

SUPPLEMENTARY DATA

**Supplementary Table 1**

Variable	Screening (Baseline)		High Carbohydrate	Low Carbohydrate	P-value H vs L
	Median	min -max	Median ±SD	Median ±SD	
†Carbohydrate intake, g/day	178	101 -238	225 ± 30	47 ± 10	*<0.001
*Calorie intake, kcal/day	1751	1145 -2386	2036 ± 265	1876 ± 278	*0.18
§Activity, steps/day	-	-	5779±1574	5602±1704	¶0.38
Weight, kg	75.2	61.0 -104.0	74.8 ± 9.6	72.9 ± 10.3	*0.35
Body mass index, kg/m <sup>2</sup>	24.6	21.9 -27.9	24.8 ± 1.5	24.6 ± 1.7	*0.80
Blood pressure, mmHg	131/76	110/59 -156/97	127/77 ± 6/5	123/70 ± 14/7	>0.05
Pulse, beats/min	65	48 -81	61 ± 14	62 ± 13	0.84

Characteristics at baseline and at study visits. Subject's habitual daily carbohydrate and calorie consumptions were assessed based on a three-day diet registry. Based on the habitual calorie intake, the dietician constructed two isocaloric diet plans for each subject. ‡The planned daily calorie intake was similar between each diet week. †The carbohydrate consumptions were registered in subject's insulin pump. §Activity was assessed by a pedometer that measured the numbers of steps per day. \*Comparisons by paired repeated measurement ANOVA adjusting for period effects and gender.

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**Supplementary Table 2**

Variable	Dose ( $\mu\text{g}$ )	Glucose			Glucagon		
		HCD	LCD	P	HCD	LCD	P
$C_f$ (mmol/l)	-	9.3 $\pm$ 0.8	8.3 $\pm$ 0.6	0.25	5.0 $\pm$ 0.8	7.0 $\pm$ 1.2	0.01
$C_0$ (mmol/l)	-	3.5 $\pm$ 0.1	3.6 $\pm$ 0.1	0.38	4.0 $\pm$ 2.1	4.4 $\pm$ 3.9	0.77
$C_{120}$ (mmol/l)	-	4.1 $\pm$ 0.3	3.1 $\pm$ 0.2	0.02	5.8 $\pm$ 0.9	8.1 $\pm$ 1.4	0.31
$C_{240}$ (mmol/l)	-	8.5 $\pm$ 0.6	5.9 $\pm$ 0.5	0.005	29.8 $\pm$ 4.6	38.6 $\pm$ 5.7	0.15
$C_{\text{max}}$ (mmol/l)	100	6.1 $\pm$ 0.5	4.9 $\pm$ 0.4	0.02	125.6 $\pm$ 23.0	124.3 $\pm$ 10.4	0.94
	500	9.7 $\pm$ 0.5	7.1 $\pm$ 0.4	0.004	508.6 $\pm$ 67.0	555.0 $\pm$ 48.8	0.55
$\Delta C_{\text{max}}$ (mmol/l)	100	2.7 $\pm$ 0.4	1.3 $\pm$ 0.3	0.002	121.6 $\pm$ 23.1	124.3 $\pm$ 10.4	0.93
	500	5.6 $\pm$ 0.5	4.1 $\pm$ 0.2	0.002	488.4 $\pm$ 61.1	488.7 $\pm$ 73.0	0.99
$T_{\text{max}}$ (min)	100	34 $\pm$ 3	30 $\pm$ 3	0.20	13.0 $\pm$ 1.3	14.5 $\pm$ 1.4	0.44
	500	52 $\pm$ 11	47 $\pm$ 12	0.20	*	*	*
PI-AUC <sub>0-120</sub> (mmol/l x min)	100	596 $\pm$ 44	476 $\pm$ 34	0.02	4204 $\pm$ 602	4869 $\pm$ 429	0.22
	500	978 $\pm$ 50	679 $\pm$ 72	0.005	24753 $\pm$ 3272	32637 $\pm$ 2790	0.07
$T_{\text{rescue}}$ (min)	100	10 $\pm$ 3.6	10 $\pm$ 2.5	0.23			
	500	10 $\pm$ 4	10 $\pm$ 3	0.49			
Duration <sub>rescue</sub> (min)	100	78 $\pm$ 15	48 $\pm$ 15	0.21			
	500	108 $\pm$ 3	108 $\pm$ 2	0.88			
Duration <sub>hypo</sub> (min)	100	43 $\pm$ 15	73 $\pm$ 15	0.20			
	500	13 $\pm$ 3	13 $\pm$ 2	0.88			
$N_{\text{rescue}}$	100	6	3	0.07			
	500	8	8	0.90			
$N_{\text{rebound}}$	100	3	0	0.06			
	500	8	3	0.04			

Pharmacodynamic and Pharmacokinetic Parameters: Data on glucose (left side) and glucagon (right side) are presented as mean $\pm$ SEM unless otherwise stated. P-values are paired comparisons of the study visits after low carbohydrate diet (LCD) versus high carbohydrate diet (HCD). Concentrations before insulin injection ( $C_f$ ), before the first ( $C_0$ ) and the second ( $C_{120}$ ) glucagon injection, and two hours after the second glucagon ( $C_{240}$ ) are presented. The peak ( $C_{\text{max}}$ ) and maximum change ( $\Delta C_{\text{max}}$ ) from baseline to 120 min after the each glucagon administration are presented. The time to peak ( $t_{\text{max}}$ ) and positive incremental area under the curve

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(PI-AUC<sub>0-120</sub>) are also given. After glucagon injection, the duration of plasma glucose above (duration<sub>rescue</sub>) and below (duration<sub>hypo</sub>) 3.9 mmol/l are shown. The number of rescue of hypoglycemia (defined as C<sub>max</sub> >4.9 mmol/L within 120 min) and rebound hyperglycemia (defined as C<sub>max</sub> >7.0 mmol/L within 120 min) after both glucagon boluses are shown. \* Blood samples were taken less frequently after the second glucagon administration, why t<sub>max</sub> and C<sub>max</sub> were not illustrated.

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**Supplementary Table 3**

Side effects (mean±SD / No.)	100 µg Glucagon			500 µg Glucagon		
	HCD	LCD	P	HCD	LCD	P
Peak nausea (VAS, cm)	0.3±0.3	0.9±0.2	0.10	3.2±1.8	2.9±1.3	≈ 1.0
Peak fatigue (VAS, cm)	2.8±3.1	2.4±2.5	0.75	1.7±2.4	6.1±6.9	0.10
Vomit (No.)	0	0	≈ 1.0	3	0	0.12
Intensity of hypoglycemia symptoms <sup>1</sup>	22±3	25±7	0.24	24±7	29±11	0.37

Peak intensity of side effects from 0-120 minutes after each glucagon administration was monitored with a visual analogue scale (VAS) with extremes from 0 to 10 cm. Side effects to glucagon were similar after both dietary interventions. <sup>1</sup>Edinburgh Hypoglycemia Score was used to assess the intensity of hypoglycemia symptoms minutes before glucagon was administered. Wilcoxon signed rank test, paired T-test and Fisher's exact test were used to compare the side effects after high (HCD) versus low carbohydrate diet (LCD).