Quali Ostacoli al “Full Closed Loop” e Come Superarli

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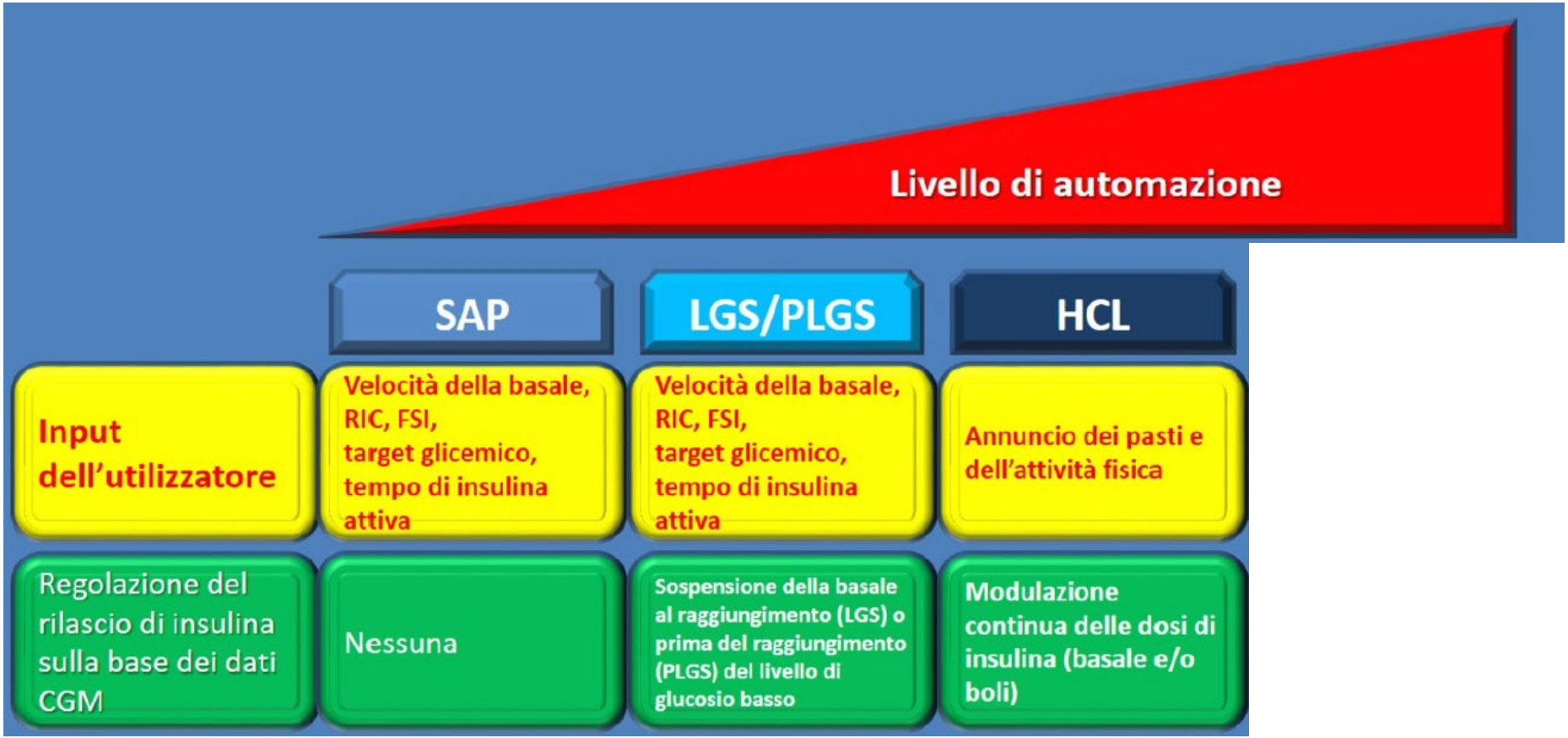
UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

Il Dr Sergio Di Molfetta dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Ascensia Diabetes Care
- Movi S.p.A
- Roche Diabetes Care Italy

Dichiara altresì il proprio impegno ad astenersi, nell’ambito dell’evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc...)

Key Developmental Milestones Towards a "Truly" Artificial Pancreas

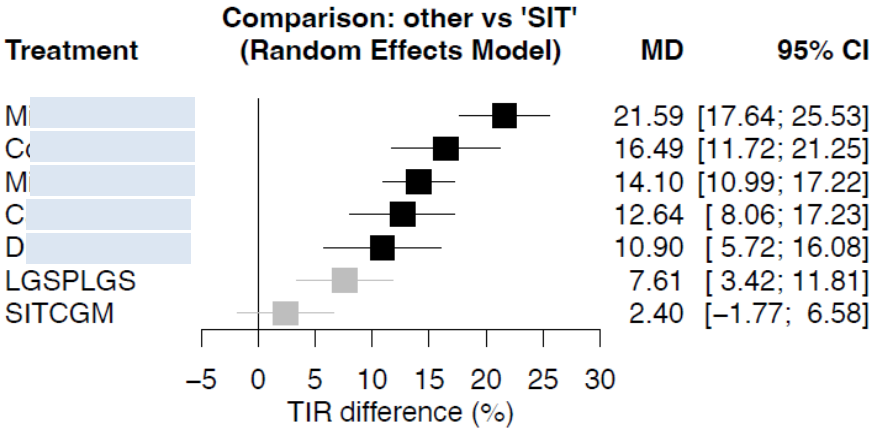


Di Molfetta S et al. L'Endocrinologo 24, 343–348 (2023)

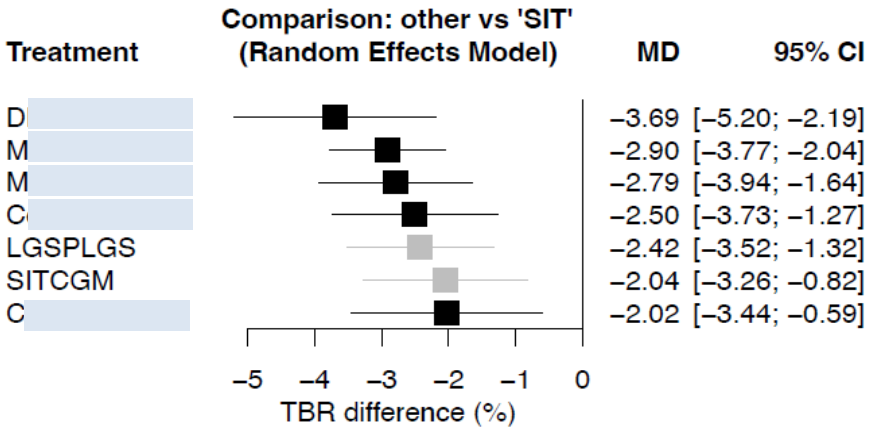
Efficacy And Safety of Different HCL Systems in People With T1D

Network Meta-Analysis; 28 Randomized Clinical Trials, n = 2,446

Time in range 70-180 mg/dL (TIR)



Time below 70 mg/dL (TBR)



HCL, hybrid closed loop; T1D, type 1 diabetes; SIT, subcutaneous insulin therapy without continuous glucose monitoring (CGM): multiple daily injections (MDI) w/o CGM, continuous subcutaneous insulin infusion (CSII) w/o CGM, mixed MDI and CSII w/o CGM; SITCGM, subcutaneous insulin therapy w/ CGM: MDI w/ real-time CGM (RT-CGM), MDI w/ intermittently scanned CGM (isCGM), mixed MDI and CSII w/ or w/o CGM, sensor-augmented pump therapy (SAPT); LGSPLGS: predictive lo glucose suspension (PLGS), mixed SAPT w/ or w/o low glucose suspension (LGS), mixed SAPT and PLGS.

Di Molfetta S, Di Gioia L, Caruso I et al. Diabetes Metab Res Rev. 2024 Sep;40(6):e3842

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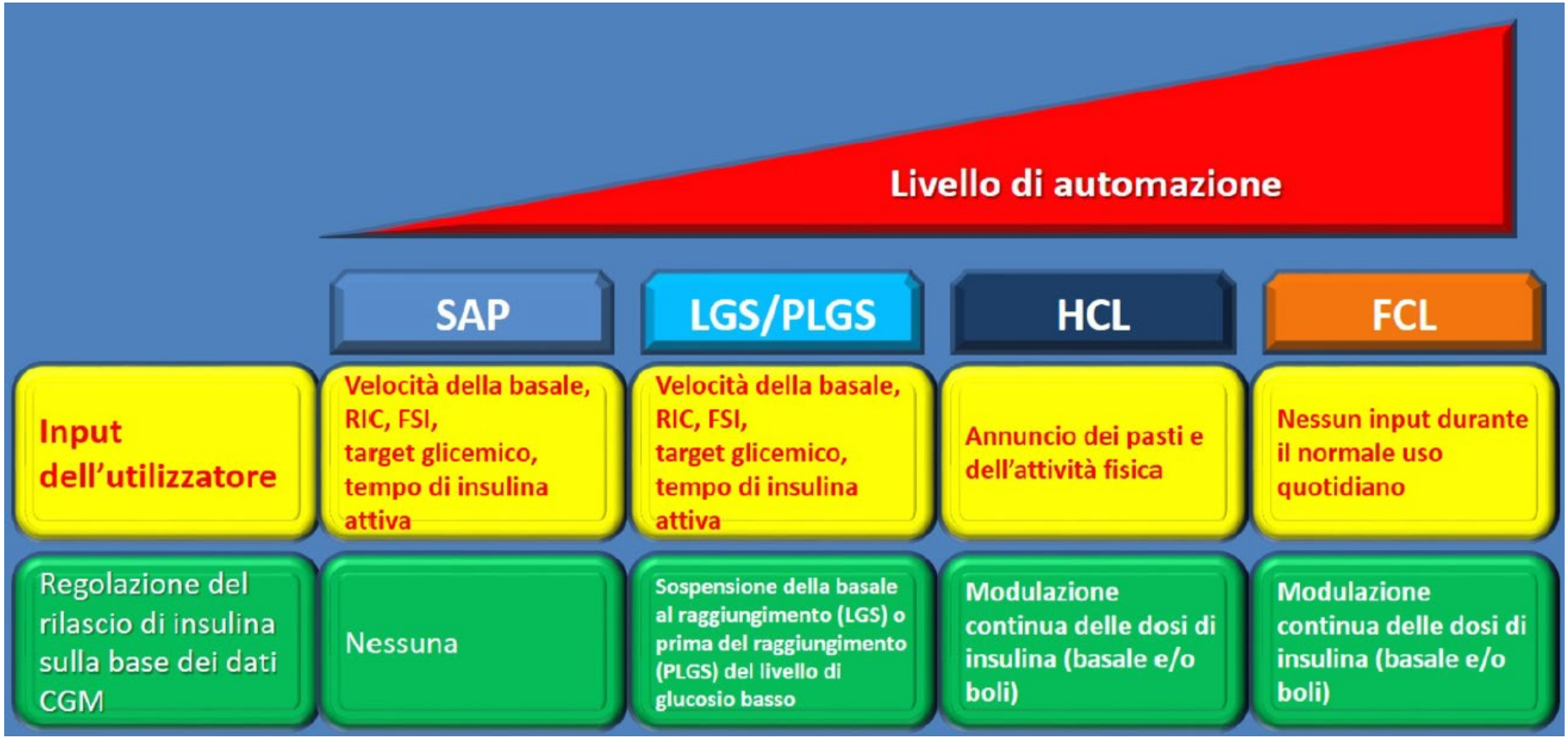

Di Molfetta S et al. L'Endocrinologo 24, 343–348 (2023)

Barriers to Full Closed Loop

- Time lag in sensor glucose values as measured in interstitial fluid vs blood
- Delayed adsorption of insulin from subcutaneous depot
- Different pharmacodynamics of applied insulin vs. physiological secreted insulin
- Peripheral vs portal delivery
- Meal and physical activity detection
- Glucose-only vs multiple-input sensing
- Insulin-only vs. multihormonal delivery
- Need for inserting and wearing multiple devices on the body

Emerging Directions in Automated Insulin Delivery

- Faster-acting insulin analogs
- Adjunct therapies
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Fully Closed-Loop Delivery With Ultrarapid-Acting Insulin Analogues

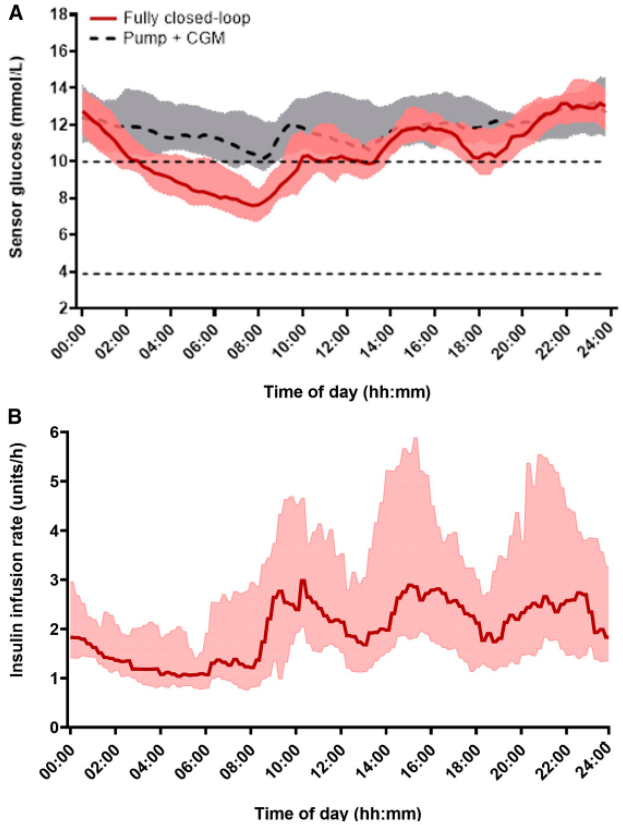
Randomized Crossover Trial, 8-week Interventions; n = 26 (T1D), Age 41±12 yrs, HbA1c 9.2±1.1%

Time in range (3.9–10.0 mmol/L) was higher during closed-loop than during pump with CGM (50.0 ± 9.6% vs. 36.2 ± 12.2%,mean difference 13.2 percentage points [95% CI 9.5, 16.9], P < 0.001)

Time with glucose >10.0 mmol/L and mean glucose (10.7 ± 1.1 vs. 12.0 ± 1.6mmol/L, mean difference 21.2 mmol/L [95% CI 21.8, 20.7], P < 0.001) were lower during closed-loop than during pump with CGM

Time with glucose <3.9 mmol/L was similar between periods (closed loop 0.88% [0.51–1.55] vs. pump with CGM0.64% [0.28–1.10], P = 0.102)

Total daily insulin requirements did not differ (closed-loop 51.9 units/day [35.7–91.2] vs. pump with CGM 50.7 units/day [34.0–70.0], P = 0.704)



Boughton CK et al. Diabetes Care. 2023 Nov 1;46(11):1916-1922

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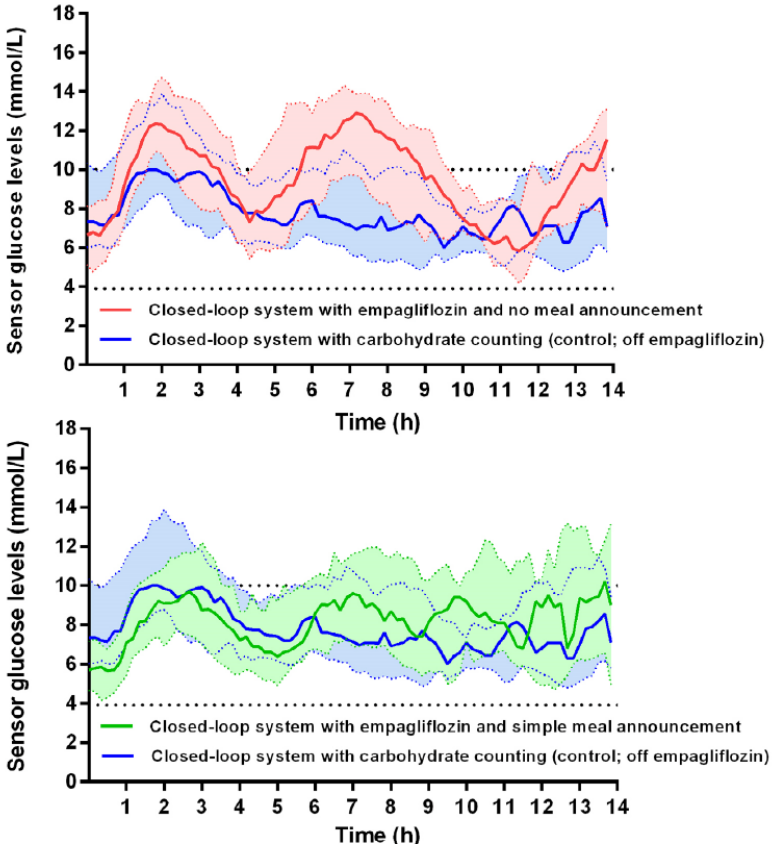
Closed-Loop Insulin Delivery With Adjunct Therapies (SGLT2 Inhibitors)

2-Month Randomized Crossover Trial; n = 30 (T1D), Age 40±15 yrs, HbA1c 7.6%±0.7%

Mean glucose level was **not** non-inferior with no meal announcement strategy and empagliflozin (10.0 ± 1.6 mmol/L) compared with the carbohydrate counting strategy and no empagliflozin (8.5 ± 1.5 mmol/L; non-inferiority p = .94 for a margin of 0.75 mmol/L)

The simple meal announcement strategy with empagliflozin and the carbohydrate-counting strategy with no empagliflozin had similar mean glucose level, times in the target range (68% ± 16% and 70% ± 23%), hyperglycaemia >10.0 mmol/L and hypoglycaemia <3.9 mmol/L, as well as CV and SD

Mean fasting ketone level was higher with empagliflozin vs. without empagliflozin (no episodes of diabetic ketoacidosis)



Haidar A et al. Diabetes Obes Metab. 2021 Jun;23(6):1272-1281

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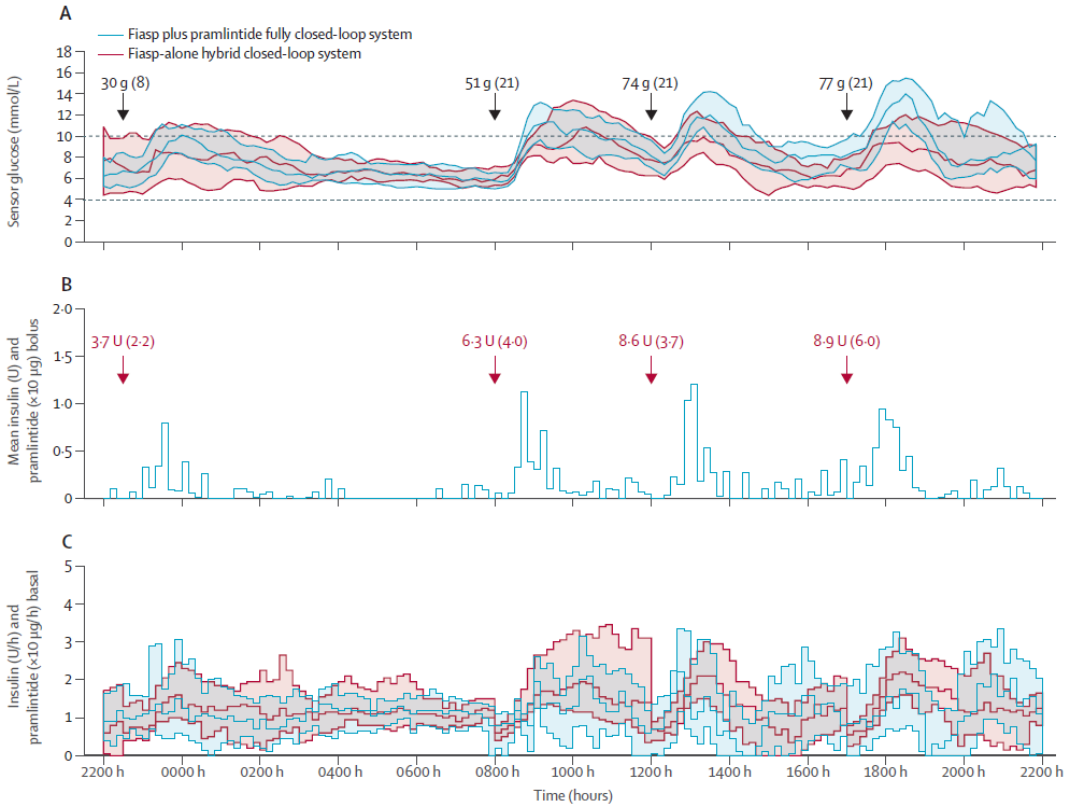
Faster Aspart Plus Pramlintide Closed-Loop System With no Meal Input

Randomized Crossover Trial, 27-h Interventions; n = 24 (T1D), Age 35±14 yrs, HbA1c 8.1±1.3%

Time spent in the target range was 74.3% [61.5–82.8] with the FCL system vs. 78.1% [66.3–87.5] with the HCL system (paired difference 2.6%, 95% CI –2.4 to 12.2; non-inferiority p=0.28)

Total daily basal insulin was 30.5 U [19.8–39.9] with the FCL system and 30.7 U [23.4–44.4; p=0.42] with the HCL. The FCL system delivered 18.8 U [13.4–23.6] of bolus compared with 27.9 U [18.6–33.1] with the HCL system

Non-mild nausea was reported by three (13%) participants and non-mild bloating by one (4%) participant with the FCL system compared with zero participants with the HCL system



Tsoukas MA et al. Lancet Digit Health. 2021 Nov;3(11):e723-e732

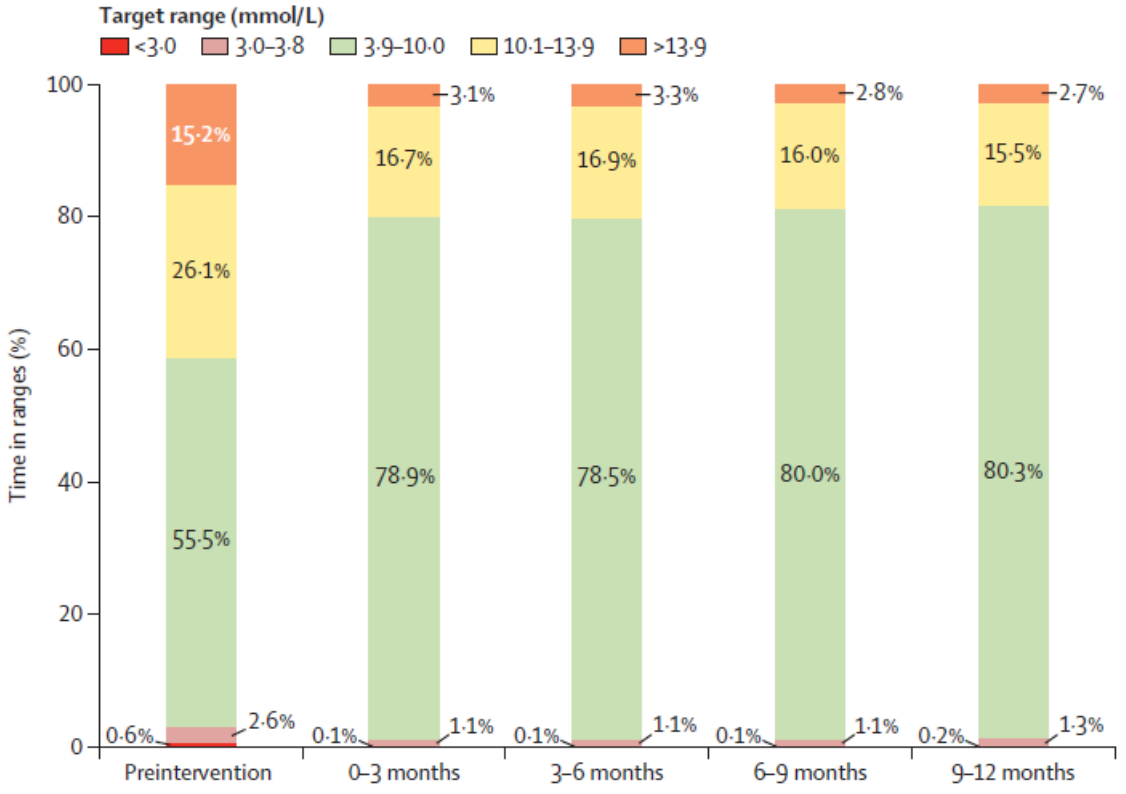
Bihormonal (Insulin And Glucagon) Fully Closed-Loop System

1-year Prospective Single-Arm Trial; n = 78 (T1D), Age 47.7±12.4 yrs, HbA1c 7.8±3.1%

Median daily insulin use was 51·9 units [34.1–83.3] after 12 months versus 44.0 units [33.0–60.8] preintervention (p<0.0001)

Questionnaire scores improved on PAID from 30.0 [18.8–41.3] preintervention to 10.0 [3.8–21.3; p<0.0001] at 12 months and on WHO-5 from 60.0 [44.0–72.0] preintervention to 76.0 [60.0–80.0; p<0.0001] at 12 months

The number of injection site reactions at the glucagon infusion site was higher than at the insulin injection site. Nausea was also reported. Occlusions of the glucagon infusion sets occurred quite frequently



van Bon AC et al. Lancet Digit Health. 2024 Apr;6(4):e272-e280

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Bolus Priming and Meal Anticipation For Improving FCL Delivery

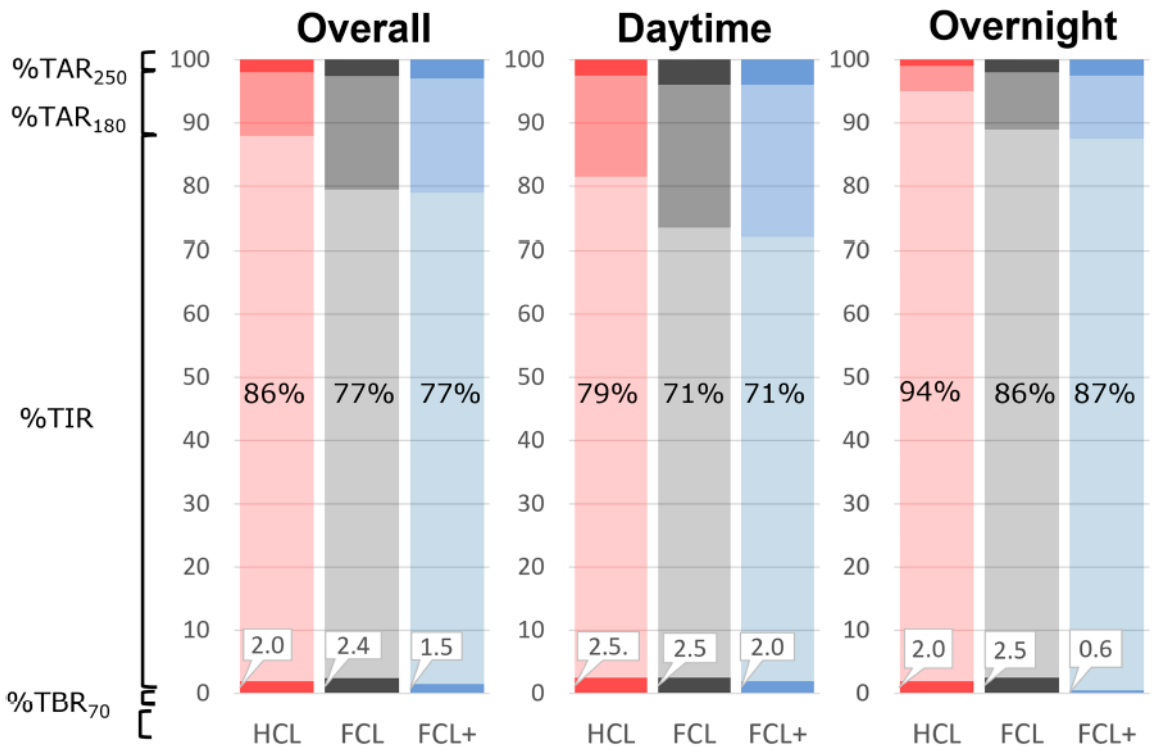
Randomized Crossover Trial, 24-h Interventions; n = 35 (T1D), Age 44.5±15.4 yrs, HbA1c 6.7±0.9%

This study compared three modalities of the latest UVA AID system:

- HCL: carbohydrate announcement
- FCL: no carbohydrate announcement with automated bolus priming
- FCL+: no carbohydrate announcement enhanced with meal anticipation

14-day baseline period for analysis of glycemic control, meal patterns, and insulin use

Modalities were tested during three supervised 24-h admissions, where breakfast, lunch, and dinner were consumed per participant's home schedule, at a fixed time, and with a 1.5 h delay, respectively



Garcia-Tirado J et al. Diabetes Care. 2023 Sep 1;46(9):1652-1658

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Anticipation of Exercise Patterns for reducing Hypoglycemia around PA

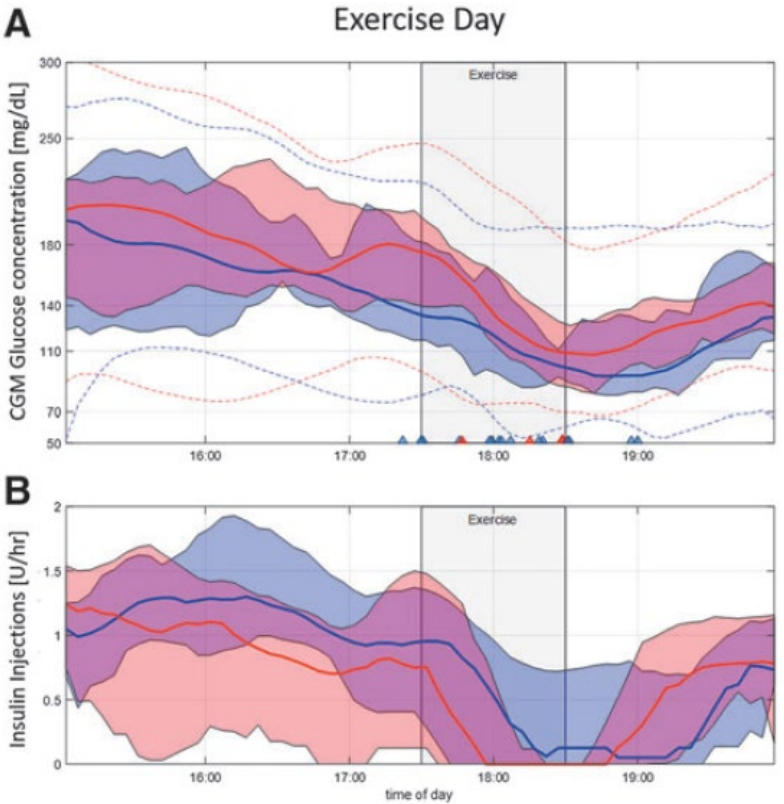
Randomized Crossover Trial; n = 15 (T1D), Age 42.0±13.5 yrs, HbA1c 6.6±1.0%

4-week at-home data collection (CGM, pump, activity tracker, user-led recording of carbohydrate intake using the pump or a dedicated app):

- Moderate-intensity exercise (target heart rate: 110–140 beats per minute) between 4 and 7 PM, for at least 30 min per day and at least four times per week

Two 32-h admissions under supervised conditions (exercise-aware artificial pancreas [APEX] vs. standard HCL algorithm):

- Day 1: at around 5:30 PM three 15-min aerobic, moderate intensity, exercise bouts on an elliptical or treadmill machine, separated by 5-min resting periods
- Day 2: sedentary activities until discharge



CGM and insulin in the hours before and after exercise are expected for **APEX** and **HCL**. Triangles are hypoglycemia treatments.

Garcia-Tirado J et al. Diabetes Technol Ther. 2021 Apr;23(4):277-285

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AHCL With Meal Bolus Based on Hand-Gesturing Algorithm

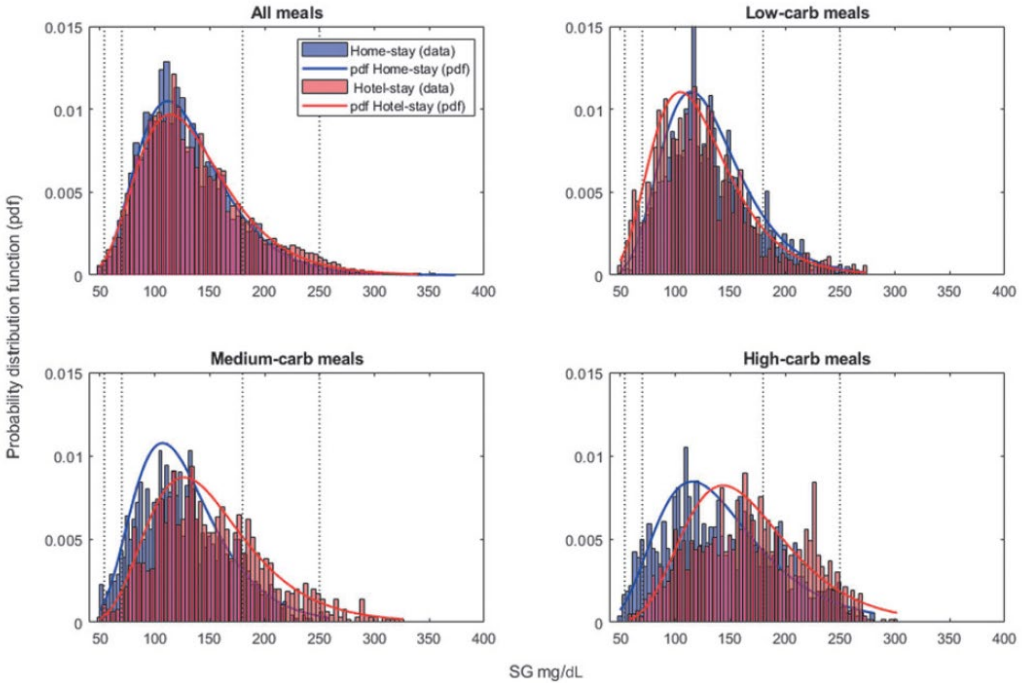
Single-Arm Feasibility Trial; n = 18 (T1D), Age 37.4±12.0 yrs, Diabetes Hystory 21.8±11.4 yrs

The “Hands-free” closed loop system consists of the M…… AHCL system and a smartwatch paired with a smartphone

- The smartwatch-based application detects eating and drinking hand gestures based on real-time data from the motion sensors in the smartwatch
- A proprietary artificial intelligence/machine learning algorithm translates the gestures to a bite-sized carb announcement that is relayed to the pump for automatic bolusing

Study period divided into two phases:

- Home-stay phase (5 days): carbohydrate counting, application disabled
- Hotel-stay phase (5 days): unannounced meals, application enabled



Roy A et al. Diabetes Technol Ther. 2024 Sep;26(9):633-643

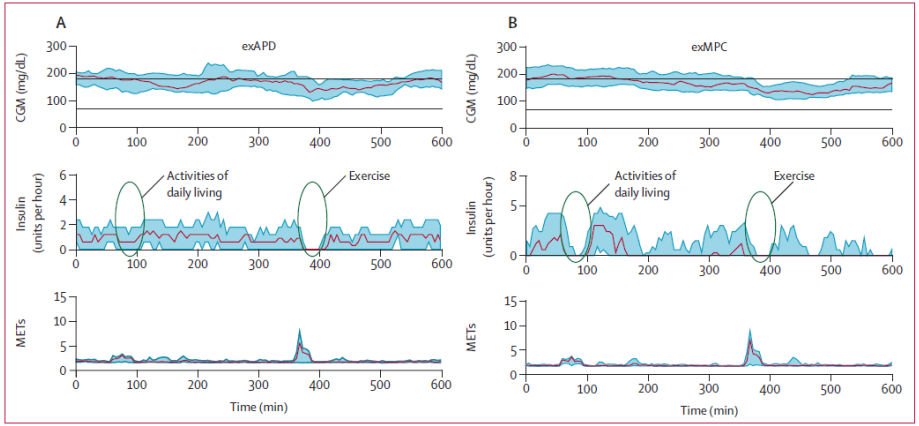
Automatic Insulin Adjustments Using Real-Time Wearable Fitness Data

Randomized Crossover Trial, 76-h Inteventions; n = 25 (T1D), Age 34.4±8.8 yrs, HbA1c 6.4±0.6%

Heart rate and accelerometry data are received wirelessly from a commercially available wrist-worn fitness monitor (smartwatch)

- Exercise-aware adaptive proportional derivative (exAPD) algorithm detects exercise, prompts the user, and shuts off insulin during exercise
- Exercise-aware model predictive control (exMPC) algorithm automates insulin adjustments using fitness data in real-time

Participants executed 1 week run-in on usual therapy followed by exAPD or exMPC for one 12 h primary in-clinic session involving meals, exercise, and activities of daily living, and 2 free-living out-patient days; a washout period of 6 d to 10 w was done before performing the next 76 h intervention on either the exMPC or exAPD depending on the first intervention arm



	exAPD	exMPC	Difference	P value (exAPD vs exMPC)	P value (sequence)	P value (period)
% time below range (<3·9 mmol/L)*	1·30 (2·16)	0·96 (1·21)	−0·33 (1·92)	0·47	0·53	0·98
% time in range (3·9–10·0 mmol/L)	75·5 (10·7)	71·2 (16·1)	−4·3 (16·4)	0·13	0·28	0·81
% high glucose (>10 mmol/L)	23·2 (10·9)	27·8 (16·0)	4·6 (16·5)	0·10	0·31	0·80
% very low glucose (<3·0 mmol/L)	0·13 (0·33)	0·05 (0·15)	−0·08 (0·33)			
% very high glucose (>13·9 mmol/L)*	4·5 (5·7)	7·0 (10·9)	2·5 (11·6)	0·27	0·17	0·92
Mean glucose (mmol/L)†	8·5 (0·9)	8·8 (1·3)	0·32 (1·3)	0·17	0·34	0·56
Rescue carbohydrate (count per day)‡	1·03 (1·34)	0·65 (0·84)	−0·38 (1·15)	0·14	0·17	0·59
Insulin (units per day)§	40·8 (16·0)	44·6 (22·6)	3·8 (11·4)	0·25	0·61	0·162

Data are mean or difference (SD). The p value for sequence indicates the significance of the sequence of doing the exAPD versus exMPC first. The p value for the period indicates whether the order of doing the intervention, regardless of the type, was significant. exAPD=exercise-aware adaptive proportional derivative. exMPC=exercise-aware model predictive control. *p values estimated using bootstrapped standard errors. †p values from mixed effects regression model on inverse-transformed glucose (mmol). ‡p values from negative binomial (count) regression model. §p values from model with log (insulin per day) as outcome.

Table 4: Outcome metrics comparing the exAPD algorithm versus the exMPC algorithm across the entire 76 h study

Jacobs PG et al. Lancet Digit Health. 2023 Sep;5(9):e607-e617

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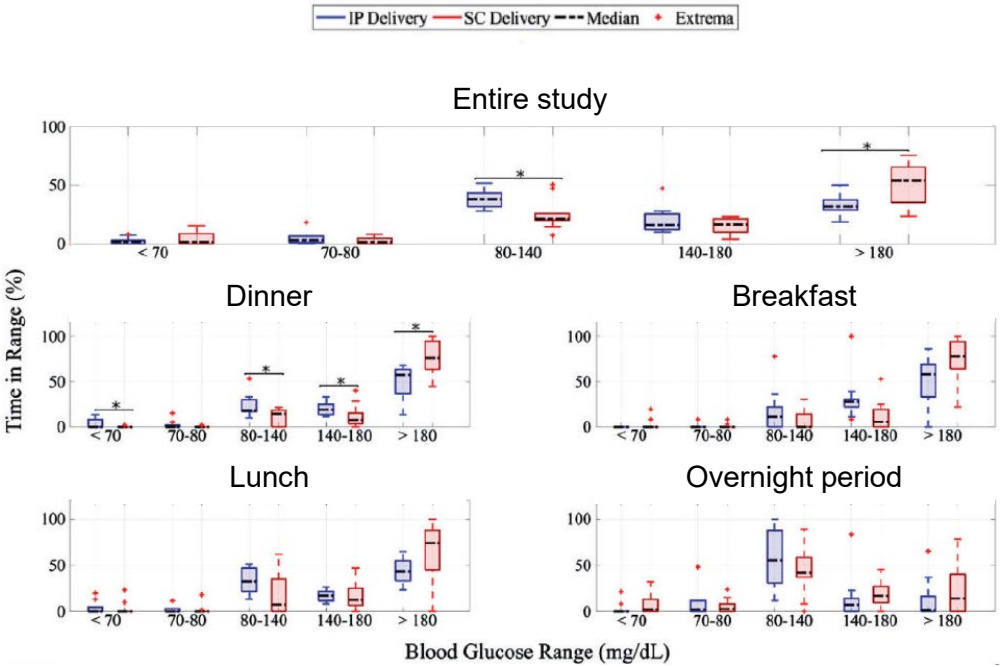
Intraperitoneal Insulin Delivery in MPC-Based Fully-Automated AP

Non-Randomized Sequential Trial; n = 10 (T1D), Age 49.0±11.0 yrs, HbA1c 7.7±1.0%

Each subject participated in two 24-hour admissions in a non-randomized, non-blinded sequential design:

- 1st admission: closed-loop system with SC fast-acting insulin analogue delivery
- 2nd admission (4 to 20 weeks from 1st admission, following implantation of the IP insulin delivery system): closed-loop system with IP regular insulin delivery

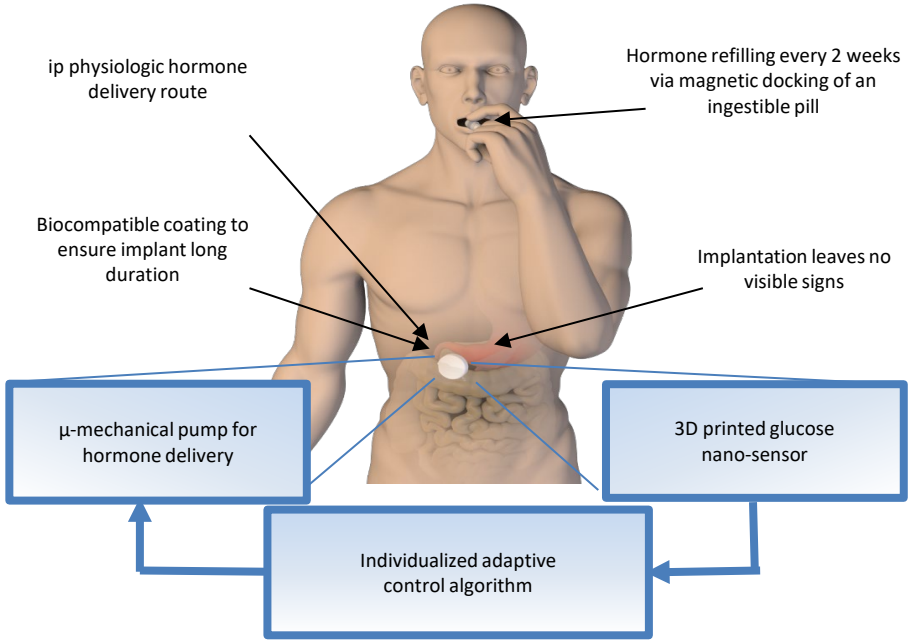
The clinical protocol included 3 unannounced meals: a 70 g-CHO dinner at ~7:00 PM, a 40 g-CHO breakfast at ~8:00 AM and a 70 g-CHO lunch at ~1:00 PM



MPC, model-predictive control; AP, artificial pancreas, SC, subcutaneous; IP, intraperitoneal; CHO, carbohydrate; *statistically significant difference between data

Dassau E et al. Diabetes Obes Metab. 2017 Dec;19(12):1698-1705

The bionic implantable pancreas : a radically new ip fully closed-loop technology



Courtesy of Cobelli C, 2024

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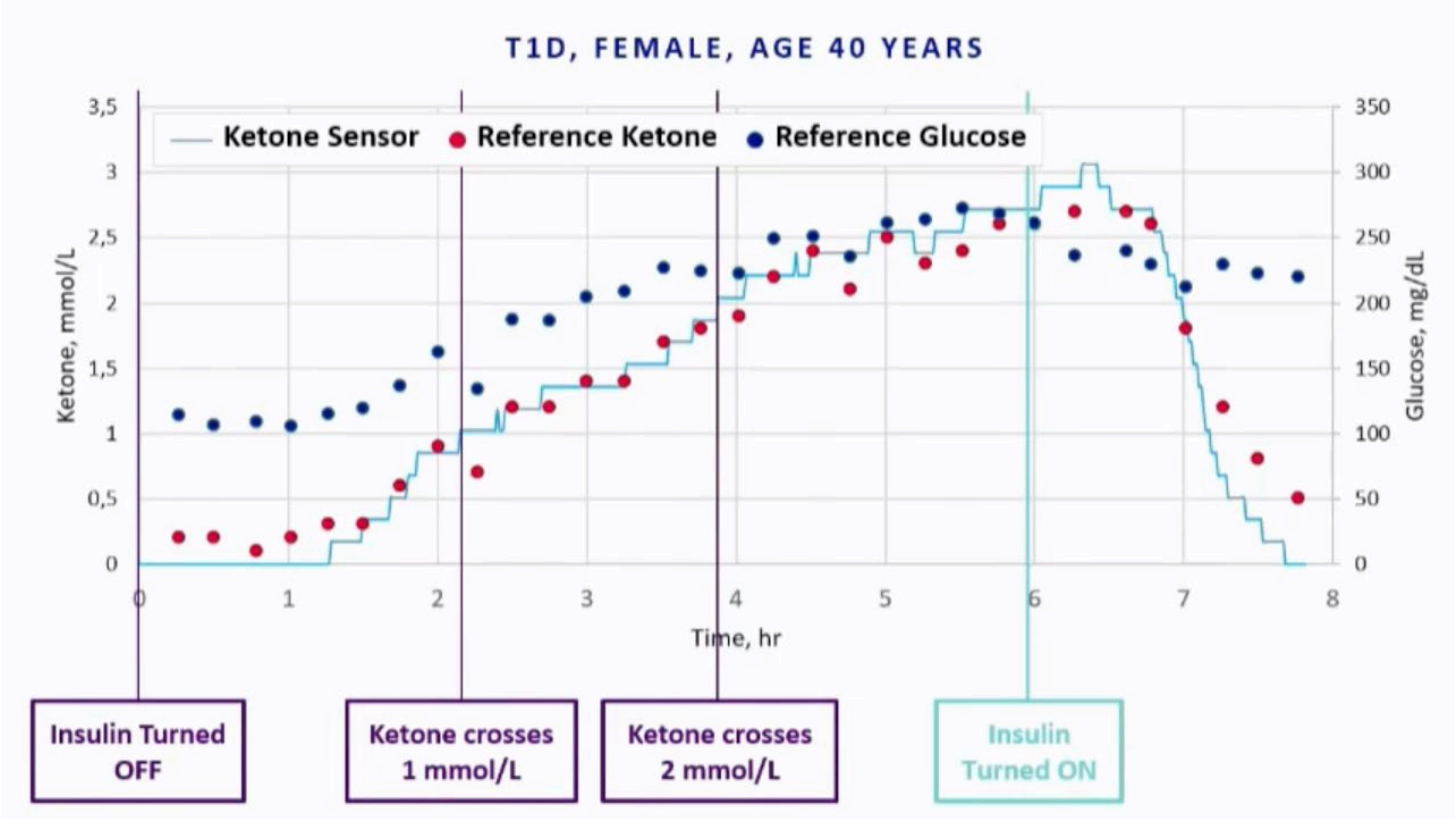
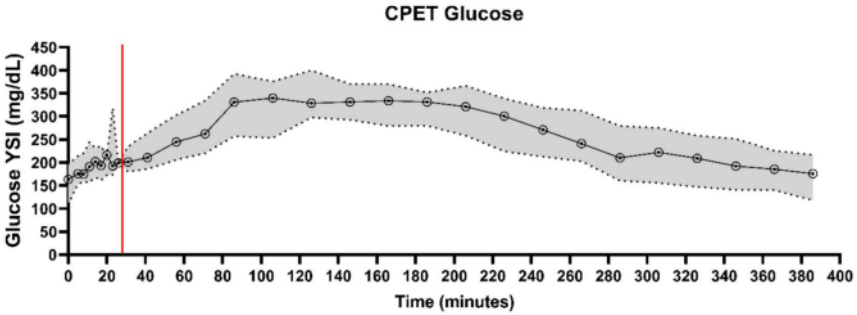
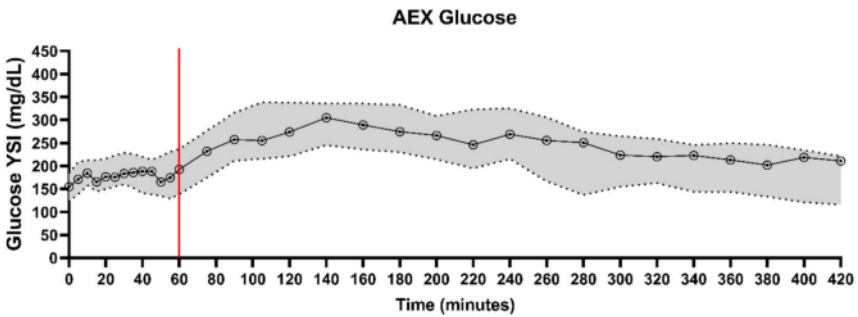
Continuous Ketone Monitoring

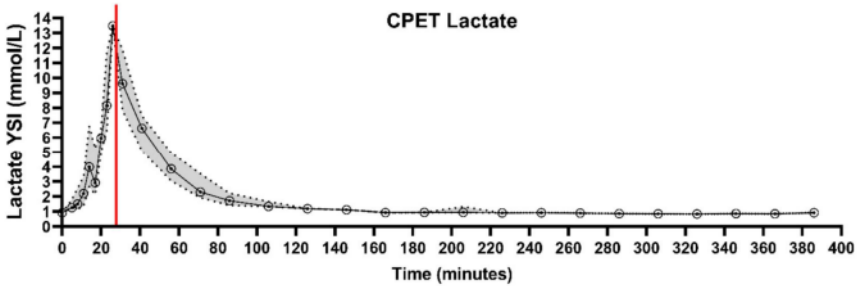


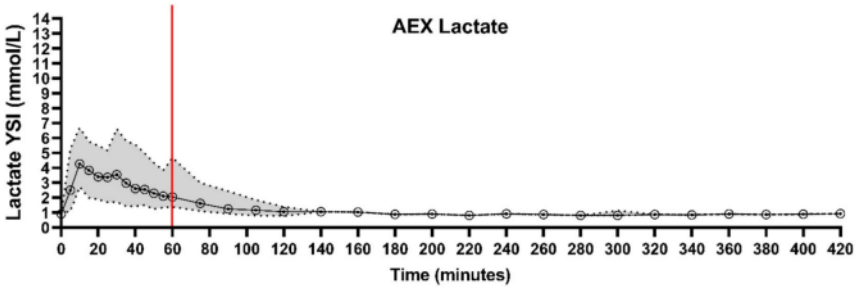
Trends of Lactate During Anaerobic And Aerobic Exercise in T1D

Prospective Pilot Study; n = 21 (T1D), Age 29 yrs [28, 38], HbA1c 7.2% [6.7–7.8]







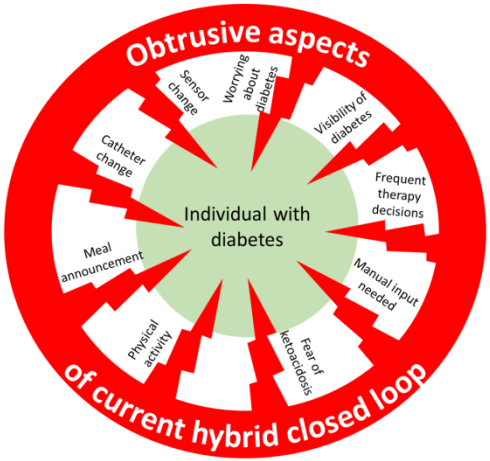


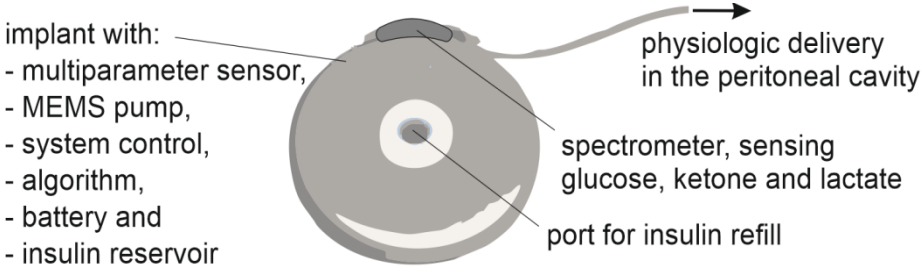
Anaerobic Exercise

Aerobic Exercise

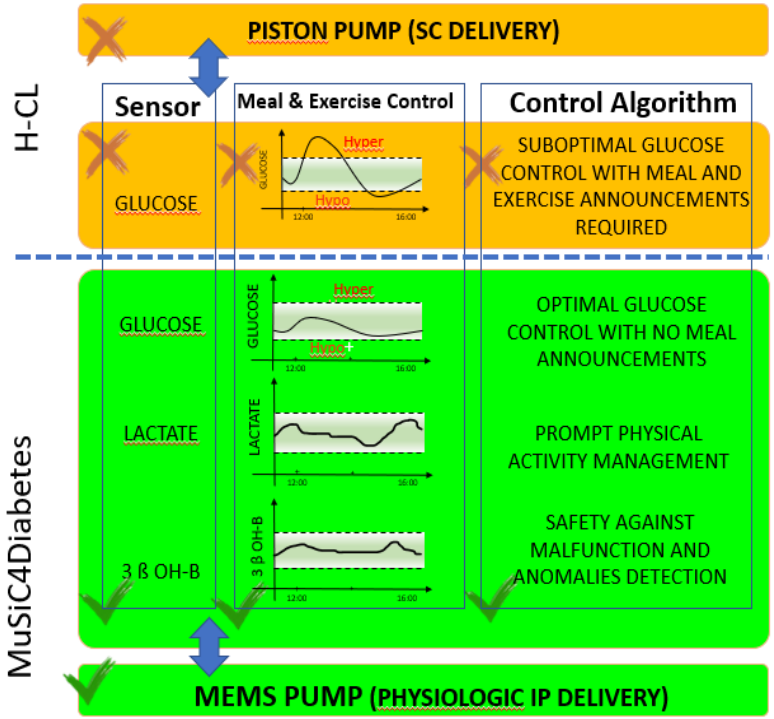
De Ridder F et al. Diabetes Metab Res Rev. 2022 Sep;38(6):e3537

Unobtrusive treatment of diabetes





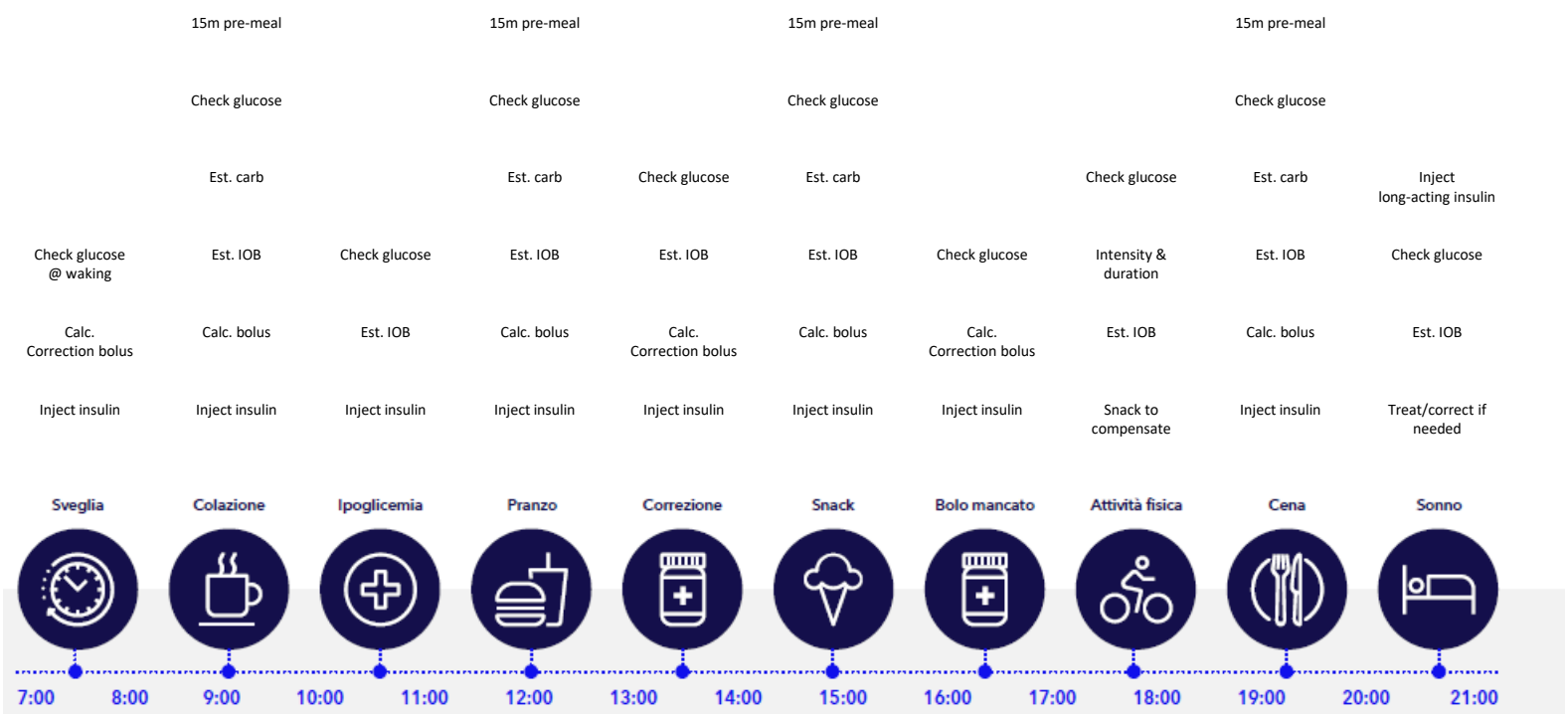
MuSiC4Diabetes: Achieving unobtrusive diabetes management



Courtesy of Cobelli C, 2024

Example Changes in The Burden of T1D Treatment Over The Last Years

Multiple Daily Injections Therapy



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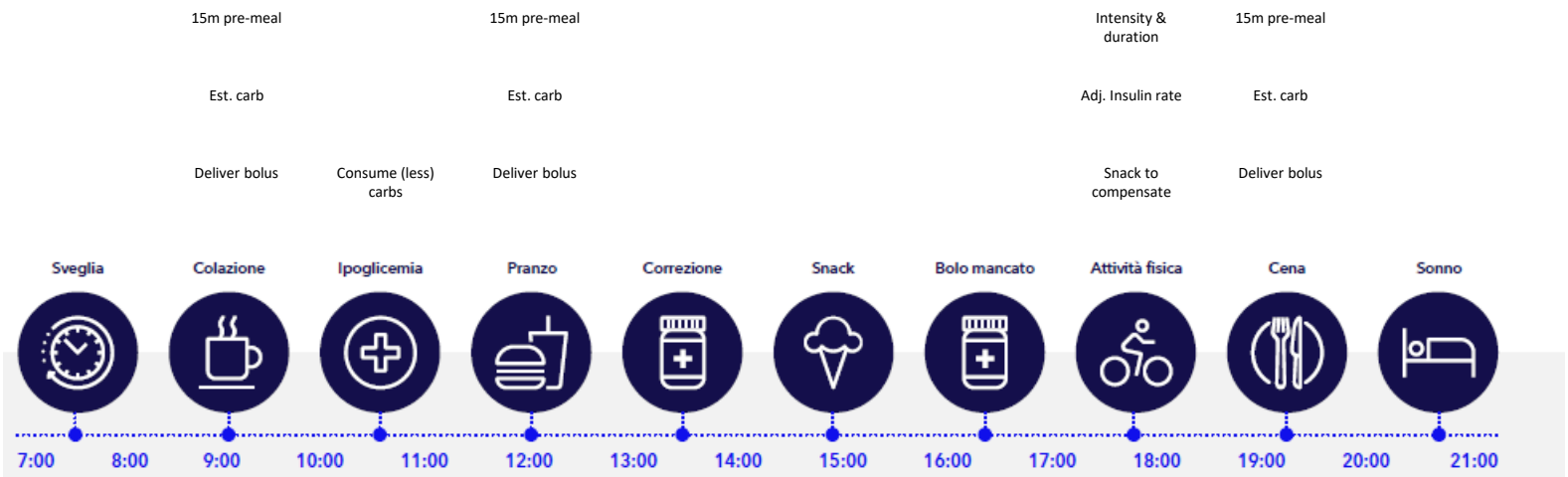
Hybrid Closed Loop Insulin Delivery



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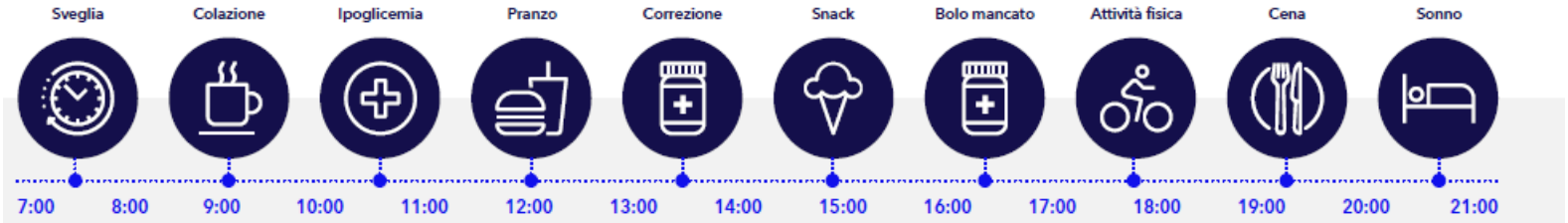
Full Closed Loop Insulin Delivery




Grazie