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diabetes  
foreningen



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SCIENTIFIC  
SESSIONS

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# Performance of a Dual-Hormone Closed-Loop System versus an Insulin-Only Closed-Loop System during Challenging Inpatient Conditions

- A Single-Blinded Randomized Controlled Crossover Study

**Ajenth G. Ranjan**, Dimitri Boiroux, Christian Laugesen, Signe Schmidt, Asbjørn T. Reenberg, John B. Jørgensen, Kirsten Nørgaard

# Presenter disclosures

Ajenthen G. Ranjan

Disclosed no conflict of interest

# Photography allowed

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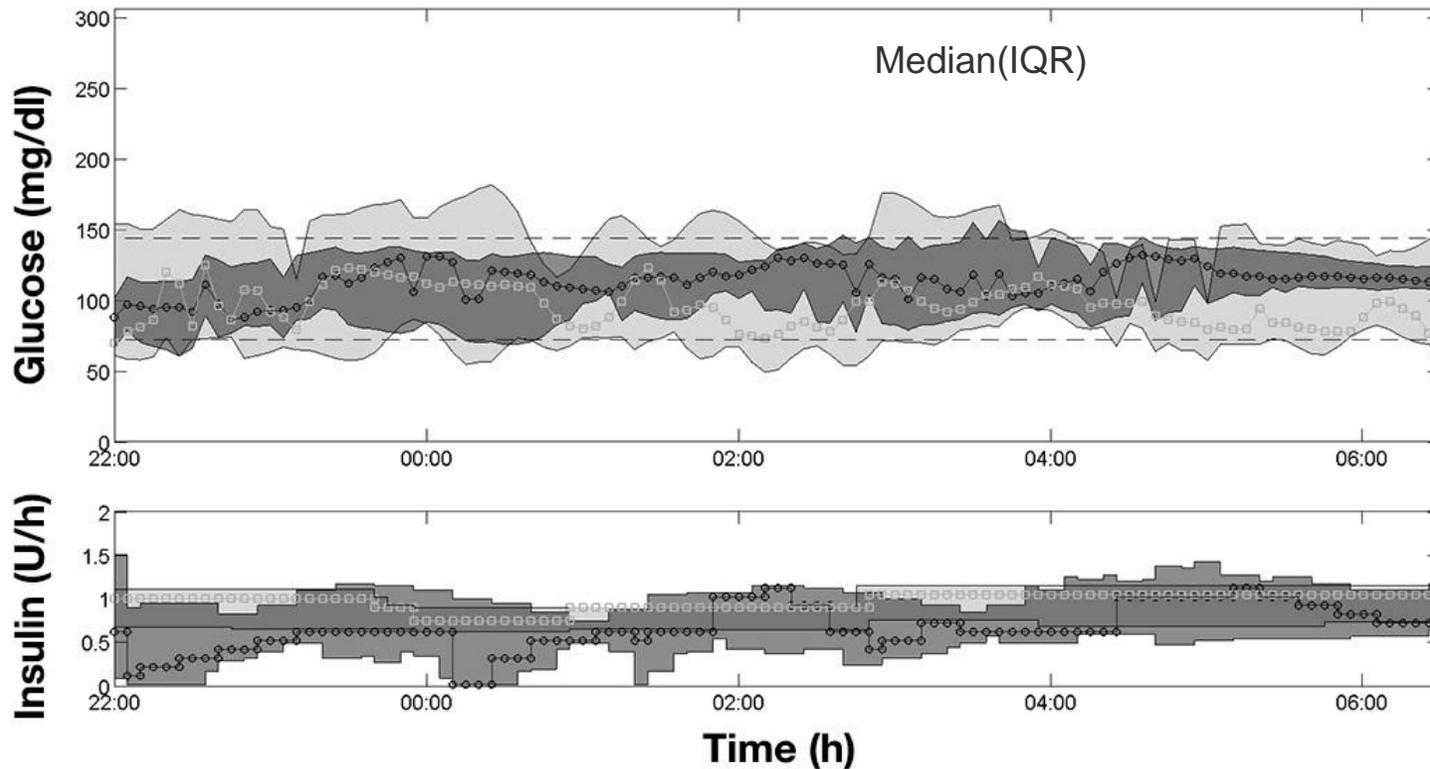


## Background

- The most technologically advanced therapy for people with type 1 diabetes is a closed-loop system
- Closed-loop systems perform better than any other technologically approaches
- Hypoglycemia remains an issue especially during challenging conditions, e.g overbolusing and exercise
- Dual-hormone closed-loop system including glucagon infusion may overcome these challenges and reduce the risk for hypoglycemia

# DIACON

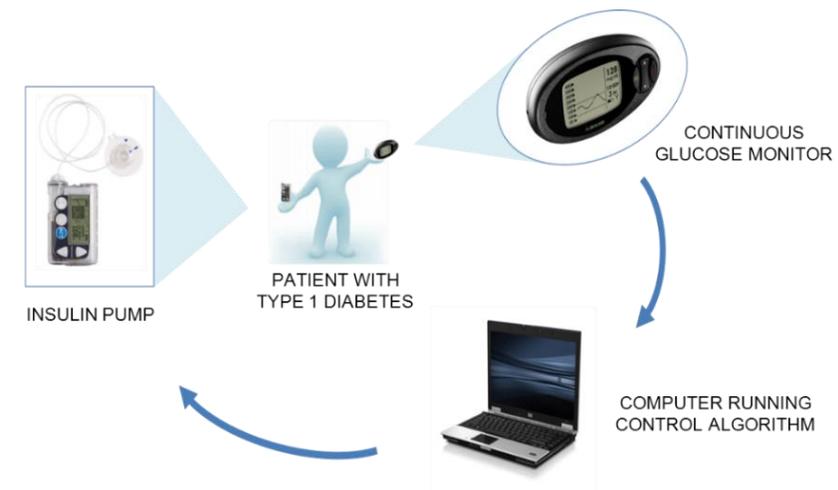
## Previous overnight study



Time in range %

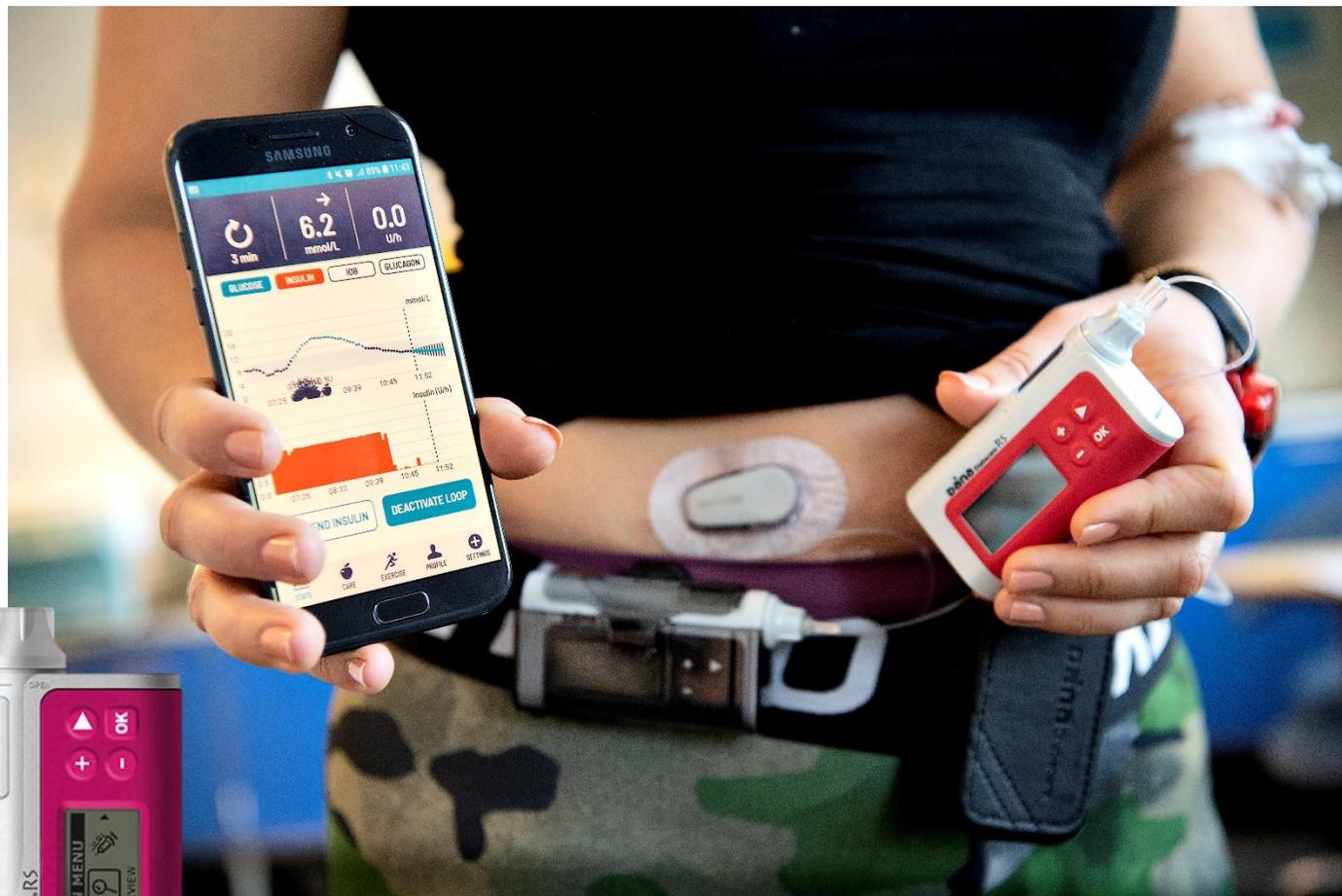
Conventional 67.9 (12.1–90.0)

Closed Loop 90.4 (84.7–99.3)



# DIACON

SINGLE- AND DUAL-HORMONE  
ARTIFICIAL PANCREAS



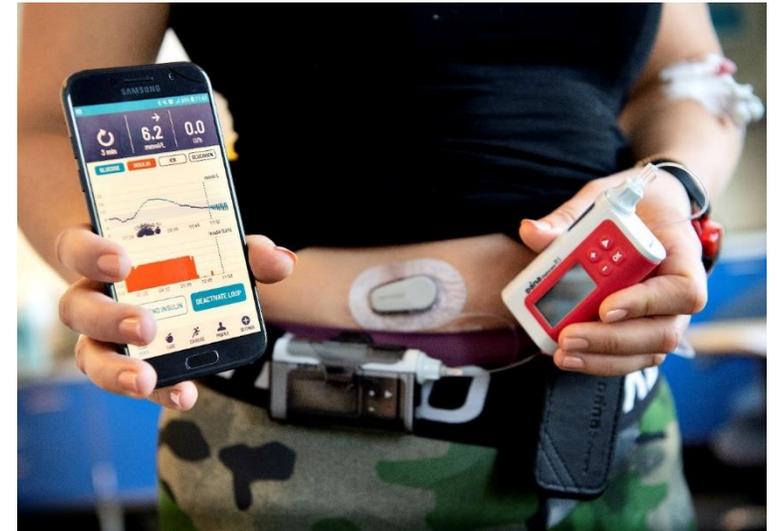
# DiaCon APS

- Model fitting based on 3-days CGM and insulin data
- Information put into the system before initiation
  - Average basal rate
  - Insulin to carbohydrate ratio
  - Insulin sensitivity
- Upper limit on basal rate, meal bolus and glucagon bolus
- Meal announcement (gram carbohydrate)
- Autocorrections only allowed for 2 hours postprandially
- No exercise announcement
- No co-administration of insulin and glucagon



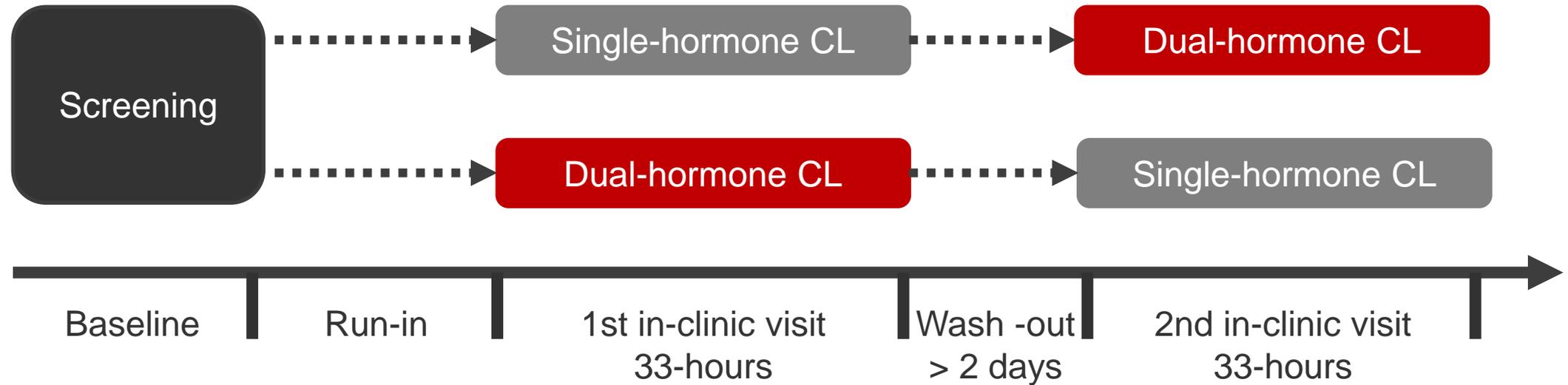
## Aim

To assess the **efficacy and safety** of an insulin-glucagon dual-hormone (DHCL) closed-loop system compared with an insulin-only single-hormone (SHCL) closed-loop system



# Design

## Single-Blinded Randomized Controlled Crossover Study



Single-hormone Closed-loop:  
Dual-hormone Closed-loop:

FiAsp and Placebo ("dummy")  
FiAsp and GlucaGen



## Eligibility criteria

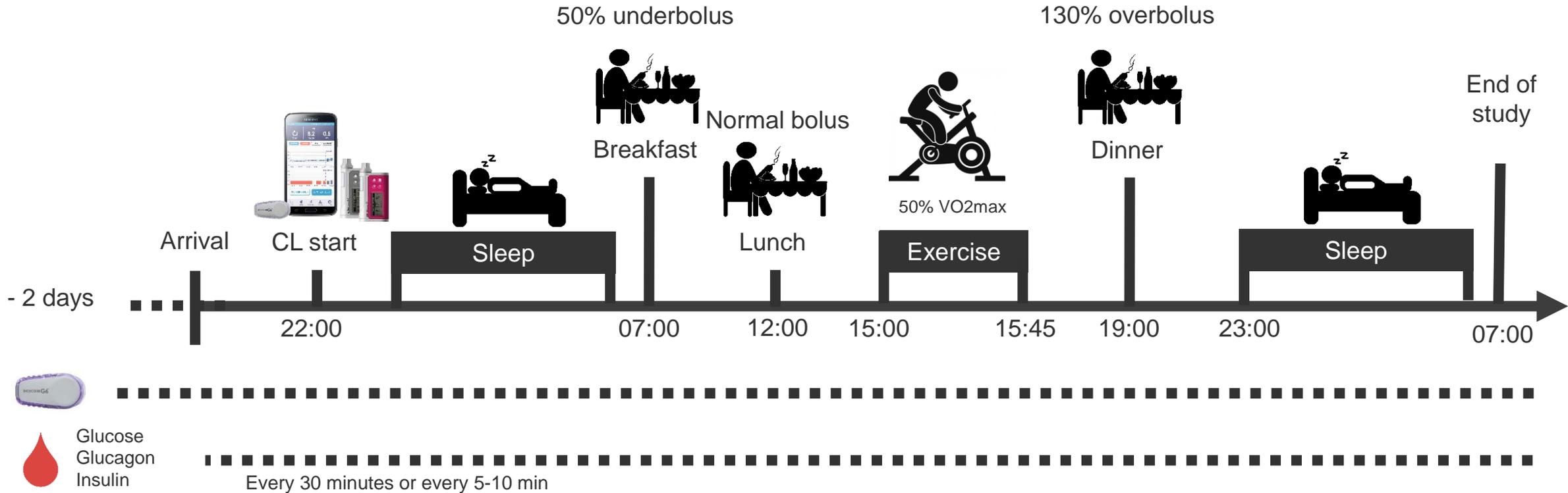
### Inclusion criteria

- Age  $\geq$  18 years
- T1D  $\geq$  2 years
- Insulin pump therapy  $\geq$  1 years
- Currently treated with FiAsp-insulin
- HbA1c  $\leq$  8.5% (69 mmol/mol)

### Exclusion criteria

- Pregnancy or nursing
- Inability to comply with procedures
- Hypoglycemia unawareness
- Use of anti-diabetic medicine (not insulin)
- History of coronary artery disease

# Study visit



# Outcomes

## Primary outcome

- Percentage of time with CGM < 3.9 mmol/l
- Number of rescue carbohydrates to hypoglycemia (PG < 3.0 mmol/l)

## Secondary outcomes

- Mean glucose level
- Glucose variability
- Number of hypoglycemic events

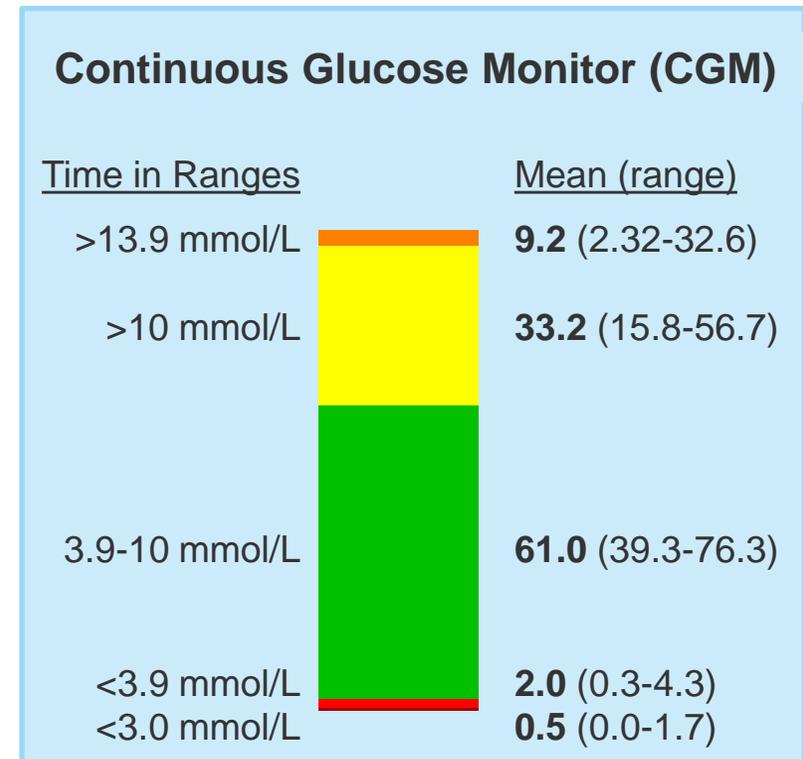
### Sample size calculation (N=13)

- Clinical effect size = 2.3%-points (30 min)
- Standard deviation = 2.7%-points<sup>1</sup>
- 80% power
- 5% significance level

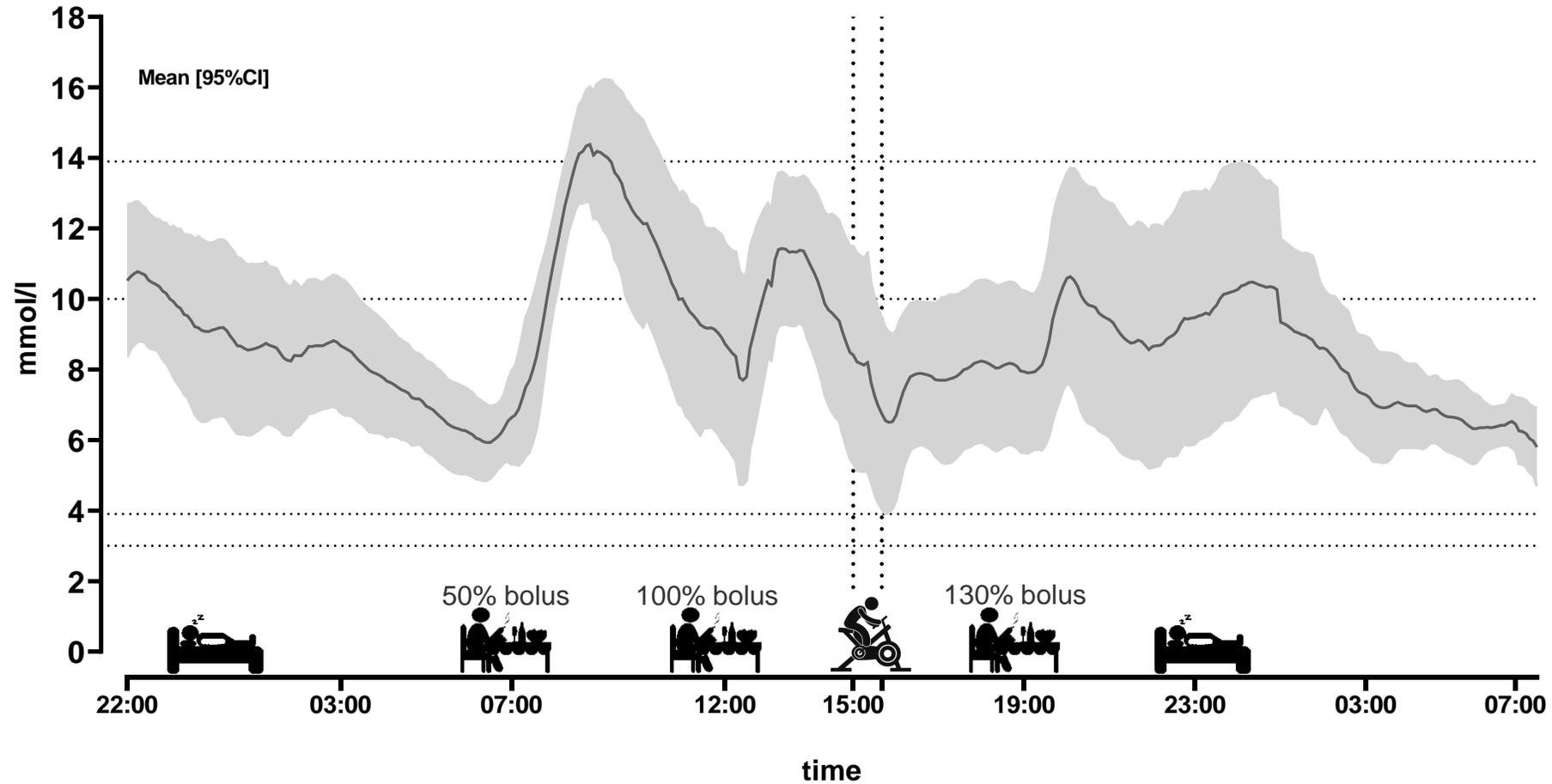
1) Haidar A. Diabetes 2014; 63 Suppl 1: A238–OR.

## Baseline Characteristic

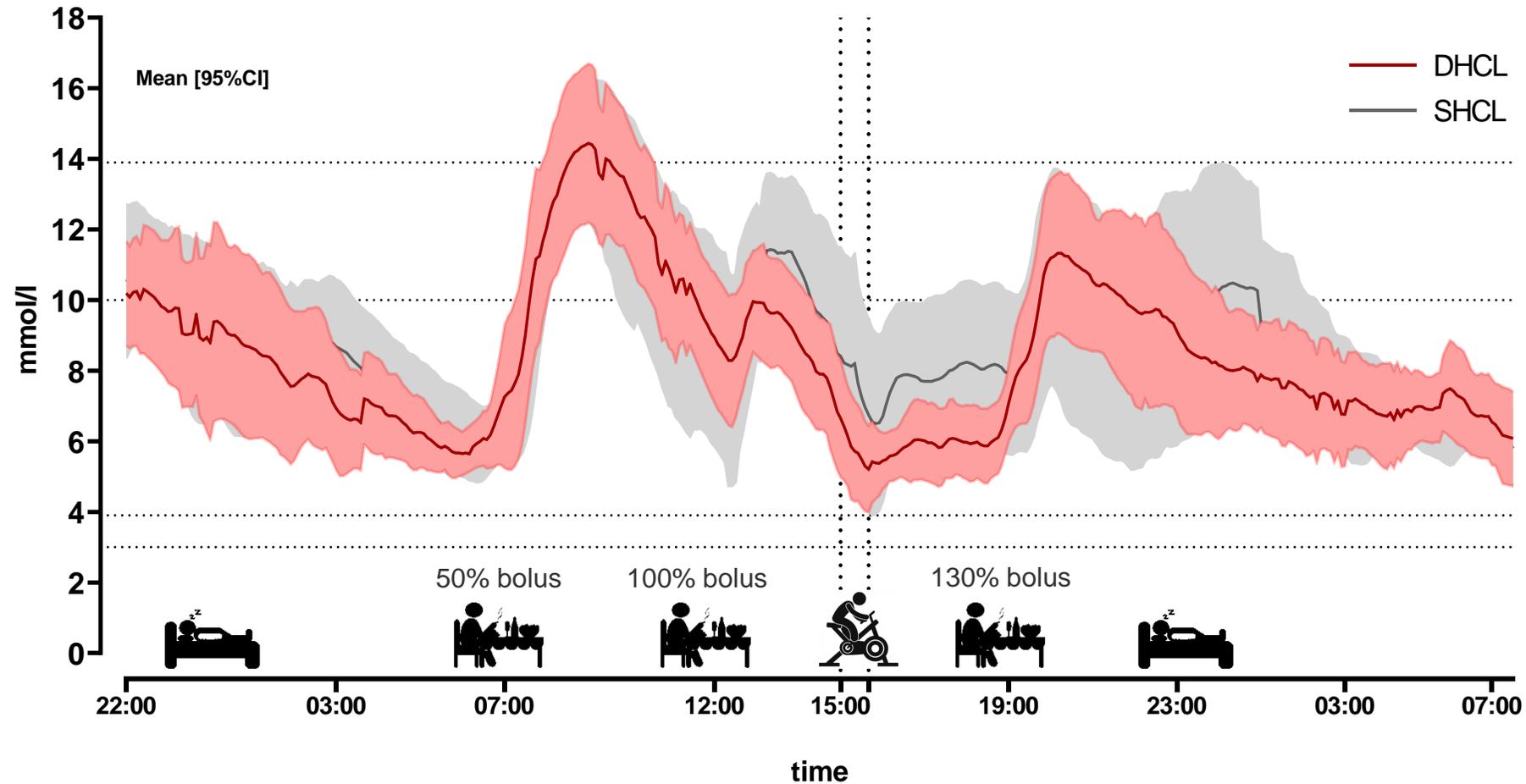
Characteristics	Mean (range)
No. of females/total	7/13
Age, years	48 (26-64)
BMI, kg/m <sup>2</sup>	28 (22.2-36.6)
HbA1c, mmol/mol	56 (44-69)
HbA1c, %	7.3 (6.2-8.5)
Diabetes duration, years	29 (17-45)
Insulin pump duration, years	8 (2-15)
CGM duration, years	4 (0-11)
Total daily insulin dose, units	46 (26-74)
Basal, %	51 (49-58)



# Sensor Glucose profiles

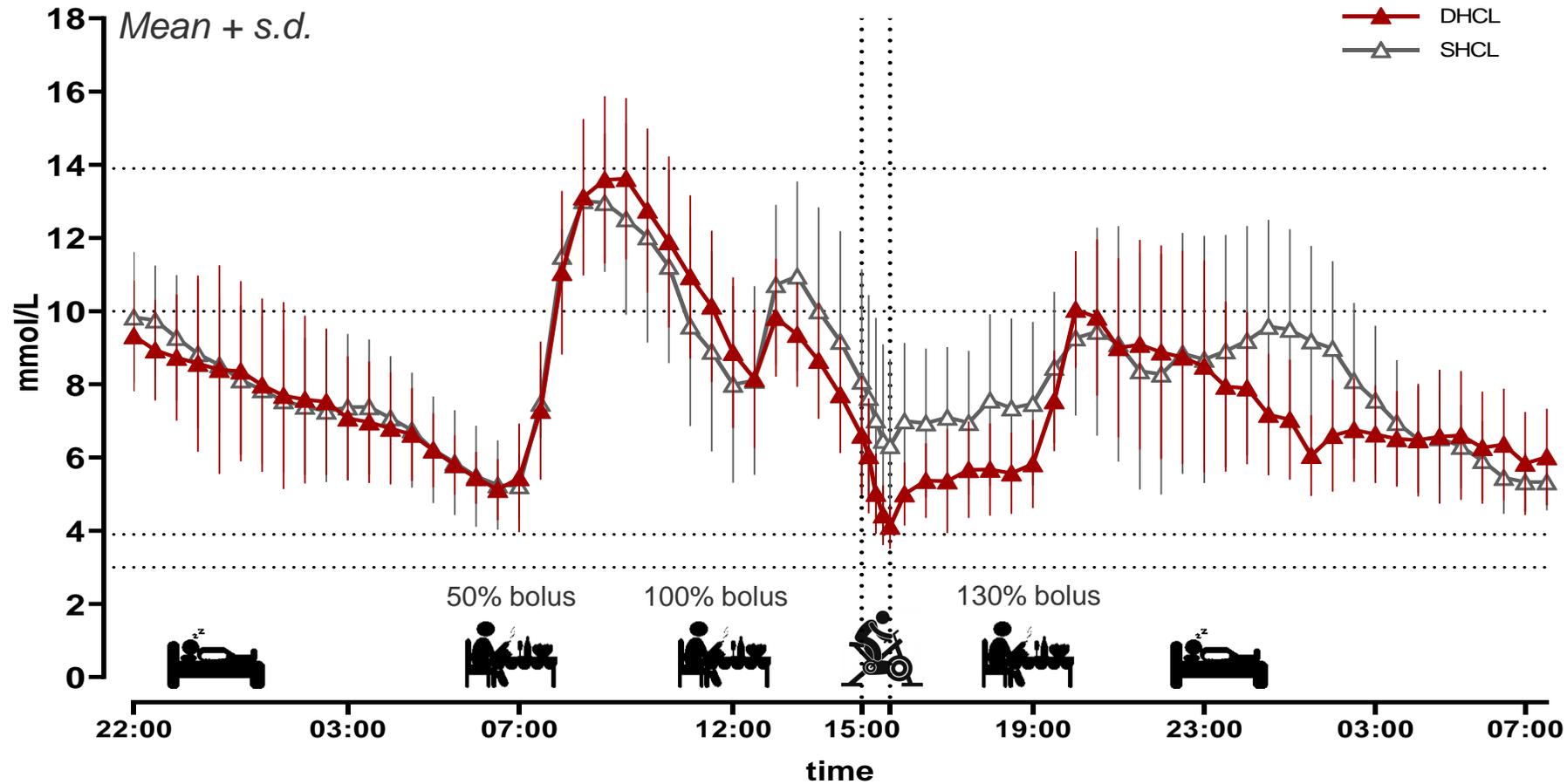


# Sensor Glucose profiles



$P_{treatment*time} = 0.23$

# Plasma Glucose Profile

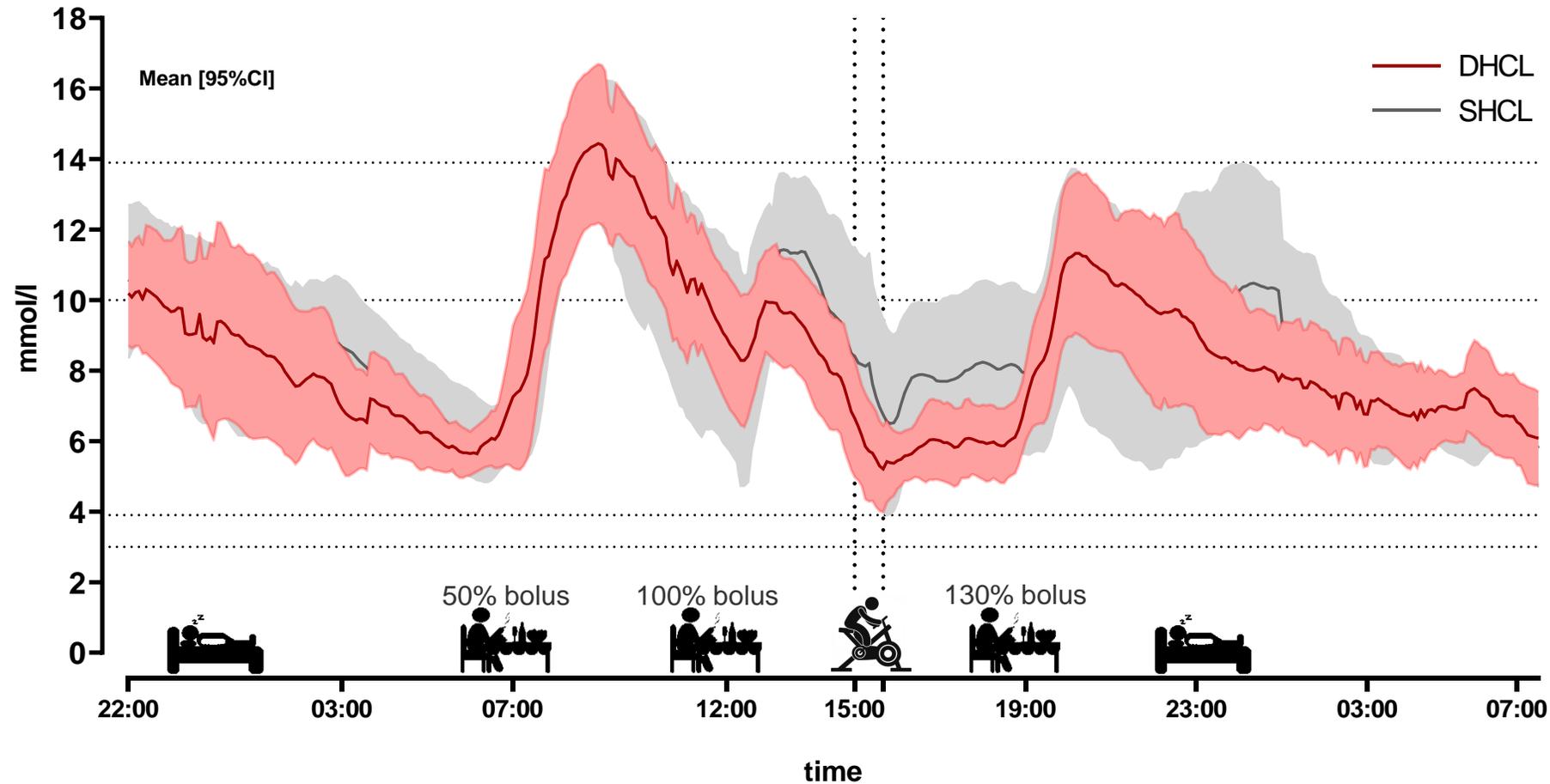


$P_{treatment*time} = 0.31$   
 $P_{AUC} = 0.38$

# Glucose parameters

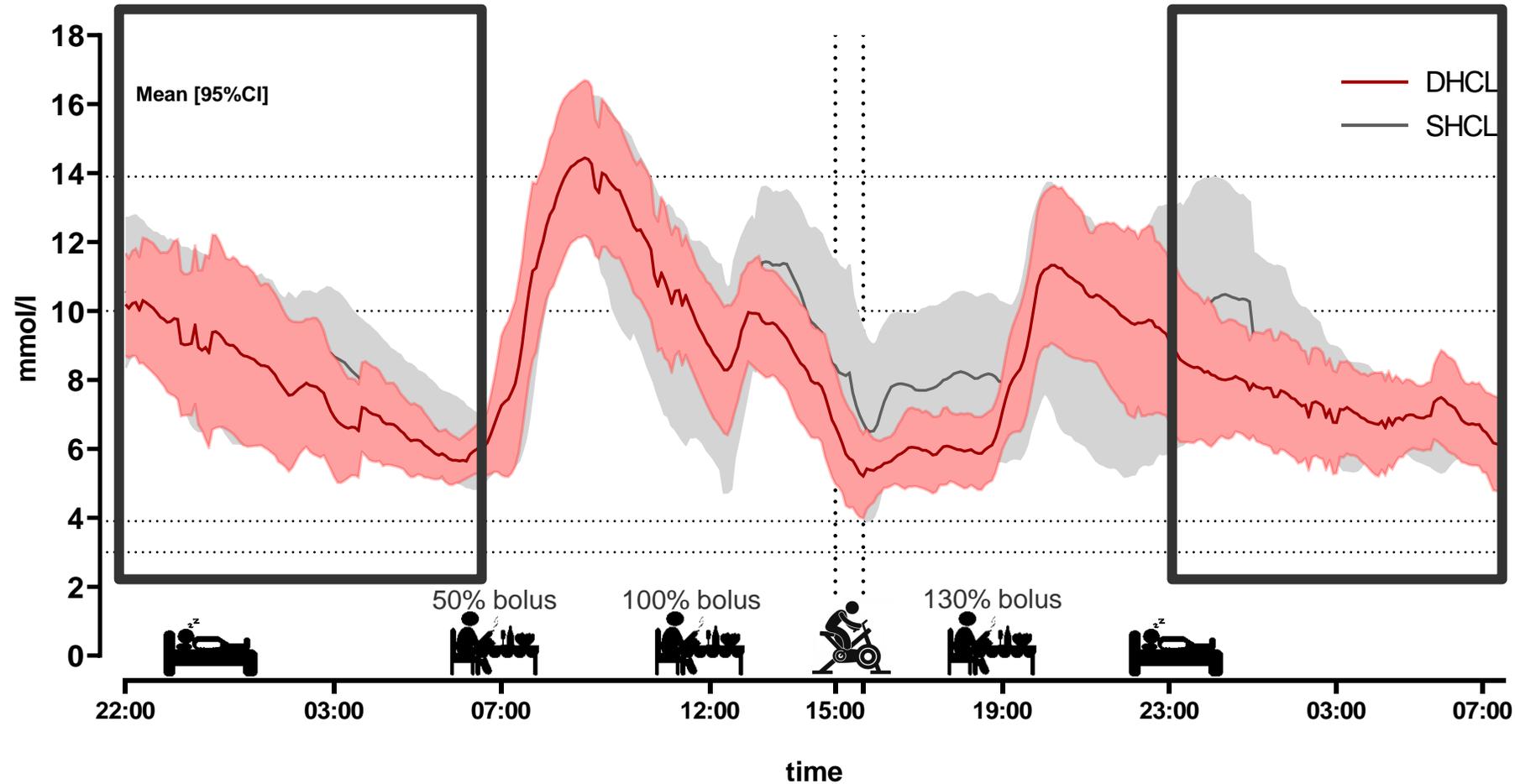
	Mean + sd	SHCL		DHCL		P-value
Sensor glucose	TAR-L2 (>13.9 mmol/L), %	11.7	6.7	8.16	6.6	0.26
	TAR-L1 (>10.0 mmol/L), %	29.2	10.4	27.5	14.8	0.46
	TIR (3.9-10.0 mmol/L), %	66.9	10.2	68.8	14.9	0.41
	TBR-L1 (<3.9 mmol/L), %	3.9	3.1	3.7	2.5	0.49
	TBR-L2 (<3.0 mmol/L), %	0.6	0.5	0.6	0.7	0.46
	Mean, mmol/L	8.62	1.0	8.32	1.2	0.30
	CV, %	39%	9%	39%	5%	0.30

# Glucose profiles



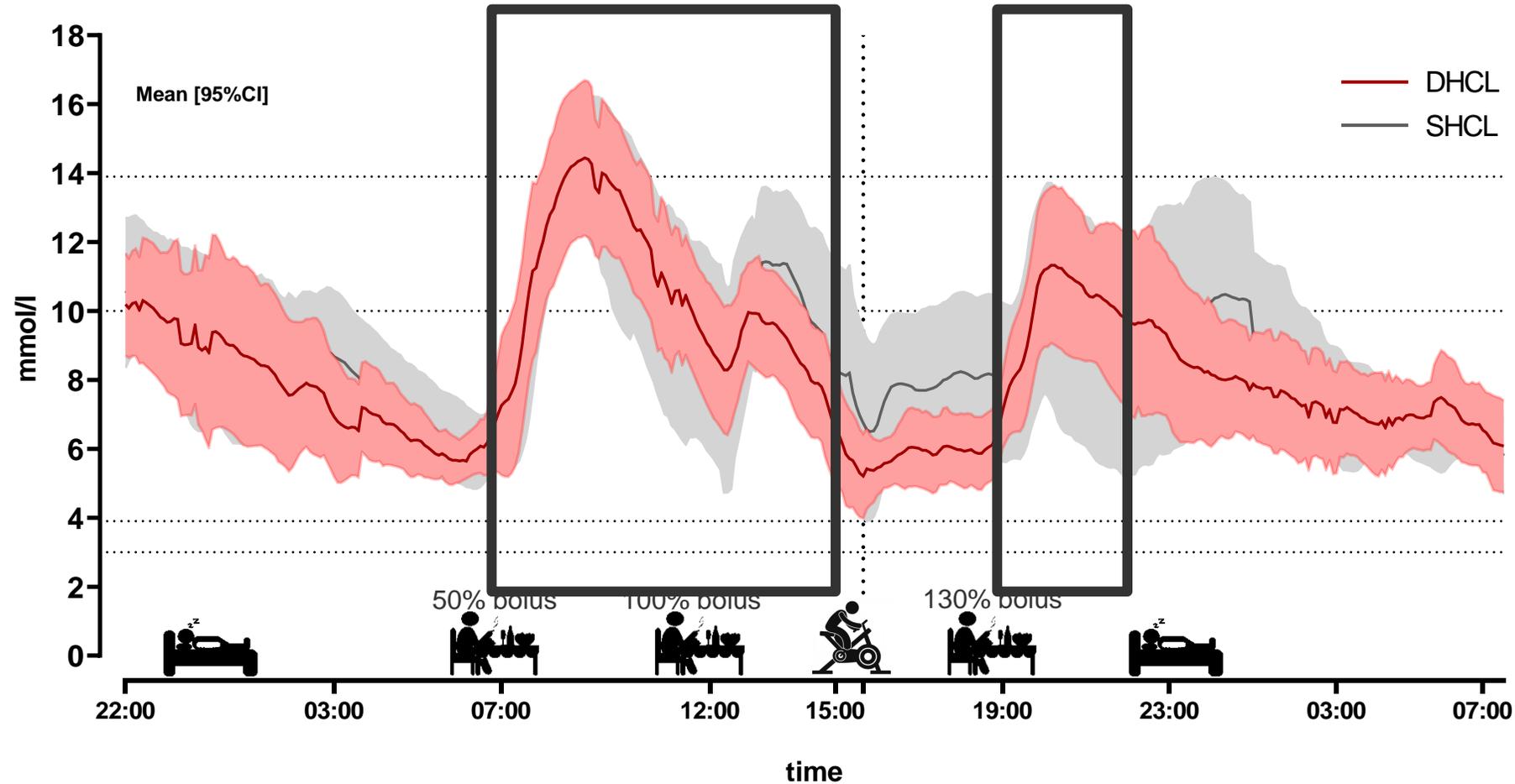
**No difference**  
1. Overall

# Glucose profiles



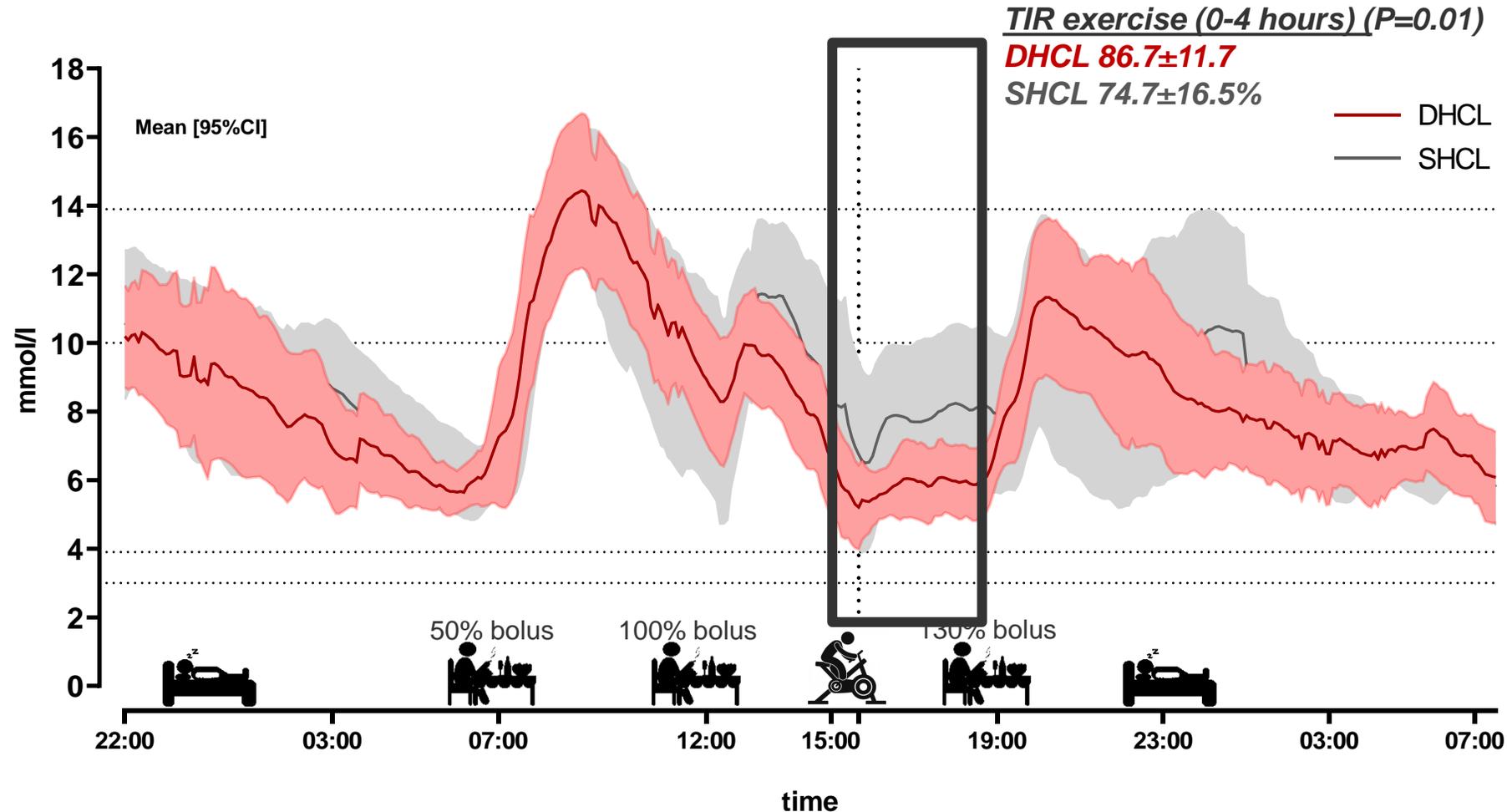
**No difference**  
1. Overall  
2. Overnight

# Glucose profiles



**No difference**  
1. Overall  
2. Overnight  
3. Postprandial (3 hours)

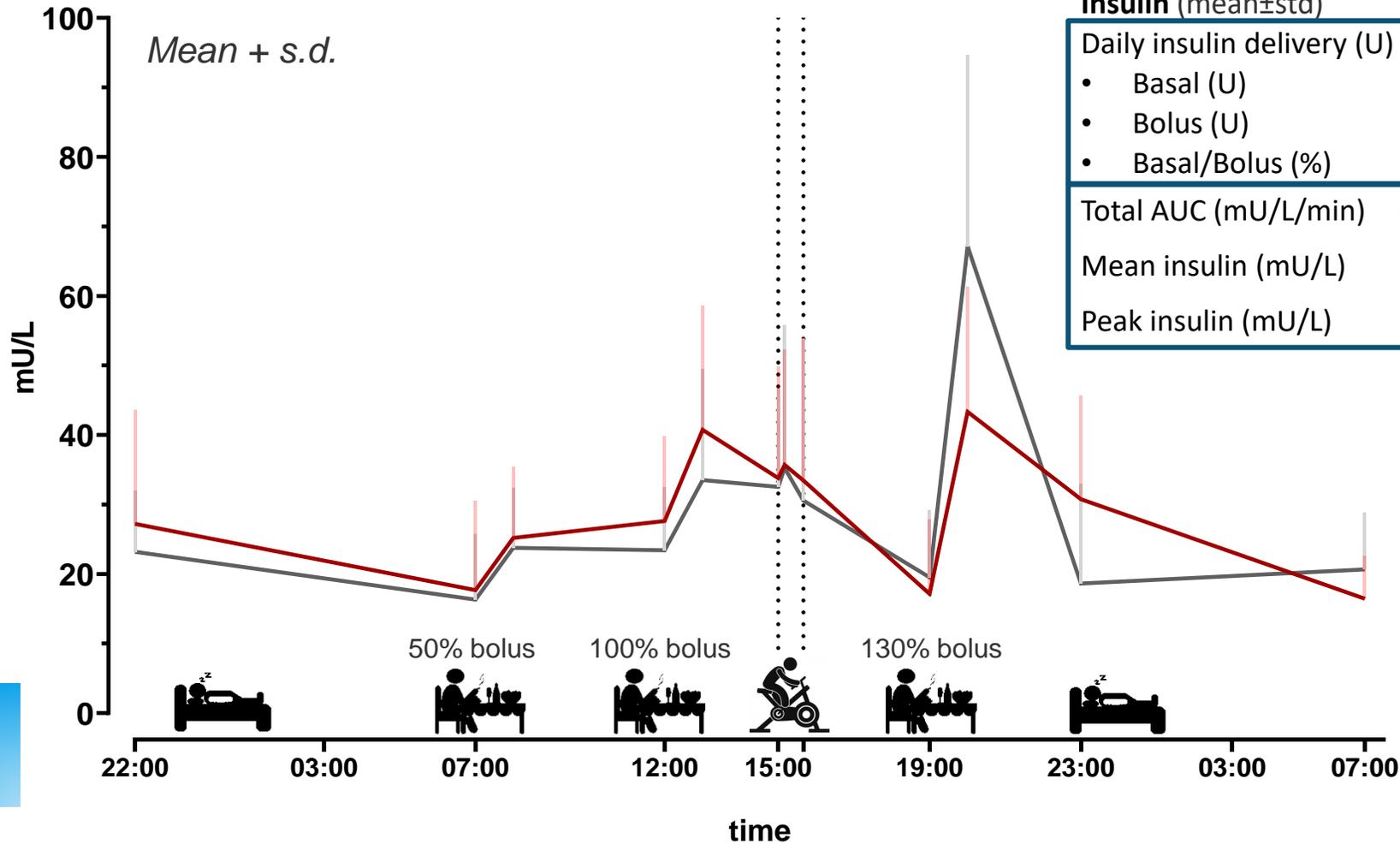
# Glucose profiles



- No difference**
1. Overall
  2. Overnight
  3. Postprandial (3 hours)

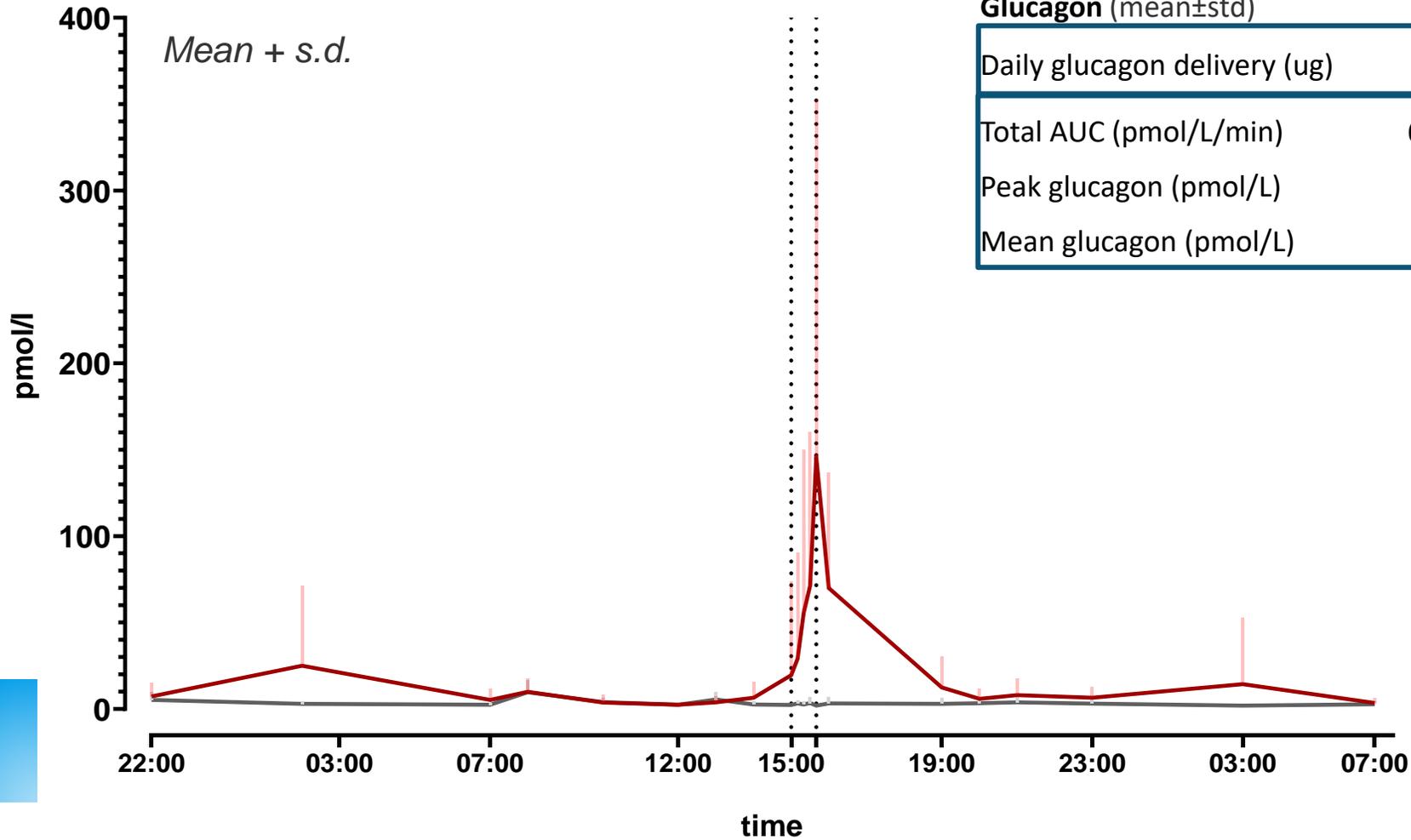
- Difference**
1. Exercise (45 min)
  2. Post-exercise (0-3 hours)

# Insulin



Insulin (mean±std)	SHCL	DHCL	P-value
Daily insulin delivery (U)	45.5 ± 11.8	40.9 ± 13.8	0.07
• Basal (U)	31.0 ± 8.3	28.8 ± 9.5	0.18
• Bolus (U)	14.5 ± 5.9	12.2 ± 6.2	0.17
• Basal/Bolus (%)	68 / 32	70/30	0.3
Total AUC (mU/L/min)	44833 ± 14153	47318 ± 19728	0.91
Mean insulin (mU/L)	27.8 ± 7.9	29.1 ± 8.8	0.72
Peak insulin (mU/L)	69.8 ± 233.9	55.9 ± 17.1	0.12

# Glucagon



Glucagon (mean±std)	SHCL	DHCL	P-value
Daily glucagon delivery (ug)	--	379±13.8 (17-889)	-
Total AUC (pmol/L/min)	6342 ± 2271	28823 ± 15922	<0.0001
Peak glucagon (pmol/L)	12 ± 5.8	182 ± 194.3	<0.0001
Mean glucagon (pmol/L)	3.5 ± 1.3	25.2 ± 19.0	<0.0001

## Adverse events

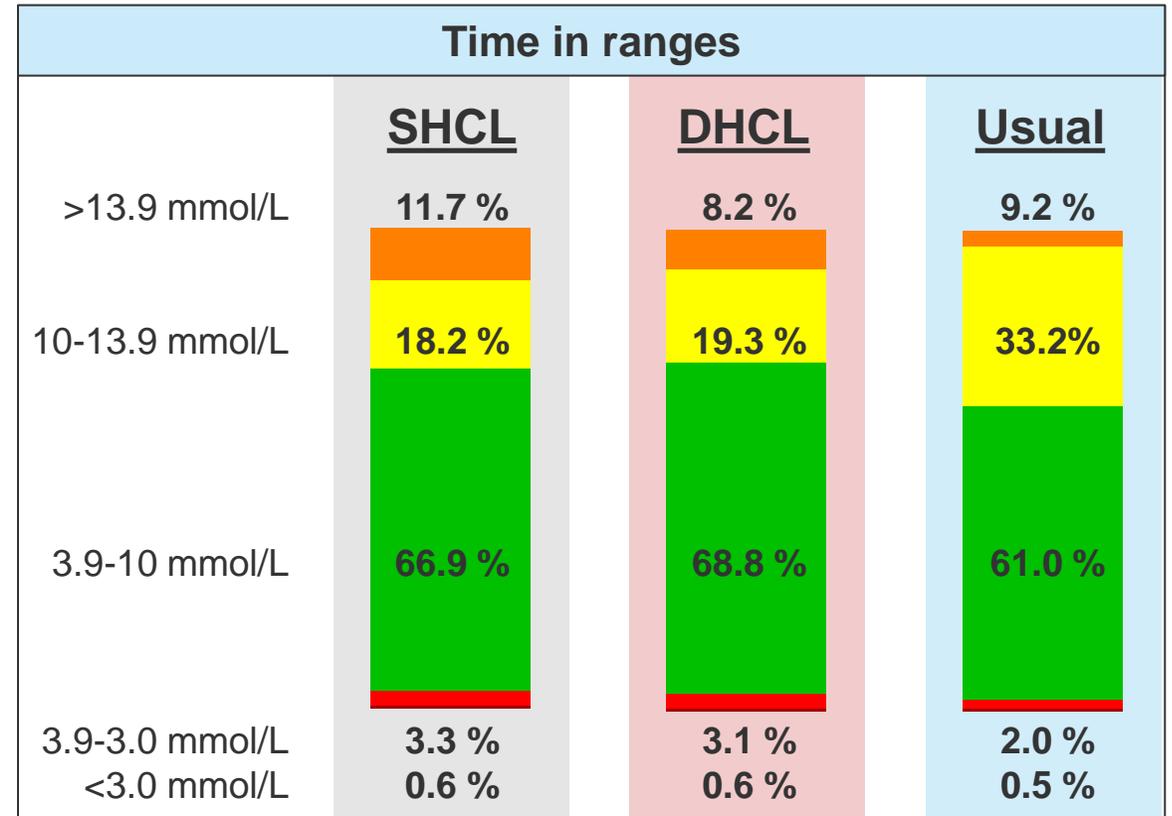
		SHCL	DHCL	P-value
Side effects*	Nausea, no.	4	5	0.73
	Headache, no.	23	17	0.28
	Vomiting, no.	1	0	0.80
	Palpitation, no.	5	1	0.09
	Hunger, no.	37	35	0.76

(\*Visual analog scale (0-100) performed 7 times per visit. 1 event = visual analog scale > 10.)

## Conclusion

Compared with DiaCon’s SHCL, the DHCL

- Had similar TBR
- Had similar TIR
- Reduced the need for rescue carbohydrate
- Had an increased TIR from 0-4 hours after exercise start
- Did not result in more adverse outcomes



# Perspectives

- Ongoing adolescents study
- Adjustment in insulin dosing algorithm
- Autocorrection
- Exercise announcement
- Adjustment in the limits of insulin and glucagon delivery



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ARTIFICIAL PANCREAS



**Steno Diabetes Center  
Copenhagen**

Kirsten Nørgaard, MD, DMSc

Christian Laugesen, MD

Signe Schmidt, MD, PhD



John Bagterp Jørgensen, MS, PhD

Dimitri Boiroux, MS, PhD

Asbjørn Thode Reenberg, MS