≥1 T1D-associated autoantibody†
- Peak C-peptide ≥0.2 pmol/mL

✕ Exclusion criteria

- Major systemic illness
- Active infection
- History of chronic infection

Treatments

- **Randomized 2:1 → teplizumab : placebo**
- **Two 12-day courses 26 weeks apart**
- Due to COVID-19 pandemic restrictions, some patients received their second course of study drug at ~Week 52 (teplizumab, n=16: placebo, n=12)

1 Primary endpoint

β-cell preservation (change from baseline in stimulated C-peptide level) at Week 78§

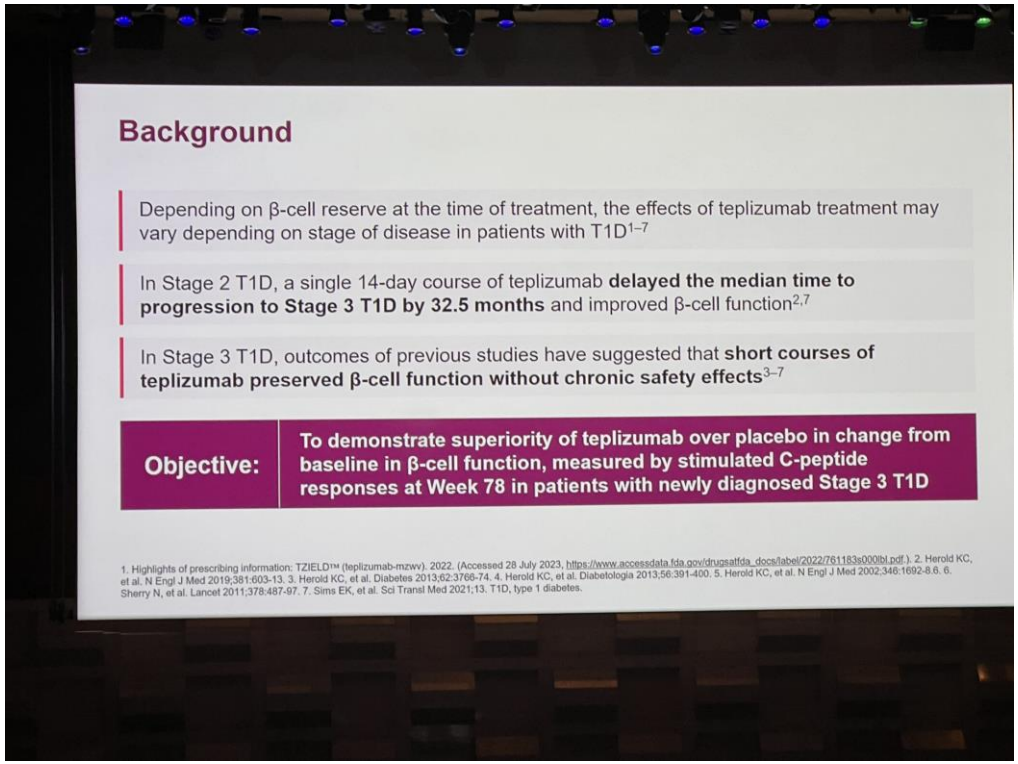
2 Secondary endpoints

- Mean total daily insulin dose
- Time in range¶
- HbA1c
- Clinically important hypoglycemic events**
- Safety

Exploratory endpoint

Clinical remission: HbA1c ≤6.5% and insulin daily dose ≤0.25 units/kg/d)

*Diagnosed using American Diabetes Association criteria. †Anti-GAD65, anti-ZnT8, anti-insulin, islet cell antibody, or anti-IA-2. Study investigators maintained glycemic control by treating to recommended target glucose levels HbA1c <7% (<53 mmol/mol). §C-peptide levels were determined from area under the concentration–time curve (AUC) during a 4-hour mixed meal tolerance test and calculated using trapezoidal rule. ¶Glucose 70–180 mg/dL (3.9–10 mmol/L). **Blood glucose <54 mg/dL (3.0 mmol/L) and/or episodes of severe hypoglycemia requiring external assistance. HbA1c, hemoglobin A1c; T1D, type 1 diabetes.


Background
Depending on β-cell reserve at the time of treatment, the effects of teplizumab treatment may vary depending on stage of disease in patients with T1D[1–7]
In Stage 2 T1D, a single 14-day course of teplizumab **delayed the median time to progression to Stage 3 T1D by 32.5 months** and improved β-cell function[2,7]
In Stage 3 T1D, outcomes of previous studies have suggested that **short courses of teplizumab preserved β-cell function without chronic safety effects**[3–7]
Objective:
To demonstrate superiority of teplizumab over placebo in change from baseline in β-cell function, measured by stimulated C-peptide responses at Week 78 in patients with newly diagnosed Stage 3 T1D
1. Highlights of prescribing information: TZIELD™ (teplizumab-mzwv). 2022. (Accessed 28 July 2023, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761183s000lbl.pdf.). 2. Herold KC, et al. N Engl J Med 2019;381:603-13. 3. Herold KC, et al. Diabetes 2013;62:3766-74. 4. Herold KC, et al. Diabetologia 2013;56:391-400. 5. Herold KC, et al. N Engl J Med 2002;346:1692-8.6. 6. Sherry N, et al. Lancet 2011;378:487-97. 7. Sims EK, et al. Sci Transl Med 2021;13. T1D, type 1 diabetes.

Primary endpoint: Preservation of β-cell function

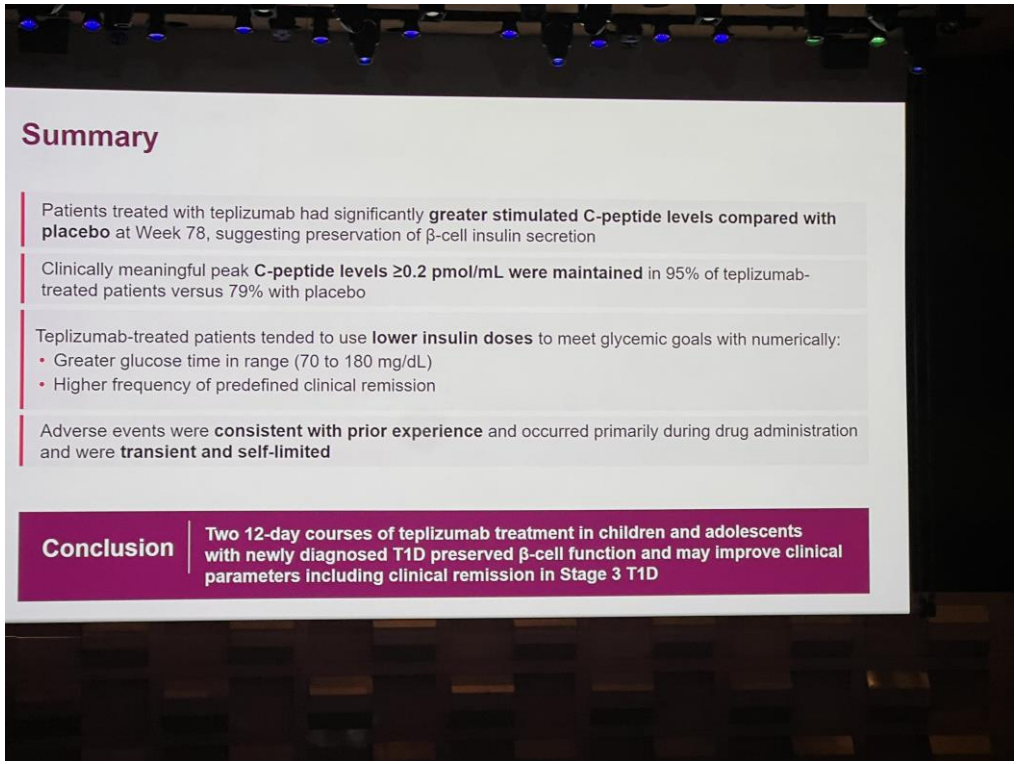
C-peptide ln(AUC+1) pmol/mL	Teplizumab (N=217)	Placebo (N=111)	Treatment difference (95% CI)*
Baseline: mean (SD; n)	0.54 (0.20; 217)	0.53 (0.17; 111)	
Week 78† mean (SD; n)	**0.46 (0.20; 188)**	**0.34 (0.21; 88)**	
LSMC from baseline	–0.09	–0.21	0.13 (0.09, 0.17)‡ **P<0.001**

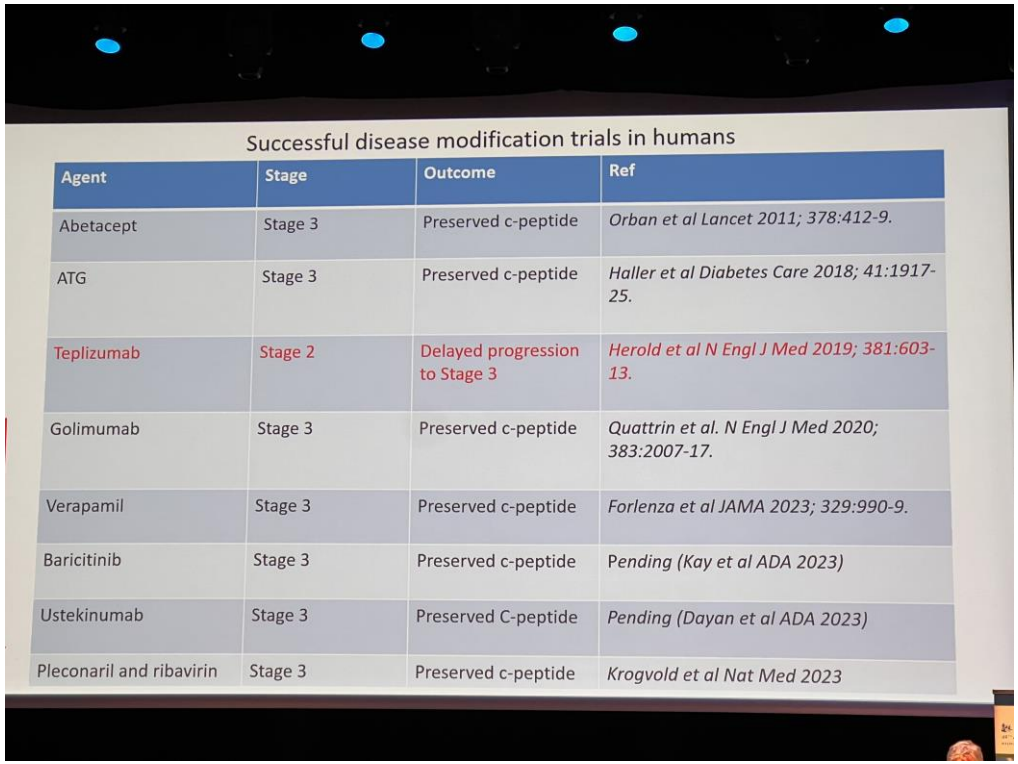
Outcome (at Week 78)	Teplizumab (N = 192)	Placebo (N = 97)
Peak C-peptide > 0.2 pmol/mL, % (95% CI)	**94.9 (89.5; 97.6)**	**79.2 (67.7; 87.4)**

Stimulated C-peptide Levels Area Under the Curve (ln(AUC+1)) Over Time

*Difference between teplizumab and placebo. †Missing data at Week 78 were multiply imputed using a pattern-mixture model under the missing not at random assumption. ‡Estimates and the P value were obtained from an ANCOVA model that included treatment, age group at randomization, and baseline C-peptide ln(AUC+1) as independent variables.
ANCOVA, analysis of covariance; AUC, area under the concentration-time curve; CI, confidence interval; LSMC, least squares mean change .


Insulin use
Teplizumab-treated patients used **lower insulin doses** to meet glycemic goals
Similar trends were observed in the pre-specified per-protocol population containing patients with ≥80% treatment compliance
Average daily insulin dose over time*
Least-squares mean daily insulin dose — units/kg/d
0.7
0.6
0.5
0.4
0.3
0.2
*P<0.05
**P<0.01
***P<0.001
Teplizumab
Placebo
Baseline
Week 12
Week 26
Week 39
Week 52
Week 65
Week 78
Teplizumab 126 130 119 94 101 95 98
Placebo 63 75 55 42 47 50 50
Insulin pump users
Teplizumab 11% 23% 26% 33% 37% 44% 48%
Placebo 12% 19% 32% 35% 48% 55% 53%
*Estimates are obtained from a mixed model of repeated measures model with treatment group, visit, and age group at randomization baseline values as fixed effects, and a treatment by visit interaction term.


Summary
Patients treated with teplizumab had significantly greater stimulated C-peptide levels compared with placebo at Week 78, suggesting preservation of β-cell insulin secretion
Clinically meaningful peak C-peptide levels ≥0.2 pmol/mL were maintained in 95% of teplizumab-treated patients versus 79% with placebo
Teplizumab-treated patients tended to use lower insulin doses to meet glycemic goals with numerically:
• Greater glucose time in range (70 to 180 mg/dL)
• Higher frequency of predefined clinical remission
Adverse events were consistent with prior experience and occurred primarily during drug administration and were transient and self-limited
Conclusion
Two 12-day courses of teplizumab treatment in children and adolescents with newly diagnosed T1D preserved β-cell function and may improve clinical parameters including clinical remission in Stage 3 T1D

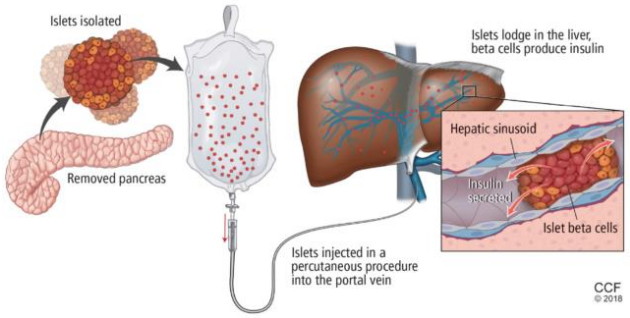


Successful disease modification trials in humans

Agent	Stage	Outcome	Ref
Abetacept	Stage 3	Preserved c-peptide	*Orban et al Lancet 2011; 378:412-9.*
ATG	Stage 3	Preserved c-peptide	*Haller et al Diabetes Care 2018; 41:1917-25.*
Teplizumab	Stage 2	Delayed progression to Stage 3	*Herold et al N Engl J Med 2019; 381:603-13.*
Golimumab	Stage 3	Preserved c-peptide	*Quattrin et al. N Engl J Med 2020; 383:2007-17.*
Verapamil	Stage 3	Preserved c-peptide	*Forlenza et al JAMA 2023; 329:990-9.*
Baricitinib	Stage 3	Preserved c-peptide	*Pending (Kay et al ADA 2023)*
Ustekinumab	Stage 3	Preserved C-peptide	*Pending (Dayan et al ADA 2023)*
Pleconaril and ribavirin	Stage 3	Preserved c-peptide	*Krogvold et al Nat Med 2023*

Beta-Cell Replacement (Islet Transplantation)

- Whole pancreas transplantation is not a viable solution; surgically, it is an aggressive and invasive procedure associated with comorbidities – except in addition to kidney transplant
- islet transplantation is considered a relatively safe procedure – usually via portal vein
- A donor pancreas contains approximately one million islets, but after purification and culture only about half of this number is successfully isolated
- As islets are avascular when transplanted, they are susceptible to apoptosis in the liver in the first few days after the procedure. Next, islets are exposed to oxidative stress, inflammation, including instant blood-mediated inflammatory reaction (IBMIR) and rejection from alloimmune and autoimmune mechanism
- leads to a less than 60% of transplanted islets successfully engrafted into the liver
- Although Islet transplantation has consistently improved over the past 20 years However, it remains a limited and inefficient therapy for the reasons mentioned previously
- Additionally, currently prolonged graft survival is achieved by using continuous immunosuppressive drugs, which when used continuously have a toxic effect.
- Currently only offered to those with complete hypoglycemic awareness



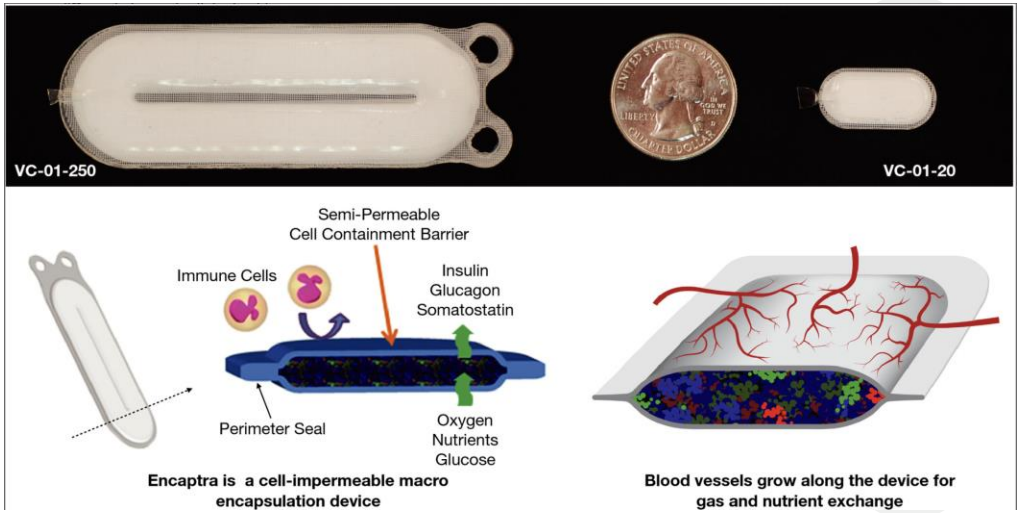
Beta-Cell Replacement (Islet Transplantation) - Encapsulation

- **Encapsulation holds the potential to shield islet or stem cells from immune attacks, using a selectively permeable and stable membrane that allows passive diffusion of glucose, insulin, oxygen, and other nutrient exchange, while preventing direct contact with immune cells**

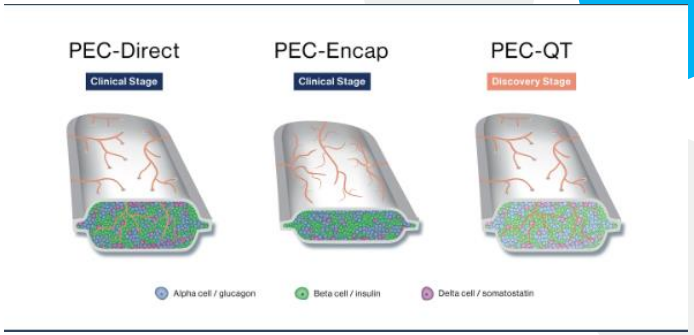
- In this sense, two approaches in encapsulations were modelled.
- **macroencapsulation** a large mass of islets is encapsulated, usually using hollow fibers or membranes
    - Larger diameter fibers limit the diffusion of nutrients which leads to cell death. Smaller diameter fibers, on the other hand, improve nutrient diffusion but make implantation harder as the risk of potential fracture is increased
    - The main disadvantages of this strategy rely on the poor oxygen diffusion through the fibers, which can compromise islet viability
- **Microencapsulation**
    - involves the encapsulation of one or a small number of islets into one semipermeable microcapsule usually measuring less than 1mm
    - Microencapsulation Although promising, microencapsulation viability in humans is still questionable and remains unsuccessful.

Viacyte

- **ViaCyte** is focused on pluripotent stem cells (PSC)
- developed advanced stem cell growth media and conditions for expanding as well as cryopreserving undifferentiated pluripotent stem cells
- pancreatic endoderm cells (also known as pancreatic precursor cells; PEC-01 cells Once implanted under the skin of a patient, PEC-01 cells, which are contained within an implantation device, have been designed to mature into functional beta cells



Viacyte



- Using gene editing on the pluripotent stem cell starting material offers the potential to protect implanted cells from the patient's immune system by ex vivo editing immune-modulatory genes in ViaCyte's CyT49 stem cell line – the CRISPR-Cas9 gene editing technology
- PEC-Direct
  - patients with type 1 diabetes with the highest risk of life-threatening acute complications. The direct vascularization of the implanted cells is intended to allow for robust and consistent engraftment but will necessitate the use of immune suppression therapy
- PEC-Encap
  - candidate as a functional cure for type 1 diabetes This device is also designed to prevent immune cells from directly contacting the implanted cells
- PEC-QT
  - ViaCyte's proprietary CyT49 pluripotent human stem cell line will be specifically engineered to avoid destruction by the patient's immune system, potentially eliminating the need for immunosuppressants

- ViaCyte and CRISPR Therapeutics formed a partn
edited allogeneic stem cell-derived therapies

Jul 11, 2022

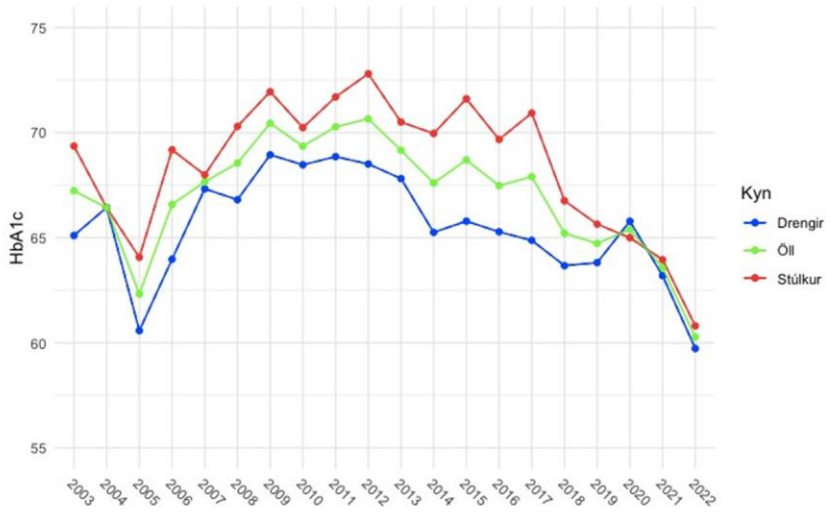
Vertex to Acquire ViaCyte, With the Goal of Accelerating its Potentially Curative VX-880 Programs in Type 1 Diabetes

- ViaCyte brings tools, technologies and assets with potential to accelerate development of VX-880, Vertex's fully differentiated, insulin-producing, stem cell derived islets -

- 157 BÖRN MEÐ INSÚLÍNHÁÐA SYKURSÝKI Í DAG Í MEÐFERÐ
- U.Þ.B 20 -25 GREINAST NÝ Á HVERJU ÁRI
- 87 % BARNA ERU Á DÆLU
- Nýgreind börn fara strax á sensor og innan nokkurra vikna á dælu en börn 5 ára og yngri fara strax á dælu

LANDSPÍTALI

SYKURSTJÓRNUN BARNA Á ÍSLANDI HEFUR ALDREI VERIÐ BETRI



Sykursýki er alvarlegur ólæknandi sjúkdómur

Stöðug aukning víðast hvar í heiminum

Mesta aukning í tíðni hjá smábörnum

Framfarir í tækni vekja von um bætta meðferð

Rannsóknir á stofnfrumum og á inngripum í

ónæmiskerfið við greiningu eru spennandi,

en ekki komin í meðferðarform

- Þrátt fyrir verulegar framfarir í lyfjaframleiðslu og tækjabúnaði er mannauðurinn, þ. e. vel þjálfað teymi
- sem starfar vel saman mikilvægasti þátturinn
- í að hjálpa sykursjúkum börnum og fjölskyldum
- þeirra að ná tökum á sjúkdómnum.

Takk fyrir