

## Supplemental Material

**Supplemental Table 1.** Indexes of insulin resistance and  $\beta$ -cell function

<i>Name</i>	<i>Formula</i>	<i>Ref</i>
<b>Indexes of insulin resistance/sensitivity</b>		
HOMA-IR	$\frac{G0 \times I0}{22.5}$	(1)
HOMA2-IR	<a href="https://www.dtu.ox.ac.uk/homacalculator/">https://www.dtu.ox.ac.uk/homacalculator/</a> *	(2)
QUICKI	$\frac{1}{\log_{10}(I0) + \log_{10}(G0)}$	(3)
HOMA2-S	<a href="https://www.dtu.ox.ac.uk/homacalculator/">https://www.dtu.ox.ac.uk/homacalculator/</a> *	(2)
Stumvoll MCR <sub>120</sub>	$19.240 - 0.281 \times \text{BMI} - 0.00498 \times I120 - 0.333 \times G120$	(4)
Matsuda ISI	$\frac{10,000}{\sqrt{(G0 \times I0) \times (G120 \times I120)}}$	(5, 6)
VAI	Men: $\left(\frac{WC}{39.68 + (1.88 \times \text{BMI})}\right) \times \left(\frac{TG}{1.03}\right) \times \left(\frac{1.31}{\text{HDL}}\right)$ Women: $\left(\frac{WC}{36.58 + (1.89 \times \text{BMI})}\right) \times \left(\frac{TG}{0.81}\right) \times \left(\frac{1.52}{\text{HDL}}\right)$	(7, 8)
LAP	Men: $(WC - 65) \times (TG)$ Women: $(WC - 58) \times (TG)$	(7)
<b>Indexes of insulin secretion/ <math>\beta</math>-cell function</b>		
Insulinogenic index	$(I30 - I0) / (G30 - G0)$	(9, 10)
First phase Stumvoll	$1,283 + 1.829 \times I30 - 138.7 \times G30 + 3.772 \times I0$	(11)
Second phase Stumvoll	$286 + 0.416 \times I30 - 25.94 \times G30 + 0.926 \times I0$	
Fasting C-peptide index (CPI) (ng/mL, mg/dL)	$\frac{Cp0}{G0} \times 100$	(12)
Total AUC <sub>Ins/Glu</sub>	$\frac{\text{AUC Insulin}}{\text{AUC Glucose}}$	(13)
HOMA2- $\beta$	<a href="https://www.dtu.ox.ac.uk/homacalculator/">https://www.dtu.ox.ac.uk/homacalculator/</a> *	(2)
Proinsulin/Insulin	$\frac{\text{Proinsulin}_0}{I0}$	
Insulin secretion sensitivity index 2 (ISSI-2)	$\frac{\text{Total AUC(Ins/Glu)}}{\text{Matsuda Index}}$	(13, 14)

HOMA-IR, QUICKI and Matsuda ISI were calculated from insulin concentrations given in mU/L. QUICKI and PCPI were calculated from glucose concentrations given in mg/dL. All other indexes were derived from the OGTT with insulin concentrations given in pmol/l, and glucose concentration given in mmol/l. VAI and LAP were calculated from triglycerides and HDL in mmol/l.

\* HOMA2 Calculator version 2.2.3 (Diabetes Trials Unit, University of Oxford, Oxford, UK).

AUC, area under the curve; BMI, body mass index; MCR, metabolic clearance rate; G0, fasting plasma glucose; G120, 2-hour post-load glucose; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; I0, fasting plasma insulin; I120, 2-hour post-load insulin; IGI, Integrated glucose-insulin; ISI, insulin sensitivity index; LAP, lipid accumulation product; Proinsulin<sub>0</sub>, fasting proinsulin; QUICKI, quantitative insulin sensitivity check index; TG= triglycerides; VAI= visceral adiposity index; WC, waist circumference.

**Supplemental Table 2.** Insulin, C-peptide and Proinsulin at the three different time points in empagliflozin vs placebo treated patients.

Factor	Empagliflozin (n=20)	Placebo (n=22)	P*	P <sub>1</sub>
<b>Baseline</b>				
FPG (mmol/L)	6.2 (6.0, 7.2)	6.3 (6.0, 6.7)		
30min-PG (mmol/L)	10.3 (9.4, 11.3)	9.9 (9.1, 11.4)		
2h-PG (mmol/L)	10.7 (8.7, 12.2)	9.7 (8.6, 12.3)		
Fasting insulin (μIU/mL)	13 (9.7, 15)	12 (8.4, 18)		
30min-insulin (μIU/mL)	62 (33, 89)	58.5 (36, 87.5)		
2h-insulin (μIU/mL)	103 (77, 177)	89 (84, 195)		
Fasting proinsulin (pmol/L)	13 (9.4, 17)	10.5 (8.4, 18)		
Fasting C-peptide (ng/mL)	1.05 (0.89, 1.4)	1.05 (0.78, 1.3)		
HbA1c (mmol/mol)	41 (39, 45)	42 (40, 47)		
Fasting mannose (μmol/L)	92.7 (82.3, 97.6)	86.1 (76.3, 90.1)		
<b>On treatment (7 months)</b>				
FPG (mmol/L)	5.6 (5.3, 6.1)	6.2 (5.8, 6.9)	<b>0.02</b>	
30min-PG (mmol/L)	9.1 (8.8, 9.5)	9.4 (8.5, 11.2)	0.30	
2h-PG (mmol/L)	9.7 (8.5, 10.6)	11.0 (8.9, 12.0)	0.06	
Fasting insulin (μIU/mL)	12.5 (5, 15)	12 (8.05, 20.5)	0.29	
30min-insulin (μIU/mL)	59 (39, 64)	41 (31, 58)	0.31	
2h-insulin (μIU/mL)	68 (48, 92)	92 (64, 152)	<b>0.02</b>	
Fasting proinsulin (ng/mL)	9.6 (4.6, 13)	9.3 (6.6, 18)	0.36	
Fasting C-peptide (ng/mL)	0.95 (0.71, 1.15)	0.94 (0.78, 1.3)	0.51	
HbA1c (mmol/mol)	42 (39, 44.5)	42 (40, 45)	0.88	
Fasting mannose (μmol/L)	83.8 (75.1, 91.7)	79.5 (69.0, 94.8)	0.53	
<b>Off treatment (10 months)</b>				
FPG (mmol/L)	6.0 (5.5, 6.4)	6.2 (5.8, 6.8)	0.26	<b>0.039</b>
30min-PG (mmol/L)	9.8 (8.8, 11.0)	10.3 (9.5, 11.2)	0.30	0.73
2h-PG (mmol/L)	11.2 (8.5, 12.3)	10.2 (8.1, 12.5)	0.85	0.10
Fasting insulin (μIU/mL)	12 (8.8, 15)	13 (8.7, 18.5)	0.55	0.25
30min-insulin (μIU/mL)	65 (41, 87)	58 (34, 66)	0.17	0.66
2h-insulin (μIU/mL)	103 (68, 129)	78 (59, 178)	0.69	<b>0.008</b>
Fasting C-peptide (ng/mL)	0.98 (0.74, 1.2)	1 (0.84, 1.3)	0.78	<b>0.048</b>
HbA1c (mmol/mol)	43.5 (39, 46)	44 (39, 46)	0.95	0.99
Fasting mannose (μmol/L)	84.6 (79.5, 92.6)	85.5 (72.3, 94.0)	0.86	0.57

Data are median (Q1, Q3).

\*P-value by Mann-Whitney U-test.

•P<sub>1</sub> = P for interaction between treatment allocation and time of visit in the repeated measures ANOVA model

**Supplemental Figure 1.** Mannose levels at the three time points in the empagliflozin and placebo groups.

