Teknoloji ve Diyabetin Kesişim Noktası: Yapay Pankreas Tedavisi

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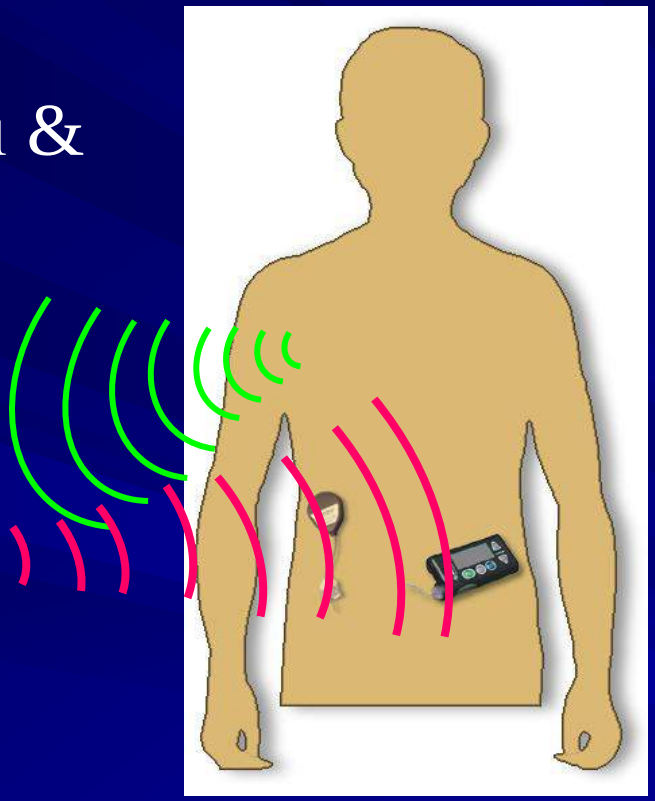
Konu Başlıkları

- Yapay pankreas kısa tarihçe
- Yapay pankreasın yapı taşları ve hız sınırlayıcı problemler

- En son yapılan çalışmalar
- Geleceğin sistemi için yapılan çalışmalar

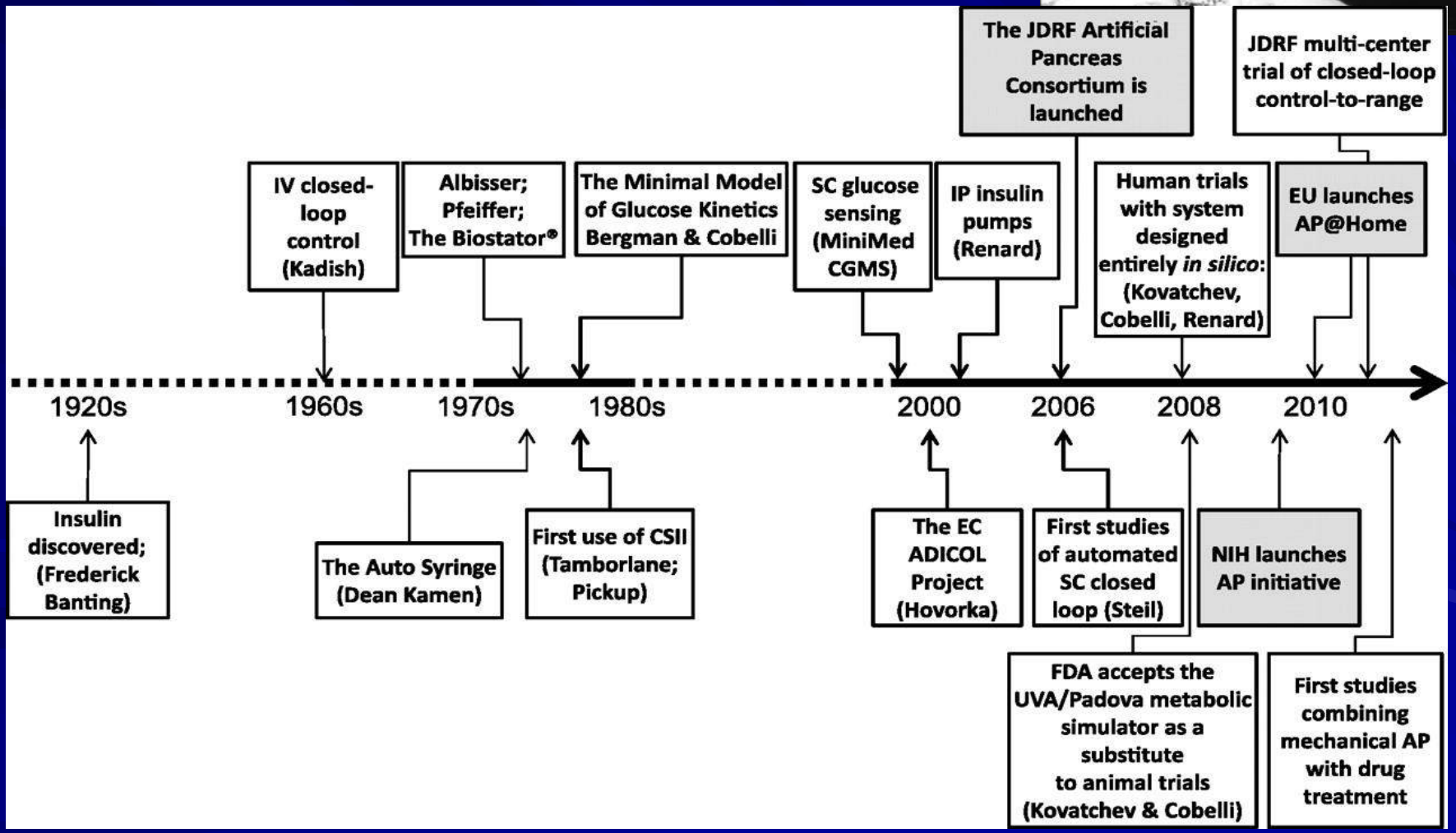
Yapay Pankreas (Closed Loop System)

- CGM
- Algoritma
- Insulin Pompası & Insülin



- CGM glukoz degerini bilgisayara gönderir, bigisayardaki algoritma glukoz degerine göre verilecek insülin miktarını hespladıktan sonra insülin pompasına iletilip infüze edilir.

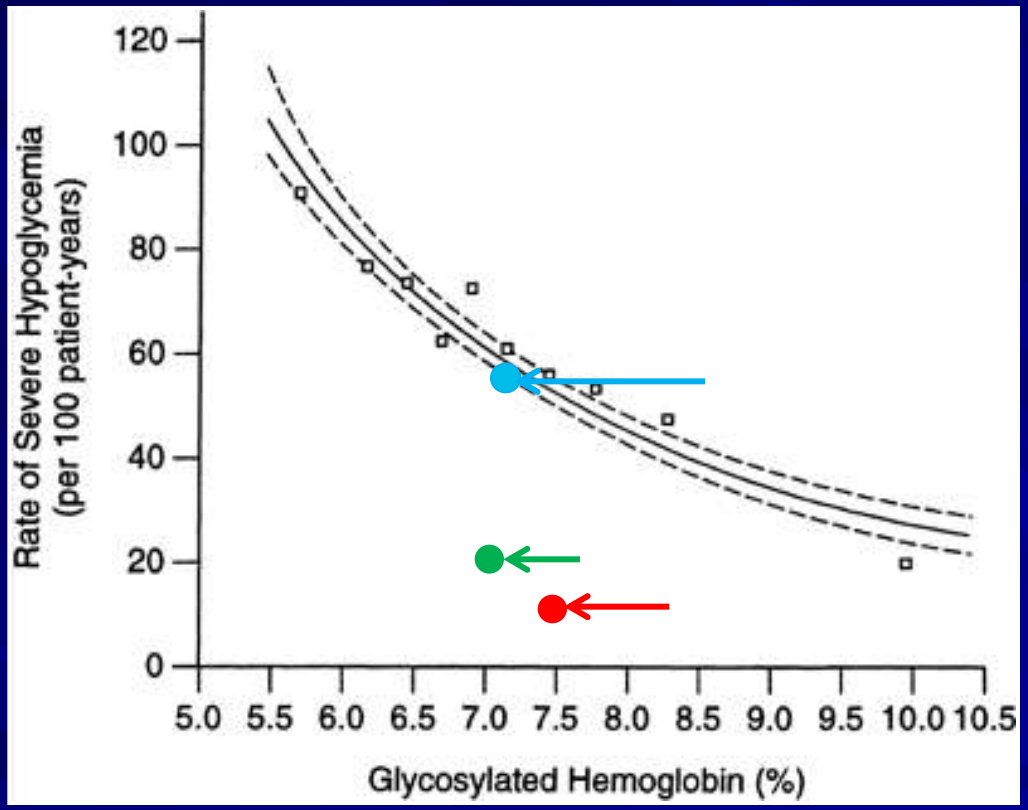
Yapay Pankreas Fikrinin Doğuşu



Neden Yapay Pankreasa İhtiyaç Var?

- Diyabet ve yok edilemeyen otoimmun reaksyon
- Erişilemeyen hedef: normal kan şekeri
- Demokles'in kılıcı: hipoglisemi

HbA1c ve Hipoglisemi: DCCT ve sonrası



- **DCCT (Adolescents & Adults)**
  Severe Hypo Rate: 62.0 per 100 pt-yrs, A1C: 9.0% → 7.2%
- **JDRF CGM (Adults, 1 Subject excluded)**
  Severe Hypo Rate: 20.0 per 100 pt-yrs, A1C: 7.6% → 7.1%
- **STAR 3 SAP (Pediatrics & Adults)**
  Severe Hypo Rate: 13.3 per 100 pt-yrs, A1C: 8.3% → 7.5%

T1DExchange (Ped)
Severe Hypoglycemia common in participants with higher HbA1c.

Nathan et al. *The New Engl J Med*. 1993; 329(14); Tamborlane et al. *The New Engl J Med.* 2008;359:1464-1476.:Bergenstal et al. *N Engl J Med*. doi:10.1056/NEJMoa1002853: Battelino et al. *Diabetologia DOI 10.1007/s00125-012-2708-9 : Cengiz et al. Pediatric Diabetes 2013, 98(8):3411-9.*

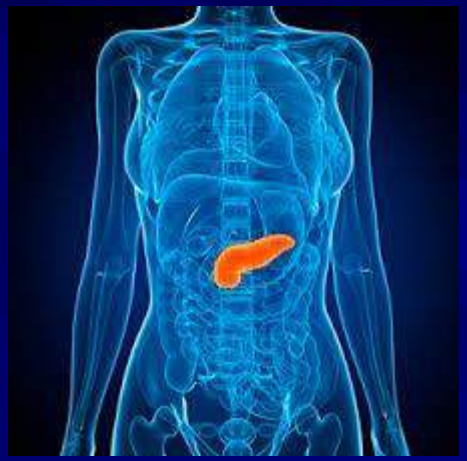
Sensorlü İnsülin Pompalarının Diyabet Tedavisine Katkısı

- HbA1c seviyesini hipoglisemiyi arttırmadan düşürebiliyor
  - STAR 3
  - Real Trend
  - SWITCH
- Hastalar ve klinisyenler üzerindeki diyabet tedavisi yükünü henüz azaltmış değil

Neden Yapay Pankreasa İhtiyaç Var?

- Diyabet ve yok edilemeyen otoimmun reaksyon
- Erişilemeyen hedef: normal kan şekeri
- Demokles'in kılıcı: hipoglisemi
- Diyabet = 24 saat kendisini unutturmayan hastalık

Elektronik Beta Hücresi



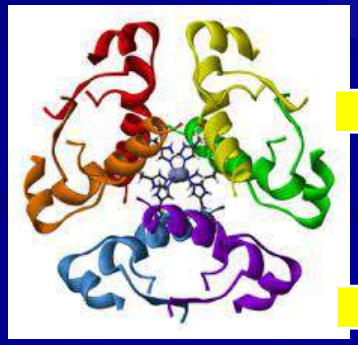
.Glucose sensing

.Insulin release, synthesis

.Glucose control

.Glucose sensor (CGM)

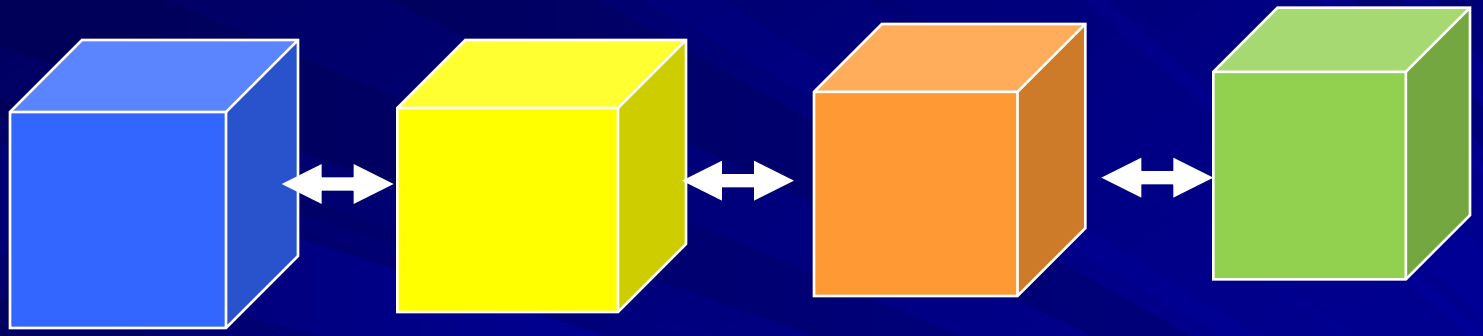
.Insulin dose calculation (Algorithm)



.Insulin delivery (Pump)

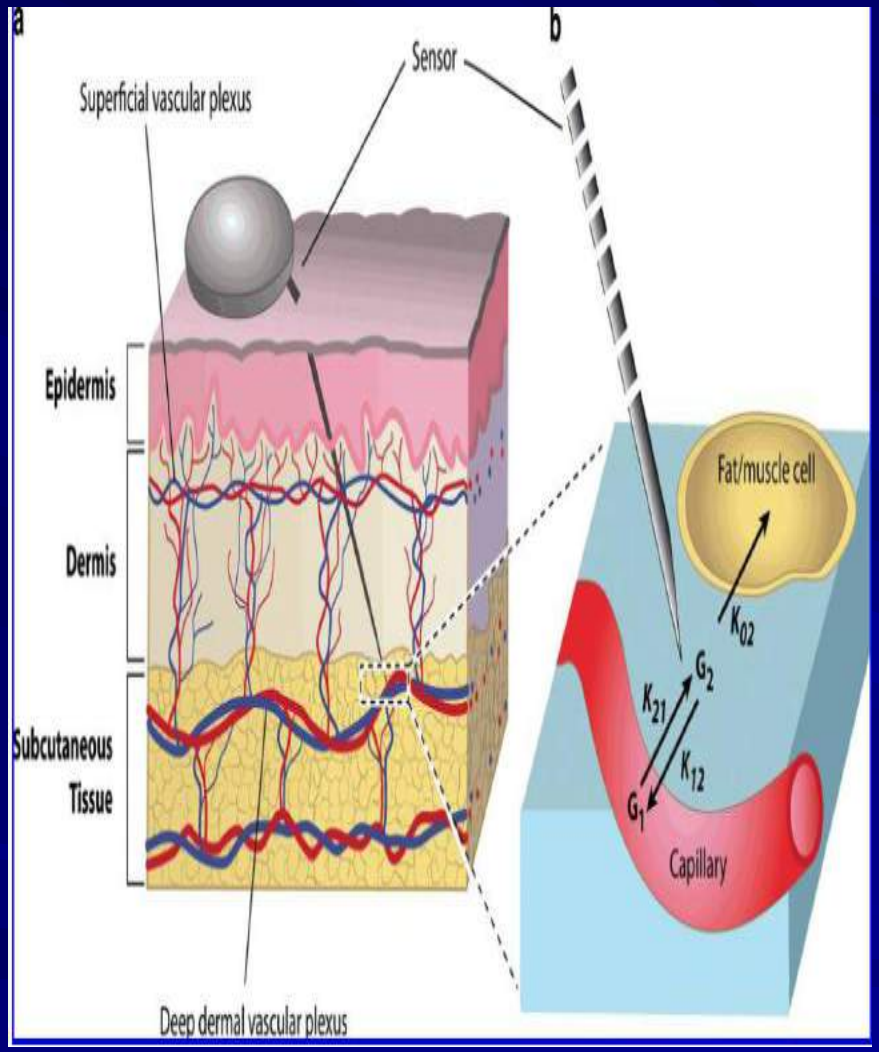
.New insulins

Yapay Pankreas



- CGM
- Algorithm
- Insulin Pump
- New Insulin Analogs

New glucose in town…CGM



Areas to improve

- Lag time
- Accuracy

-MARD: average error compared to a reference value

- Signal drop

Glucometer BG Testing

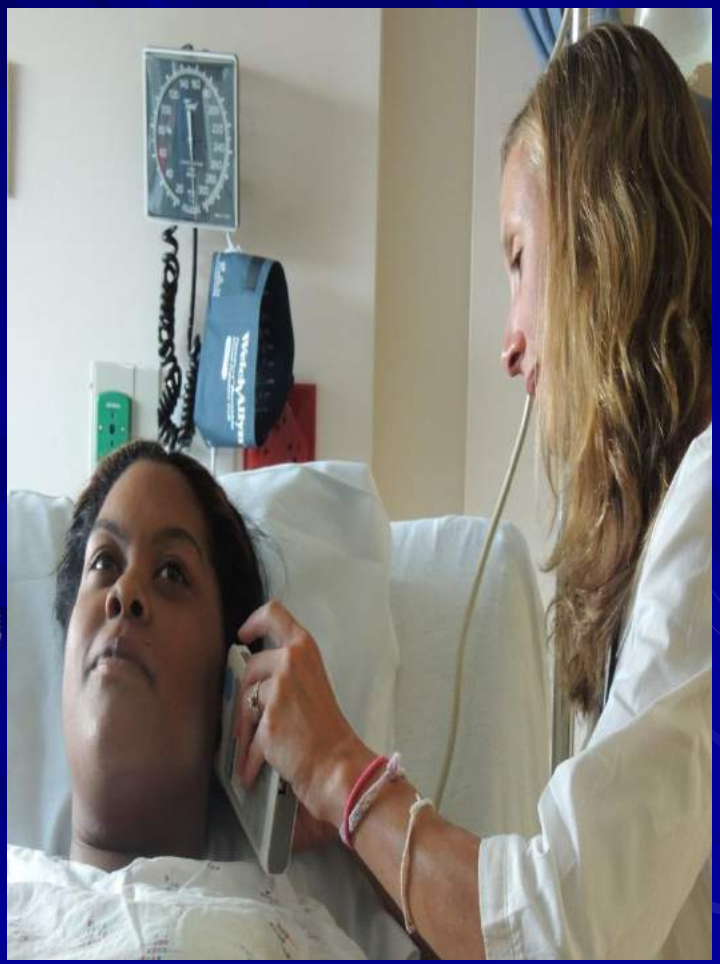
Cengiz & Tamborlane, DTT 2009

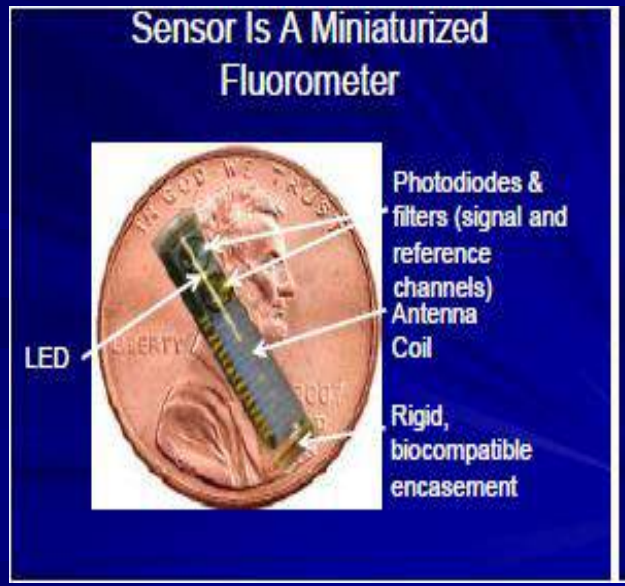
Commercially Available CGMs and Accuracy

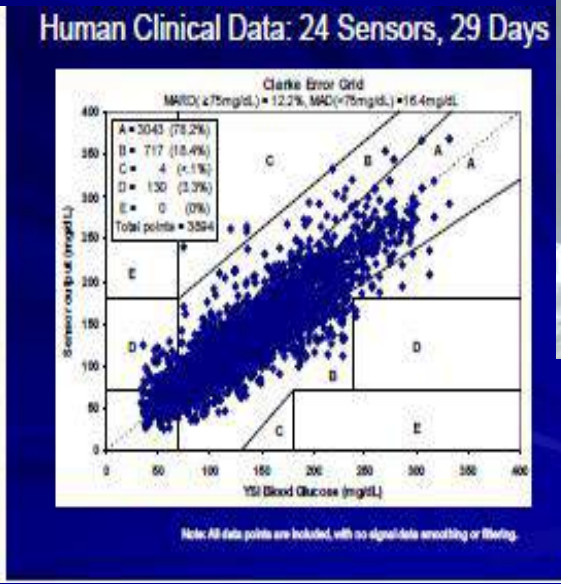
Continuous glucose-monitoring system	Mean absolute relative difference (MARD)	Precision absolute relative difference (PARD)
Abbott Navigator	12.4 ± 3.6%	10.1 ± 4.1%
Medtronic Enlite	16.4 ± 6.9%	16.7 ± 3.8%
Dexcom SEVEN PLUS	16.7 ± 3.8%	15.4 ± 4.2%
Dexcom G4 PLATINUM	10.9 ± 1.5%	7.3 ± 1.9%

Gelişmekte Olan CGM Teknolojisi

- Implanted Fluorescent
- Glucose Binding Protein
- Cell based glucose sensing
- Lazer kan sekerı



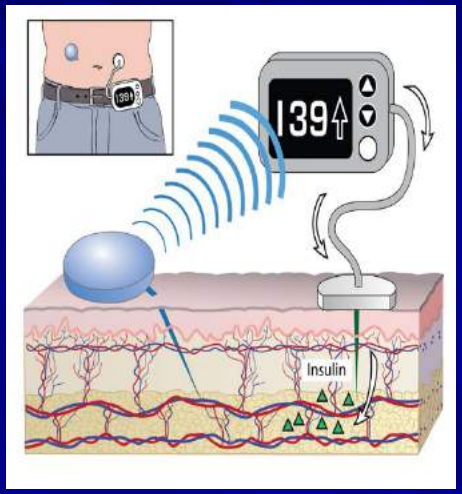




Insulin Pumps




Medtronic
Insulet-Omnipod
Roche
Tandem- TSlim



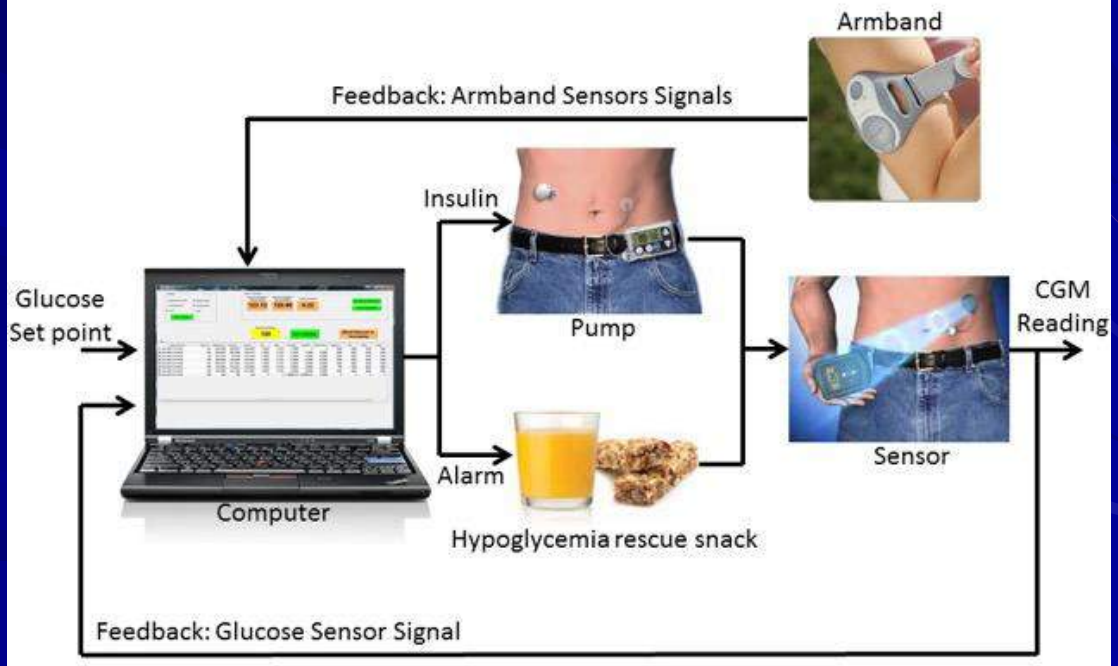
Patch Pumps

Closed-Loop Algorithms

- PID with Insulin Feedback
- Fuzzy Logic
- Model Predictive
- Model Predictive with Mutivariable Adaptive

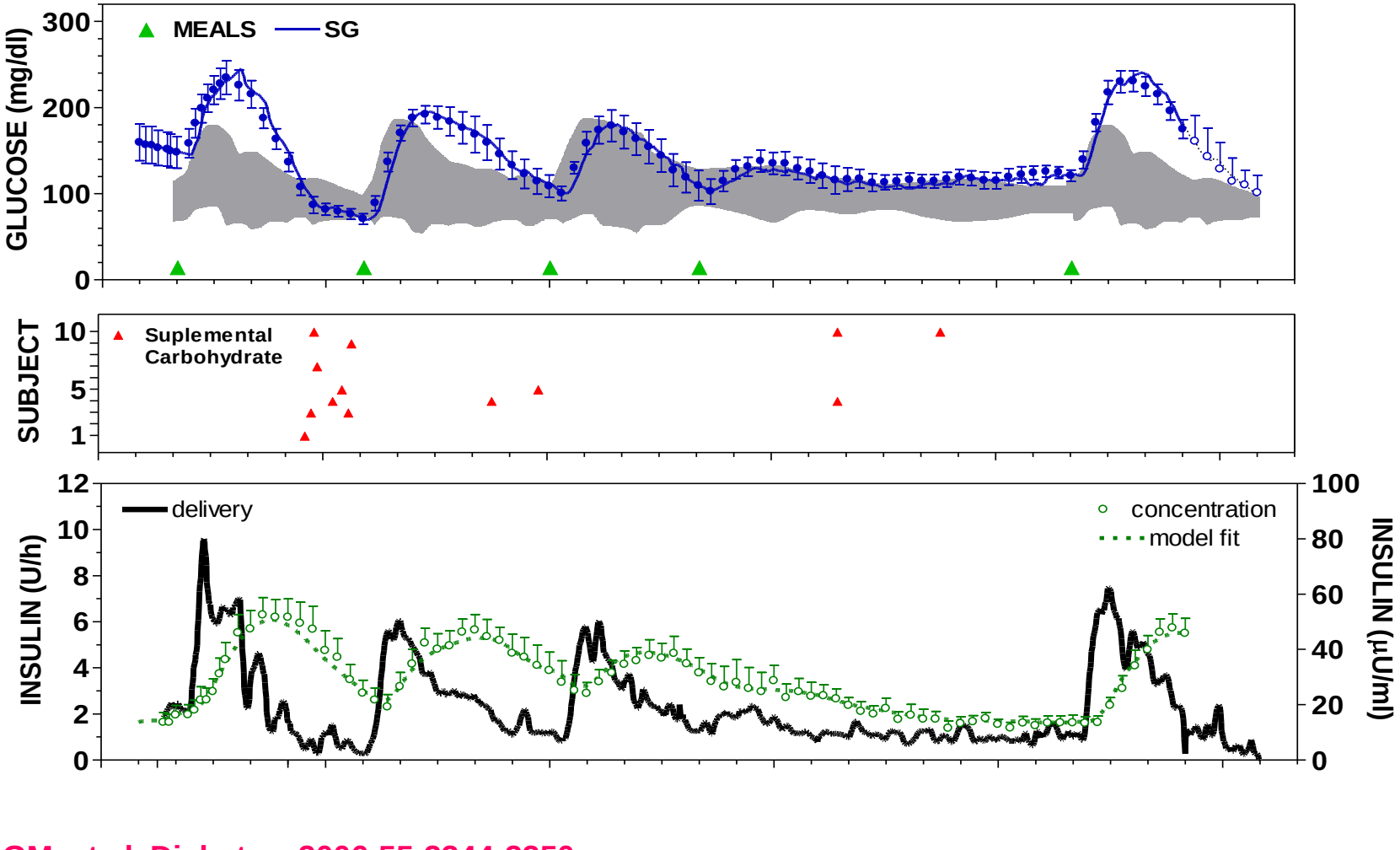
Multivariable Adaptive Closed-Loop Control of an Artificial Pancreas Without Meal and Activity Announcement

Kamuran Turksoy, BS,[1] Elif Seyma Bayrak, BS,[2] Lauretta Quinn, PhD, RN,[3] Elizabeth Littlejohn, MD,[4] and Ali Cinar, PhD[1,2]



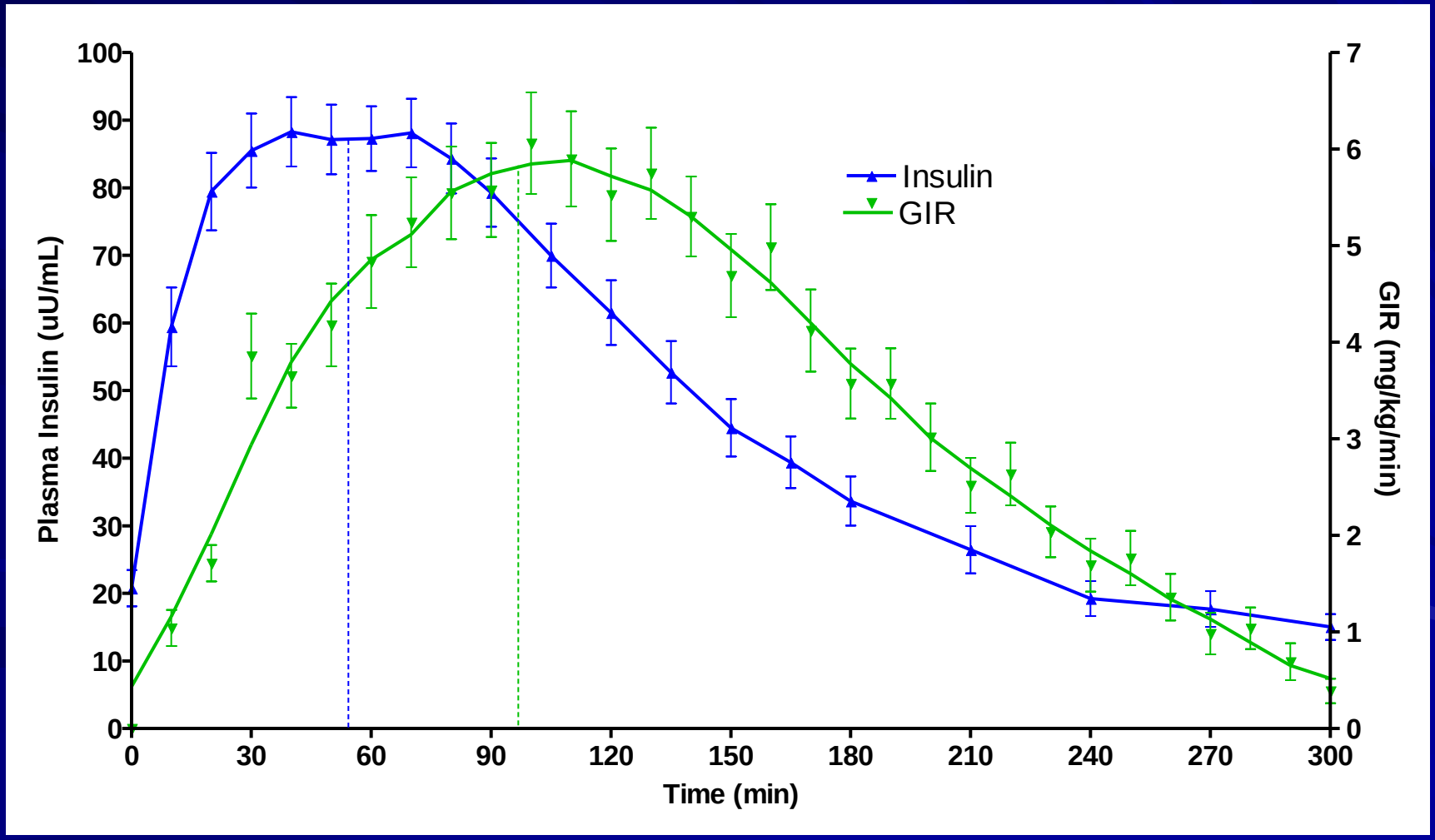
DIABETES TECHNOLOGY & THERAPEUTICS
Volume 15, Number 5, 2013

İnsülin ve Yapay Pankreas: Medtronic ePID UCLA araştırması



Steil GM, et al. Diabetes. 2006;55:3344-3350.

Pharmacokinetics vs. Pharmacodynamics of Rapid Acting Insulin Analogs

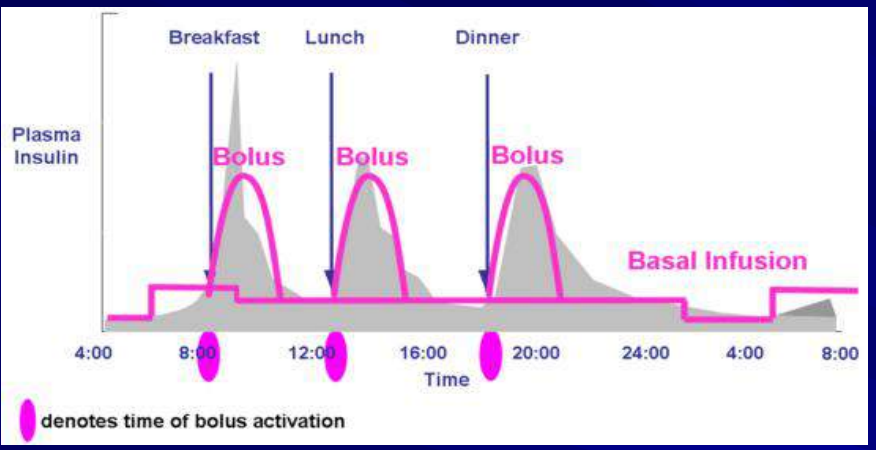


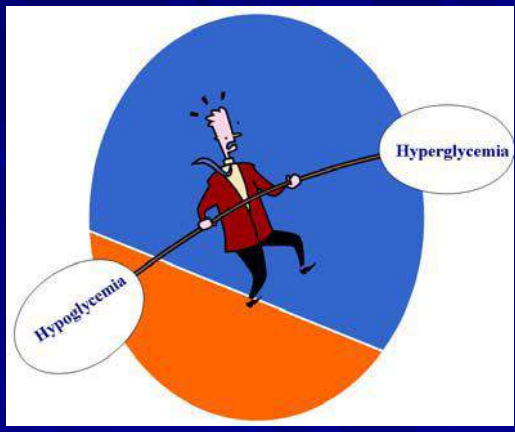
Subkutan Insülin Etkisindeki Tehlikeli Gecikmeler

1. Kimyasal yapıdan kaynaklanan gecikmeler

2. Dokuya bağlı gecikmeler

Insulin Tedavisi ve Kan Sekeri Seviyesini Dengelemek





Treatment of Hyperglycemia (High Blood Sugar)

Exogenous Insulin

Risk of Hypoglycemia (Low Blood Sugar)

Too little insulin or too much food

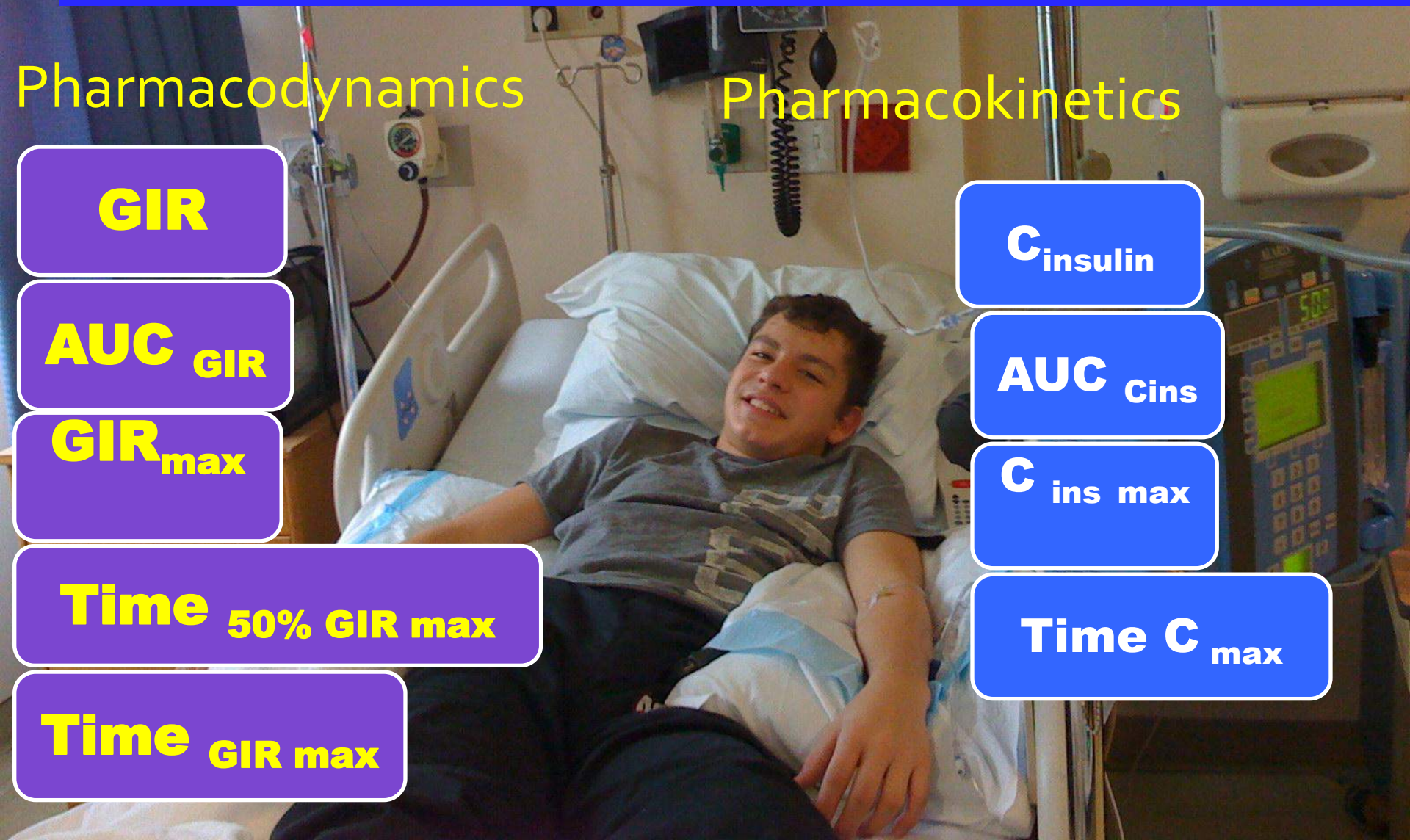
Too much insulin

YaIe İnsülin Farmakoloji Araştırmaları

- Pharmacokinetics & pharmacodynamics of rapid acting insulin analogs (PK-PD)
- Amaç

İnsülinin vücüda verildikten sonraki fonksyonunu etkileyen faktörleri T1D olan çocuklarda ve adolesan hastalarda «euglycemic clamp» metodu ile araştırmak

YaIe İnsülin Farmakoloji Araştırmaları: Euglycemic Clamp



Pharmacodynamics

- GIR
- AUC_{GIR}
- GIR_{max}
- $Time_{50\%\ GIR\ max}$
- $Time_{GIR\ max}$

Pharmacokinetics

- $C_{insulin}$
- AUC_{Cins}
- $C_{ins\ max}$
- $Time\ C_{max}$

İnsülin Clamp Çalışmaları Sonuçları

- Çocuklarda ve adolesan dönemde insülin etki mekanizması
- Değişik insülin analogları arasındaki farklar
- Ergenlikte insülin rezistansı
- Uzun etkili ve kısa etkili insülin beraber enjekte edildiğinde oluşan ters etkileşme
- İnsülin etki mekanızmasındaki gecikmeler

PK-PD
U-F.A.I.R. PROJESİ

Ultra-Fast Acting Insulin Research

(Ultra Hızlı İnsülin Projesi)

Amaç:

İnsülin etki mekanızmasını hızlandıracak yeni analog ve metodların araştırılması.

Yapay Pankreasa Tedavisine Uygulama

İnsülin hızını arttırmak için potansiyel çözümler

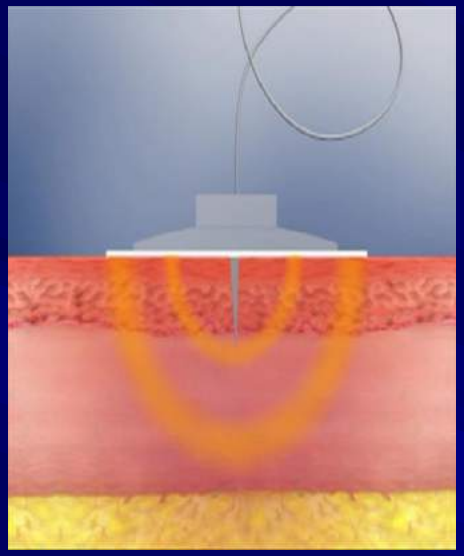
- Cilt ısını arttırmak
  - Insuline (InsuPatch)
- Ultra hızlı insülin
  - Novo Nordisk
  - Biodel
- Hyaluronidase
  - Halozyme
- Yeni metodlar

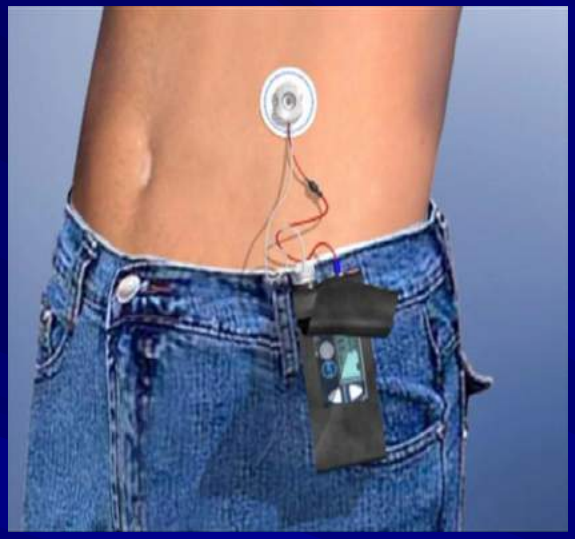
-Intra-dermal micro-needle infusion sets (BD)

-Inhaled insulin

-Intraperiotenal insulin delivery (DiaPort)

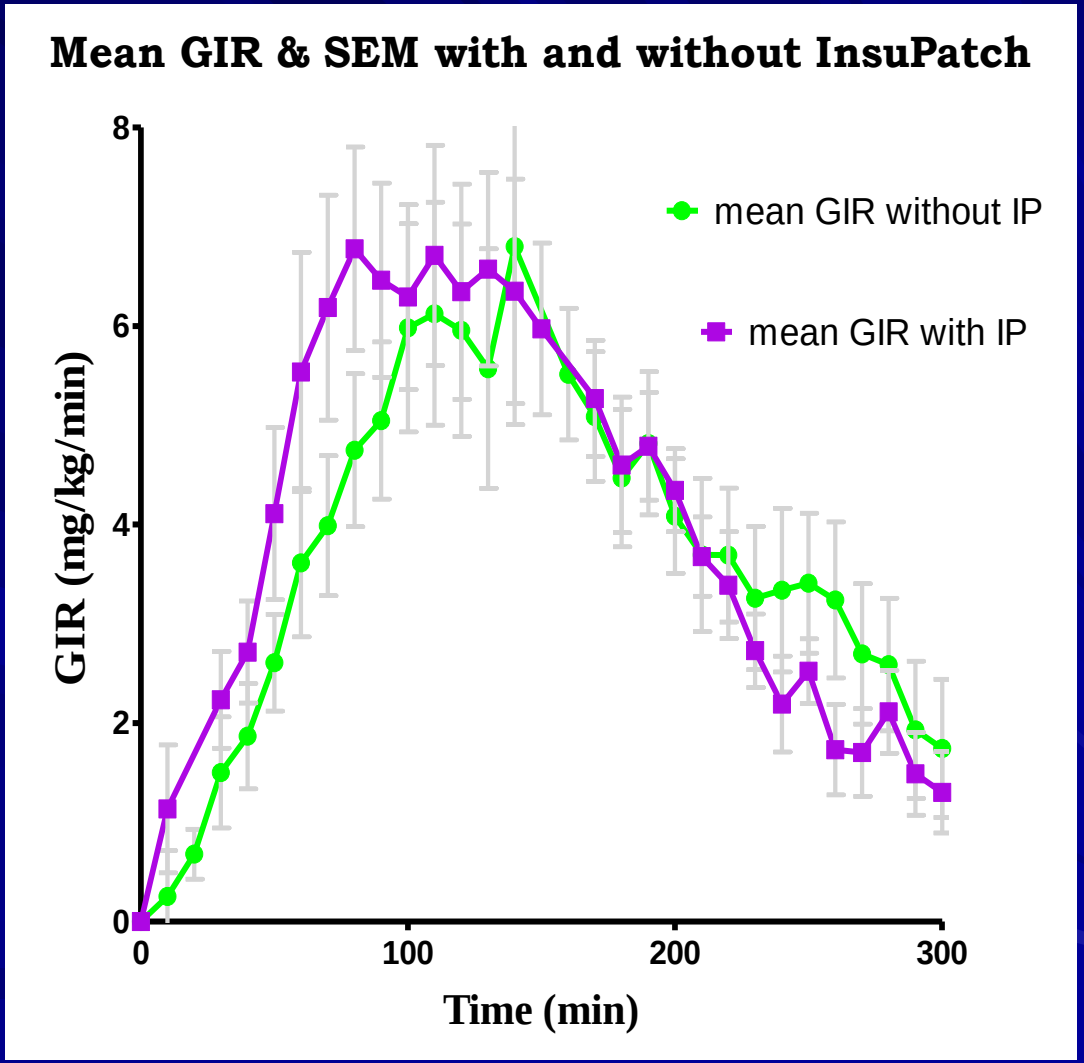
InsuPatch





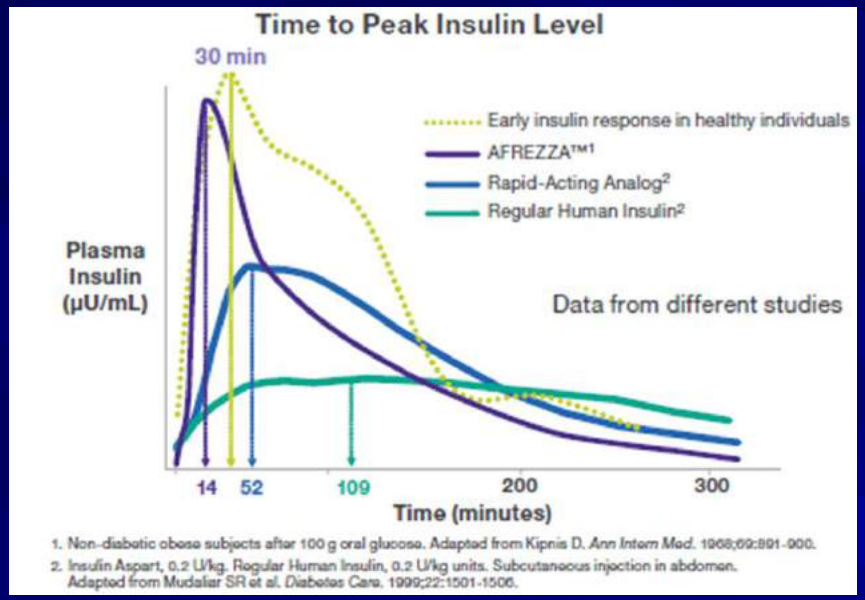
- The InsuPatch™ : insülin infüzyon sahasına kontrollü ısı tatbiki

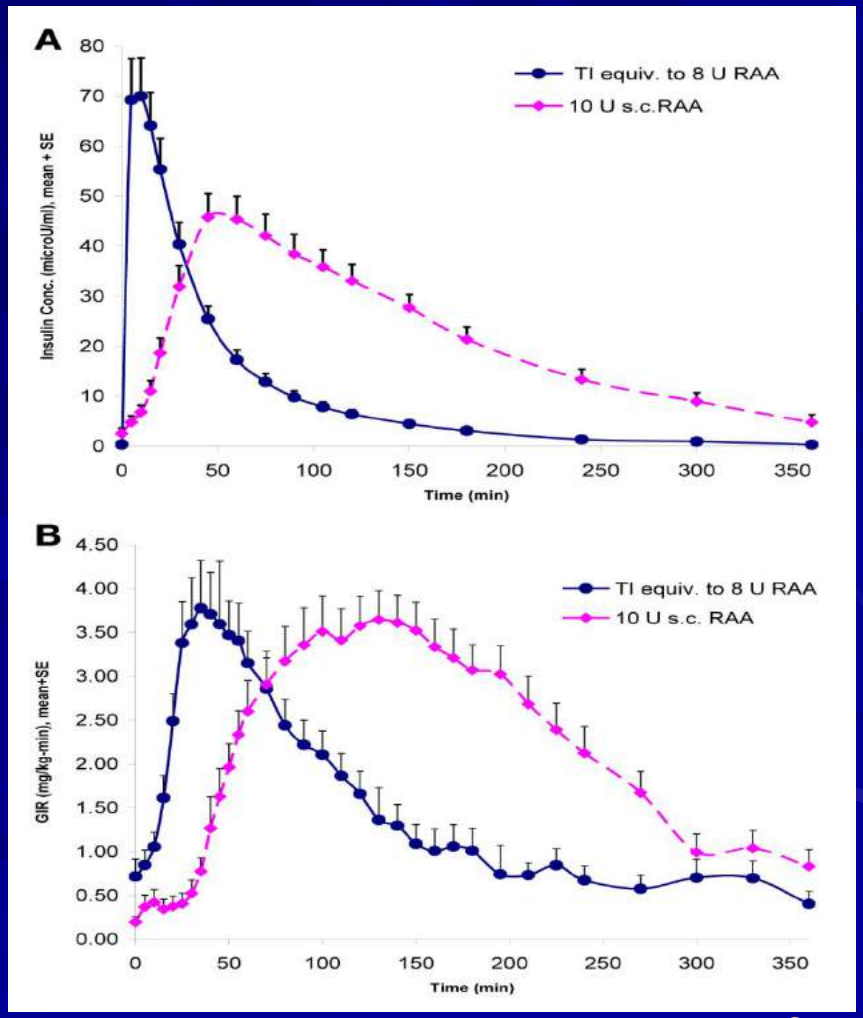
İnsülin Zaman Etki Grafiği : InsuPatch kullanılarak ve kullanılmadan



Hyaluronidase Mechanism of Action

Bir nefeslik insulin? Afrezza





Akıllı İnsülinler, yeni analoglar

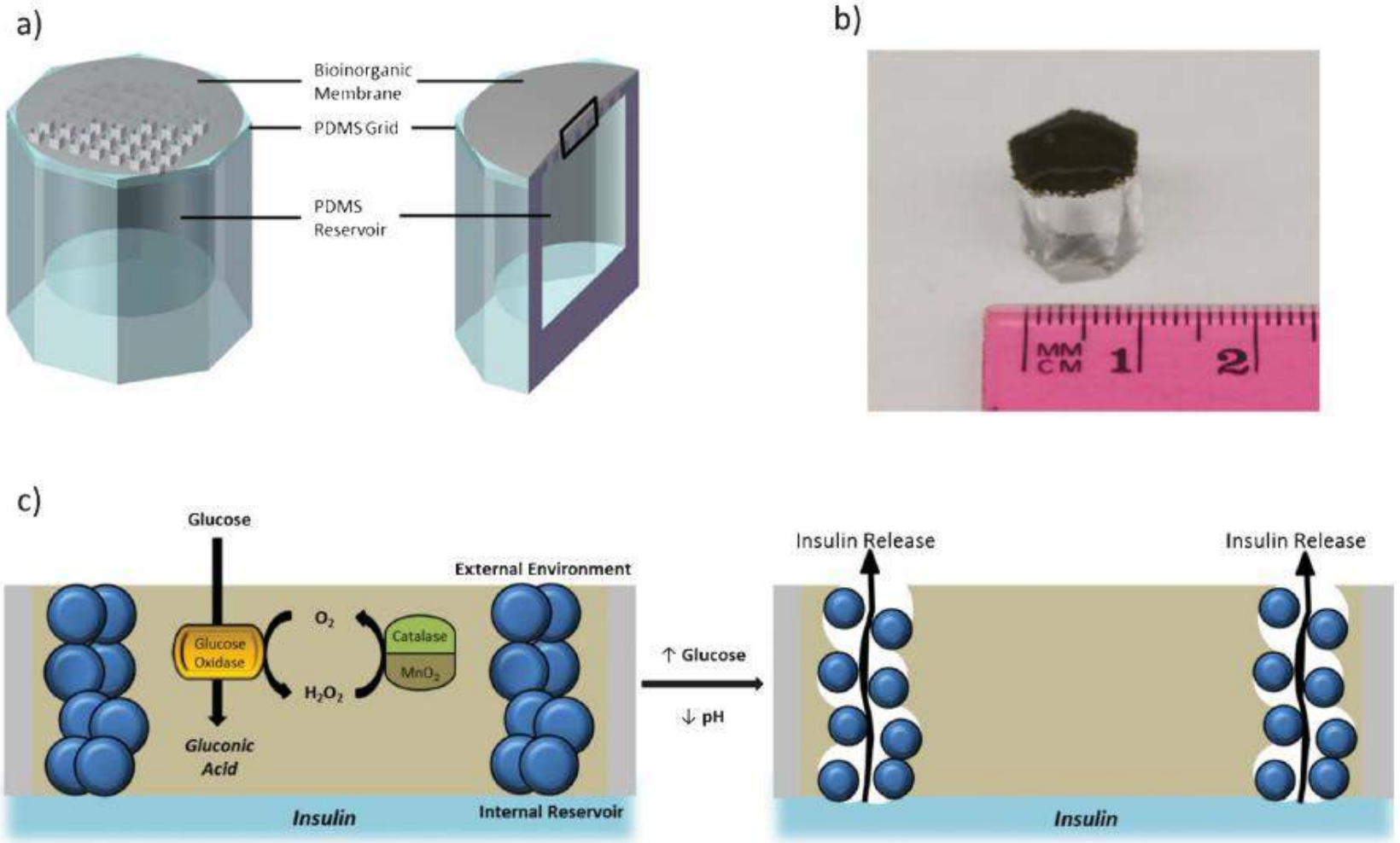
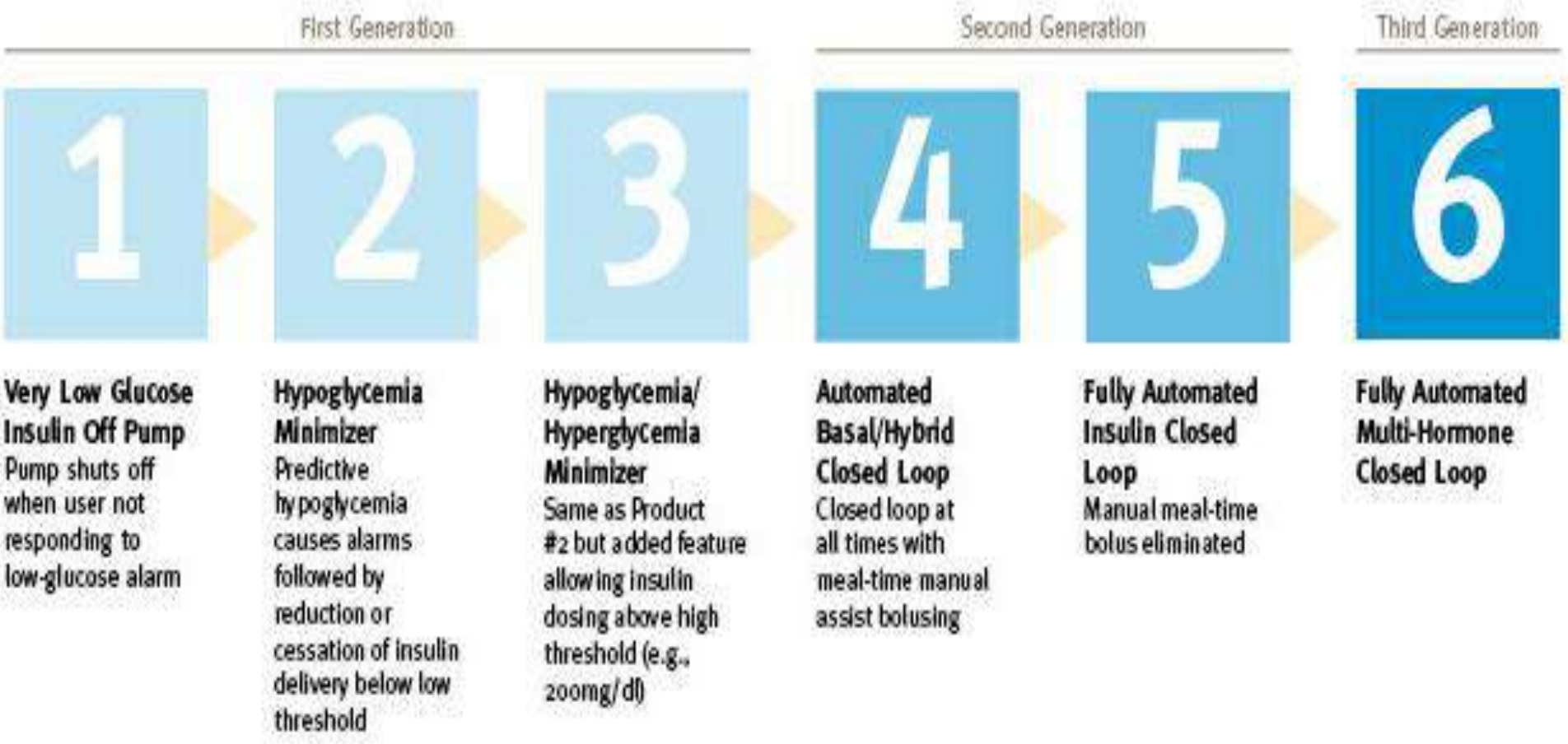
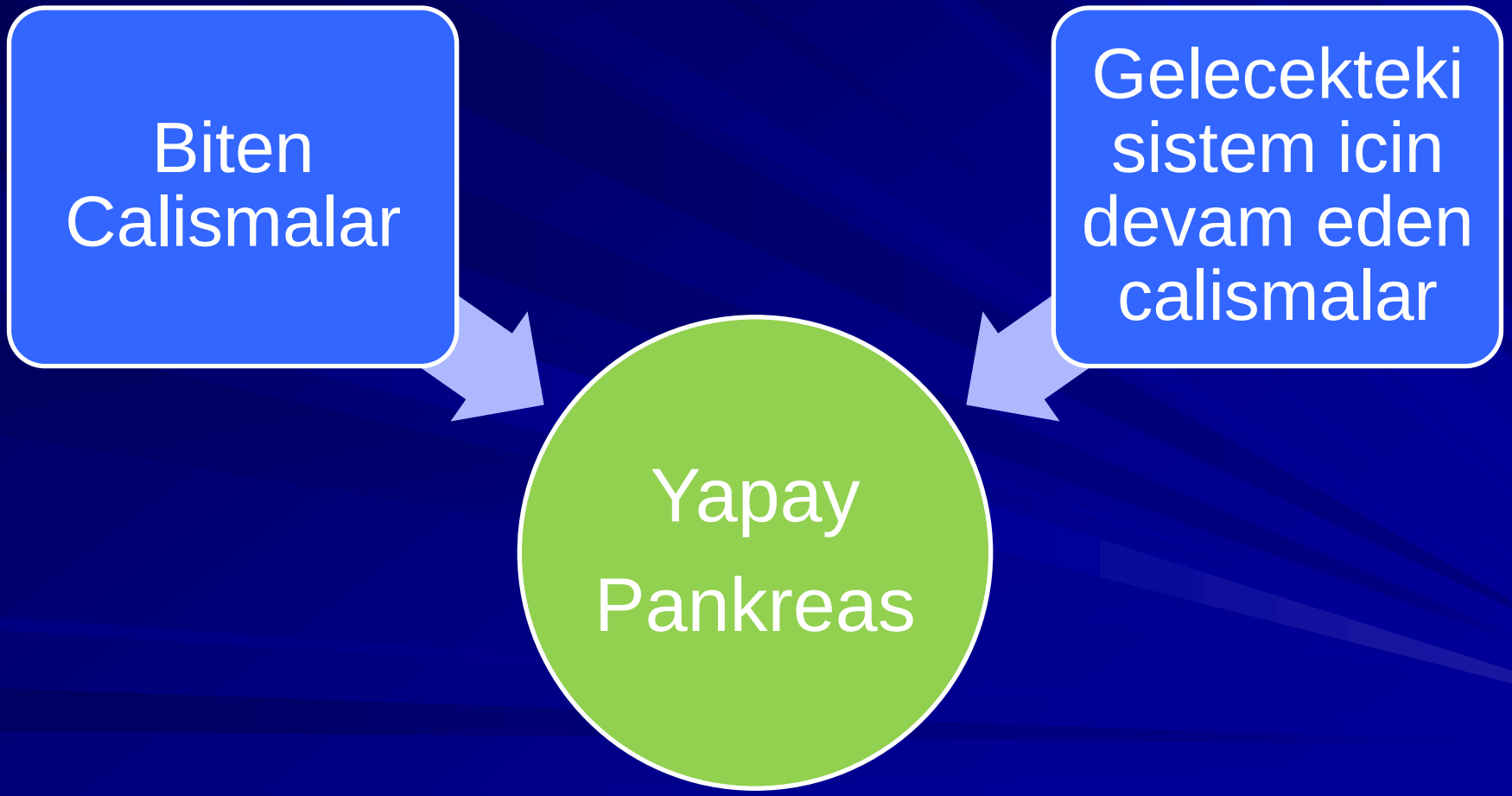


Fig. 1 (a) Schematic of the PDMS grid–gel microdevice with integrated bioinorganic membrane (with inset for (c)). (b) Size comparison of completed PDMS grid–bioinorganic gel membrane microdevices. (c) Cross-sectional diagram showing triggered insulin release in a glucose-rich environment to form open 'nano-pores'.

Yapay Pankreas Araştırmalarında Yolun Neresindeyiz ?

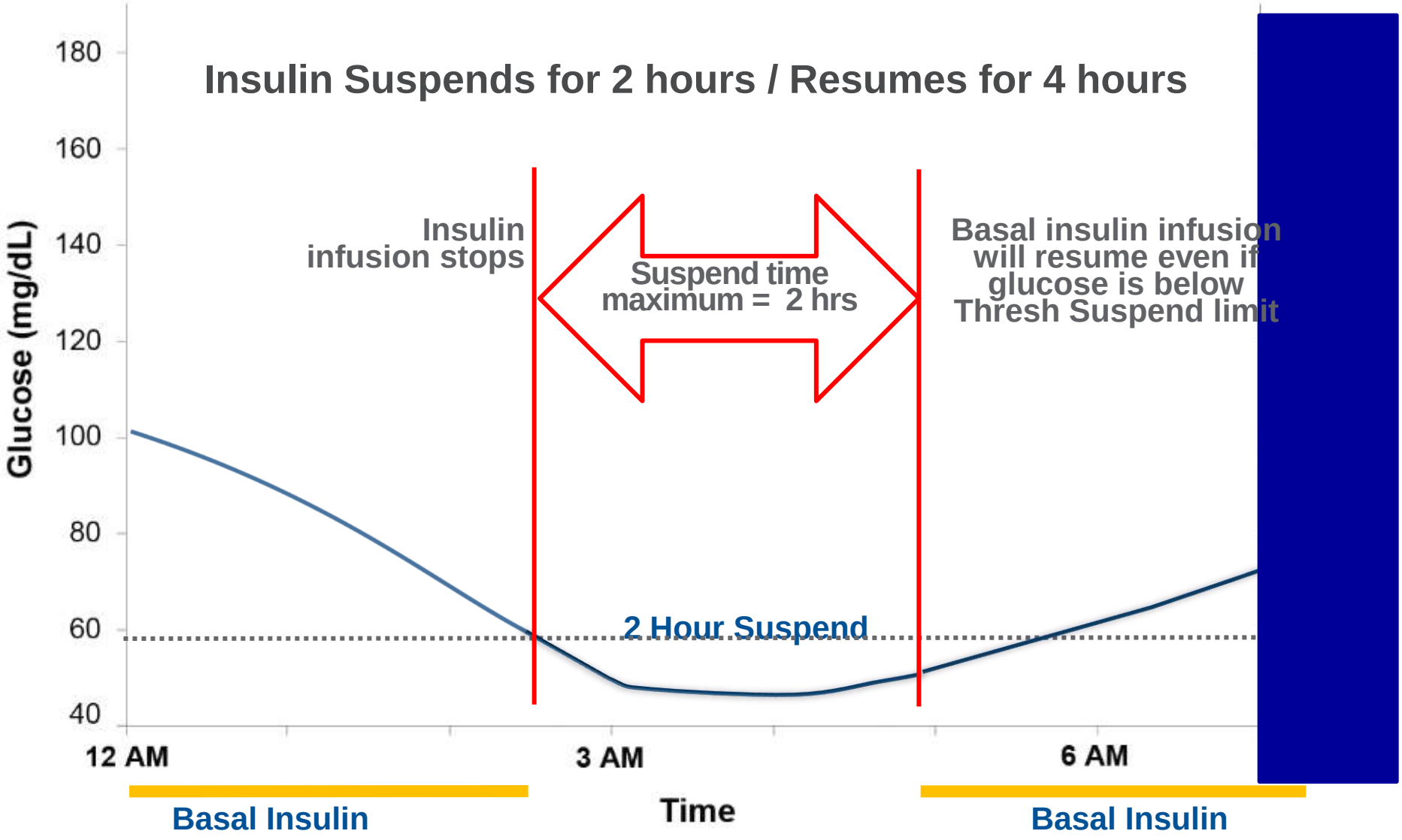
JDRF Yapay Pankreas Haritası



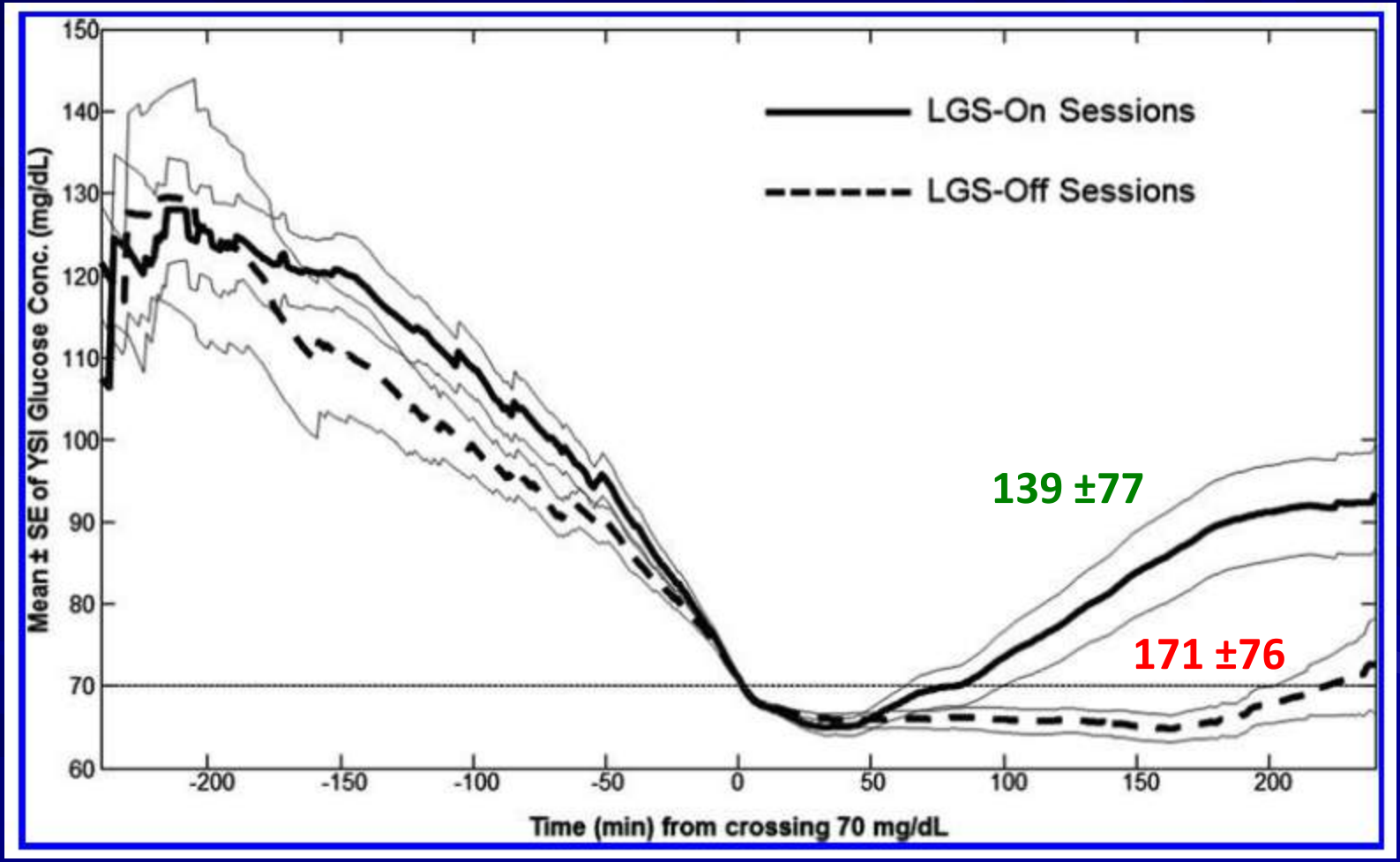

Biten Calismalar
Gelecekteki sistem icin devam eden calismalar
Yapay Pankreas

Example of Threshold Suspend Cycle

Automatically suspends insulin delivery if sensor glucose reaches the user-set limit

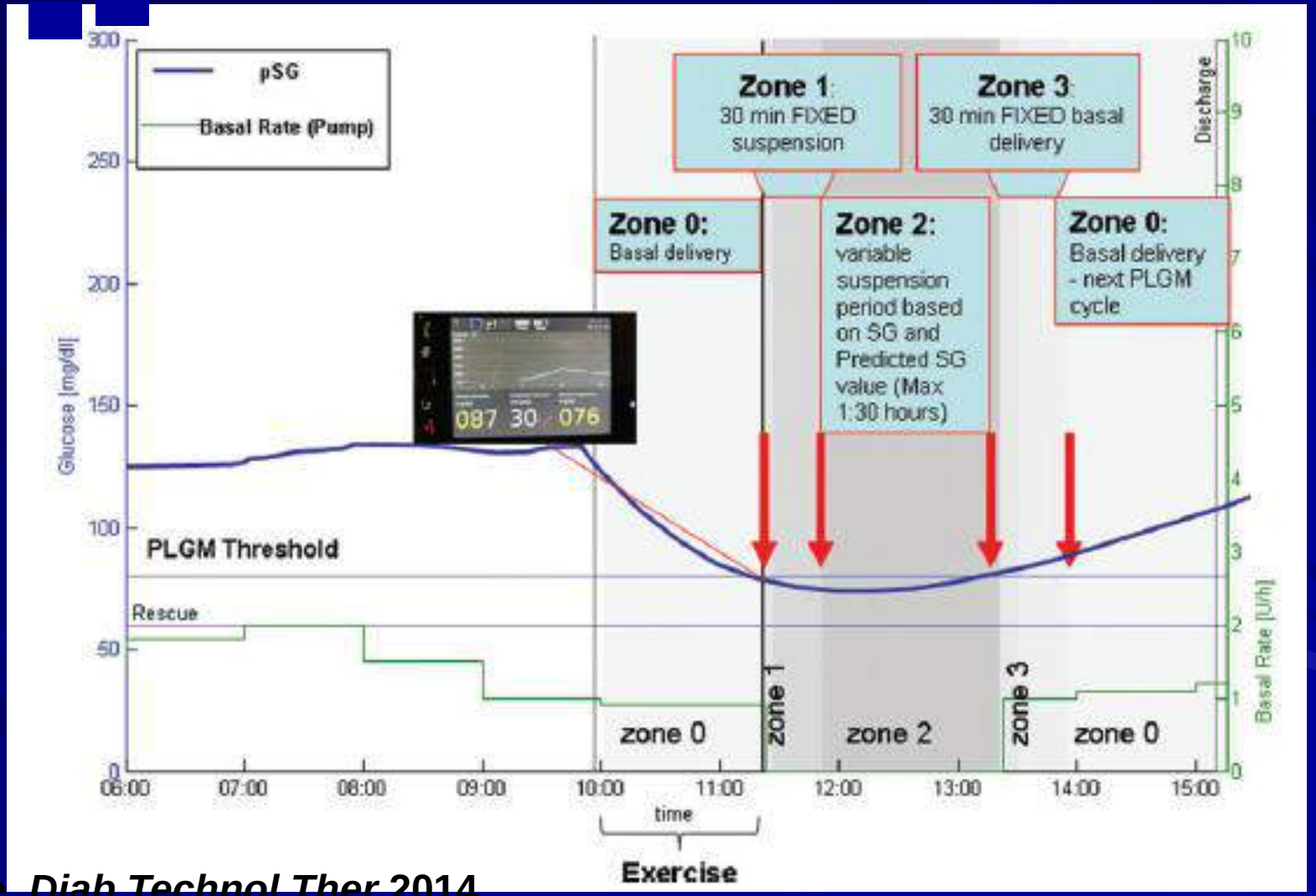


ASPIRE Low-Glucose Suspend Study



Garg S, Diabetes Technol Ther 2012; 14: 205-9

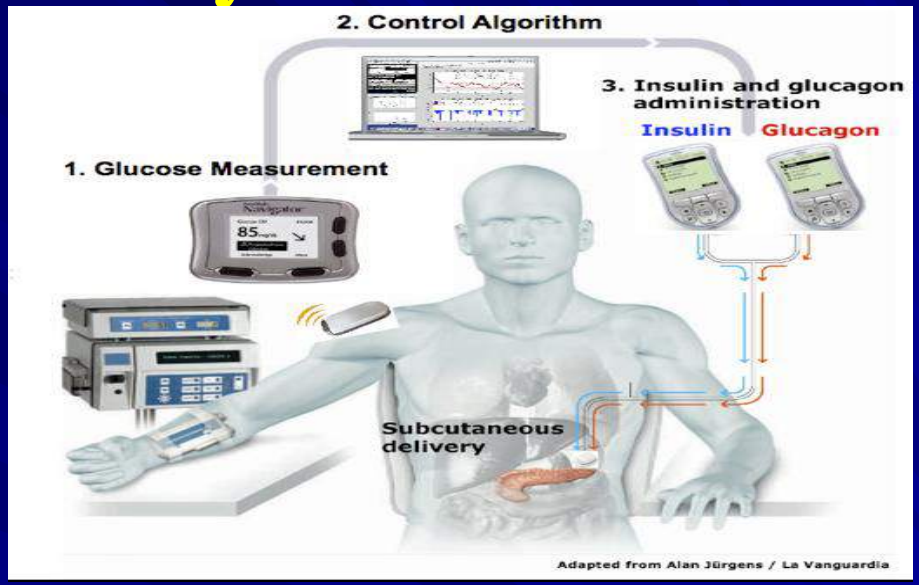
Predictive Low Glucose Suspend

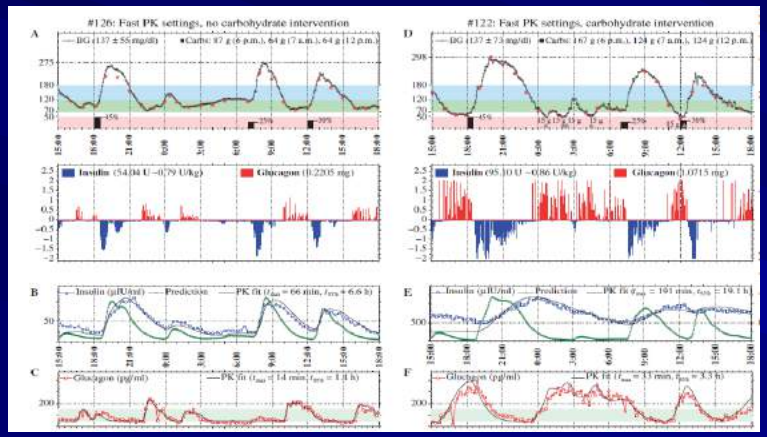


Danne, *Diab Technol Ther* 2014

Artificial Pancreas (Closed-Loop): Bi-hormonal Systems

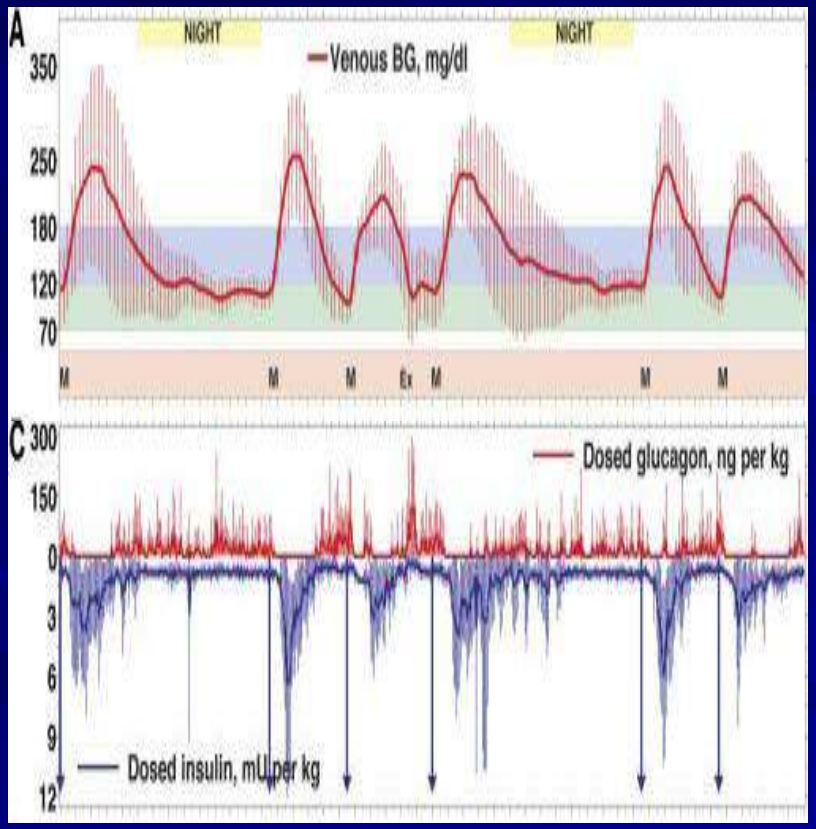
- Insulin + Glucagon
  - to prevent hypoglycemia





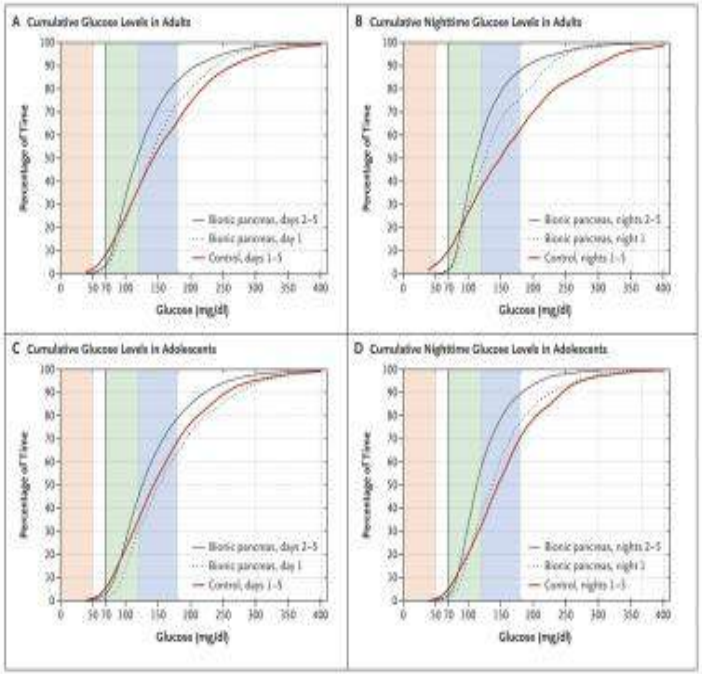
- Insulin + Pramlintide
  - to reduce post-meal excursions and the risk of hypoglycemia by slowing rate of gastric emptying

Hybrid Closed-Loop – multiple hormone (glucagon) plus standardized pre-meal bolus



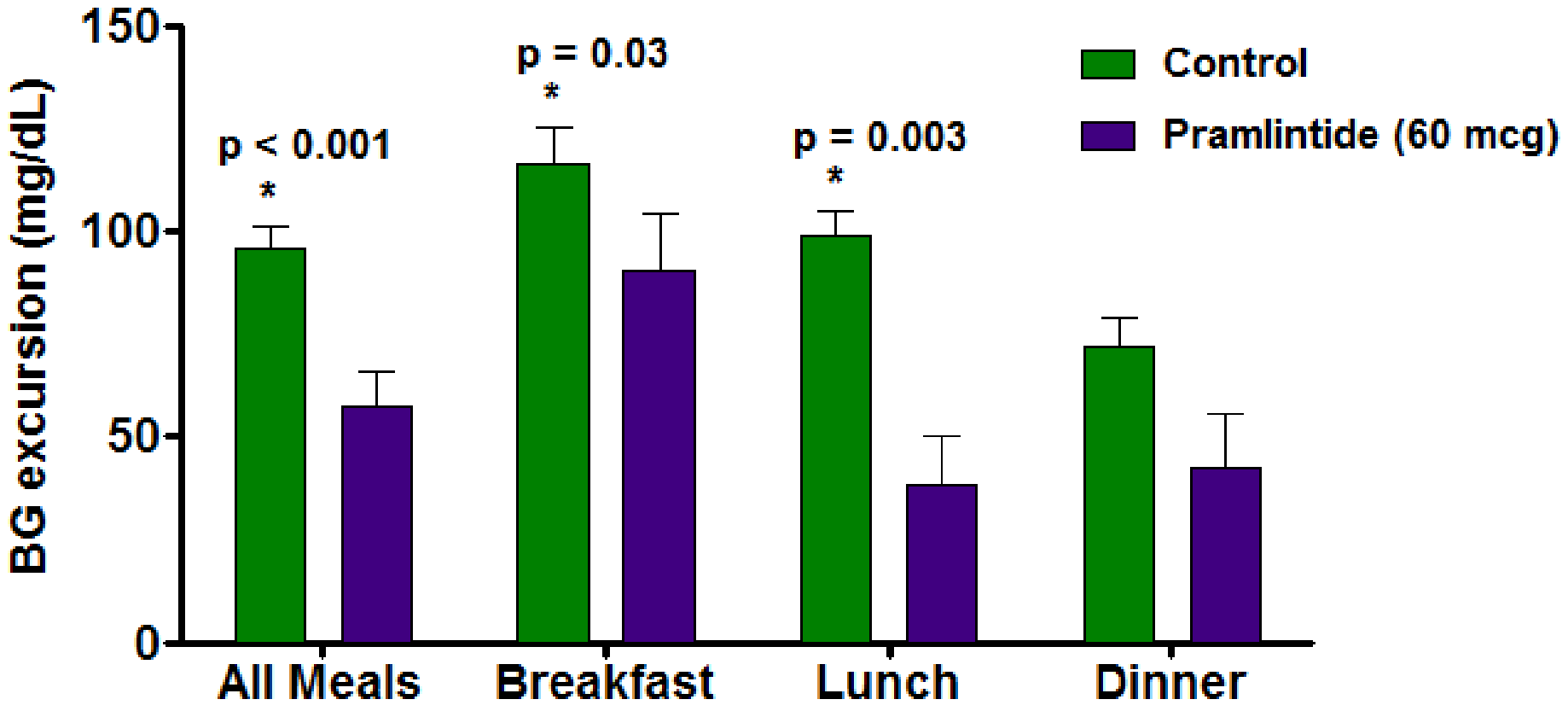
Russell, *Diab Care* 2012

- N=6, 48 hr



Russell SJ et al. N Engl J Med 2014;371:313-325.

Pramlintide reduced peak post-meal BG spikes

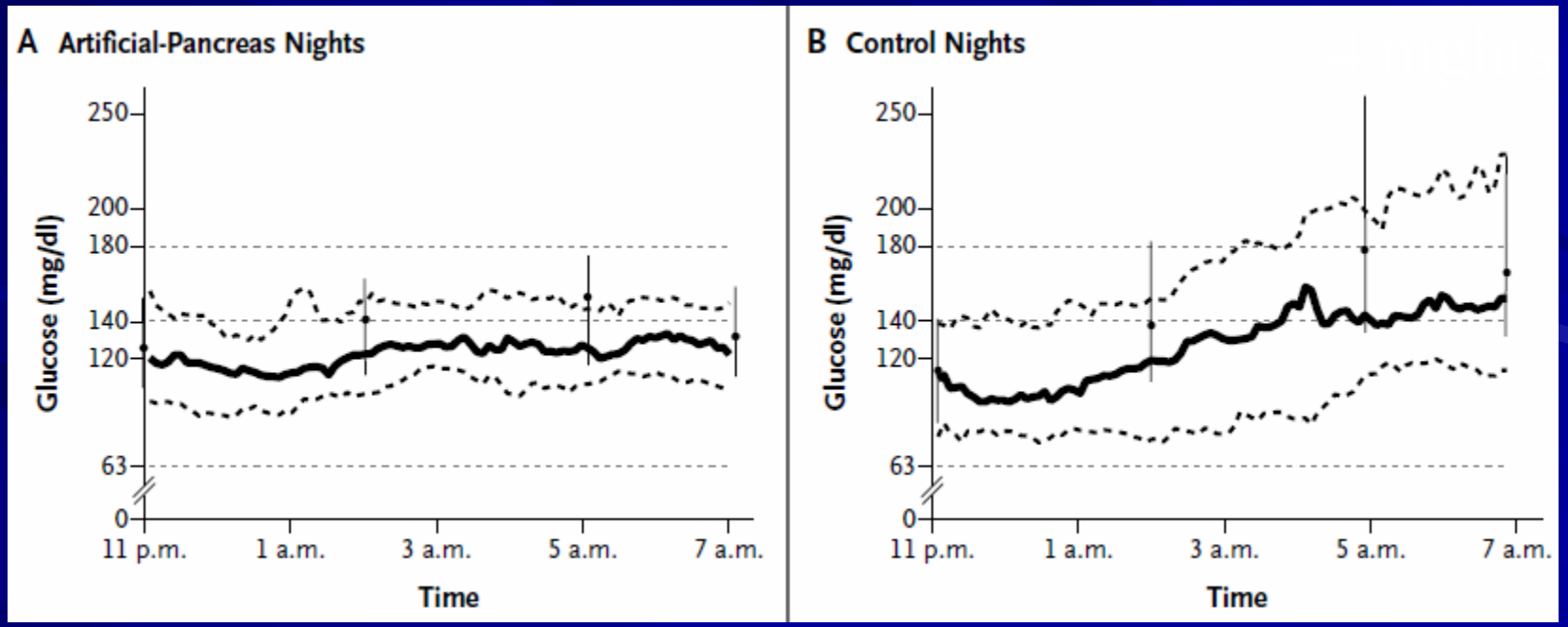


Transition to Outpatient Studies: Testing the CL System in Real Life Conditions

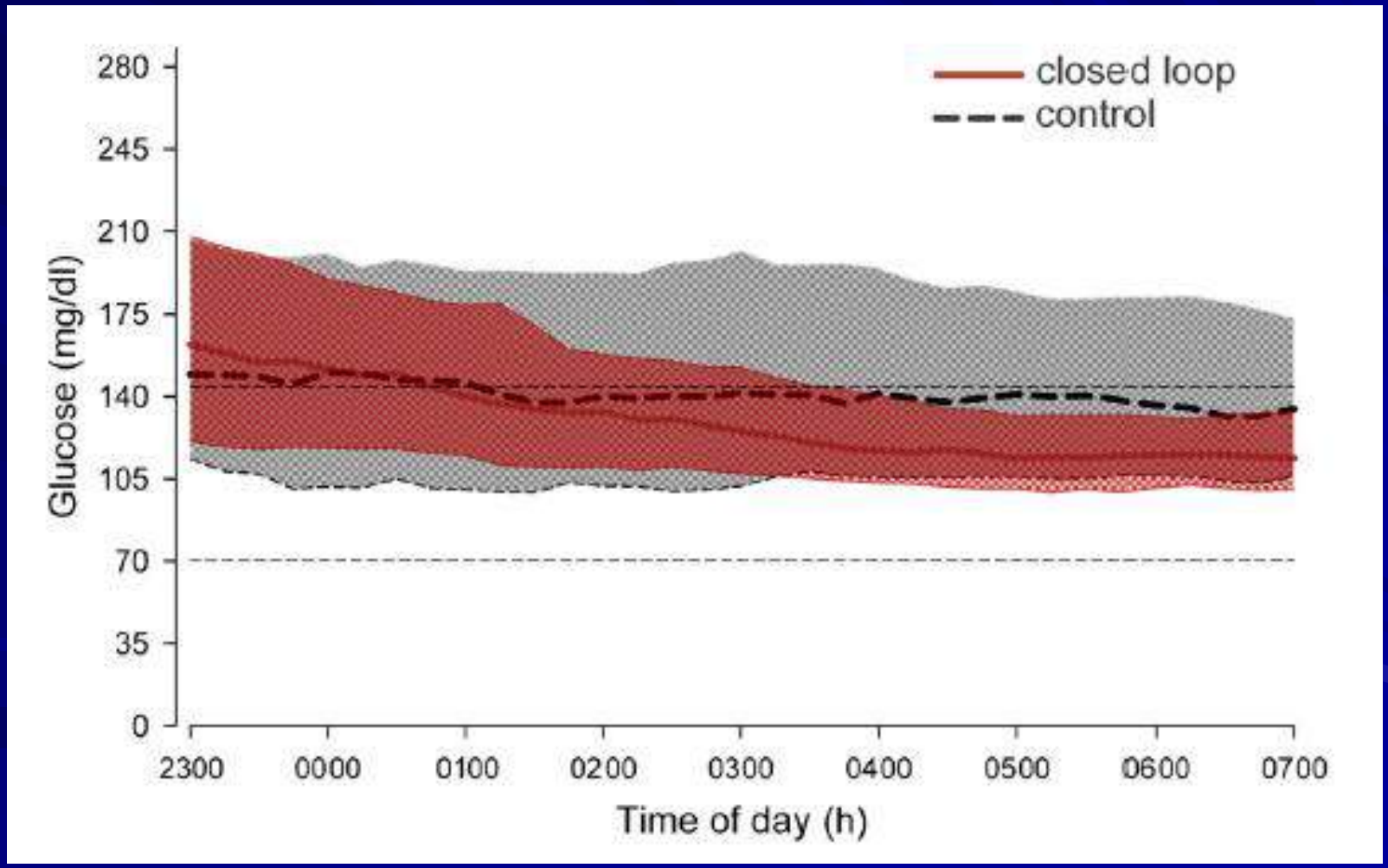
Nocturnal Glucose Control with an Artificial Pancreas at a Diabetes Camp

Moshe Phillip, M.D., Tadej Battelino, M.D., Eran Atlas, M.Sc., Olga Kordonouri, M.D., Natasa Bratina, M.D., Shahar Miller, B.Sc., Torben Biester, M.D., Magdalena Avbelj Stefanija, M.D., Ido Muller, B.Sc., Revital Nimri, M.D., and Thomas Danne, M.D.

5,



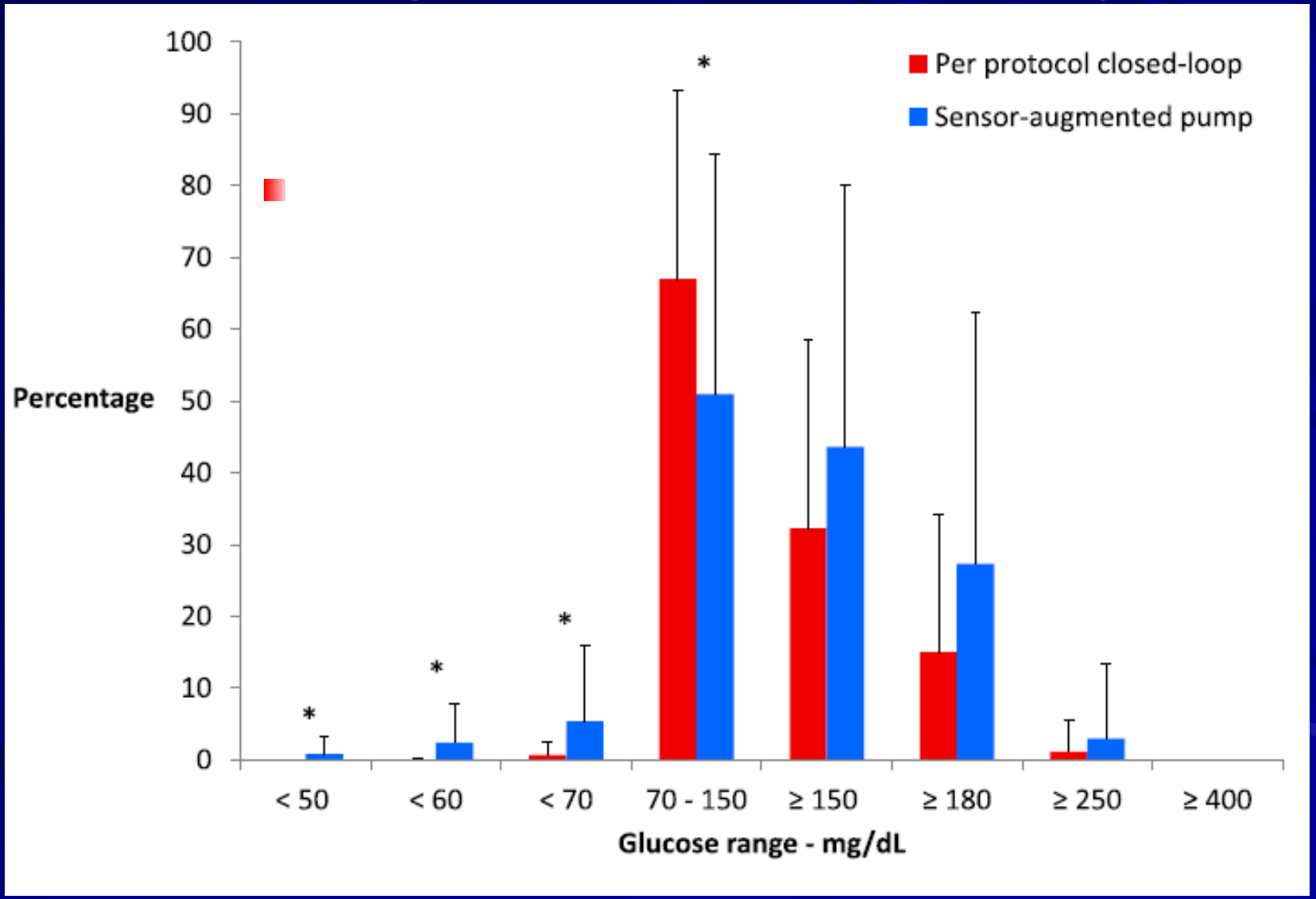
Overnight CL – Longest duration outpatient study yet



- N=16, 3 weeks

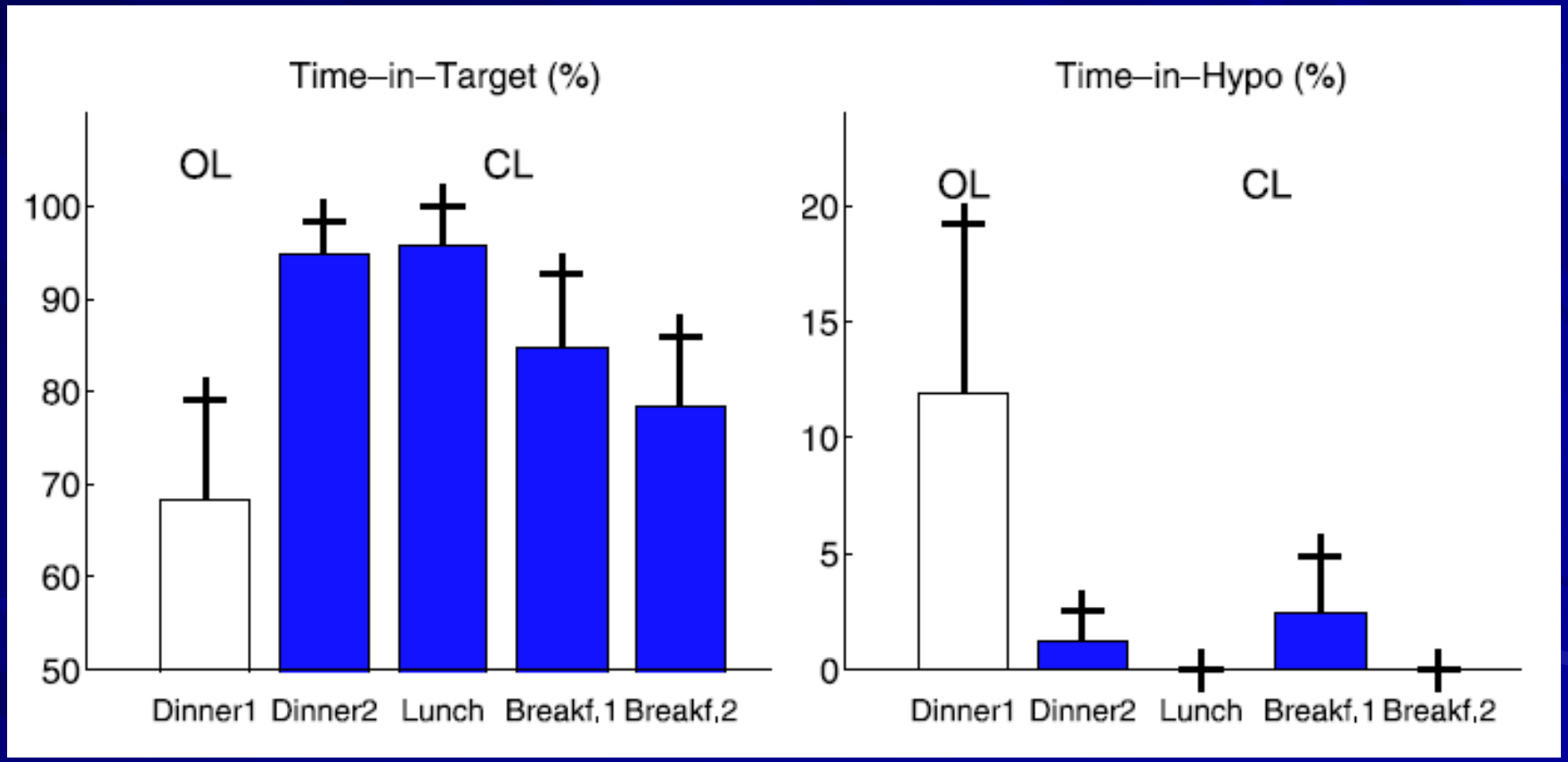
Hovorka, *Diab Care* 2014

Overnight CL Camp Study



Ly, *Diab Care* 2014

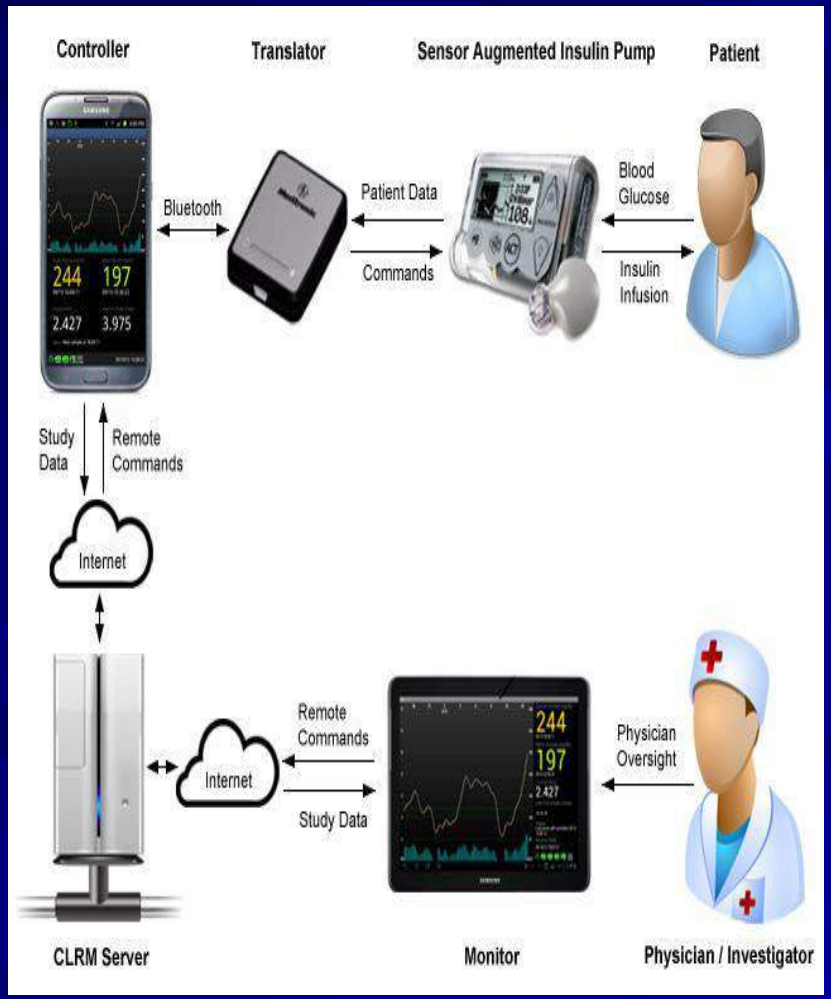
Outpatient Full-Day Hybrid Closed-Loop

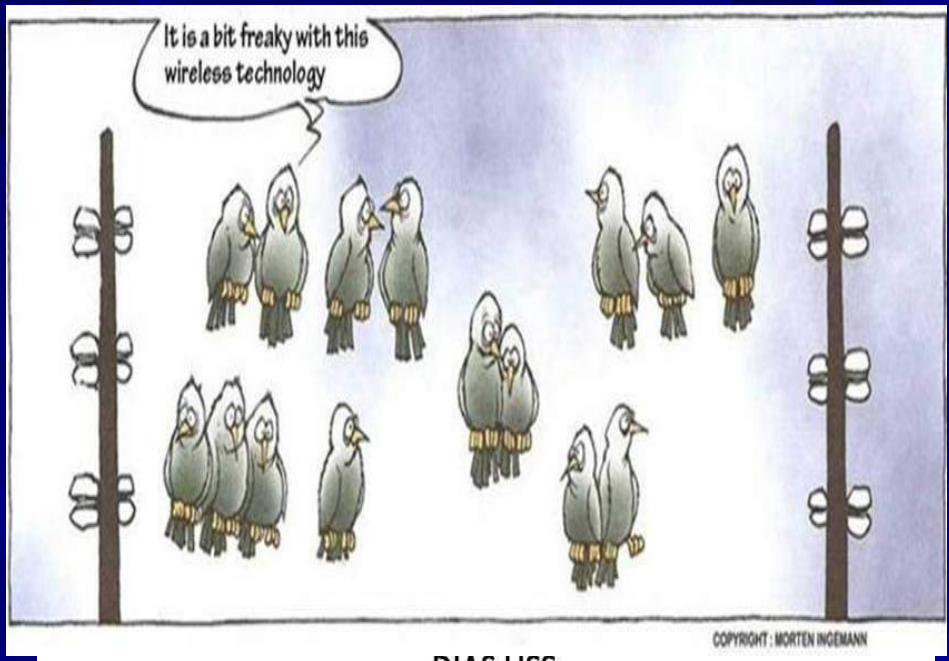


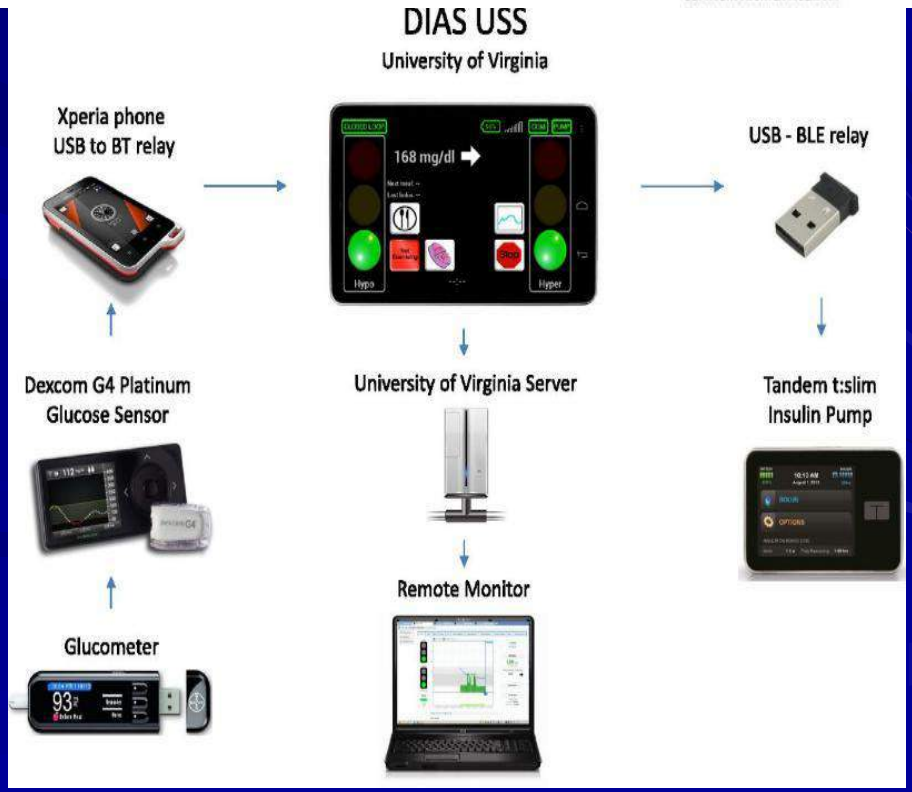
- N=6, 28 hr on CL

Del Favero, *Diab Care* 2014

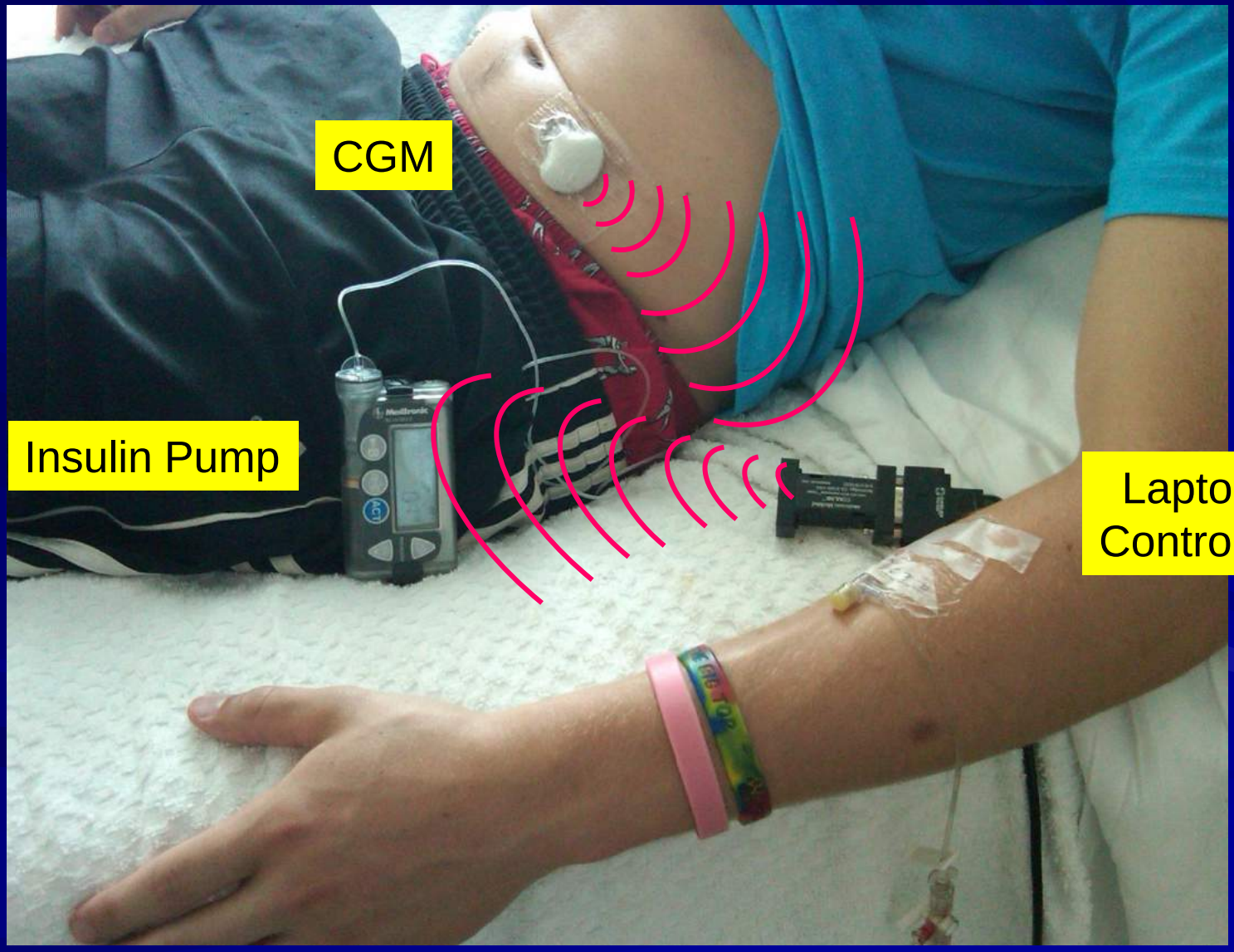
Ambulatory Closed-Loop Systems





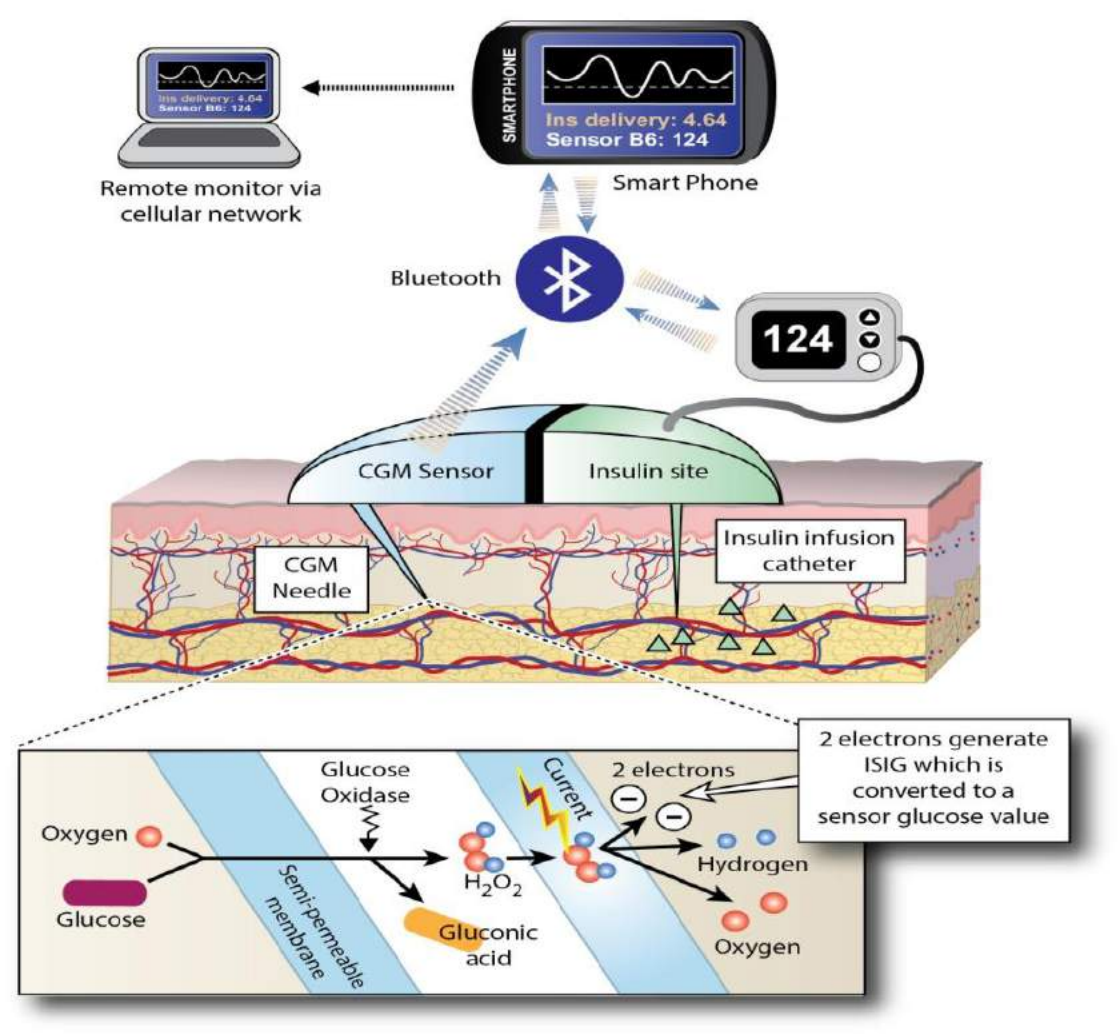


Yale Yapay Pankreas Sistemi - 2007



Outpatient Hybrid CL Study -- in Action! "The Hotel Study" 2015

Yakın Gelecekteki Yapay Pankreas Sistemi



- Yeni ve gelişmiş CGM (dual sistem)
- Remote access
- Biyometrik data
- Ek ilaçlar

(GLP1; SGLT1,2 inhibitors)

- Ultrahızlı insülinler (tamamen otomatik sistem)

Cengiz 2015, *in submisson*

Bizim Takım

- Yale Pediatric Diabetes Clinic & Research Teams

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