Lifestyle Intervention Strategy to Treat Diabetes in Older Adults: A Randomized Controlled Trial

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ONLINE SUPPLEMENTAL MATERIAL

Supplementary Table 1—Summary of Adverse Events

	HL (N = 50)	ILI (N = 50)
Serious adverse events		
	Angina (n = 4)	Acute kidney injury (n = 1)
	Pneumonia (n = 3)	Anemia from GI bleed (n = 1)
	Costochondritis (n = 1)	Angina (n = 1)
	Gastroenteritis (n = 1)	Cholecystitis (n = 1)
	Hyperkalemia (n = 1)	Congestive heart failure (n = 1)
	Level 3 hypoglycemia (n = 1)*	COPD exacerbation (n = 1)
	Lymphoma (n = 1)	Myocardial infarction (n = 1)
	Osteomyelitis (n =1)	Orthostatic hypotension (n = 1)
	Renal cancer (n =1)	Pancreatic cancer (n = 1)
	Syncope, etiology unknown (n = 1)	Pneumonia (n = 1)
		Syncope, etiology unknown (n = 1)
Nonserious adverse events		
	Level 1 hypoglycemia (n = 19)*	Level 1 hypoglycemia (n = 29)*
	Back pain (n = 2)	Dizziness/orthostasis (n = 5)
	Level 2 hypoglycemia (n = 2)	Level 2 hypoglycemia (n = 1)*
	Dehydration (n = 1)	Angina (n = 2)
	Fall without injury (n = 1)	Asthma exacerbation (n = 2)
	Finger fracture (n = 1)	Back pain (n = 2)
	Leg pain (n = 1)	Amaurosis fugax (n = 1)
	Back pain (n = 2)	Avulsed toenail (n = 1)
	Dehydration (n = 1)	Fall without injury (n = 1)
	Migraine (n = 1)	Leg bruise (n = 2)
	Tooth fracture (n = 1)	Otitis media (n = 1)
	Vasovagal syncope (n = 1)	Toe fracture (n = 1)
	Wrist fracture (n = 1)	Wrist sprain (n = 1)

* Hypoglycemia levels: 1=glucose ≤70 mg/dL (3.9 mmol/L)—sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy; 2=glucose <54 mg/dL (3.0 mmol/L)—sufficiently low to indicate serious, clinically important hypoglycemia; 3=no specific glucose threshold— hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery. Hypoglycemia episodes were recurrent in 4 participants (3–5 episodes/participant) in the ILI group that occurred during months 1–3 of the 1-year intervention. Hypoglycemia episodes were recurrent in 5 participants (2-3 episodes/participant) in the HL group that occurred during months 4–8 of the 1-year intervention. Hypoglycemic episodes that occurred in other participants were isolated.

Supplementary Table 2—Diabetes Medication Change*

Diabetes medication changes	**HL N (%)**	**ILI N (%)**	**Overall**
Oral agent			
Yes	5 (10)	7 (14)	12 (12)
No	45 (90)	43 (86)	88 (88)
Insulin and other injectables			
Yes	7 (14)	12 (24)	19 (19)
No	43 (86)	38 (76)	81 (81)

* Change is defined by any of the following: change in dose of any 1 hypoglycemic medication by more than two-fold, change in dose of insulin and other injectables of >10%, addition or subtraction of an oral glucose lowering agent or insulin and other injectables. HL, healthy lifestyle; ILI, intensive lifestyle intervention

† Note: P value = 0.76 and 0.31 for the between-group differences in changes in oral agent and insulin and other injectables, respectively based on Fisher's exact test

Supplementary Table 3— Effect of Lifestyle Intervention on Primary and Secondary Outcomes After Controlling for Changes in Fat Mass*

	HL (N = 50)	ILI (N = 50)	Difference (95% CI)	*P* value†
Primary outcome				
HbA_{1c} (%)				
Baseline	7.3 ± 0.2	7.5 ± 0.2		
Change at 6 mo	-0.2 ± 0.1	-0.4 ± 0.1		
Change at 1 yr	-0.0 ± 0.1	-0.3 ± 0.2	0.3 (-0.1, 0.7)	0.24
Secondary outcomes				
Glucose tolerance variables				
Fasting glucose (mmol/L)				
Baseline	7.1 ± 0.3	7.6 ± 0.3		
Change at 6 mo	-0.0 ± 0.4	-0.1 ± 0.4		
Change at 1 yr	0.3 ± 0.4	0.1 ± 0.3	0.2 (-0.9, 1.3)	0.79
2-hour glucose (mmol/L)				
Baseline	14.9 ± 0.8	16.4 ± 0.7		
Change at 6 mo	0.3 ± 0.6	-1.3 ± 0.7		
Change at 1 yr	0.2 ± 0.5	-1.0 ± 0.6	1.2 (-0.4, 2.8)	1.00
Glucose AUC (mmol/L per 2h)				
Baseline	1573 ± 65	1644 ± 51		
Change at 6 mo	27 ± 56	-78 ± 56		
Change at 1 yr	69 ± 77	-89 ± 86	158 (-63, 380)	0.35
Insulin AUC ($x10^3$ pmol/L per 2h)				
Baseline	64.9 ± 9.1	66.2 ± 9.5		
Change at 6 mo	-0.1 ± 4.6	-10.5 ± 4.6		
Change at 1 yr	0.3 ± 4.0	-5.3 ± 4.5	5.5 (-5.8, 16.9)	0.44
C-peptide AUC (nmol/L per 2h)				
Baseline	340.9 ± 32.4	324.4 ± 31.8		
Change at 6 mo	0.3 ± 12.6	-15.9 ± 14.9		
Change at 1 yr	1.3 ± 12.6	-23.8 ± 13.9	25.2 (-10.6, 60.9)	0.60
Glucagon AUC (ng/L per 2h)				
Baseline	2429 ± 178	2416 ± 175		
Change at 6 mo	31 ± 119	-155 ± 108		
Change at 1 yr	74 ± 116	-174 ± 130	248 (-89, 584)	0.42

* Baseline values are observed means ± SEs; change score values are least-squares adjusted means ± SE from repeated measures ANCOVAs. HL, healthy lifestyle; ILI, intensive lifestyle intervention; AUC, area under the curve.

† *P* values for the comparison between the groups of changes from baseline to the 1 yr were calculated with the use of mixed-model repeated-measures analysis of variance (with baseline values, sex, and changes in fat mass as covariates).

Benjamini-Hochberg correction for multiple comparisons was used to adjust the P values in the secondary outcomes.

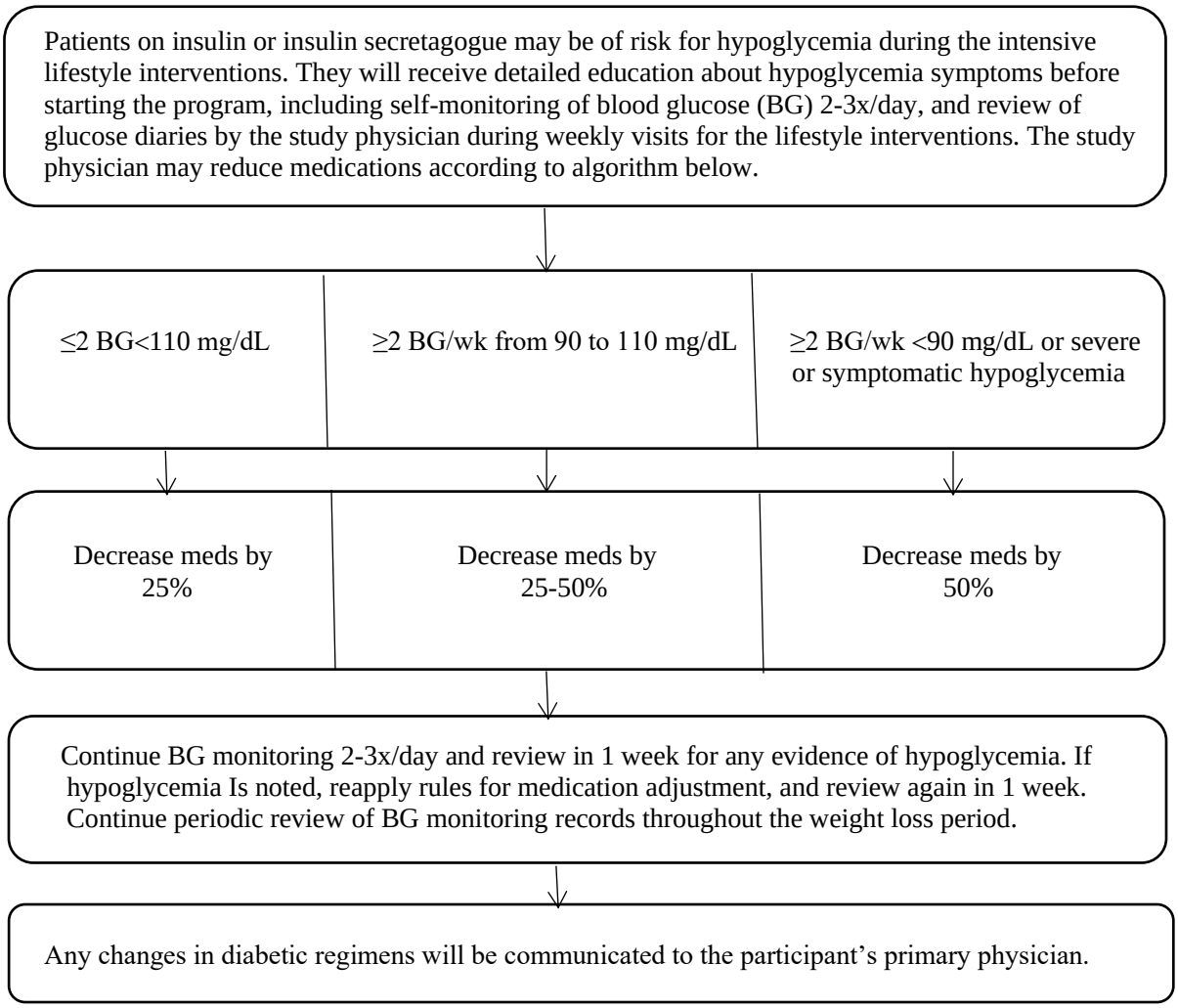
Supplementary Table 4— Effect of Lifestyle Intervention on Primary and Secondary Outcomes After Controlling for Changes in VO_{2peak}*

	HL (N = 50)	ILI (N = 50)	Difference (95% CI)	*P* value†
Primary outcome				
HbA_{1c} (%)				
Baseline	7.3 ± 0.2	7.5 ± 0.2		
Change at 6 mo	-0.2 ± 0.2	-0.7 ± 0.2		
Change at 1 yr	-0.1 ± 0.2	-0.5 ± 0.2	0.4 (-0.1, 1.0)	0.16
Secondary outcomes				
Glucose tolerance variables				
Fasting glucose (mmol/L)				
Baseline	7.1 ± 0.3	7.6 ± 0.3		
Change at 6 mo	0.1 ± 2.5	-0.1 ± 0.3		
Change at 1 yr	0.4 ± 0.3	-0.4 ± 0.3	0.9 (0.1, 2.0)	1.00
2-hour glucose (mmol/L)				
Baseline	14.9 ± 0.8	16.4 ± 0.7		
Change at 6 mo	0.0 ± 0.7	-1.4 ± 0.6		
Change at 1 yr	1.6 ± 10.7	-1.0 ± 0.6	1.1 (-0.6, 2.8)	0.75
Glucose AUC (mmol/L per 2h)				
Baseline	1573 ± 65	1644 ± 51		
Change at 6 mo	26 ± 42	-19 ± 42		
Change at 1 yr	97 ± 45	-23 ± 46	121 (-35, 277)	0.45
Insulin AUC ($x10^3$ pmol/L per 2h)				
Baseline	64.9 ± 9.1	66.2 ± 9.5		
Change at 6 mo	0.5 ± 3.4	-7.7 ± 3.5		
Change at 1 yr	0.5 ± 3.7	-6.4 ± 3.8	6.8 (-6.4, 20.0)	0.47
C-peptide AUC (nmol/L per 2h)				
Baseline	340.9 ± 32.4	324.4 ± 31.8		
Change at 6 mo	2.0 ± 12.9	-5.6 ± 13.2		
Change at 1 yr	-2.3 ± 14.2	-23.2 ± 13.9	17.2 (-32.1, 66.2)	0.76
Glucagon AUC (ng/L per 2h)				
Baseline	2429 ± 178	2416 ± 175		
Change at 6 mo	-50 ± 84	-175 ± 85		
Change at 1 yr	104 ± 91	-173 ± 95	278 (-56, 611)	0.52

* Baseline values are observed means ± SEs; change score values are least-squares adjusted means ± SE from repeated measures ANCOVAs. HL, healthy lifestyle; ILI, intensive lifestyle intervention; AUC, area under the curve.

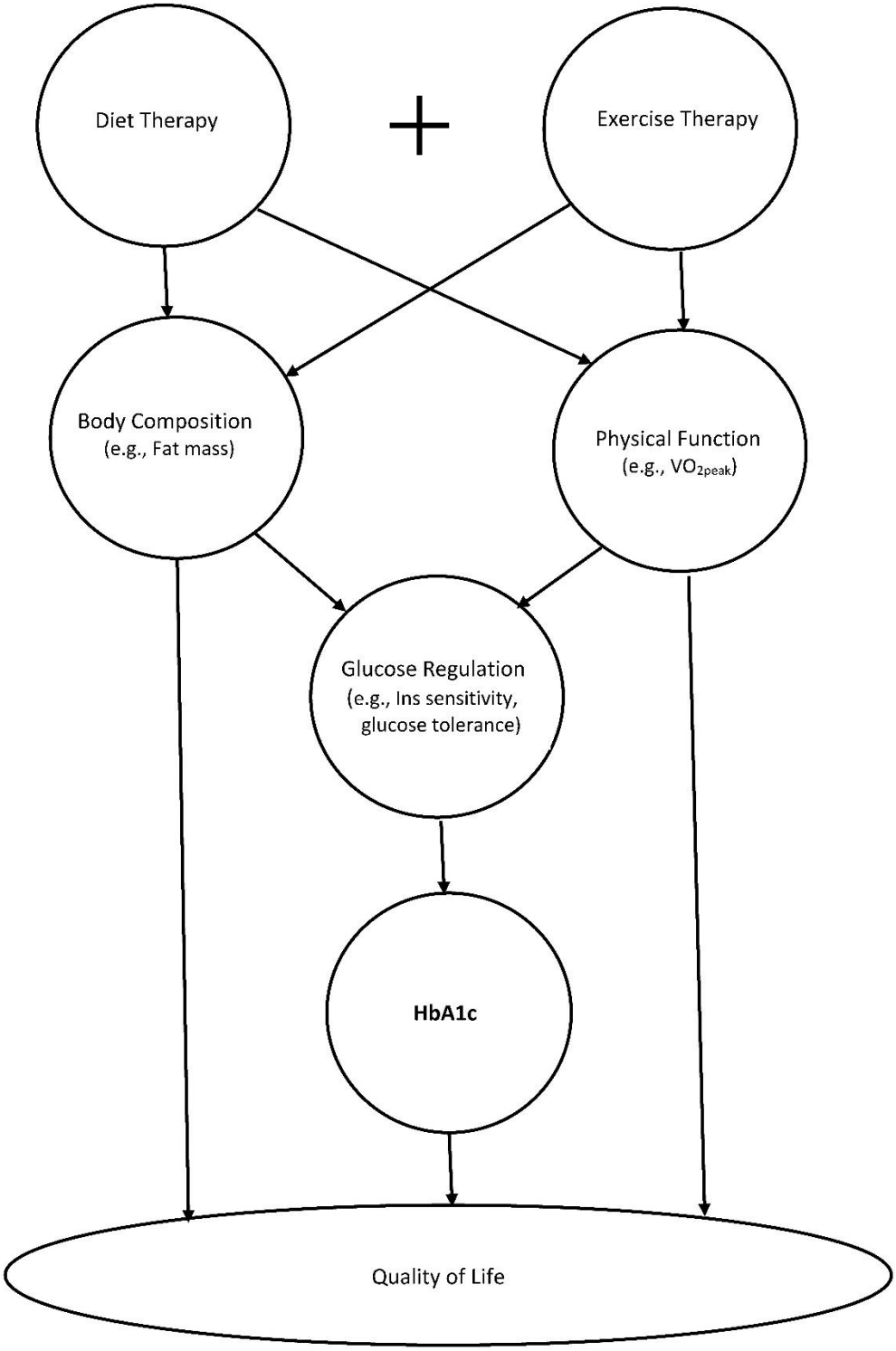
† *P* values for the comparison between the groups of changes from baseline to the 1 yr were calculated with the use of mixed-model repeated-measures analysis of variance (with baseline values, sex, and changes in VO_{2peak} as covariates).

Benjamini-Hochberg correction for multiple comparisons was used to adjust the P values in the secondary outcomes.

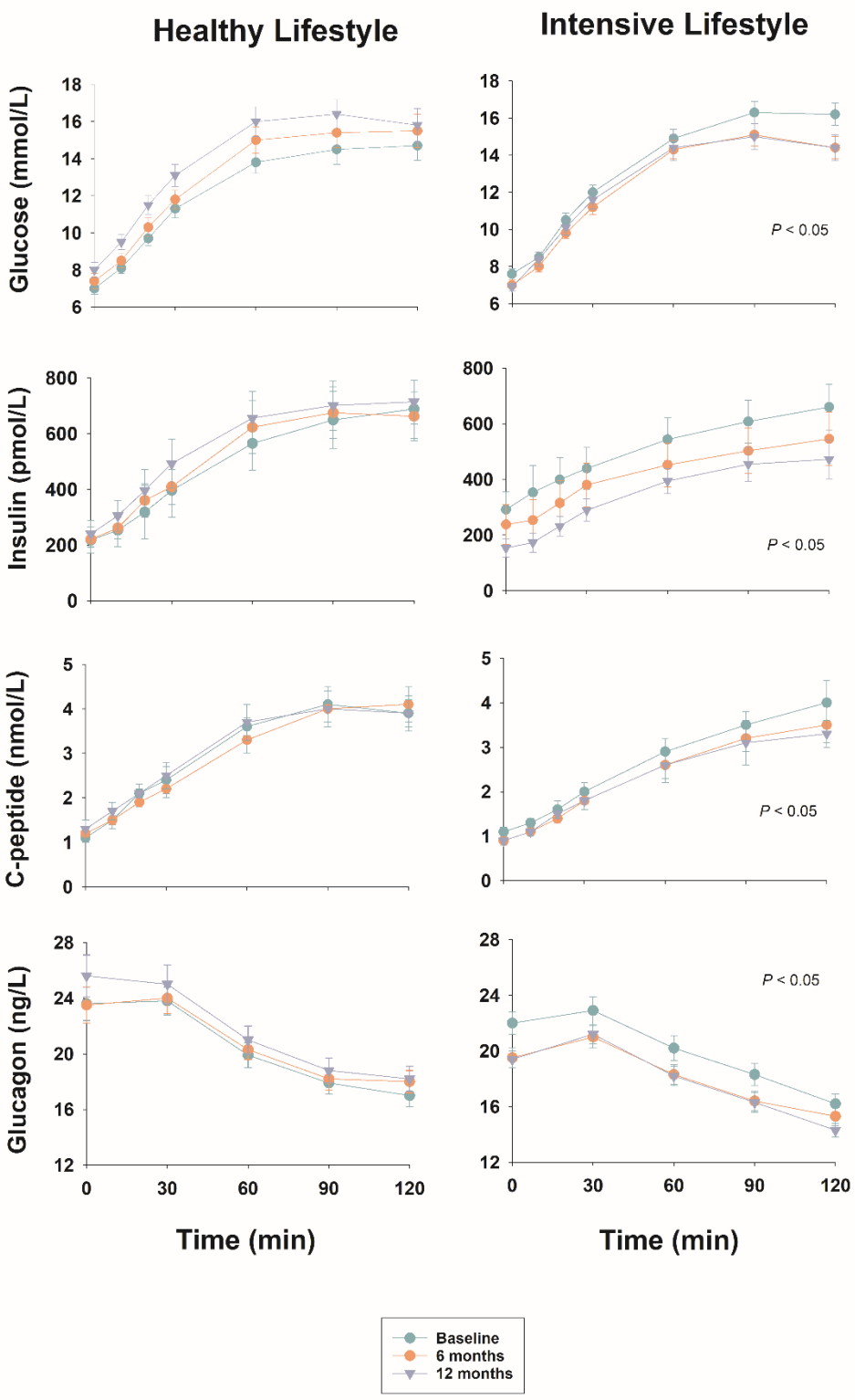


Supplementary Fig. 1—Evaluation/Management of Diabetes Medications during Intensive Lifestyle Intervention.

In addition, because exercise has an insulin-like effect, exercise-induced hypoglycemia is a risk at the time of exercise in those on insulin (and to a lesser degree, insulin secretagogue). To minimize the risk of hypoglycemia during exercise sessions, the following precautions are followed (2009 ACSM's Guidelines for Exercise Testing and Prescription, 8th edition): 1) BG will be measured before, during, and after exercise; 2) insulin dosages will be decreased before exercise, according to the exercise intensity and duration; insulin dosage reductions may amount to ~50% of daily insulin requirements; 3) during exercise, easily absorbable carbohydrates may be consumed; and 4) after exercise, an extra carbohydrate (~30 grams) may be necessary. Only participants with adequate diabetes control will be enrolled in the study (see inclusion criteria). In general, BG between 100 and 140 mg/dl will be considered safe to begin exercise sessions. If BG is <100 mg/dl, the subject will be provided with a carbohydrate snack (e.g., piece of fruit, three graham crackers) before starting; alternatively, based on medical judgment, the planned exercise session may be cancelled. If BG >140 mg/dl during any subsequent follow-up, the subject will be carefully evaluated whether it is safe to resume exercise (e.g., review of history/physical exam, any interval events, and glucose diaries). BG >240 mg/dl will be considered a relative contraindication to exercise participation, in which case potential causes or exacerbating events (e.g., acute medical problems, noncompliance) will be evaluated and accordingly, the participant may be referred to their primary physician for further evaluation and management.



Supplementary Fig. 2—Conceptual relationship of biomarkers to HbA1c and weight outcomes



Supplementary Fig. 3—Plasma glucose, insulin, C-peptide, and glucagon concentrations during the 2-h frequently sampled oral glucose tolerant test. Values are mean ± s.e. *P* values indicate the significance of the differences between area under the curve values before and after treatment and differences in the change in areas under the curve between groups.