Supplementary Online Content

Solomon TPJ, Malin SK, Karstoft K, Haus JM, Kirwan JP. The influence of hyperglycemia on the therapeutic effect of exercise on glycemic control in patients with type 2 diabetes mellitus. *JAMA Internal Med*. Published online July 1, 2013. doi:10.1001/jamainternmed.2013.7783

eMethods
eTable. Subject Characteristics

This supplementary material has been provided by the authors to give readers additional information about their work.

e*Methods*

Subjects. The purpose of this report is to examine trends within the data from exercise training studies that have been conducted in our laboratory. This study includes data from subjects who had adhered to >90% of prescribed exercise training in our studies. Some subject data was previously published for purposes not related to the primary outcome of this paper (Solomon *et al*. Am J Clin Nutr 2010, 92:1359-1368; Karstoft *et al*. Diabetes Care 2013, 36:228-236; and Solomon *et al*. J Appl Physiol 2008, 104:1313-1319). Potential subjects from the local community underwent medical evaluation (medical history, physical examination, 75 g OGTT, and blood chemistry) as part of eligibility screening. Volunteers who were engaged in regular exercise training or weight loss programs, smokers, pregnant women, and those exhibiting symptoms of chronic pulmonary, hepatic, renal, cardiovascular, or hematological disease were excluded from participation. All subjects had impaired glucose tolerance or type 2 diabetes according to American Diabetes Association criteria. Participants with type 2 diabetes were recently diagnosed (4.8±0.9 years) and were being treated with the following anti-diabetic medications: N=14 metformin, N=6 sulfonylureas, N=2 GLP-1-analogues, N=1 DPP-4-inhibitors. No subject was insulin-treated. Medications were held for 5-days prior to metabolic testing.

Measurements. For 3-days prior to testing, subjects continued their typical dietary/activity habits and completed diet and exercise records. Clinical assessments were conducted at the Clinical Research Unit at the Cleveland Clinic (Ohio, USA) and in the clinical research laboratory of the Centre of Inflammation and Metabolism (Copenhagen, Denmark). Body composition (height, weight, dual-energy x-ray absorptiometry to determine body fat) and aerobic fitness (VO_2max measured by indirect calorimetry during an incremental work-load exercise test to exhaustion on a treadmill) were measured. Glycemic control was determined by HbA_{1c}, fasting plasma glucose, and the 2-hour plasma glucose

response to a standard 75 g OGTT. All tests were conducted at baseline and repeated 2-4-days after the final exercise training bout.

Intervention. All subjects participated in an aerobic exercise training intervention of 12-16 weeks. Exercise consisted of supervised walking or cycling exercise performed for ~60 min/day, on 4-5 days/week, at an intensity of ~75% of VO_2max. VO_2max was measured every 2-4 weeks during the intervention to modify the absolute work load of exercise so as to maintain the appropriate relative intensity. Full details of our standard exercise intervention are published (Solomon et al J Appl Physiol 2008, 104:1313-1319).

Biochemical Analyses. HbA_{1c} was measured in whole blood by high-pressure liquid-chromatography (Tosho G7, San Francisco, CA). Samples for glucose analysis were collected into heparin-containing syringes and immediately analyzed (YSI Stat, Yellow Springs, OH; ABL 700, Radiometer, Copenhagen, Denmark).

Statistics. Exercise-induced changes between pre- and post-intervention means were examined using paired two-tailed *t*-tests. Exercise-induced changes in variables (delta; Δ) were calculated as post-minus pre-exercise mean. Relationships between variables were determined by linear and non-linear regression. In order to calculate the rate of loss of improvement in a variable following exercise training (y) in relation to a pre-training variable (x), the quadratic functions of y were derivatized with respect to x (dy/dx) to solve x at the minimum value of y. Then, the linear function that described the relationship between y and x above this minimum value was derivatized (dy/dx) to calculate the rate of loss of improvement in y (= slope, m, in $y=mx+c$). Data represent mean±S.E.M. and statistical significance was accepted when $P<0.05$. All statistical analyses were conducted using Prism (v6, GraphPad. San Diego, CA).

Study approval. This study was approved by the Institutional Review Board at the Cleveland Clinic (Cleveland, Ohio, USA) and by the Ethical Committee of the Capital Region of Denmark. All study subjects provided informed consent before participation in the study.

e*Table* – Subject Characteristics

	PRE			POST				Delta (Δ)		
Sex (M/F)	46	/	59							
Age (years)	61	±	1							
Weight (kg)	94.8	±	1.7	89.7	±	1.5	***	-4.6	±	0.5
BMI (kg/m^2)	33.2	±	0.5	31.5	±	0.5	***	-1.6	±	0.2
Fat (%)	40.7	±	0.8	38.8	±	0.9	***	-1.9	±	0.3
VO_2max (L/min)	2.15	±	0.06	2.37	±	0.07	***	0.23	±	0.03
VO_2max (mg/kg/min)	22.7	±	0.5	26.5	±	0.6	***	3.8	±	0.4
Plasma glucose (mmol/L)										
HbA_{1c} (%)	6.09	±	0.11	6.06	±	0.13		-0.01	±	0.06
Fasting	6.42	±	0.15	6.08	±	0.16	***	-0.35	±	0.08
2-hour OGTT	11.0	±	0.4	10.2	±	0.4	***	-0.8	±	0.2

Subjects (N=105) with impaired glucose tolerance or newly-diagnosed type 2 diabetes underwent 12-16 weeks of moderate-intensity aerobic exercise training, 5 days/week, 60 minutes/day. Body composition, aerobic fitness (VO_2max), and glycemic control were measured. M = male; F = female; HbA_{1c} = glycosylated hemoglobin (N=54). Delta values represent the exercise-induced change for each variable. Data indicate mean±SEM. Paired t-tests were used to compare pre- vs. post-exercise means. Statistical significance is represented by ***P<0.001.