Yapay Pankreasda Güncel Durum ve Gelecek…

6/2021

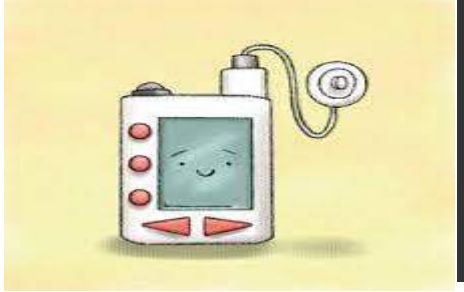
Eda Cengiz, MD, MHS, FAAP

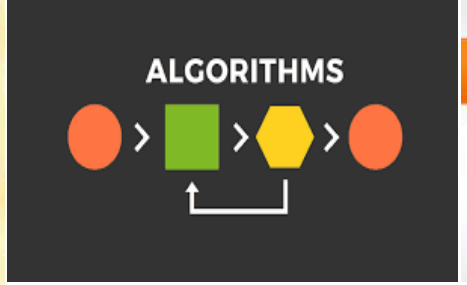
Genel Başliklar

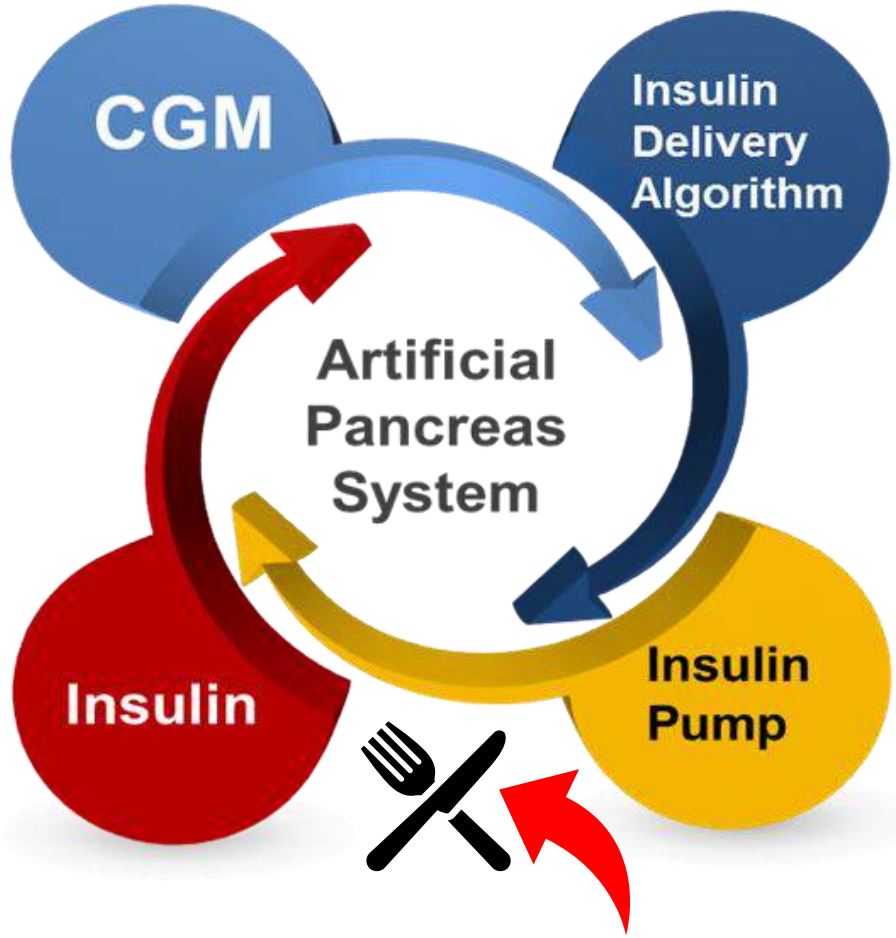
- Yapay pankreas sistemini olusturan elementler
- Geçmişten günümüze Yapay Pankreas Sistemleri
- Yapay Pankreasin araştirma ve klinik sonuçlari
- Geleceğin Yapay Pankreas Sistemleri

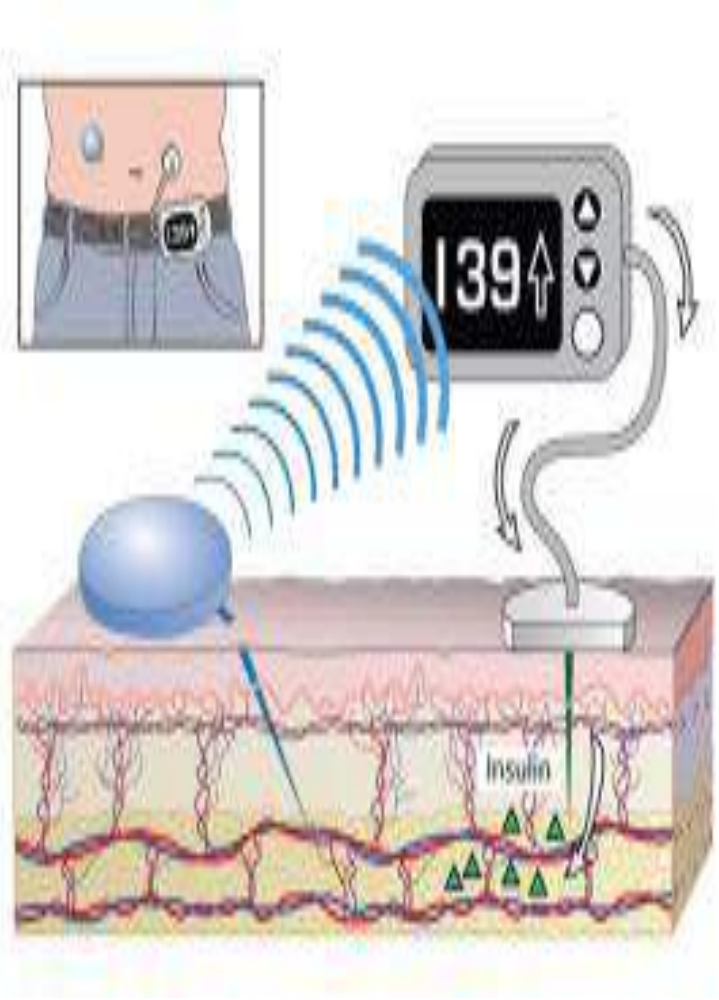
Yapay Pankreas

1.Insulin pompasi
2. Algoritma
3.CGM









Cengiz & Tamborlane, DTT 2009

Yapay Pankreas'ın Evrimi

Sensor Destekli Insulin Pompa Tedavisi: Akıll İnsulin Tedavi Sistemlerine Basamakli Geçiş…

Insulin Pump + CGM=
Sensor Augmented Pump Therapy (SAP)
+ Insulin Delivery Algorithms
(Insulin Pump's Brain!)

Diabetes Care Volume 41, October 2018 2155

Check for updates

Predictive Low-Glucose Suspend Reduces Hypoglycemia in Adults, Adolescents, and Children With Type 1 Diabetes in an At-Home Randomized Crossover Study: Results of the PROLOG Trial

Gregory P. Forlenza,[1] Zoey Li,[2] Bruce A. Buckingham,[3] Jordan E. Pinsker,[4] Eda Cengiz,[5] R. Paul Wadwa,[1] Laya Ekhlaspour,[3] Mei Mei Church,[4] Stuart A. Weinzimer,[5] Emily Jost,[1] Tatiana Marcal,[3] Camille Andre,[4] Lori Carria,[5] Vance Swanson,[6] John W. Lum,[2] Craig Kollman,[2] William Woodall,[2] and Roy W. Beck[2]

Diabetes Care 2018;41:2155–2161 | https://doi.org/10.2337/dc18-0771

İlk FDA Onayi Alan Yapay Pankreas Sistemi: Medtronic 670G Hybrid Closed-loop (HCL)

HCL System

Insulin only System

1st FDA Approved HCL for ≥14yo with T1D

Study Population

Pediatric & Adult

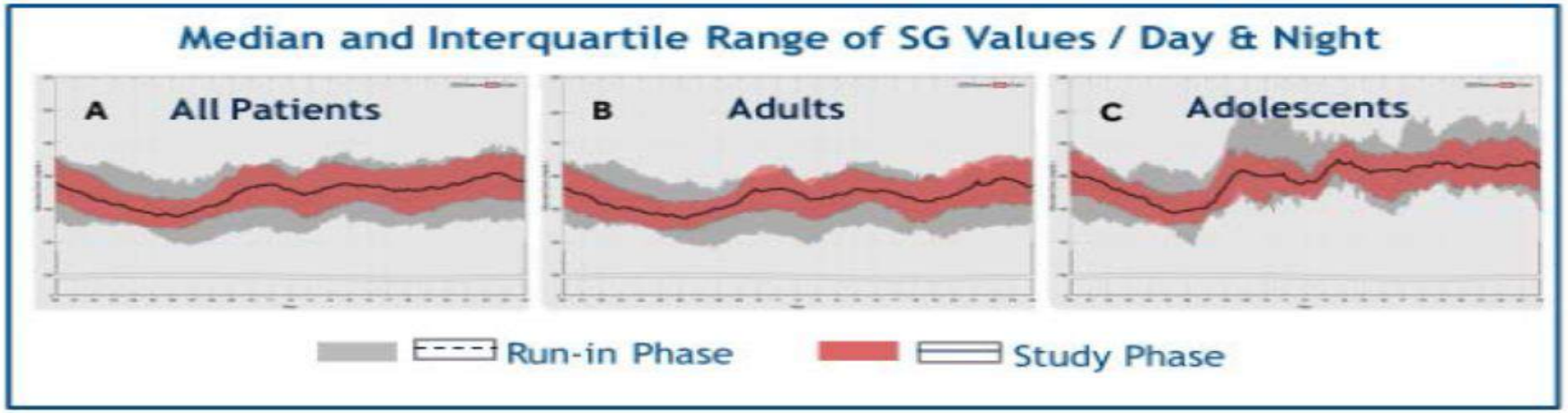
Study & Outcomes

-2 week run-in; 3 month, non-randomized study HCL vs. SAP

-One week hotel, rest of time AT HOME

-124 subjects, 10 centers

MODAL DAY SENSOR GLUCOSE TRACINGS



- *Adult Group:*

-Hypoglycemia reduction

Adolescent Group:

-Hyperglycemia reduction

- **0.5% reduction in A1c, bringing subjects from a low initial A1c of 7.4% to 6.9%**

Bergenstal RM, et al. *JAMA*. Published online September 15, 2016 ; Garg SK, et al. DTT 2017

One Year Clinical Experience of the First Commercial Hybrid Closed-Loop

https://doi.org/10.2337/dc19-0855

Rayhan A. Lal,[1,2,3] Marina Basina,[1,3] David M. Maahs,[2,3] Korey Hood,[2,3] Bruce Buckingham,[2,3] and Darrell M. Wilson[2,3]

670G Otomatik Sistem Kullanımı 12 ay icinde 74% den 35% e düşüyor!

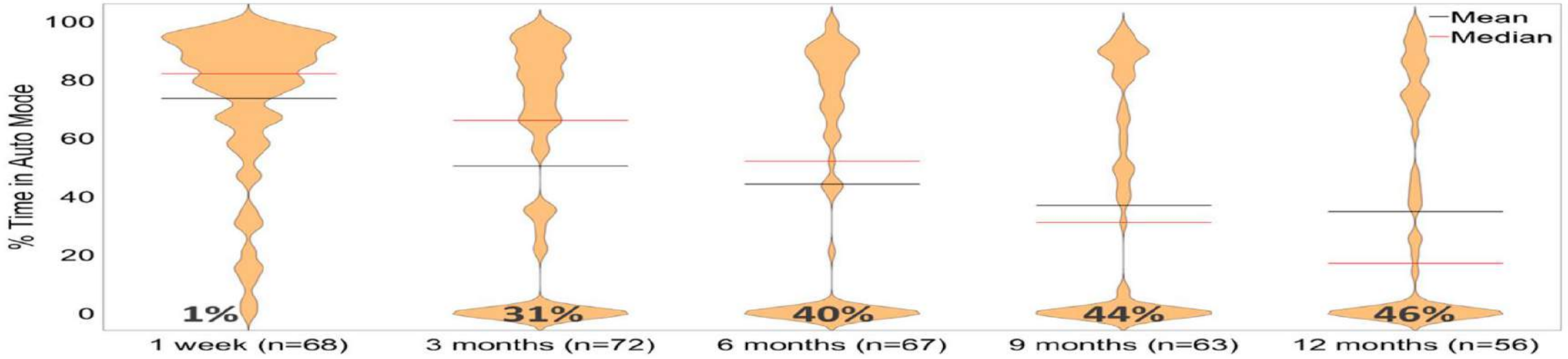


Figure 1—Violin plot reflecting percentage of time in Auto Mode by time of follow-up, with the number of participants with available data noted. For the available data, usage of Auto Mode diminishes over time. At 1 week, mean 74% and median 82%; 3 months, mean 50% and median 66%; 6 months, mean 44% and median 52%; 9 months, mean 37% and median 31%; and 12 months, mean 35% and median 17%.

-Yeni ve gelişmiş yapay pankreas sistemlerine gereksinim var.

Değişen ve Gelişen Yapay Pankreas

- I. Insulin Pompa, CGM (Sensor) ve diğer sistem gelişimleri
- II. Yan dal gelişmeler

Akıllı Insulin Pompaları ve Teknolojik Interoperabilite

- ACE Pump
  - **“alternate controller-enabled”**
- iCGM
  - **“integrated continuous glucose monitor”**
- iAGC
  - **“interoperable automated glycemic controller”**

FDA’in Tandem İnsulin Pompası ile farklı sensorler arasinda iletişim izni ve onayını kabul etmesi ile gelişen diyabet teknolojisi.

Yapay Pankreas İnsulin Pompaları

Medtronic
Minimed

Tandem
tSlim
Control IQ

Omnipod 5

iLet
Beta
Bionics

Tidepool
Loop

Lilly-
Ypsomed

bigfoot™
BIOMEDICAL

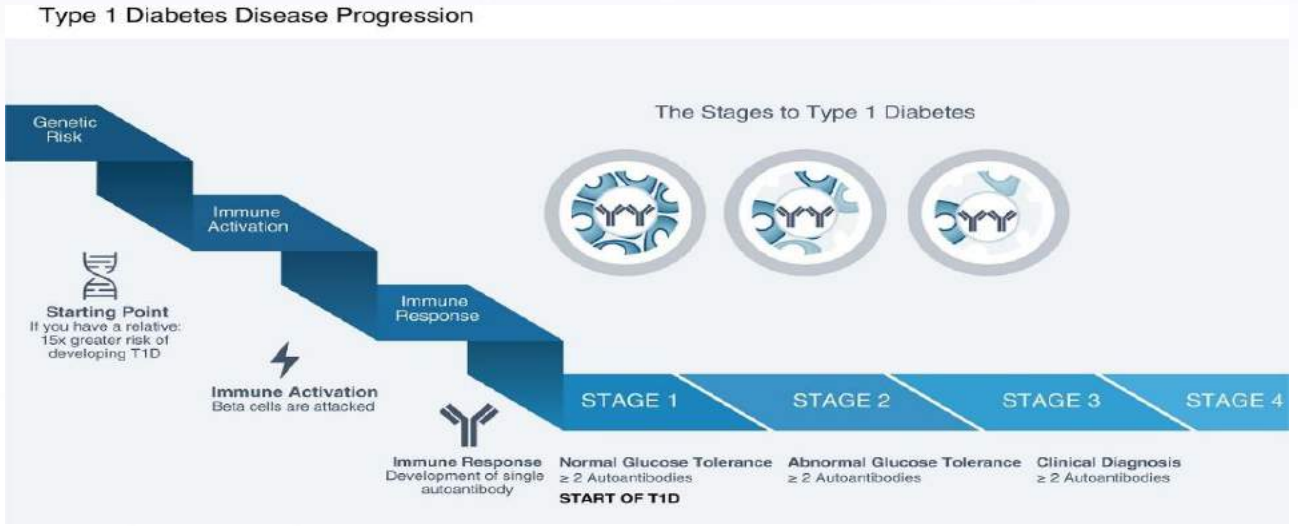
Glukoz Sensorleri (CGM)

Dexcom G6, G7

Eversense

Freestyle Libre

Medtronic



- Trial of Early Initiation of CGM-Guided Insulin Therapy in Stage 2 T1D (TESS)
- Clinical Trials.gov: NCT04335513

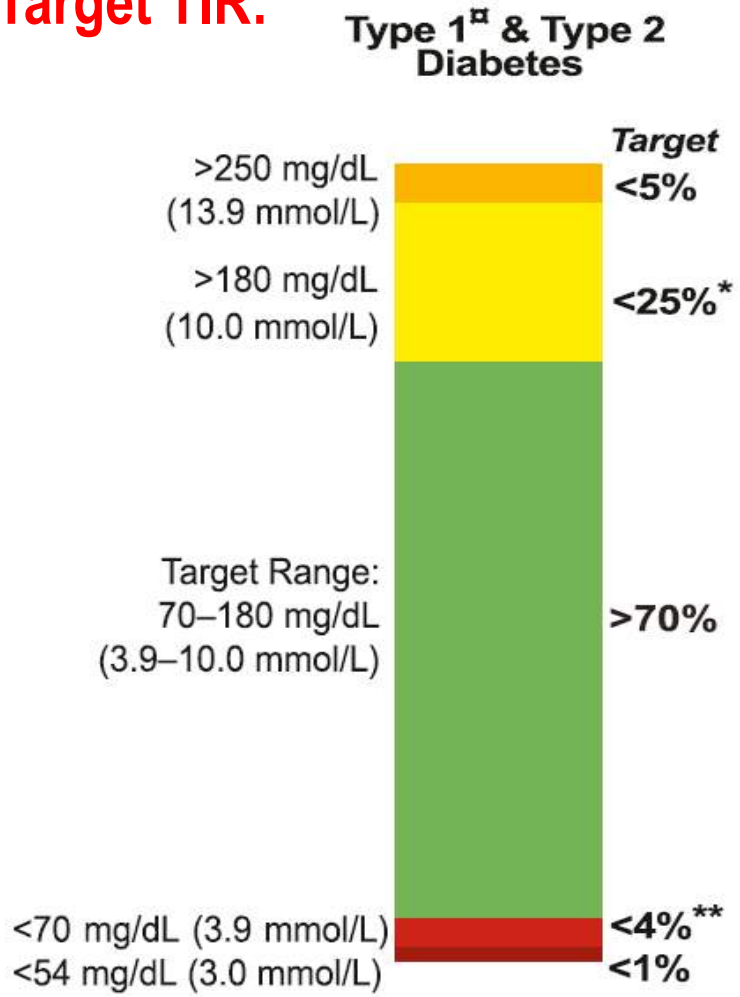
Sensor'un Diyabet Tedavisine Sundugu Ölçüm: Time in Range (TIR)

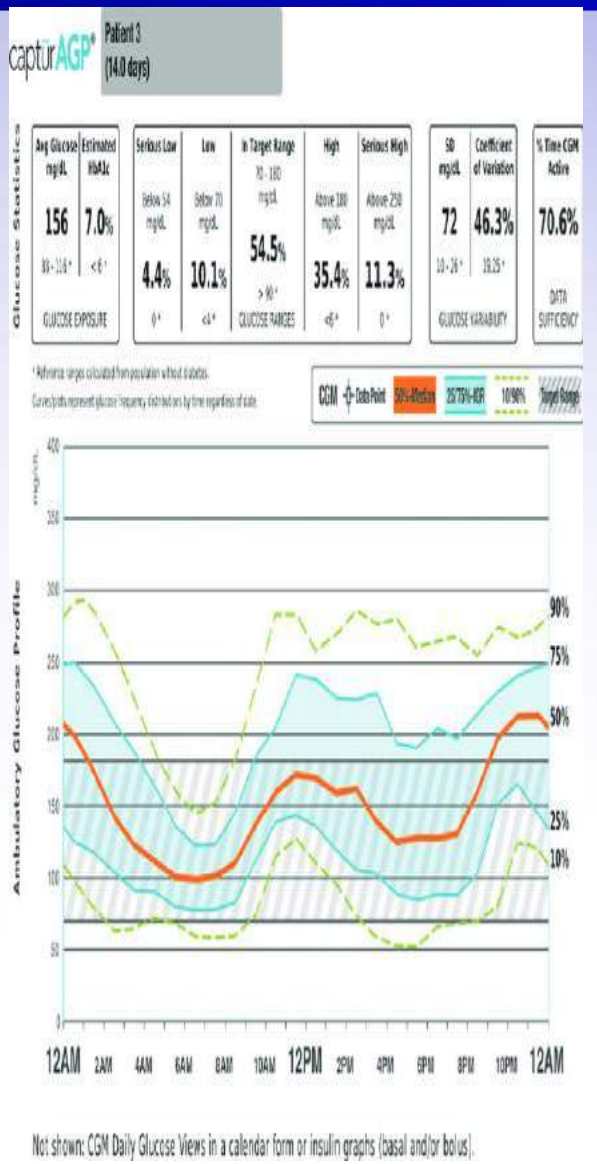
- Sensor data ve data pattern tanima programlari
- Klinisyen ve diyabetliler icin sensor data tanimlama ve yorumlama
- CGM data'dan HbA1c tahmini
- Time in Range (TIR),Time Above Range (TAR), Time Below Range (TBR)

- *HbA1c nin TIR ile belirlenmesi:*
- **TIR 70% =HbA1c 7% (53mmol/mol)**
- **10% TIR iyilesme = HbA1c de 0.5% (5mmol/mol) azalma**

Beck et al., JDST, 2019

Target TIR:





Battelino et al., Diabetes Care, 2019

Uzun Süre Kullanılabilen İnsulin İnfüzyon Setleri

7 gunluk infuzyon seti (Medtronic)

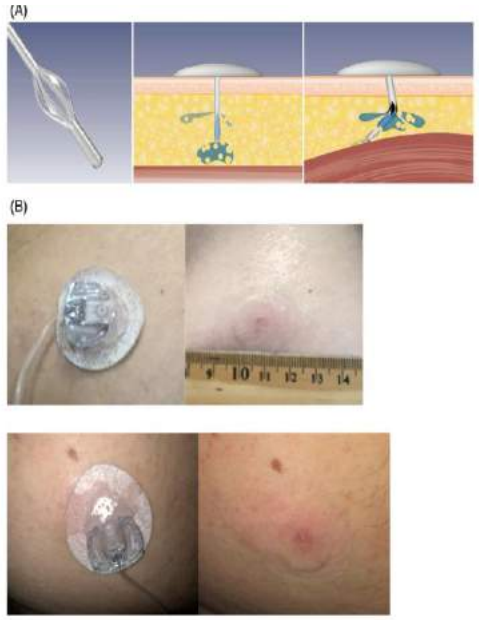
-600,700 insulin pompa sistemleri ile uyu

-81% 7 gun kullanim (eski tip infuzyon se
77% 3 gun kullanim)
- Insulin israfi azaliyor (senede 5-10 vial)

-10 gunluk infuzyon seti kullanimi:

- 45% 10 gun (median kullanim: 7-10gun)
- set problemleri (50% yapiskan,33% hiperglisemi, 8% hiperglisemi+keton, 8% enfeksyon)

Lal et al, JDST 2021

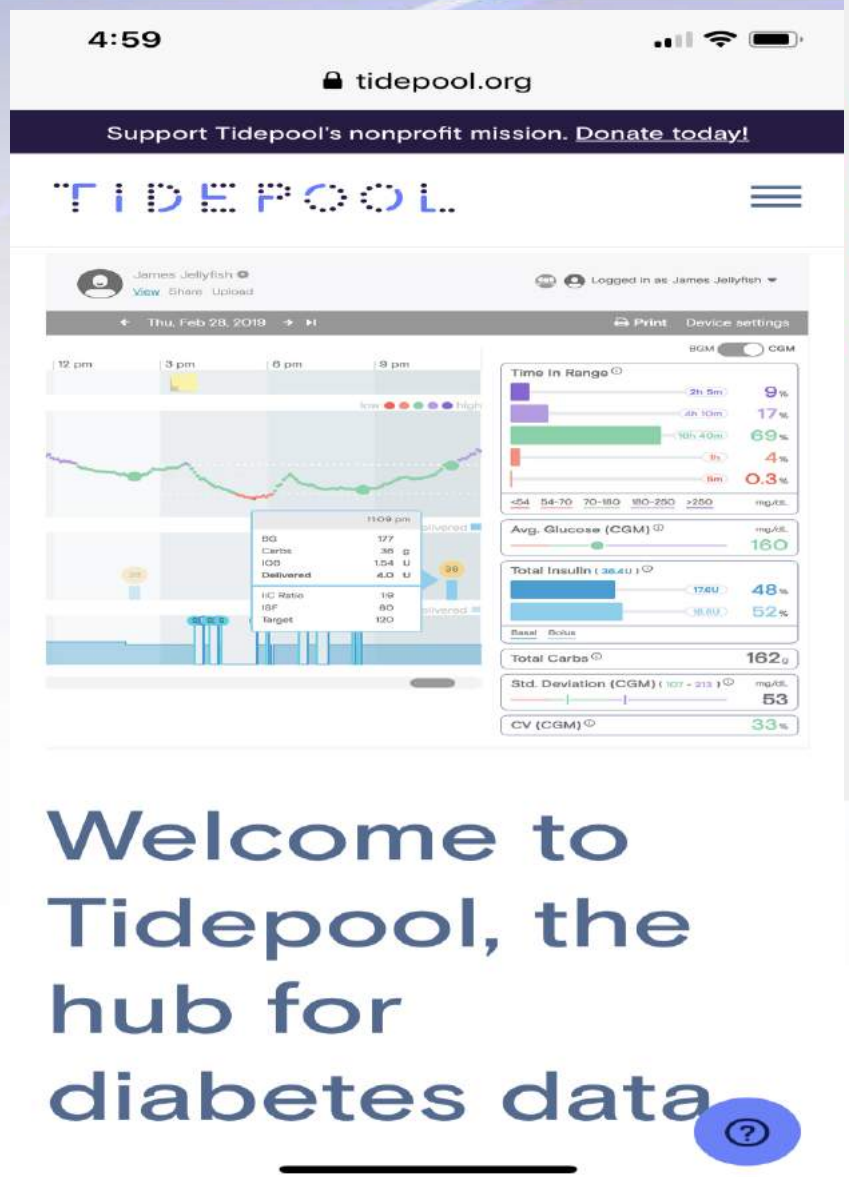


Degisen ve Gelisen Yapay Pankreas

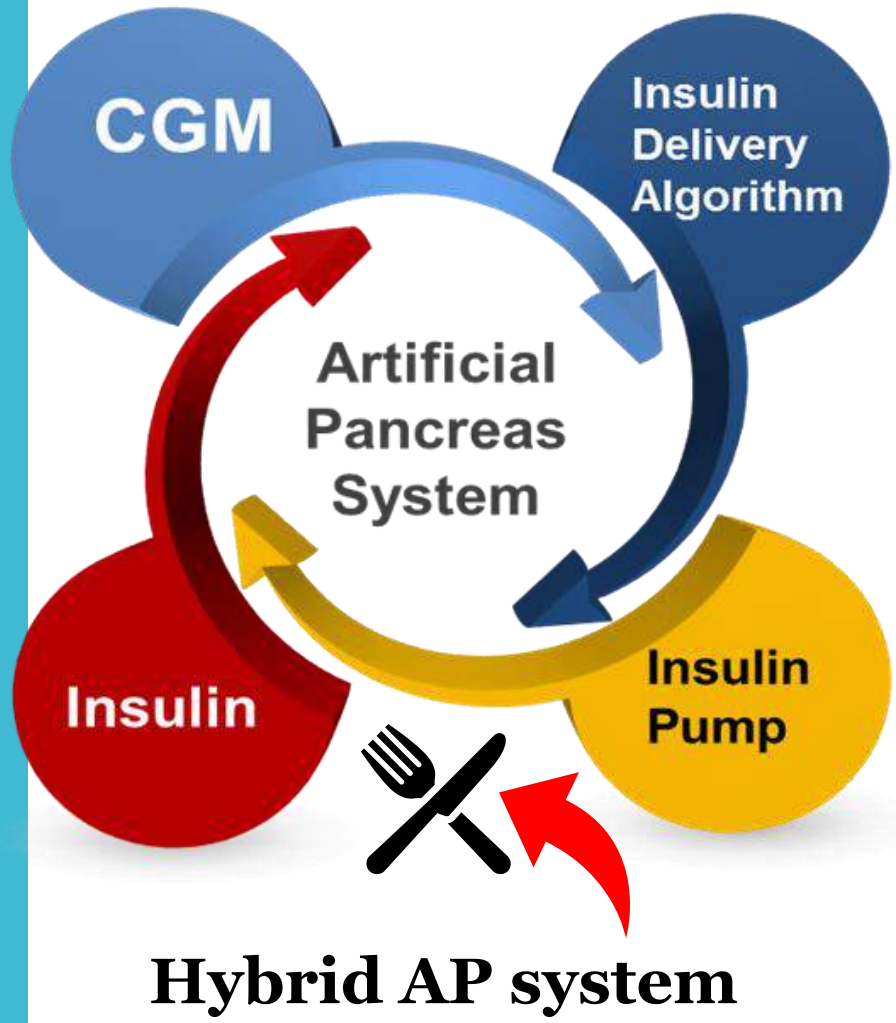
- I. Insulin Pompa, CGM (Sensor) ve diğer sistem gelişimleri
- **II. Yan dal gelişmeler**

eSaglik, Akıllı Telefon Applikasyonları…

- Akıllı telefon applikasyonlari
- eSaglik (Telehealth)
- Diyabet Hayat Koçluğu



Hibrid Yapay Pankreas: Tek Hormon ve Çoklu Hormon Sistemler



- Tek Hormon: Insulin
- Çoklu Hormon:
- Glukagon vb. ek hormonlar
- Esas Hedef: **Tam otomatik, kapalı sistem yapay pankreas**

Yeni Jenerasyon Glukagon

Intranasal Glukagon

Stabil ve Uzun Omurlu Glukagon

GVOKE HypoPen™ (glucagon injection) | Gvoke™ PFS (glucagon injection) PRE-FILLED SYRINGE

Ultra hızlı İnsulinler: Hızlı yapay pankreasa uyabilecek glukodinamik etki

- UVA/Padova simulator: Eriskin diyabetli
- Yemek sonrasi kan sekeri simulasyonu
- Hem kapali (closed-loop) hem acik (open-loop) sistemde simulasyon

- Insulin algoritmasinin ayarlanmasi
(delivery algorithm aggressiveness)
- **+** insulin glukodinamik hiz arttirma

- **<u>Closed-loop</u>**

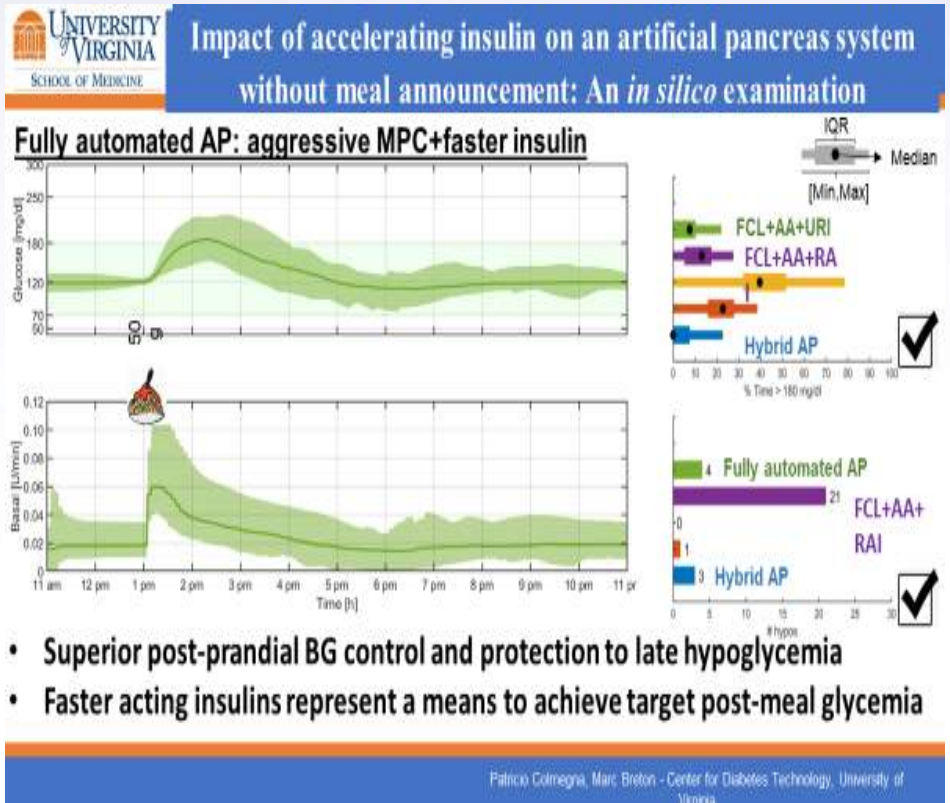
➢ Hybrid

➢ Fully-automated (unannounced meals)

Diabetes Science and Technology 2020 Jun 17

Impact of Accelerating Insulin on an Artificial Pancreas System Without Meal Announcement: An In Silico Examination

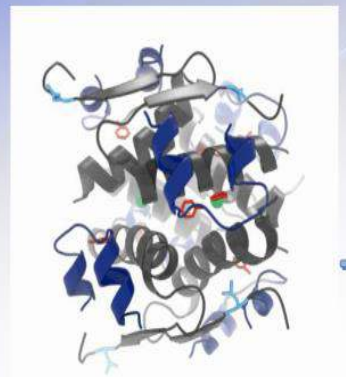
Patricio Colmegna, PhD[1,2], Eda Cengiz, MD, MHS[3,4], Jose Garcia-Tirado, PhD[1], Kristen Kraemer, BS[3], and Marc D. Breton, PhD[1]



Ultra Hızlı İnsulinler

Afrezza Insulin

Faster Acting Aspart



Insulin Aspart

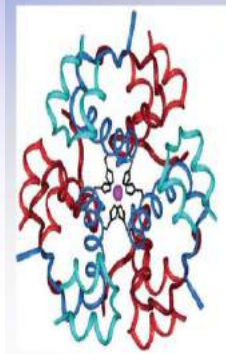
+ Niacinamide: absorption modifier

+ L-Arginine: supports stability

→ Acceleration of Insulin absorption & action

Fiasp
insulin aspart injection 100 units/mL

BioChaperone Lispro



Insulin Lispro

+ BioChaperone

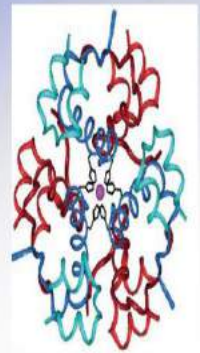
Polymer that accelerates insulin delivery

+ Citrate: increase vascular permeability

→ Acceleration of Insulin absorption & action

ADOCIA

Ultra Rapid Insulin Lispro



Insulin Lispro

+ Treprostinil: local vasodilator

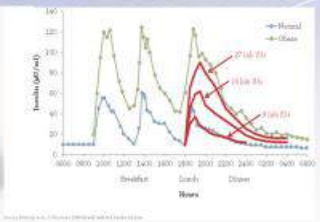
+ Citrate: increase vascular permeability

→ Acceleration of Insulin absorption action

More Insulins in the pipeline...

Inhaled Insulin Dance-501

Multidose insulin Dispenser



Liquid formulation of insulin
vibrating mesh micropump technology
Phase I/II Study - Samba-01: single low dose of inhaled insulin in 12 patients with Type 1 diabetes.
Phase II Study - Samba-02: (9, 18 and 27 inhaled units) in 23 patients with Type 2 diabetes.[1]

1. https://www.dancebiopharm.com/(accessed 2/7/2018)

Ultra-Rapid Acting Insulin Arecor

- Excipients that both accelerate the onset of action & ensure product stability
- Ultra-rapid onset & stability validated in a diabetic pig model
- Human clinical trials in 2018

http://arecor.com/products/ultra-rapid-acting-insulin/ (accessed 2/8/2018)

58

DiaPort

The DiaPort is a port system for continuous intraperitoneal insulin infusion.

- The port is connected with an insulin pump which infuse the insulin continuously in the body
- The catheter tip is placed in the peritoneal cavity where the insulin is directly infused.

Akıllı İnsulin Kalem Sistemi:

Bigfoot Unity System

- Abbott's FreeStyle® Libre 2 system

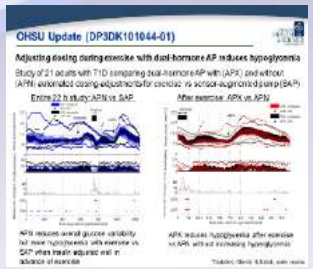
bigfoot™ BIOMEDICAL

Yapay Pankreas : Closed-loop Systems (Artificial Pancreas, Bionic Pancreas)

Medtronic 670G

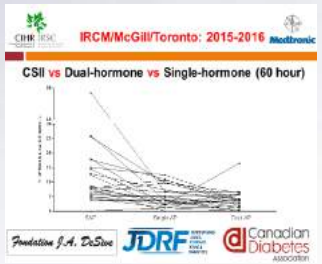
DiAs – Type Zero

iLet-BetaBionics



OHSU

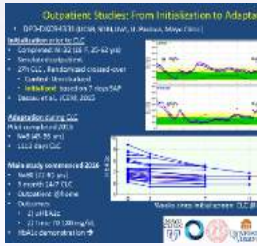
Diabeloop (DBLG1)-France



CLASS

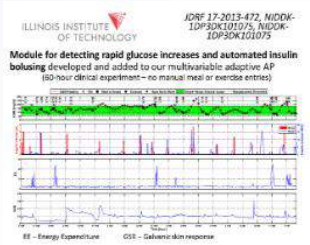
BCH/Harvard Med.

DSC



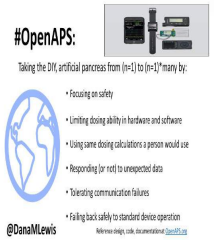
ZMPC

Medtronic 770G, 780G



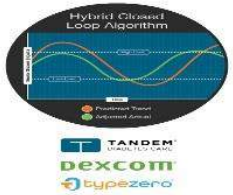
IMAPP

BigFoot



#OpenAPS

Omnipod 5



Tandem-Type Zero

Camdiab FX

Lilly
Menarini
Roche

?

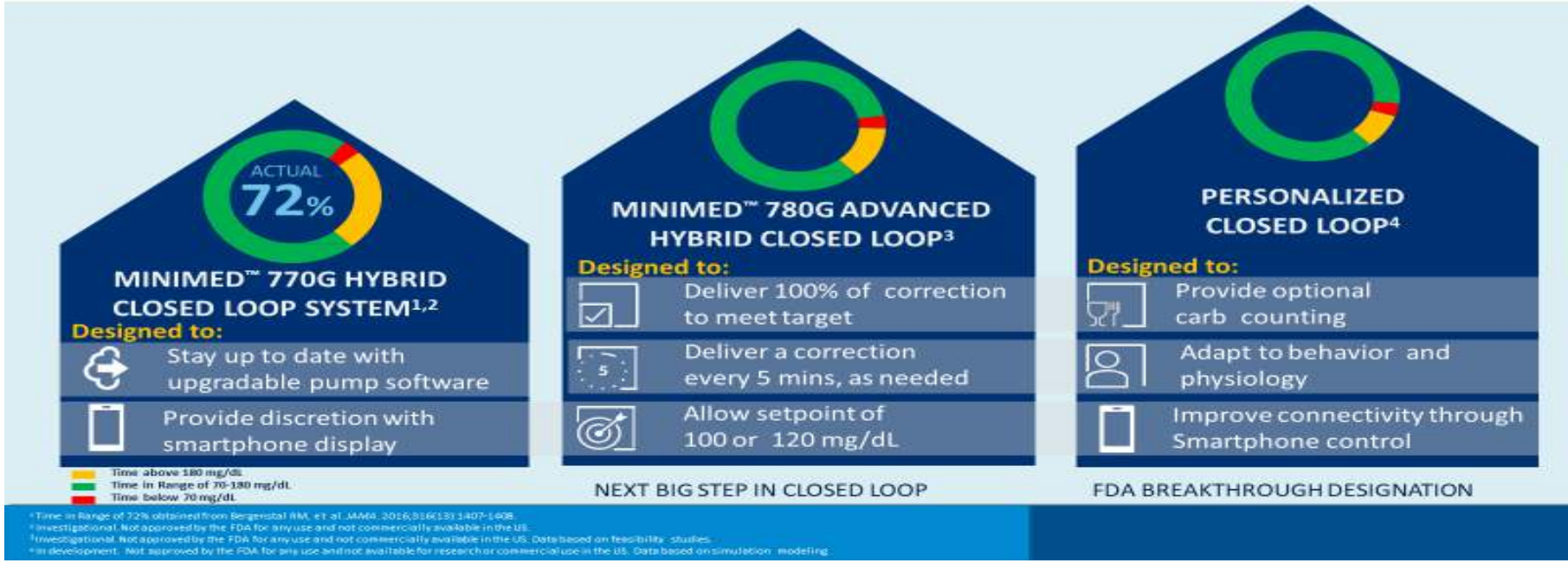
670G

770G

780G

Yeni Yapay Pankreas Sistemleri

-Minimed



PERSONALIZED CLOSED LOOP SYSTEM

SIMPLIFYING THERAPY MANAGEMENT

**With FDA Breakthrough Designation

Algorithm

Fizyolojiye adapte olarak çalişan sistem

Otomatik yemek insulin dozu düzenlemesi
“Automated Meal Handling”
Reduced Carb counting

100% Auto Mode Capable
TIR goal of >85%

Design Goals

Comfort
Personalization
Meaningful outcomes

Sensor & Key Features

50% daha küçük ve kullanılıp atılabilen sensor (CGM)

10 saniyede sensor takabilme
o
özelliği

Akıllı telefon ile kontrol edilebilir

Development programs not approved by the FDA; not investigational nor commercially available

** Priority review and communication with FDA. Breakthrough Devices Program. www.FDA.gov. Accessed April 23, 2019.

Kişiye Özel Yapay Pankreas Tedavisi

Precision Medicine & Diabetes Technology

Kadın tip 1 diyabetli olan kişiler icin özel yapay pankreas algoritmasi

ClinicalTrials.gov : NCT02693938

Principal Investigator: Cengiz

Control IQ System

Control IQ-Tandem Tslim

-Control-IQ kullanan çocuklar **67% time in range (TIR)**, SAP(kontrol) kullanan çocuklar 55%.

-**Gece control IQ 80% TIR**, 54% (kontrol)

-**Control IQ ile 6 saat daha uzun sureli TIR**

-Control IQ gercek hayat kullanim (n=1659):
Hb A1c 7.2% den 6.9% geriledi
Yapay pankreas kullanimi :96%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes

Marc D. Breton, Ph.D., Lauren G. Kanapka, M.Sc., Roy W. Beck, M.D., Ph.D., Laya Ekhlaspour, M.D., Gregory P. Forlenza, M.D., Eda Cengiz, M.D., Melissa Schoelwer, M.D., Katrina J. Ruedy, M.S.P.H., Emily Jost, M.P.H., R.D., C.D.E., Lori Carria, M.S., Emma Emory, R.N., Liana J. Hsu, B.S., Mary Oliveri, C.C.R.C., Craig C. Kollman, Ph.D., Betsy B. Dokken, Ph.D., Stuart A. Weinzimer, M.D., Mark D. DeBoer, M.D., Bruce A. Buckingham, M.D., Daniel Cherñavvsky, M.D., and R. Paul Wadwa, M.D., for the iDCL Trial Research Group*

Yapay Pankreasin Önündeki Engel: Yemek Sonrasi Kan Şekeri Kontrolü

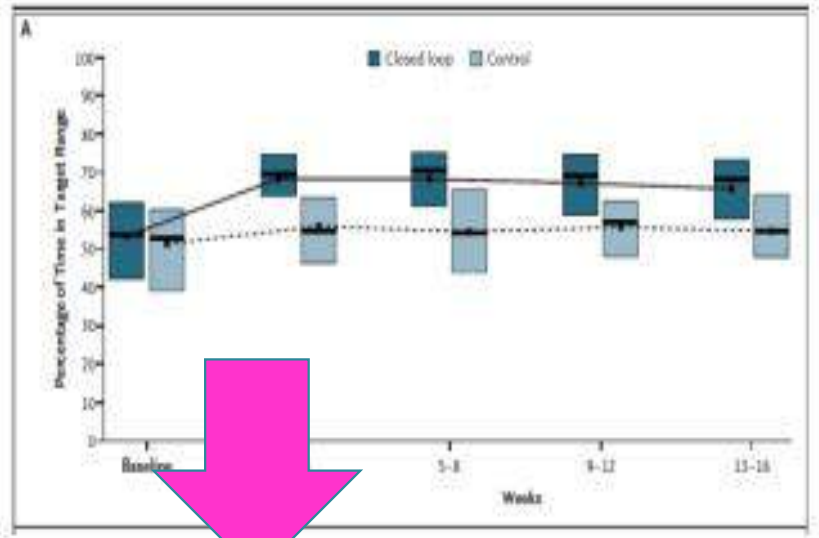
Control IQ-Tandem Tslim

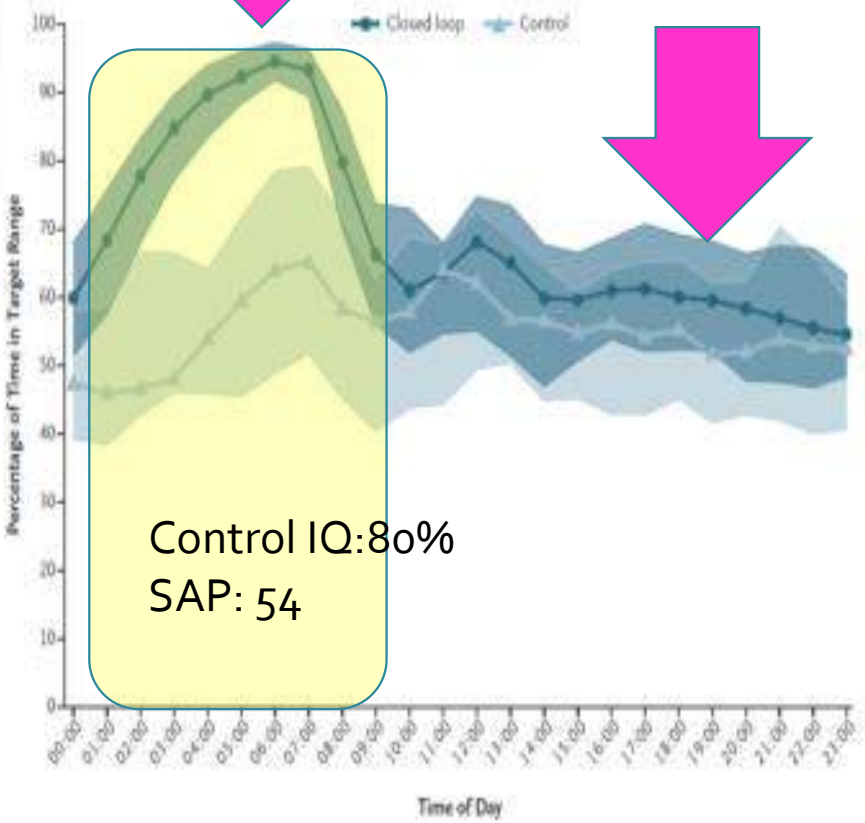
-Children using Control-IQ spent 67% time in range, compared to 55% for children using a sensor-augmented pump.

-Overnight 80% time in range overnight, compared to 54% in the control group

-Six hours more daily time in range with control IQ

-Real-life use data (1659 participants):
estimated Hb A1c fell from 7.2% to 6.9%
Users spent 96% time in closed-loop

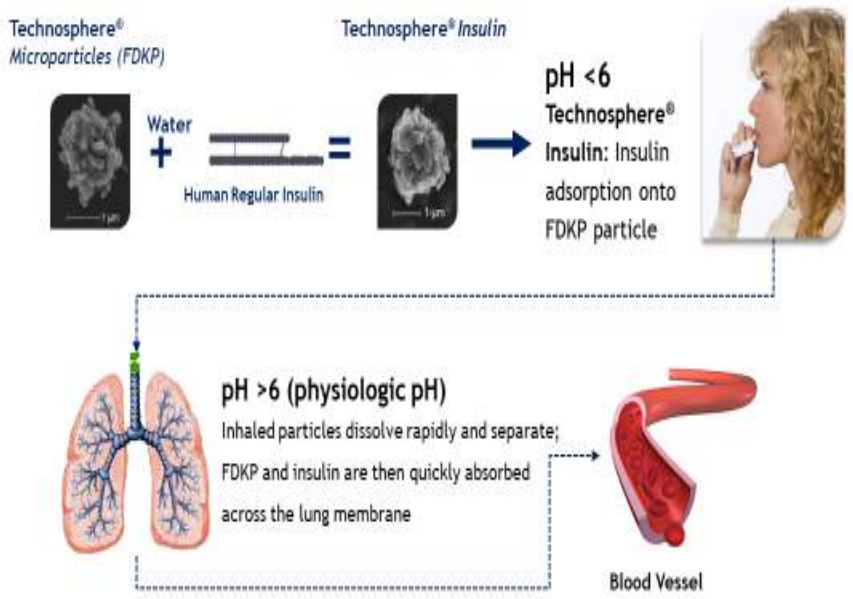




Control IQ:80%
SAP: 54

Afrezza: Ultra-hızlı Inhale İnsulin ve Akıllı Inhaler

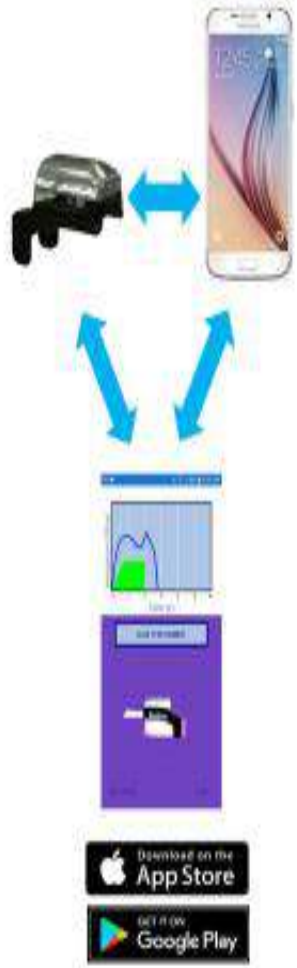
Oral Inhalation Insulin Delivery: One-of-a-kind therapy



Afrezza® (insulin human) Inhalation Powder Presentation. MannKind Corporation. FDA Endocrinologic and Metabolic Advisory Committee Meeting. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM392919.pdf. Accessed November 4, 2014.

BluHale – Digital Health Space

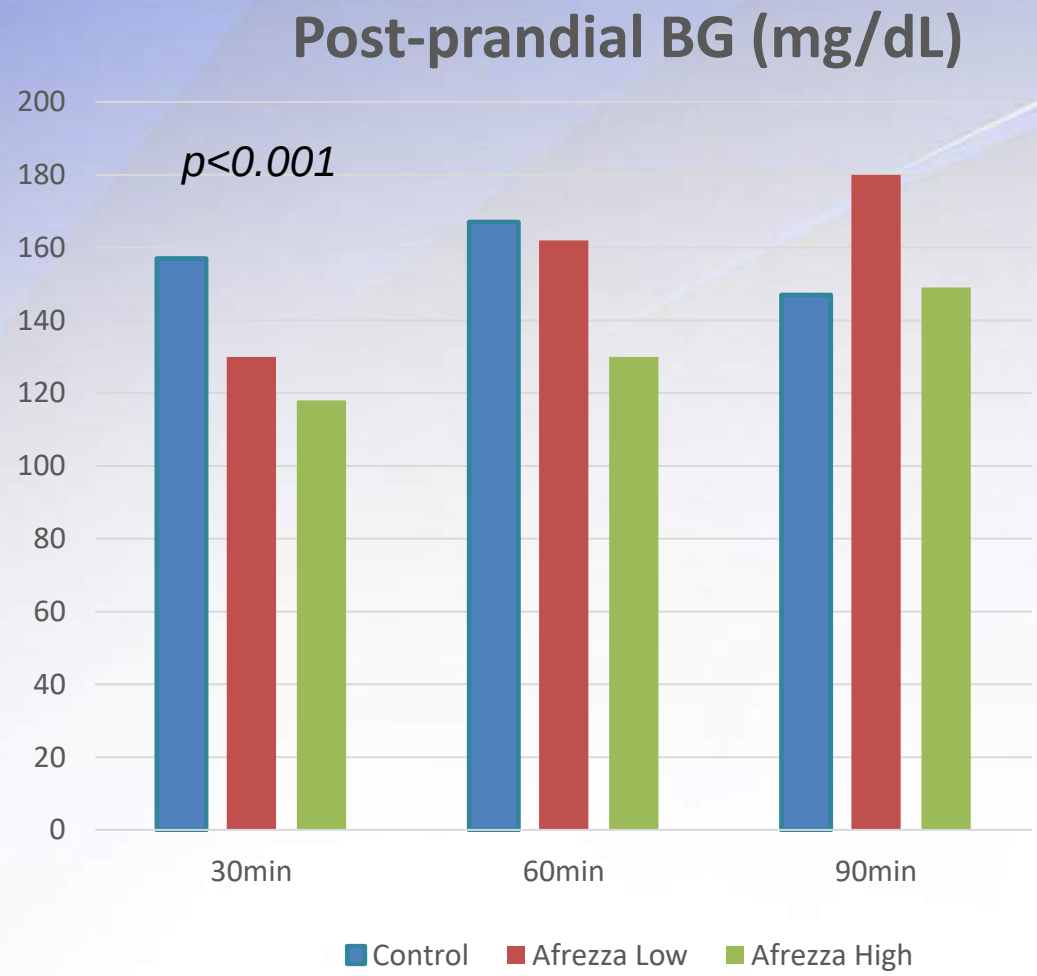
- Components
  - BluHale Accessory (attachment onto DreamBoat inhaler)
  - Smart device (Droid or Apple)
  - Application
- Features:
  - Teach best inhalation efforts (with or without app)
  - Provide handling guidance



BluHale Scored a 4.4 out of 5 on Ease of Use
Over 97% Rating it a 4 or 5 on scale 1-5

- ***Afrezza*** : *Ultra Fast-in & Fast-out Action*

Afrezza Hibrid Yapay Pankreas Klinik Calışması



Effect of Afrezza on Glucose Dynamics During HCL Treatment

Alfonso Galderisi,[1,2] Nathan Cohen,[3] Peter Calhoun,[3] Kristen Kraemer,[1] Marc Breton,[4] Stuart Weinzimer,[1] and Eda Cengiz[1,5]

https://doi.org/10.2337/dc20-0091

# of meals requiring CH rescue for hypoglycemia :

Control : 9

Afrezza low : 2

Afrezza high : 2

Mean Insulin (U)	41 (31, 51)	38 (29, 54)	49 (42, 68)	P=0.61

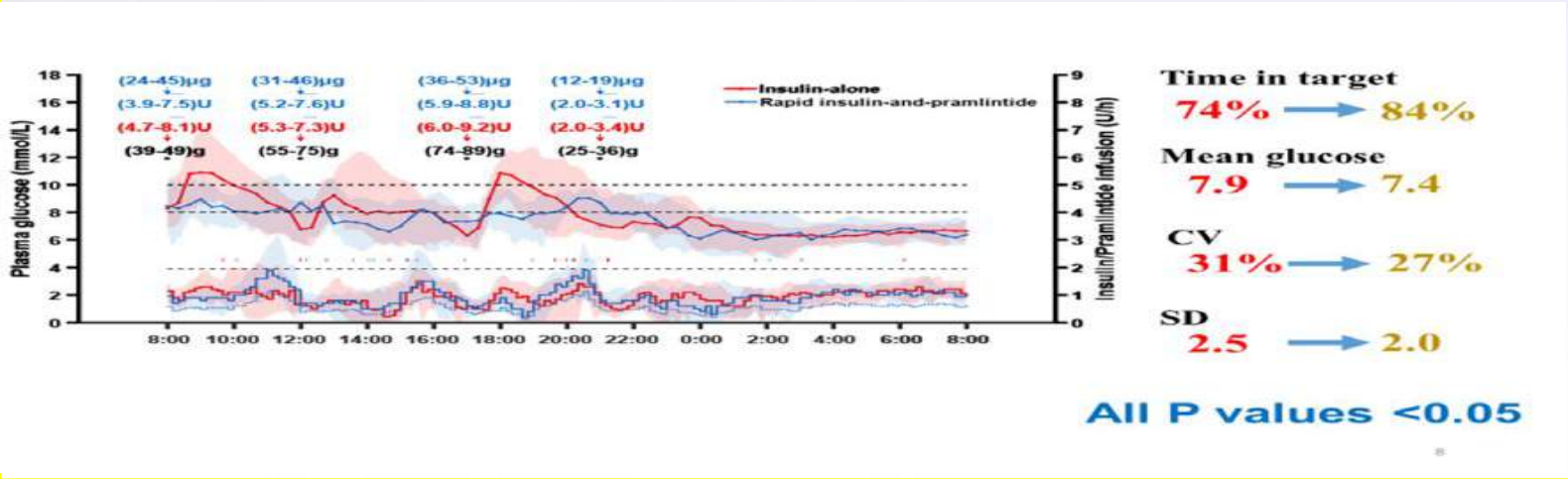
Yapay Pankreas Yemek Sonrası Kan Şekeri Kontrolü: Insuline Ek İlaç Kullanımı

-Ek ilaclar

- Adjunctive pramlintide, liraglutide: Delaying and blunting of peak post- meal hyperglycemia
  Sherr et al, Diabetes Care2016; 39:1127-134
  Galderisi et al, J Clin Endocrinol Metab. 2018 Mar 1;103(3):1088-1094

-Adjunctive DPP4 inhibitors

Underland et al., J Diabetes Sci Technol. 2017 May;11(3):602-610.



Haidar et al, ATTD 2019

- **Adjunctive Therapies to Optimize Closed-loop Glucose Control**
  Shylaja Srinivasan MD, Laya Ekhlaspour MD, and Eda Cengiz MD, MHS
  In submission

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 23, Number 6, 2021
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2020.0546

DTT

ORIGINAL ARTICLE

First Outpatient Evaluation of a Tubeless Automated Insulin Delivery System with Customizable Glucose Targets in Children and Adults with Type 1 Diabetes

Omnipod 5

-Patch pump
-Hedef kan şekeri değiştirme fonksyonu
-14 gun standard tedavi , 14 gün Omnipod 5
-Hba1c -1.3% (MDI), -0.9% (pompa)

Forlenza et al., DTT 2021

iLet
Beta Bionics
-insulin
-insulin+glukagon

- İnsulin ve çoklu hormon sistem (insulin+glucagon)
- İnsulin rezervuar yerine kartuş sistemi

open source do-it-yourself (DIY) Loop code base

Tidepool-Loop

#OpenAPS:

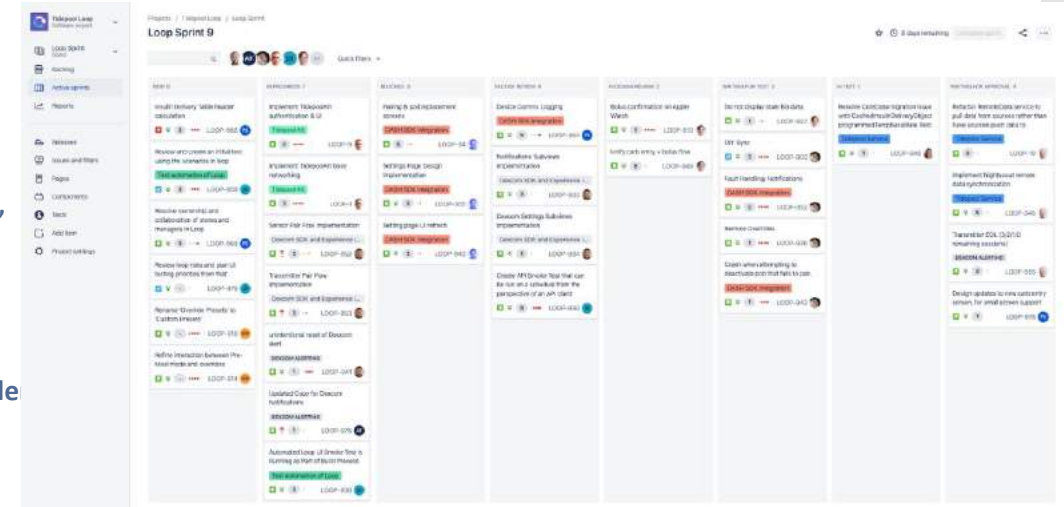
Taking the DIY, artificial pancreas from (n=1) to (n=1)*many by:

- Focusing on safety
- Limiting dosing ability in hardware and software
- Using same dosing calculations a person would use
- Responding (or not) to unexpected data
- Tolerating communication failures
- Failing back safely to standard device operation

@DanaMLewis

Reference design, code, documentation at OpenAPS.org

- ACE Pump
  - **“alternate controller-enabled”**
- iCGM
  - **“integrated continuous glucose monitor”**
- iAGC
  - **“interoperable automated glycemic controlle**
- #WeAreNotWaiting



Yakin Gelecekte Gorecegimiz Gelismeler

- CGM+infuzyon seti kombinasyonlari
- Micro CGM, insulin pompalar
- Çoklu tedavi: Insulin ile koformulasyon ve kombine diger tedaviler (Adjunct)
- Çoklu bilgi toplayan sensorla güçlendirilmis sistemler
- Kişiye özel insulin tedavisi

(precision medicine)

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

Yale Center for Clinical Investigation

NIH National Institute of Diabetes and Digestive and Kidney Diseases

ISPAD International Society for Pediatric and Adolescent Diabetes

BAU Bahçeşehir University

UNIVERSITY OF VIRGINIA 1819

Robert E. Leet and Clara Guthrie Patterson Foundation

JCHR JAEB CENTER FOR HEALTH RESEARCH

MannKind Corporation