SUPPLEMENTARY DATA

Supplementary Table S1. Effect of liraglutide versus placebo on anthropometric and biochemical variables

	Treatmenteffect		Difference	95% CI	p-value
	Liraglutide	Placebo			
Weight, kg	-4.17 (3.49)	-0.98 (2.62)	-3.18 (4.31)	-4.79 to -1.57	<0.001
Systolicblood pressure, mmHg	-8.10 (17.27)	-3.17 (16.07)	-4.93 (23.68)	-13.78 to 3.91	0.263
Diastolicblood pressure, mmHg	-3.13 (12.11)	-3.83 (8.75)	0.70 (17.06)	-5.67 to 7.07	0.826
HbA1c, %	-0.42 (0.34)	-0.04 (0.43)	-0.37 (0.54)	-0.57 to -0.17	<0.001
HbA1c, mmol/mol	-4.70 (3.98)	-0.60 (4.90)	-4.10 (6.02)	-6.35 to -1.85	<0.001
LDL-cholesterol, mmol/L	-0.25 (0.72)	-0.17 (0.63)	-0.08 (0.96)	-0.47 to 0.30	0.657
HOMA IR, pmol/L	-1.35 (3.18)	-0.57 (2.41)	-0.78 (3.24)	-2.01 to 0.45	0.336
Fasting plasma insulin, pmol/L	-11.73 (57.54)	-1.69 (43.79)	-10.04 (68.27)	-36.01 to 15.93	0.469
Fasting bloodglucose, mmol/L	-0.99 (1.11)	-0.62 (0.96)	-0.36 (1.06)	-0.76 to 0.03	0.125

Data are expressed as the mean (SD). BMI, body mass index; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HOMA IR, homeostasis model analysis of insulin resistance.

Supplementary Table S2. Regression coefficients (β), R-squared values and p-values from linear regression analysis.

Dependent variabel	Independent variabel	Placebo			Liraglutide		
		β	R^2	p-value	β	R^2	p-value
ΔHR	ΔResting systolic blood pressure	0.070	0.024	0.440	-0.024	0.002	0.812
ΔHR	ΔResting diastolic blood pressure	0.410	0.254	0.007	0.130	0.031	0.377
ΔHR	ΔWeight	-0.713	0.076	0.165	-0.089	0.001	0.852
ΔHR	ΔHbA1C	-2.848	0.032	0.373	3.670	0.022	0.465
ΔHR	ΔFasting blood glucose	-1.026	0.025	0.434	0.662	0.009	0.645
ΔSDNN	ΔmeanNN	0.045	0.015	0.542	0.080	0.133	0.061
ΔSDNN	ΔWeight	-1.881	0.033	0.362	0.097	0.000	0.928
ΔSDNN	ΔHbA1C	-2.452	0.002	0.848	-17.125	0.091	0.126
ΔSDNN	ΔFasting blood glucose	-2.558	0.010	0.625	-2.169	0.018	0.504
ΔSDNN	ΔHR	-0.226	0.003	0.778	-0.764	0.113	0.086
ΔRMSSD	ΔHF	0.117	0.634	<0.001	0.178	0.770	<0.001
ΔRMSSD	ΔLF	0.070	0.391	0.001	0.082	0.480	<0.001
ΔRMSSD	ΔHFnorm	287.72	0.470	<0.001	409.03	0.616	<0.001
ΔRMSSD	ΔLFnorm	212.88	0.296	0.004	384.16	0.533	<0.001

HbA1C, glycated hemoglobin; HR, heart rate; SDNN, standard deviation of all normal RR-intervals; HF, high frequency power; LF, low frequency power; TP, total power

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Supplementary Table S3.List of total adverse events in study.

Group	Event	Liraglutide periode, n(%)	Placebo periode, n(%)	Washout periode, n(%)
Abnormalblood test	Amylaseincreased	1 (1.1)	0 (0)	0 (0)
Abnormalblood test	Anemia	1 (1.1)	0 (0)	0 (0)
Abnormalblood test	CreatinineIncreased	1 (1.1)	0 (0)	1 (7.7)
Abnormalblood test	PSA Elevated	1 (1.1)	1 (2.6)	0 (0)
Cardiac	Atrial Fibrillation	0 (0)	1 (2.6)	1 (7.7)
Cardiac	Non CardiacChestPain	0 (0)	0 (0)	2 (15.4)
Cardiac	ChestPainCardiac	2 (2.2)	3 (7.9)	1 (7.7)
Cardiac	Dyspnea	1 (1.1)	1 (2.6)	0 (0)
Cardiac	MyocardialInfarction	2 (2.2)	0 (0)	0 (0)
Cardiac	Palpitations	1 (1.1)	1 (2.6)	0 (0)
Cardiac	Sinus Tachycardia	2 (2.2)	0 (0)	0 (0)
Gastrointestinal	Anorexia	12 (13.2)	1 (2.6)	0 (0)
Gastrointestinal	Bloating	1 (1.1)	0 (0)	0 (0)
Gastrointestinal	Constipation	5 (5.5)	2 (5.3)	0 (0)
Gastrointestinal	Dehydration	0 (0)	1 (2.6)	0 (0)
Gastrointestinal	Diarrhea	7 (7.7)	4 (10.5)	1 (7.7)
Gastrointestinal	Gastroesophageal RefluxDisease	8 (8.8)	1 (2.6)	0 (0)
Gastrointestinal	Gastroenteritis	0 (0)	1 (2.6)	1 (7.7)
Gastrointestinal	Nausea	18 (19.8)	3 (7.9)	0 (0)
Gastrointestinal	StomachPain	1 (1.1)	2 (5.3)	0 (0)
Gastrointestinal	Vomiting	4 (4.4)	0 (0)	0 (0)
Infection	Chills	1 (1.1)	0 (0)	0 (0)
Infection	Infectioneye	0 (0)	1 (2.6)	0 (0)
Infection	InfectionsOther Cold	1 (1.1)	3 (7.9)	1 (7.7)
Infection	Sinusitis	2 (2.2)	1 (2.6)	0 (0)
Infection	Skin Infection	0 (0)	0 (0)	2 (15.4)
Muscle	Myalgia	0 (0)	1 (2.6)	1 (7.7)
Neurological	Dizziness	5 (5.5)	3 (7.9)	2 (15.4)
Neurological	ErectileDysfunction	0 (0)	1 (2.6)	0 (0)
Neurological	Headache	2 (2.2)	0 (0)	0 (0)
Neurological	Insomnia	0 (0)	2 (5.3)	0 (0)
Neurological	Libido Decreased	1 (1.1)	0 (0)	0 (0)
Neurological	Concussion	1 (1.1)	0 (0)	0 (0)
Neurological	Somnolence	2 (2.2)	0 (0)	0 (0)
Other	Fat BiopsyRelatedComplication	2 (2.2)	0 (0)	0 (0)
Renal, urine	Proteinuria	1 (1.1)	0 (0)	0 (0)
Renal, urine	Discoloration of Urine	0 (0)	1 (2.6)	0 (0)

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Skin	Pruritus	2 (2.2)	0 (0)	0 (0)
Skin	MaculopapularRash	1 (1.1)	1 (2.6)	0 (0)
Vascular	Allergicreaction	0 (0)	1 (2.6)	0 (0)
Vascular	Hot flash	1 (1.1)	1 (2.6)	0 (0)
Vascular	VascularDisorders - Hypotension	1 (1.1)	0 (0)	0 (0)
Total events		**91**	**38**	**13**

Data are expressed as number of events (% of total events during treatment period).

SUPPLEMENTARY DATA

Supplementary Figures 1A to 1H. Diurnal variation in changes in heart rate variability (HRV) parameters during each treatment period: (A) heart rate (HR); (B) log transformed values of the root mean square of successive differences in NN-intervals (RMSSD); (C) log transformed values of the mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording (SDNN-index); (D) log transformed values of low frequency (LF) power; (E) log transformed values of high frequency (HF) power; (F) log transformed values of normalized values of LF power (LFnorm); (G) log transformed values of normalized values of HF power (HFnorm) (H) log transformed values of LF/HF ratio. Error bars: mean+/- SE. * = p<0.05 for the comparison of the change during liraglutide period vs the change during placebo period for each hour. X-axis represents time of the day from (7 am to 6 am).