The effects of different doses of exercise on pancreatic β-cell function in patients with newly diagnosed type 2 diabetes

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BACKGROUND AND RATIONAL

The etiology, pathophysiology and treatment of type 2 diabetes (T2D) are undeniably multifactorial and the understanding of T2D is increasing rapidly, but reducing obesity remains essential to improve β-cell function. However, a residue β-cell capacity appears to be essential for remission emphasizing the need for lifestyle intervention early in the clinical management [1].

While exercise is less recognized as an efficient therapy for weight loss, dietary therapy is [2]. With the recent advantages in the role of very low-calorie diets on β-cell function [1, 3], it is important to study the role of exercise therapy in combination with dietary-induced weight loss to fully understand the implications for patient care. However, only a few studies have focused on the effects of exercise on pancreatic β-cell function in T2D and discrepancies regarding the effect exist [4-8]. The discrepancies may relate to the assessment of β-cell function [9], failure to correct for the change in peripheral insulin sensitivity, concomitant pharmacological therapy and the pre-trial insulin secretory capacity. Moreover, exercise intensity, volume and modality may play an essential role in the reduction of HbA1c [10-14]. Thus, current evidence suggests that physical activity may *directly* improve β-cell mass and β-cell function[15], and may also *indirectly* improve β-cell function and mass by inducing β-cell rest via reductions in systemic inflammation and metabolic stress (i.e. gluco- and lipotoxicity). However, evidence is limited from human studies investigating the relationship of exercise volume, intensity, frequency, and dose-dependency on β-cell function[15]. As a consequence, knowledge about the exercise training dose needed to reduce micro- and macrovascular complications in T2D is almost non-existing [12, 16-23]. As most clinical exercise interventions in T2D base their conclusions on HbA1c, the significance of exercise training in the clinical care of prevalent T2D is challenged [11, 23-25] and investigating β-cell function with different volumes of exercise in addition to a diet-induced weight loss is of clinical relevance. A full description of the rationale behind the study has been published elsewhere[26]. We propose that combining a moderate diet-induced weight loss with exercise training may dose-dependently improve pancreatic β-cell function.

OBJECTIVES

Primary aim: To investigate the effect of exercise training volume on pancreatic β-cell function after 16 weeks in patients with short standing T2D.

Secondary aims: To investigate the effect of exercise training volume on mechanisms underlying β–cell function.

Primary objective: To compare the effect of high (HED) *or* moderate (MED) volumes of exercise in combination with a dietary intervention, relative to the control (CON) *or* diet (DCON) comparator, on changes in the late-phase disposition index (DI) during the final 30 minutes of hyperglycemic phase of the hyperglycemic clamp from baseline to week 16, in patients with short standing T2D.

Major secondary objective: To compare the effect of high (HED) *or* moderate (MED) volumes of exercise in combination with a dietary intervention, relative to the control (CON) *or* diet (DCON) comparator, on changes in insulin secretion rate and insulin sensitivity derived from hyperglycemic clamp AND oral insulinogenic and insulin sensitivity index derived from the mixed meal tolerance test (MMTT) from baseline to week 16, in patients with short standing T2D.

Other objectives: To compare the effect of high (HED) *or* moderate (MED) volumes of exercise in combination with a dietary intervention, relative to the control (CON) *or* diet (DCON) comparator on changes in glucose disposal, postprandial glycemic control, GLP-1 and arginine stimulated insulin secretion, fasting blood glucose control, fasting blood lipids, blood pressure, physical function from baseline to week 16, in patients with short standing T2D.

HYPOTHESIS

Primary: The effect of exercise training on pancreatic β-cell function (assessed as late-phase disposition index) increases with increasing volumes of exercise in combination with a diet intervention across a 16-week intervention in patients with T2D of short duration. Specifically, it is expected that both moderate volume and high volumes of exercise in combination with a dietary intervention are superior to the control intervention in improving pancreatic β-cell function.

The hierarchy of the hypotheses and subsequent claims for the primary outcome are as follows;

1. High-volume exercise and diet group (HED) is superior to the control intervention (CON) in increasing the late phase disposition index from baseline (visit 1) to follow-up (visit 7). Superiority is claimed if the difference in change between the groups favours the HED group.

2. Medium-volume exercise and diet group (MED) is superior to the control intervention in increasing the late phase disposition index from baseline (visit 1) to follow-up (visit 7). Superiority is claimed if the difference in change between the groups favours the MED group.

3. The diet control group (DCON) is superior to the control intervention in increasing the late phase disposition index from baseline (visit 1) to follow-up (visit 7). Superiority is claimed if the difference in change between the groups favours the DCON group.

4. HED is superior to the DCON intervention in increasing the late phase disposition index from baseline (visit 1) to follow-up (visit 7). Superiority is claimed if the difference in change between the groups favours the HED group.

5. MED is superior to the DCON intervention in increasing the late phase disposition index from baseline (visit 1) to follow-up (visit 7). Superiority is claimed if the difference in change between the groups favours the MED group.

6. HED is superior to the MED intervention in increasing the late phase disposition index from baseline (visit 1) to follow-up (visit 7). Superiority is claimed if the difference in change between the groups favours the HED group.

TRIAL DESIGN, DATA COLLECTION AND OUTCOMES ASSESSMENT

All procedure and detailed information about the trial design, eligibility and methods, including a detailed description of the interventions has been published elsewhere [26]. Briefly, the study is a parallel-group, 4-arm assessor-blinded, randomised, clinical trial with 16 weeks of intervention. Participants are randomly allocated (1:1:1:1, stratified by sex) to four groups; 1) No intervention, 2) Dietary intervention, 3) Dietary intervention + moderate volume exercise (3 sessions/week), 4) Dietary intervention + high volume exercise (6 sessions/week). The study is registered at www.clinicaltrials.gov (NCT03769883) and approved by the Scientific Ethical Committee of the Capital Region of Denmark (approval number H-18038298) prior to commencement of any study procedures. Primary place of study execution and data collection is the Centre for Physical Activity Research (CFAS), Rigshospitalet, section 7641, Tagensvej 20, DK-2200 Copenhagen (visiting address); Blegdamsvej 9, DK-2100 Copenhagen (postal address), Telephone: (+45) 3545 7641.

It is expected that an exercise intervention will increase late-phase disposition index derived from a hyperglycemic clamp by 1.5 (au.) more than the control group, with a standard deviation of 1.5 (au.) of the change in the exercise and 1.0 (au.) in the control group[4]. For a contrast in a one-way ANOVA with four means (1.5, 1.0, 0.5, 0.0) and contrast coefficients (1, 0, 0, -1) using a two-sided significance level of 0.05, assuming an error standard deviation of 1.5 and a balanced design, a total sample size of 80 participants corresponds to an approximate statistical power of 87.7%. Thus, at least 20 participants are recruited per group.

OUTCOMES

The domains and measurements for this article as well the hierarchal structure of the hereof are based on the pre-specified designation located in the trial registration (published prior to recruitment initiation) and our published protocol published prior to last patient-last-visit (described in Table 5)[26].

Primary outcome (change, timeframe 0 to 16 weeks)

Domain: beta-cell function

Measurement: hyperglycemic clamp

- Late-phase disposition index during the last 30 minutes of the glucose infusion in the hyperglycemic clamp

Major outcomes (change, timeframe 0 to 16 weeks)

Domain: beta-cell function

Measurement: hyperglycemic clamp

- Late-phase insulin sensitivity index (mean Glucose infusion rate over last 30 min of the hyperglycemic clamp phase/ (mean insulin $\times$ glucose))
- Late-phase insulin secretion rate (mean deconvoluted C-peptide measurements over last 30 min of the hyperglycemic clamp phase/ mean glucose)

Domain: post-prandial glycemic control

Measurement: mixed meal tolerance test:

- Oral disposition index
- Oral insulin sensitivity index (Matsuda index)
- Oral insulin secretion index

Other secondary outcomes (change, timeframe 0 to 16 weeks).

Domain: β cell function

Measurement: hyperglycemic clamp

- GLP-1 stimulated insulin secretion rate and C-peptide
- Arginine stimulated insulin secretion rate and C-peptide
- First phase C-peptide and insulin secretion defined as the peak concentration during the initial 10 minutes of the hyperglycemic clamp
- Basal rate of glucose disappearance (R_d)
- Basal rate of endogenous glucose appearance (R_a)
- Rate of glucose disappearance (R_d) during steady-state hyperglycemia
- Rate of glucose endogenous appearance (R_a) during steady-state hyperglycemia

Domain: post-prandial glycemic control

Measurement: mixed meal tolerance test:

- iAUC of glucose, insulin, glucagon and C-peptide
- tAUC of glucose, insulin, glucagon and C-peptide
- Glucagon like peptide-1
- Gastric inhibitory peptide

- Gastric emptying

Domain: Body anthropometrics and composition

- Body weight
- Body mass index (BMI)

Domain: Clinical, functional markers of mechanism

Measurement: fasting blood samples (plasma)

- Glycated hemoglobin A1c
- Glucose
- C-peptide
- Insulin
- Triglyceride
- Low density lipoprotein

Domain: Blood pressure

Measurement: Home blood pressure monitoring

- Avg. home systolic blood pressure
- Avg. home diastolic blood pressure

Domain: Physical function

Measurements: VO2max test (indirect calorimetry and 1 repetition max in chest press and leg-extensions)

- Maximal oxygen consumption
- Maximal oxygen consumption relative to body weight
- Upper and lower body maximal strength

STUDY POPULATION, ANALYSIS SET AND STATISTICAL PRINCIPLES

Inclusion and exclusion criteria have been published elsewhere [26].The primary analysis will be based on the family of the intention-to-treat population, defined as the *as-observed population* (missing data will not be imputed in the primary analysis) [27, 28], and the set of participants who are as close as possible to the intended intervention protocol, i.e. per-protocol (criteria described in the box 1) as a sensitivity analysis. The 'Full Analysis Set' for the intention-to-treat will thus be derived from the set of all randomized participants by minimal and justified elimination of participants. Therefore, all participants allocated to a treatment group (CON, DCON, MED or HED) will be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment.

P-values and 95% confidence intervals will be presented for the between-group difference in change comparisons and only 95% confidence intervals will be presented for the within-group (0-16 weeks) differences. Statistical significance will be claimed if the null hypothesis is rejected at the alpha level of 0.05 (two-sided). No corrections for multiplicity will be performed. To maintain the family-wise type 1 error rate on the primary outcome, a hierarchical analytic approach is engaged [29]; if we fail to progress from any of the subsequent steps (p > 0.05) we will interpret p-values and CI's numerically as indicators of associations.

Between group comparisons for effect size estimation (difference in change from 0-16 weeks, based on a superiority assumption) will be completed for all outcomes in the following order:

1) CON vs. HED. If a difference is present (p < 0.05, 2-sided) then the next between group comparison is performed. If not – then sequence is terminated.
2) CON vs. MED. If a difference is present (p < 0.05, 2-sided) then the next between group comparison is performed. If not – then sequence is terminated.
3) CON vs. DCON. If a difference is present (p < 0.05, 2-sided) then the next between group comparison is performed. If not – then sequence is terminated.
4) DCON vs. HED. If a difference is present (p < 0.05, 2-sided) then the next between group comparison is performed. If not – then sequence is terminated.
5) DCON vs. MED. If a difference is present (p < 0.05, 2-sided) then the next between group comparison is performed. If not – then sequence is terminated.
6) MED vs. HED.

All non-hypothesis-based comparisons (i.e. on the secondary outcomes) are per definition considered exploratory and supportive to the interpretation of the primary outcome.

BOX 1 Per-protocol definition (all criteria present)

Control group:
- The primary outcome is assessed at both baseline and after 16 weeks follow-up (i.e. complete case).

Diet control group:
- The primary outcome is assessed at both baseline and after 16 weeks follow-up (i.e. complete case).
- Do not exceed +/- 30% of the prescribed energy intake as assessed by their dietary records (assessed as the mean energy intake across that latter 16 weeks, excluding 1-week vacation administered following week 2 of the intervention)

Exercise and diet groups:
- The primary outcome is assessed at both baseline and after 16 weeks follow-up (i.e. complete case).
- ≥ 70% of the prescribed exercise volume across the intervention period (excluding the initial two weeks of familization and potentially one week of vacation permitted after week two of the intervention). Exercise volume is calculated separately for aerobic and resistance training and ≥ 70% of the volume of each type should be achieved. For aerobic training ≥ 70% of prescribed training time (minutes) should be within the target heart rate zones. For resistance training, ≥ 70% of prescribed sets should be performed at or below the prescribed maximum RIR.
- Do not exceed +/- 30% of the prescribed energy intake as assessed by their dietary records (assessed as the mean energy intake across that latter 16 weeks, excluding 1-week vacation administered following week 2 of the intervention).

Harms and adverse events as defined in the protocol will be reported if the incidence is ≥ 5 % in any of the groups. All serious adverse events will be reported. Harms and adverse events will be reported as number and percentages of participants experiencing the event by system organ class and will be subject to null-hypothesis testing.

Sensitivity analyses will be performed using the potentially biased but conservative non-responder imputation (*baseline observation carried forward* technique) as well as the current best practice multiple imputation procedure[27]. Patterns of missing data will be investigated. *A priori*, the less restrictive missing at random (MAR) assumption is considered more reasonable than data missing completely at random (MCAR). Assuming that the data on potential dropouts are MAR, multiple imputation procedures will be applicable to handle missing data for all participants with baseline measurements.

STATISTICAL METHODS

The analyses of the primary outcome will be performed using a repeated measures analysis of covariance applied using mixed linear modelling [28, 30]. Mean change score of DI will be applied as the dependent outcome variable, whereas group, time, the interaction between time and group, sex, the baseline value of DI are included as independent (fixed) variables and participant identifier as random effect. The potentially biased *per-protocol* population analysis will be adjusted for putative confounders: sex, age, diabetes duration, baseline maximal oxygen consumption. If the global test indicates between-group differences ($H_{0,DCON} = H_{0,MED} = H_{0,HED} = H_{0,CON}$; $p \leq 0.1$), pairwise between-group differences, in the order described above, will be explored. The same statistical method will be applied to the other continues outcomes.

The assumptions for using the linear models will be checked to confirm normal distribution of the residuals and the homogeneity of the variance (standardized residuals vs. the predicted values). Variables not meeting the model assumptions will be transformed using appropriate transformations. If no suitable transformation is identified, the median change with interquartile ranges will be reported and testing will be performed using suitable non-parametric statistical tests (e.g. quantile regression).

Dichotomous outcomes (i.e. discontinuation, reduction or intensification of medications according to the predefined treatment algorithm) at 16 weeks follow-up compared to baseline) will be analyzed using logistic regression. If the dichotomous outcome data are sparse, the asymptotic results can be unreliable; therefore, Fisher's exact tests will be used to calculate the exact probability of the possible (2×4) tables allowing estimation of the Wald-test-associated variance, which corresponds to the ratio of its estimate (log-odds ratio [OR]) to its standard error. By default, no imputations will be used (statistical or otherwise) for the analysis, but robustness will be assessed via sensitivity analyses which evaluate missing data to explore the effect of departures from the assumption made in the main analysis (missing at random).

Statistical code for the primary analysis
```
*************************************************************************
mixed dDI i.group##i.time DI_0 i.sex ||ID:,
contrast i.group##i.time (note: omnibus test)
pwcompare i.group##i.time (note: pairwise comparisons if the omnibus test allows)
*************************************************************************
```

The variable *dDI* is the change in late-phase disposition index from baseline (0 weeks) to end follow-up (16 weeks). *Group* is the treatment variable; *sex* describes the sex of the participants and *DI_0* is the baseline late-phase disposition index. The model includes treatment (group, 4 levels), time (2 levels), sex (2 levels), and the possible interaction between treatment and time (8 levels) as fixed effects, with the baseline value of the relevant variable as a covariate.

DEVIATIONS FROM THE ORIGINAL PROTOCOL

Due to new data on the effects of medical discontinuation, following protocol changes were made prior to initiation of the study (Date for amendment Dec. 18th, 2018);

- Complete medical discontinuation upon inclusion was abandoned and excluded from the *per-protocol definition*.

Due to a slow recruitment rate and exclusion of a clinically relevant group of potential participants, we modified the following eligibility criteria (Date for amendment Sep. 2nd, 2019);

- "No known lung disease" was changed to "No lung disease, other than asthma that can be managed with beta2-agonists and does not exhibit seasonal variation.
- "No known thyroid disease" was changed to "No changes in hypothyroid disease treatment within the last 3 three months prior to enrolment"
- "No known liver disease" was changed to "No known liver disease - defined as ALAT or ASAT elevated three times above upper limit."
- "No known autoimmune disease" was changed to "No psoriasis disease requiring systemic treatment or cutaneous elements bigger than a total area of 25 cm^2"
- "No diagnose of depression or treatment with anti-depressive medication, ongoing or within the last three months before enrolment" was changed to "No changes in symptoms or anti-depressive medication three months prior to enrolment."
- " Protein or glucose in the urine at pre-screening" was changed to "Macroalbuminuria at pre-screening"
- "No biochemical sign of other major diseases" was changed to "Biochemical sign of other major diseases"

The majority of participants were not able to attend the 4- and 12-week visits following an overnight fast, thus fasting blood sampling at these timepoint were abandoned.

Change from 2-hour to 1-hour hyperglycemia + GLP-1 infusion as we were not able to maintain hyperglycemia and with excessive high coefficients of variation.

In the event of malfunctioning heart rate monitoring, the participant was carefully instructed to train in accordance to the Borg scale corresponding to target heart rate zones (i.e. %HRmax) in harmony with the specific training program[31].

Six participants have had their intervention prolonged 3 weeks in order to ensure that they were no longer infected or infectious. The participant group distribution consisted of 1 CON, 2 DCON, 2 MED and 1 HED.

IMPLEMENTATION OF THE SAP

Upon SAP approval by and signatures of the writing committee, the statistical analysis plan will published at The Centre for Physical Activity website (www.aktivsundhed.dk) prior to commencing any statistical analyses.

EXPECTED WRITING COMMITTEE

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EXPECTED OUTLINE OF THE REPORT

The study report will be aimed at a clinical journal, thus the report will contain 3500-4000 words and 4 to 6 main figures and tables depending on the journal.

OVERVIEW OF CONTENT (Unformatted tables with specific variables are placed at the end of the text)

TABLES (In paper)

- Table 1 Baseline characteristics
- Table 2 Within group changes in the primary and major secondary outcomes
- Table 3 Pairwise comparisons of the change in the primary outcome and major secondary outcomes
- Table 4 Within group changes in other outcomes reflecting underlying mechanisms of β cell function
- Table 5 Pairwise comparisons of the change in other outcomes reflecting underlaying mechanisms of β cell function

FIGURES (In paper)

- Figure 1: Table of graphs (2x3 panel) depicting the within-group change (baseline to 16 weeks) in the primary outcome and major secondary outcomes. Data are presented as least-squares-means (bar charts overlaid with individual values) with 95% confidence intervals.
  - Figure 2a: Change in late phase disposition index (primary outcome) by group
  - Figure 2b: Change in late phase insulin sensitivity index by group
  - Figure 2c: Change in late phase insulin secretion rate by group
  - Figure 2d: Change in oral disposition index by group
  - Figure 2e: Change in oral insulin sensitivity index by group
  - Figure 2f: Change in oral insulinogenic index by group

ONLINE ONLY (Tables)

- eTable 1 Self-reported adherence to diet
- eTabel 2 Self-reported adherence to pharmacological treatment and management
- eTable 3 Free-living physical activity
- eTable 4 Intensity and duration in aerobic training. Intensity measured as %HRmax in intervention in MED and HED group. Intensity is reported as duration in moderate intensity (60-79% HRmax) and duration in high intensity (80-100% HRmax).
- eTable 5 Resistance training in the large muscle groups. Intensity measured as repetitions in reserve in resistance training intervention in MED and HED group.
- eTable 6 Volume load (tonnage) in resistance training in the large muscle groups. Volume load measured as tonnage (kg x repetitions x sets).
- eTable 7 Exercise modification and causes in aerobic training in MED and HED group.
- eTable 8 Exercise modification and causes in resistance training in MED and HED group.
- eTabel 9 Adherence for aerobic and resistance training in MED and HED group.
- eTable 10 Coefficient of variation and precision during the hyperglycemic clamp
- eTable 11 Sensitivity analyses - Pairwise comparisons of the change in the primary and major outcomes
- eTable 12 Baseline values and within group changes (0-16 weeks) in the primary outcome and other secondary outcomes derived from the hyperglycemic clamp
- eTable 13 Other Pairwise comparisons of secondary outcomes derived from the mixed meal tolerance test
- eTable 14 Baseline values and within group changes (0-16 weeks) cardiometabolic, body composition and fitness
- eTable 15 Pairwise comparisons of the change in cardiometabolic, body composition and fitness
- eTable 16 Adverse events after randomization

ONLINE ONLY (Figures)

- eFigure 1: Flow of participants

- eFigure 2: Figure describing the pre-defined algorithms for pharmacological management of blood glucose, blood pressure and blood lipids including therapeutic targets.

- eFigure 3: Table of graphs describing the insulin secretion rates (least-squares-means, concentration on the y-axis) across the clamp (time in minutes on x-axis) by group (1a, 1b, 1c, 1d) with pre and post values and standard errors in the same graph (overlay graphs)

- eFigure 4: Table of graphs describing the glucose infusion rates (least-squares-means, concentration on the y-axis) across the clamp (time in minutes on x-axis) by group (1a, 1b, 1c, 1d) with pre and post values and standard errors in the same graph (overlay graphs)

- eFigure 5: Table of graphs describing the GLP-1 (least-squares-means, concentration on the y-axis) across the hyperglycemic clamp (time in minutes on x-axis) by group (1a, 1b, 1c, 1d) with pre and post values and standard errors in the same graph (overlay graphs)

- eFigure 6: Table of graphs describing the glucose (least-squares-means, concentration on the y-axis) response during the mixed meal tolerance test (time in minutes on x-axis) by group (1a, 1b, 1c, 1d) with pre and post values and standard errors in the same graph (overlay graphs)

- eFigure 7: Table of graphs describing the insulin (least-squares-means, concentration on the y-axis) response during the mixed meal tolerance test (time in minutes on x-axis) by group (1a, 1b, 1c, 1d) with pre and post values and standard errors in the same graph (overlay graphs)

- eFigure 8: Table of graphs describing the c-peptide (least-squares-means, concentration on the y-axis) response during the mixed meal tolerance test (time in minutes on x-axis) by group (1a, 1b, 1c, 1d) with pre and post values and standard errors in the same graph (overlay graphs)

- eFigure 9: Table of graphs describing the GLP-1 (least-squares-means, concentration on the y-axis) response during the mixed meal tolerance test (time in minutes on x-axis) by group (1a, 1b, 1c, 1d) with pre and post values and standard errors in the same graph (overlay graphs)

- eFigure 10: Table of graphs describing the GIP (least-squares-means, concentration on the y-axis) response during the mixed meal tolerance test (time in minutes on x-axis) by group (1a, 1b, 1c, 1d) with pre and post values and standard errors in the same graph (overlay graphs)

- eFigure 11: Table of graphs describing the paracetamol (least-squares-means, concentration on the y-axis) response during the mixed meal tolerance test (time in minutes on x-axis) by group (1a, 1b, 1c, 1d) with pre and post values and standard errors in the same graph (overlay graphs)

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UNFORMATTED TABLES WITH INTENDED CONTENT

Table 1 Baseline characteristics					
	CON	DCON	MED	HED	Total
Age (years)					
Sex (N (%) female)					
Type 2 diabetes duration (years)					
Glycemic control					
HbA1c (mmol/mol)					
HbA1c (%)					
Fasting glucose (mmol/l)					
Fasting insulin (pmol/l)					
Fasting C-peptide (pmol/l)					
Lipids					
Low Density lipoprotein					
Fasting triglycerides					
Blood pressure					
Systolic (mmHg)					
Diastolic (mmHg)					
Glucose-lowering medication, N (%)					
None					
Biguanide					
Biguanide + SGLT2i **or** DPP4i					
Biguanide + SGLT2i + DPP4i					
Lipid-lowering medication, No (%)					
None					
Statin					
Blood pressure lowering medication, No (%)					
None					
ARB **or** ACEi					
ARB **or** ACEi + Thiazide **or** CCB					
ARB **or** ACEi + Thiazide + CCB					
Physical function					
Absolute VO_2 max (ml/min)					
Relative VO_2 max (ml/kg/min)					
Watt max (W/kg)					
1 RM chest press (kg)					
1 RM leg extension (kg)					
Body composition					
Body weight (kg)					
BMI (kg/m^2)					
Diet					
Energy intake (kcal/day)					
Physical activity level					
Moderate and vigorous physical activity (hours/day)					
Stepping (steps/day)					
Sitting (hours/day)					
Hyperglycemic clamp					
Basal					
Mean insulin secretion rate					
Glucose R_a (mg * kg^{-1} * min^{-1})					
Glucose R_d (mg * kg^{-1} * min^{-1})					
Early phase hyperglycemia					
Mean GIR (mg * kg^{-1} * min^{-1})					
Mean insulin secretion rate					
Peak insulin secretion rate					

Table 1 cont'd					
Steady state hyperglycemia					
Late phase disposition index					
Late phase insulin sensitivity index					
Late phase insulin secretion rate					
Mean GIR (mg * kg^{-1} * min^{-1})					
Peak insulin secretion rate					
Glucose R_a (mg * kg^{-1} * min^{-1})					
Glucose R_d (mg * kg^{-1} * min^{-1})					
Hyperglycemia and GLP-1					
Mean GIR (mg * kg^{-1} * min^{-1})					
Mean insulin secretion rate					
Peak insulin secretion rate					
Hyperglycemia, GLP-1 and Arginine					
Mean insulin secretion rate					
Peak insulin secretion rate					
Mixed meal tolerance test					
0-30 min					
tAUC glucose					
tAUC C-peptide					
tAUC insulin					
tAUC GLP-1$_{total}$					
tAUC GLP-1$_{active}$					
tAUC GIP$_{total}$					
tAUC paracetamol					
0-120 min					
Oral disposition index					
Oral insulin sensitivity index					
tAUC glucose					
tAUC C-peptide					
tAUC insulin					
tAUC GLP-1$_{total}$					
tAUC GLP-1$_{active}$					
tAUC GIP$_{total}$					
tAUC paracetamol					

Data are presented as mean (SD) or median (IQR). CON, control group, DCON: Diet control group: MED: Moderate volume exercise, HED: High volume exercise, HbA1c: glycated hemoglobin A1c, LDL: low-density lipoprotein, BMI: body mass index (calculated as weight in kilograms divided by height in meters squared). SLGT2i: selective sodium glucose co-transporter 2 inhibitors, DPP4i: dipeptidyl peptidase 4 inhibitors, ARB: angiotensin II receptor blockers, ACEi: angiotensin converting enzyme inhibitors, CCB: calcium channel blockers. Ra: Rate of appearance, Rd: Rate of disappearance, GIR: Glucose infusion rate

	CON		DCON		MED		HED	
Table 2 Within-group changes from baseline to 16-week follow-up in the primary and major secondary outcomes								
	Change	95% CI	Change	95% CI	Change	95% CI	Change	95% CI
Primary outcome								
Late-phase Disposition index								
Major Secondary outcomes								
Late-phase insulin secretion rate								
Late-phase insulin sensitivity								
Oral disposition index								
Oral insulin sensitivity index								
Oral insulinogenic index								
Data are least-squares means. CI: confidence intervals, CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise,								

	HED vs. CON		MED vs. CON		DCON vs. CON		HED vs. DCON		MED vs. DCON		HED vs. MED		P
Table 3 Pairwise comparisons of the change in the primary outcome and major secondary outcomes

	HED vs. CON		MED vs. CON		DCON vs. CON		HED vs. DCON		MED vs. DCON		HED vs. MED		P
	MD	95% CI	MD	95% CI	MD	95% CI	MD	95% CI	MD	95% CI	MD	95% CI	
Primary outcome													
Late-phase Disposition index													
Major Secondary outcomes													
Insulin secretion rate													
Insulin sensitivity													
Oral disposition index													
Oral insulin sensitivity index													
Oral insulinogenic index													

MD: Mean difference, CI: confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise

	CON		DCON		MED		HED	
Table 4 Within-group changes from baseline to 16-week follow-up in in other outcomes reflecting underlaying mechanisms of beta-cell function	Change	95% CI	Change	95% CI	Change	95% CI	Change	95% CI
Basal								
Mean insulin secretion rate								
Glucose R_a (mg * kg^{-1} * min^{-1})								
Glucose R_d (mg * kg^{-1} * min^{-1})								
Early state hyperglycemia								
Mean GIR (mg * kg^{-1} * min^{-1})								
Mean insulin secretion rate								
Peak insulin secretion rate								
Steady state hyperglycemia								
Mean GIR (mg * kg^{-1} * min^{-1})								
Peak insulin secretion rate								
Glucose R_a (mg * kg^{-1} * min^{-1})								
Glucose R_d (mg * kg^{-1} * min^{-1})								
Hyperglycemia and GLP-1								
Mean GIR (mg * kg^{-1} * min^{-1})								
Mean insulin secretion rate								
Peak insulin secretion rate								
Hyperglycemia, GLP-1 and Arginine								
Mean insulin secretion rate								
Peak insulin secretion rate								
0-30 min								
tAUC glucose								
tAUC C-peptide								
tAUC insulin								
tAUC GLP-1$_{total}$								
tAUC GLP-1$_{active}$								
tAUC GIP$_{total}$								
tAUC paracetamol								
0-120 min								
tAUC glucose								
tAUC C-peptide								
tAUC insulin								
tAUC GLP-1$_{total}$								
tAUC GLP-1$_{active}$								
tAUC GIP$_{total}$								
tAUC paracetamol								
Data are least-squares means. CI: confidence intervals, CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, GIR: glucose infusion rate, Ra: Rate of appearance, Rd: Rate of disappearance: GLP-1: Glucagon-like-peptide 1, GIP: Gastric inhibitory polypeptide, tAUC: Total area under the curve								

Table 5 Pairwise comparisons of the change in other outcomes reflecting underlying mechanisms of beta-cell function												
	HED vs. CON		MED vs. CON		DCON vs. CON		HED vs. DCON		MED vs. DCON		HED vs. MED	
	MD	95% CI	MD	95% CI	MD	95% CI	MD	95% CI	MD	95% CI	MD	95% CI
	Hyperglycemic clamp											
Basal												
Mean insulin secretion rate												
Glucose R_a (mg * kg^{-1} * min^{-1})												
Glucose R_d (mg * kg^{-1} * min^{-1})												
Early state hyperglycemia												
Mean GIR (mg * kg^{-1} * min^{-1})												
Mean insulin secretion rate												
Peak insulin secretion rate												
Steady state hyperglycemia												
Mean GIR (mg * kg^{-1} * min^{-1})												
Peak insulin secretion rate												
Glucose R_a (mg * kg^{-1} * min^{-1})												
Glucose R_d (mg * kg^{-1} * min^{-1})												
Hyperglycemia and GLP-1												
Mean GIR (mg * kg^{-1} * min^{-1})												
Mean insulin secretion rate												
Peak insulin secretion rate												
Hyperglycemia, GLP-1 and Arginine												
Mean insulin secretion rate												
Peak insulin secretion rate												
	Mixed meal tolerance test											
0-30 min												
tAUC glucose												
tAUC C-peptide												
tAUC insulin												
tAUC GLP-1$_{total}$												
tAUC GLP-1$_{active}$												
tAUC GIP$_{total}$												
tAUC paracetamol												
0-120 min												
tAUC glucose												
tAUC C-peptide												
tAUC insulin												
tAUC GLP-1$_{total}$												
tAUC GLP-1$_{active}$												
tAUC GIP$_{total}$												
tAUC paracetamol												
MD: Mean difference, CI: confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, GIR: glucose infusion rate, Ra: Rate of appearance, Rd: Rate of disappearance: GLP-1: Glucagon-like-peptide 1, GIP: Gastric inhibitory polypeptide, tAUC: Total area under the curve												

eTable 1 Adherence to diet									
	Baseline (N=)	Week 4 (N=)	% adherence	Week 12 (N=)	% adherence	Week 16 (N=)	% adherence	% adherence after randomization	Mean reduction after randomization (% from baseline)
Total energy intake (Kcal/kg/day)									
CON									
DCON									
MED									
HED									
Total carbohydrate (% of total energy intake)									
CON									
DCON									
MED									
HED									
Fiber (% of total energy intake)									
CON									
DCON									
MED									
HED									
Total fat (% of total energy intake)									
CON									
DCON									
MED									
HED									
Saturated fat (% of total energy intake)									
CON									
DCON									
MED									
HED									
Protein (% of total energy intake)									
CON									
DCON									
MED									
HED									
Alcohol (% of total energy intake)									
CON									
DCON									
MED									
HED									
Data are mean and standard deviation or median and interquartile range. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise									

eTabel 2 self-reported adherence to pharmacological treatment[a] and management																
	Baseline				Week 4				Week 12				Week 16			
	CON	DCON	MED	HED	CON	DCON	MED	HED	CON	DCON	MED	HED	CON	DCON	MED	HED
Proportion of participants attending consultation																
Self-reported adherence to Glucose-lowering medication																
Several times per week																
Once a week																
Several times per month																
Once a month																
Never																
Not relevant																
Does not take prescribed medication																
Missing values																
Self-reported adherence to blood pressure-lowering medication																
Several times per week																
Once a week																
Several times per month																
Once a month																
Never																
Not relevant																
Does not take prescribed medication																
Missing values																
Self-reported adherence to lipid-lowering medication																
Several times per week																
Once a week																
Several times per month																
Once a month																
Never																
Not relevant																
Does not take prescribed medication																
Missing values																
Glucose-lowering medication, N (%)																
None																
Biguanide																
Biguanide + SGLT2i or DPP4i																
Biguanide + SGLT2i + DPP4i																
Lipid-lowering medication, No (%)																
None																
Statin																
Blood pressure lowering medication, No (%)																
None																
ARB or ACEi																
ARB or ACEi + Thiazide or CCB																
ARB or ACEi + Thiazide + CCB																

Data presented as N (%)

There were five adherence categories in relation to how often the participants would forget to take their medicine: 1) several times per week 2) once a week 3) several times per month 4) once a month 5) never.

Adherence (%) in these categories is calculated as follows: Total N - (does not take the prescribed medicine + numbers of participants with no medication + missing values) since adherence is calculated based on the participants that are prescribed medication and taking the medication. Not the total number of participants (N).

[a]How often does the participant forget the medication

eTable 3 Free-living physical activity				
	Baseline (N=)	Week 4 (N=)	Week 12 (N=)	Week 16 (N=)
Valid days (N)				
CON				
DCON				
MED				
HED				
Wear time (hours/day)				
CON				
DCON				
MED				
HED				
Total physical activity (counts per minute)				
CON				
DCON				
MED				
HED				
MVPA (min/day)				
CON				
DCON				
MED				
HED				
Sitting time (min/day)				
CON				
DCON				
MED				
HED				
Stepping (steps/day)				
CON				
DCON				
MED				
HED				
Data are mean and standard deviation or median and interquartile range. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, MVPA: Moderate and vigorous physical activity				

eTable 4 Intensity and duration in aerobic training					
Intensity (internal and external load) in aerobic training					
Familiarization week 1-2	Average %HRmax, N (%)	Number of minutes 60-79% HRmax, (N=)	Number of minutes 80-100% HRmax, (N=)	Minutes spent in 80-100% HRmax, N (%)	Average watt, (N=)	
MED						
HED						
Week 3-10	Average %HRmax, N (%)	Number of minutes 60-79% HRmax, (N=)	Number of minutes 80-100% HRmax, (N=)	Minutes spent in 80-100% HRmax, N (%)	Average watt, (N=)	Increase in average watt from week 1-2 to 3-10 N (%)
MED						
HED						
Week 11-16	Average %HRmax, N (%)	Number of minutes 60-79% HRmax, (N=)	Number of minutes 80-100% HRmax, (N=)	Minutes spent in 80-100% HRmax, N (%)	Average watt, (N=)	Increase in average watt from week 3-10 to week 11-16 N (%)
MED						
HED						
Week 3-16	Number of minutes 60-79% HRmax, (N=)	Number of minutes 80-100% HRmax, (N=)	Number of minutes within target %HRmax, N (%)	Minutes spent in 80-100% HRmax, N (%)	Average watt, (N=)	Increase in average watt from week 3 to week 16, N (%)
MED						
HED						
Duration of aerobic training					
Familiarization week 1-2	Number of minutes prescribed pr. week, (N=)	Number of minutes performed pr week, (N=)	Number of minutes completed from prescribed, N (%)	Number of minutes performed within target %HRmax, N (%)	Number of minutes pr. sessions, (N=)	Number of sessions pr. week, (N=)
MED						
HED						
Week 3-10	Number of minutes prescribed pr. week, (N=)	Number of minutes performed pr week, (N=)	Number of minutes completed from prescribed, N (%)	Number of minutes performed within target %HRmax, N (%)	Number of minutes pr. sessions (N=)	Number of sessions pr. week, (N=)
MED						
HED						
Week 11-16	Number of minutes prescribed pr. week, (N=)	Number of minutes performed pr week, (N=)	Number of minutes completed from prescribed, N (%)	Number of minutes performed within target %HRmax, N (%)	Number of minutes pr. sessions (N=)	Number of sessions pr. week, (N=)
MED						
HED						
Week 3-16	Number of minutes prescribed pr. week, (N=)	Number of minutes performed pr week, (N=)	Number of minutes completed from prescribed, N (%)	Number of minutes performed within target %HRmax, N (%)	Number of minutes pr. sessions (N=)	Number of sessions pr. week, (N=)
MED						
HED						
Data are mean and standard deviation or median and interquartile range. HRmax: Maximum heart rate, MED: Moderate volume exercise, HED: High volume exercise					

eTable 5 Resistance training in the large muscle groups				
Familiarization week 1-2	Number of sets prescribed pr. week, (N=)	Number of sets performed pr. week, (N=)	Number of sets completed from prescribed, N (%)	Number of sets performed within target RIR, N (%)
MED				
Leg press				
Leg extension				
Leg curl				
Chest press				
Back row				
Total				
HED				
Leg press				
Leg extension				
Leg curl				
Chest press				
Back row				
Total				
Week 3-10	Number of sets prescribed pr. week, (N=)	Number of sets performed pr. week, (N=)	Number of sets completed from prescribed, N (%)	Number of sets performed within target RIR, N (%)
MED				
Leg press				
Leg extension				
Leg curl				
Chest press				
Back row				
Total				
HED				
Leg press				
Leg extension				
Leg curl				
Chest press				
Back row				
Total				
Week 11-16	Number of sets prescribed pr. week, (N=)	Number of sets performed pr. week, (N=)	Number of sets completed from prescribed, N (%)	Number of sets performed within target RIR, N (%)
MED				
Leg press				
Leg extension				
Leg curl				
Chest press				
Back row				
Total				
HED				
Leg press				
Leg extension				
Leg curl				
Chest press				
Back row				
Total				
Week 3-16	Number of sets prescribed pr. week, (N=)	Number of sets performed pr. week, (N=)	Number of sets completed from prescribed, N (%)	Number of sets performed within target RIR, N (%)
MED				
Leg press				
Leg extension				
Leg curl				
Chest press				
Back row				
Total				
HED				
Leg press				
Leg extension				
Leg curl				
Chest press				
Back row				
Total				
Data are mean and standard deviation or median and interquartile range. RIR: repetitions in reserve, MED: Moderate volume exercise, HED: High volume exercise				

eTable 6 Volume load (tonnage) in resistance training in the large muscle groups

Familiarization week 1-2	Number of repetitions pr week, (N=)	Number of repetitions pr. set, (N=)	Average kilogram lifted pr. set, (N=)	Number of sets performed pr week, (N=)	Tonnage pr week, (N=)	
MED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
HED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
Week 3-10	Number of repetitions pr week, (N=)	Number of repetitions pr. set, (N=)	Average kilogram lifted pr. set, (N=)	Number of sets performed, (N=)	Tonnage pr week, (N=)	Tonnage increase from week 1-2 to week 3-10, N (%)
MED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
HED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
Week 11-16	Number of repetitions pr week, (N=)	Number of repetitions pr. set, (N=)	Average kilogram lifted pr. set, (N=)	Number of sets performed, (N=)	Tonnage pr week, (N=)	Tonnage increase from week 3-10 to week 11-16, N (%)
MED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
HED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
Week 3-16	Number of repetitions pr week, (N=)	Number of repetitions pr. set, (N=)	Average kilogram lifted pr. set, (N=)	Number of sets performed, (N=)	Tonnage, (N=)	Tonnage increase from week 3 to week 16, N (%)
MED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
HED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						

Data are mean and standard deviation or median and interquartile range. Tonnage: weight (kg) x repetitions x sets, MED: Moderate volume exercise, HED: High volume exercise

eTable 7 Exercise modification and causes in aerobic training							
Familiarization week 1-2	Fatigue, (N=)	Musculoskeletal discomfort, (N=)	Motivational, (N=)	Other reasons, (N=)	Missed exercises, (N=)	Number of participants with ≥1 modification (%)	Number of sessions with ≥1 modification (%)
MED							
HED							
Week 3-10	Fatigue, (N=)	Musculoskeletal discomfort, (N=)	Motivational, (N=)	Other reasons, (N=)	Missed exercises, (N=)	Number of participants with ≥1 modification (%)	Number of sessions with ≥1 modification (%)
MED							
HED							
Week 11-16	Fatigue, (N=)	Musculoskeletal discomfort, (N=)	Motivational, (N=)	Other reasons, (N=)	Missed exercises, (N=)	Number of participants with ≥1 modification (%)	Number of sessions with ≥1 modification (%)
MED							
HED							
Week 3-16	Fatigue, (N=)	Musculoskeletal discomfort, (N=)	Motivational, (N=)	Other reasons, (N=)	Missed exercises, (N=)	Number of participants with ≥1 modification (%)	Number of sessions with ≥1 modification (%)
MED							
HED							
Data are mean and standard deviation or median and interquartile range. MED: Moderate volume exercise, HED: High volume exercise							

eTable 8 Exercise modification and causes in resistance training						
Familiarization week 1-2	Fatigue, (N=)	Musculoskeletal discomfort, (N=)	Motivational, (N=)	Other reasons, (N=)	Missed exercises, (N=)	Number of participants with ≥1 modification (%)	Number of sessions with ≥1 modification (%)
MED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
HED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
Week 3-10	Fatigue, (N=)	Musculoskeletal discomfort, (N=)	Motivational, (N=)	Other reasons, (N=)	Missed exercises, (N=)	Number of participants with ≥1 modification (%)	Number of sessions with ≥1 modification (%)
MED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
HED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
Week 11-16	Fatigue, (N=)	Musculoskeletal discomfort, (N=)	Motivational, (N=)	Other reasons, (N=)	Missed exercises, (N=)	Number of participants with ≥1 modification (%)	Number of sessions with ≥1 modification (%)
MED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
HED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
Week 3-16	Fatigue, (N=)	Musculoskeletal discomfort, (N=)	Motivational, (N=)	Other reasons, (N=)	Missed exercises, (N=)	Number of participants with ≥1 modification (%)	Number of sessions with ≥1 modification (%)
MED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
HED						
Leg press						
Leg extension						
Leg curl						
Chest press						
Back row						
Total						
Data are mean and standard deviation or median and interquartile range. MED: Moderate volume exercise, HED: High volume exercise						

eTabel 9 Adherence for aerobic and resistance training			
Familiarization week 1-2	Aerobic training, N (%)	Resistance training, N (%)	Total training, N (%)
MED			
HED			
Week 3-10	Aerobic training, N (%)	Resistance training, N (%)	Total training, N (%)
MED			
HED			
Week 11-16	Aerobic training, N (%)	Resistance training, N (%)	Total training, N (%)
MED			
HED			
Week 3-16	Aerobic training, N (%)	Resistance training, N (%)	Total training, N (%)
MED			
HED			Total training, N (%)
Total	Aerobic training, N (%)	Resistance training, N (%)	
MED			
HED			
Data are mean and standard deviation or median and interquartile range. RIR: repetitions in reserve, MED: Moderate volume exercise, HED: High volume exercise. Adherence: For prescribed aerobic training $\geq$ 70% of minutes should be within the target heart rate zones. For prescribed resistance training, $\geq$ 70% of the sets should be performed at or below the maximum RIR.			

	CON		DCON		MED		HED	
eTable 10 Coefficient of variation and precision during the hyperglycemic clamp								
	0 weeks (SD or IQR)	16 weeks (SD or IQR)	0 weeks (SD or IQR)	16 weeks (SD or IQR)	0 weeks (SD or IQR)	16 weeks (SD or IQR)	0 weeks (SD or IQR)	16 weeks (SD or IQR)
Coefficient of variance (%)								
Basal								
Early phase hyperglycemia								
Steady phase hyperglycemia								
Hyperglycemia + GLP-1								
Hyperglycemia + GLP-1 + Arginine								
Off-target								
Steady phase hyperglycemia								
Hyperglycemia + GLP-1								
Data are means and standard deviations/median or interquartile ranges at baseline or follow-up or estimated within-group difference in change from baseline to follow-up with 95% confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, GIR: glucose infusion rate, Ra: Rate of appearance, Rd: Rate of disappearance: GLP-1: Glucagon-like-peptide 1								

	HED vs. CON	P-value		MED vs. CON	P-value		DCON vs. CON	P-value		HED vs. DCON	P-value		MED vs. DCON	P-value		HED vs. MED	P-value
eTable 11 Sensitivity analyses - Pairwise comparisons of the change in the primary outcome and indices of beta-cell function and insulin sensitivity																		
Per protocol#																		
Primary outcome																		
Late-phase Disposition index (hyperglycemic clamp)																		
Major Secondary outcomes																		
Late-phase insulin sensitivity (hyperglycemic clamp)																		
Late-phase insulin secretion rate (hyperglycemic clamp)																		
Oral disposition index (MMTT)																		
Oral insulin sensitivity (MMTT)																		
Oral insulinogenic index (MMTT)																		
Imputation																		
Primary outcome																		
Late-phase Disposition index (hyperglycemic clamp)																		
Secondary outcomes																		
Late-phase insulin sensitivity (hyperglycemic clamp)																		
Late-phase insulin secretion rate (hyperglycemic clamp)																		
Oral disposition index (MMTT)																		
Oral insulin sensitivity (MMTT)																		
Oral insulinogenic index (MMTT)																		

Data are estimated mean difference in changes between groups with 95% confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, MMTT: Mixed meal tolerance test

Adjusted for sex, age, diabetes duration, baseline maximal oxygen consumption

eTable 12 Baseline values and within group changes (0-16 weeks) for other outcomes from the mixed meal tolerance test derived outcomes											
	CON			DCON			MED			HED	
	0 weeks (SD or IQR)	Change (95% CI)		0 weeks (SD or IQR)	Change (95% CI)		0 weeks (SD or IQR)	Change (95% CI)		0 weeks (SD or IQR)	Change (95% CI)
0-15 min											
Incremental AUC											
iAUC glucose											
iAUC C-peptide											
iAUC insulin											
iAUC GLP-1$_{total}$											
iAUC GLP-1$_{active}$											
iAUC GIP$_{total}$											
iAUC paracetamol											
Total AUC											
tAUC glucose											
tAUC C-peptide											
tAUC insulin											
tAUC GLP-1$_{total}$											
tAUC GLP-1$_{active}$											
tAUC GIP$_{total}$											
tAUC paracetamol											
0-30 min											
Incremental AUC											
iAUC glucose											
iAUC C-peptide											
iAUC insulin											
iAUC GLP-1$_{total}$											
iAUC GLP-1$_{active}$											
iAUC GIP$_{total}$											
iAUC paracetamol											
Total AUC											
tAUC glucose											
tAUC C-peptide											
tAUC insulin											
tAUC GLP-1$_{total}$											
tAUC GLP-1$_{active}$											
tAUC GIP$_{total}$											
tAUC paracetamol											
0-60 min											
Incremental AUC											
iAUC glucose											
iAUC C-peptide											
iAUC insulin											
iAUC GLP-1$_{total}$											
iAUC GLP-1$_{active}$											
iAUC GIP$_{total}$											
iAUC paracetamol											
Total AUC											
tAUC glucose											
tAUC C-peptide											
tAUC insulin											
tAUC GLP-1$_{total}$											
tAUC GLP-1$_{active}$											
tAUC GIP$_{total}$											
tAUC paracetamol											
0-180 min											
Incremental AUC											
iAUC glucose											
iAUC C-peptide											
iAUC insulin											
iAUC GLP-1$_{total}$											

iAUC GLP-1$_{active}$										
iAUC paracetamol										
Total AUC										
tAUC glucose										
tAUC C-peptide										
tAUC insulin										
tAUC GLP-1$_{total}$										
tAUC GLP-1$_{active}$										
tAUC paracetamol										

Data are means and standard deviations/median or interquartile ranges at baseline or follow-up or estimated within-group difference in change from baseline to follow-up with 95% confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, GLP-1: Glucagon-like-peptide 1, GIP: Gastric inhibitory polypeptide, tAUC: total area under the curve, iAUC: incremental area under the curve.

eTable 13 Other Pairwise comparisons of secondary outcomes derived from the mixed meal tolerance test													
	HED vs. CON	P-value		MED vs. CON	P-value		DCON vs. CON	P-value		HED vs. DCON	P-value		MED vs. DCON	P-value		HED vs. MED	P-value

	HED vs. CON	P-value	MED vs. CON	P-value	DCON vs. CON	P-value	HED vs. DCON	P-value	MED vs. DCON	P-value	HED vs. MED	P-value
Total AUC												
0-15 min												
tAUC C-peptide												
tAUC insulin												
tAUC GLP-1$_{total}$												
tAUC GLP-1$_{active}$												
tAUC GIP$_{total}$												
tAUC paracetamol												
0-60 min												
tAUC glucose												
tAUC C-peptide												
tAUC insulin												
tAUC GLP-1$_{total}$												
tAUC GLP-1$_{active}$												
tAUC GIP$_{total}$												
tAUC paracetamol												
0-180 min												
tAUC glucose												
tAUC C-peptide												
tAUC insulin												
tAUC GLP-1$_{total}$												
tAUC GLP-1$_{active}$												
tAUC GIP$_{total}$												
tAUC paracetamol												
Incremental AUC												
0-15 min												
iAUC glucose												
iAUC C-peptide												
iAUC insulin												
iAUC GLP-1$_{total}$												
iAUC GLP-1$_{active}$												
iAUC GIP$_{total}$												
iAUC paracetamol												
0-30 min												
iAUC glucose												
iAUC C-peptide												
iAUC insulin												
iAUC GLP-1$_{total}$												
iAUC GLP-1$_{active}$												
iAUC GIP$_{total}$												
iAUC paracetamol												
0-60 min												
iAUC glucose												
iAUC C-peptide												
iAUC insulin												
iAUC GLP-1$_{total}$												
iAUC GLP-1$_{active}$												
iAUC GIP$_{total}$												
iAUC paracetamol												
0-180 min												
iAUC glucose												
iAUC C-peptide												
iAUC insulin												
iAUC GLP-1$_{total}$												
iAUC GLP-1$_{active}$												
iAUC paracetamol												

Data are estimated mean difference in changes between groups with 95% confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, GLP-1: Glucagon-like-peptide 1, GIP: Gastric inhibitory polypeptide, tAUC: total area under the curve, iAUC: incremental area under the curve

eTable 14 Within-group changes (0-16 weeks) cardiometabolic, body composition and fitness								
	CON		DCON		MED		HED	
	Change	95% CI	Change	95% CI	Change	95% CI	Change	95% CI
Glycemic control								
HbA1c (mmol/mol)								
HbA1c (%)								
Fasting glucose (mmol/l)								
Fasting insulin (pmol/l)								
Fasting C-peptide (pmol/l)								
Glucose-lowering medication, No (%)								
Reduction[a]								
Discontinuation[b]								
Intensification[c]								
Lipid-lowering medication, No (%)								
Reduction[a]								
Discontinuation[b]								
Intensification[c]								
Blood pressure lowering medication, No (%)								
Reduction[a]								
Discontinuation[b]								
Intensification[c]								
Lipids								
LDL cholesterol (mmol/l)								
Fasting triglycerides (mmol/l)								
Blood pressure								
Systolic (mmHg)								
Diastolic (mmHg)								
Fitness								
Absolute VO$_2$ max (ml/min)								
Relative VO$_2$ max (ml/kg/min)								
Watt max (W/kg)								
1 RM chest press (kg)								
1 RM leg extension (kg)								
Body composition								
Body weight (kg)								
BMI (kg/m^2)								

Data are least-squares means. CI: confidence intervals, CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise

[a]Reduction defined as at least one step down on the pre-defined algorithm.

[b]Discontinuation defined as, discontinuation of all drugs when therapeutic target was met.

[c]Intensification defined as at least one step up on the pre-defined algorithm.

	HED vs. CON	P-value		MED vs. CON	P-value		DCON vs. CON	P-value		HED vs. DCON	P-value		MED vs. DCON	P-value		HED vs. MED	P-value
eTable 15 Pairwise comparisons of the change in cardiometabolic, body composition and fitness																	
Glycemic control																	
HbA1c (mmol/mol)																	
HbA1c (%)																	
Fasting glucose (mmol/l)																	
Fasting insulin (pmol/l)																	
Fasting C-peptide (pmol/l)																	
Glucose-lowering medication, No (%)																	
Reduction																	
Discontinuation																	
Intensification																	
Lipid-lowering medication, No (%)																	
Reduction																	
Discontinuation																	
Intensification																	
Blood pressure lowering medication, No (%)																	
Reduction																	
Discontinuation																	
Intensification																	
Lipids																	
Total cholesterol (mmol/l)																	
LDL cholesterol (mmol/l)																	
Fasting triglycerides (mmol/l)[a]																	
Blood pressure																	
Systolic (mmHg)																	
Diastolic (mmHg)																	
Fitness																	
Absolute VO$_2$ max (ml/min)																	
Relative VO$_2$ max (ml/kg/min)																	
Watt max (W/kg)																	
1 RM chest press (kg)																	
1 RM leg extension (kg)																	
Body composition																	
Body weight (kg)																	
BMI (kg/m^2)																	

Data are estimated mean difference in changes between groups with 95% confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, HbA1c: Glycated hemoglobin 1Ac, GLP-1: Glucagon-like-peptide 1, GIP: Gastric inhibitory polypeptide

eTable 16 Adverse events after randomization					
Event	All n (%)	CON n (%)	DCON n (%)	MED n (%)	HED n (%)
Serious AE					
All AE					
Gastrointestinal					
Nausea					
Vomiting					
Diarrhea					
Constipation					
Dyspepsia					
Flatulens					
Abdominal distension					
Abdominal pain					
Other					
Infections					
Musculoskeletal pain and discomfort					
Back pain					
Lower extremities					
Upper extremities					
other					
Musculoskeletal injury, defined as pain or discomfort resulting in inability to exercise for ≥7days					
Back pain					
Lower extremities					
Upper extremities					
other					
Complications associated with clinical or experimental procedures					
Metabolism and nutrition disorders					
Decreased appetite					
Increased appetite					
Hunger					
Other					
Nervous system disorders					
Headache					
Dizziness					
Other					
Events related to dysglycemia					
Events related to blood pressure management					
Other					
Values are number and percentage (%) of participants with adverse event for each group. All events are self-reported to reported to the study nurse, dietitian or trainers and occurred after randomization.					