Hindawi Publishing Corporation
Journal of Obesity
Volume 2012, Article ID 309196, 12 pages
doi:10.1155/2012/309196

Clinical Study

Lifestyle Intervention Improves Heart Rate Recovery from Exercise in Adults with Type 2 Diabetes: Results from the Look AHEAD Study

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Received 18 May 2012; Accepted 14 September 2012

Academic Editor: Jonathan N. Myers

The primary aims of this paper were (1) to evaluate the influence of intensive lifestyle weight loss and exercise intervention (ILI) compared with diabetes support and education (DSE) upon Heart Rate Recovery (HRR) from graded exercise testing (GXT) and (2) to determine the independent and combined effects of weight loss and fitness changes upon HRR. In 4503 participants (45–76 years) who completed 1 year of intervention, HRR was measured after a submaximal GXT to compare the influence of (ILI) with (DSE) upon HRR. Participants assigned to ILI lost an average 8.6% of their initial weight versus 0.7% in DSE group ($P < 0.001$) while mean fitness increased in ILI by 20.9% versus 5.8% in DSE ($P < 0.001$). At Year 1, all exercise and HRR variables in ILI improved ($P < 0.0001$) versus DSE: heart rate (HR) at rest was lower (72.8 ± 11.4 versus 77.7 ± 11.7 b/min), HR range was greater (57.7 ± 12.1 versus 53.1 ± 12.4 b/min), HR at 2 minutes was lower (89.3 ± 21.8 versus 93.0 ± 12.1 b/min), and HRR was greater (41.25 ± 22.0 versus 37.8 ± 12.5 b/min). Weight loss and fitness gain produced significant separate and independent improvements in HRR.

1. Introduction and Purpose

Type 2 diabetes (T2DM) is defined by chronic hyperglycemia and results from combined defects in insulin secretion and action [1]. A long-term consequence of T2DM is an increased risk of complications leading to increased morbidity and mortality from cardiovascular diseases [2]. One of the mechanisms that contributes to this increased cardiovascular disease risk is autonomic nervous system dysfunction, which may be associated with the metabolic syndrome and endothelial dysfunction [3, 4]. Autonomic nervous system dysfunction is detected by a variety of measures including heart rate variability (HRV) at rest, chronotropic incompetence during exercise, and impaired recovery after exercise [5]. However, the chronic imbalance of the autonomic nervous system, as reflected in simple heart rate measures, is not widely recognized by clinicians as a prevalent and potent risk factor for cardiovascular events [3], despite abundant evidence linking it to a sedentary lifestyle, obesity, T2DM, and cardiovascular morbidity and

mortality. Previous concerns about emerging patterns of increasing obesity and increasing sedentary behavior have led to major clinical trials in Finland [6] and the United States [7] using weight loss diet and physical activity interventions. These early trials have demonstrated that these interventions are successful in delaying the onset of T2DM in individuals with glucose intolerance [8] as well as reversal of established diabetes. However, until the Look AHEAD (Action for Health in Diabetes) Trial [9], no large-scale multicenter randomized clinical trials have examined the longitudinal influence of behavioral intervention upon HRR and autonomic dysfunction using diet and exercise interventions in overweight/obese individuals with T2DM.

The primary aims of this paper were (1) to examine the influence of one year of an intensive weight loss diet and exercise intervention (ILI) upon autonomic dysfunction as measured by Heart Rate Recovery (HRR) from exercise stress testing and (2) to evaluate the separate and combined effects of weight loss and fitness changes.

2. Methods

2.1. Subjects. A detailed description of the baseline characteristics of Look AHEAD participants has been published elsewhere [10]. Data from 4,503 individuals who completed the assessment of fitness by treadmill testing at baseline and 1 year were available. At baseline, all participants were diagnosed with T2DM with mean duration of diabetes of 6.7 ± 4.5 years, and HbA1c level of 7.3 ± 1.2% were 58.7 ± 6.8 years old with a BMI or 35.8 ± 5.8 $kg/m^2$and received general medical care and treatment for their diabetes from their personal healthcare provider. While participants with and without β-blocker use were combined for initial analyses, subsequent separate analyses were conducted on those participants ($N = 3371$) not on β-blocker medication due to the known influence of β-blockers on all heart rate variables.

2.2. Intervention

2.2.1. Intensive Lifestyle Intervention Group (ILI). Specific details of the lifestyle intervention used in the Look AHEAD Study have been published previously [11]. Briefly, for months 1–6, participants attended weekly on-site treatment sessions that included three group sessions and one individual meeting with their Lifestyle Counselor each month. During months 7–12, participants attended two group meetings and one individual session per month and one motivational campaign to promote adherence to the recommended weight loss behaviors. The 1-year weight loss goal for individual participants was 10% of their body weight.

2.2.2. Diabetes Support and Education Intervention Group (DSE). The DSE group has previously been described [11]. Individuals randomly assigned to DSE received general recommendations related to healthful eating and physical activity, and safety recommendations for an individual with type 2 diabetes. Participants attended an initial diabetes education session and were invited to attend 3 additional group sessions, that addressed topics related to diet, physical activity, and social support but were not provided individual strategies to change diet or physical activity.

2.3. Assessments. Though Look AHEAD assessment method have been published in detail [11, 12], selected methods relevant to the present paper are presented below.

2.3.1. Cardiorespiratory Fitness. A graded exercise treadmill test was used to assess cardiorespiratory fitness at baseline and at 1 year. The speed of the treadmill was set at 1.5, 2.0, 2.5, 3.0, 3.5, or 4.0 mph for the baseline test based on the participant's preferred walking speed and their heart rate response during the first minute of the test; this speed remained constant throughout the test. The grade of the treadmill was initially set at 0% and increased by 1% at 1-minute intervals throughout the test. Heart rate was assessed at rest, during the last 10 seconds of each exercise stage, and at the point of test termination using a 12-lead ECG. Rating of perceived exertion (RPE) was assessed using the Borg 15-category scale (range is on a scale from 6–20) during the last 15 seconds of each stage and at the point of test termination. Blood pressure was assessed using a manual sphygmomanometer and stethoscope during the last 45 seconds of each even minute stage (e.g., 2 min, 4 min, etc.).

Baseline Test. The baseline test was terminated at the point of volitional exhaustion or at the point where ACSM [13] test termination criteria were observed, that is, serious arrhythmias, angina, and signs of myocardial ischemia, and so forth. A baseline test was considered valid if the maximal heart rate was ≥85% of age-predicted maximal heart rate (HR_{Max} = 220 minus age) if the participant was not taking a β-blocking medication. If the participant was taking a β-blocker medication, the baseline test was considered valid if RPE was ≥18 at the point of termination. In addition, to be eligible, all participants needed to achieve ≥4 metabolic equivalents (METs) on the baseline graded exercise test, where 1 MET is equal to 3.5 mL/kg/min of oxygen uptake.

1-Year Test. This test was a submaximal test [14]. It was performed at the same walking speed as the baseline test and was terminated at the time when the participant first achieved or exceeded 80% of age-predicted maximal heart rate (HR_{Max} = 220 minus age), if the participant was not taking a β-blocker at either the baseline or 1-year assessment period. If the participant was taking a β-blocker at either the baseline or 1-year assessment, then the submaximal test was terminated at the point when the participant first reported achieving or exceeding a rating of 16 on the 20 point RPE scale, that is, 80% of RPE = 20. Cardiorespiratory fitness was defined as the estimated metabolic equivalent (MET) level based on the treadmill work load (i.e., speed and grade) [13] using either the criteria of attaining 80% of maximal heart rate or an RPE of ≥16 for those on a β-blocker. Data from 4503 individuals who completed the assessment of fitness at baseline and 1 year were available.

Heart Rate Recovery (HRR). Heart Rate Recovery is a measurement of how much the heart rate falls during the first few minutes after peak exercise, that is, the ability of the heart to return itself to a resting state after being elevated during exercise [15]. Normal heart rate recovery is defined as a decrease in pulse of 15 to 25 beats per minute. Abnormal heart rate recovery is defined as a decrease in pulse of 12 or fewer beats per minute. Heart rate was recorded immediately after exercise and every 2 minutes. For the purpose of this analysis, Heart Rate Recovery (HRR) is defined as HRR = HR at peak-HR at 2 minutes.

2.3.2. Statistical Analysis. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). Normality of the outcome variable, Heart Rate Recovery (HRR) at Year 1, was examined prior to the fit of multiple linear regression models. Spearman's correlation coefficients were used to assess the bivariate associations between the outcome variable and continuous measures at baseline as well as 1-year changes in weight and fitness. The analysis of variance (ANOVA) approach was used to examine bivariate associations between the outcome and categorical variables such as treatment group, gender, diabetes medication usage, CVD history, and hypertension. Multivariate analyses were conducted, examining the separate and combined effects of weight loss and fitness change on HRR at Year 1. Variables that were significantly associated with the outcome in bivariate analyses were entered into two separate multiple linear regression models: one for assessing the treatment group effect on year 1 HRR after adjusting for baseline covariates; the other for assessing the combined effect of weight loss and fitness change using a derived categorical variable with five levels. Least square means and standard errors were obtained from these two models along with pairwise P values for comparing ILI and DES or pairs of two LSMEANs of the five categories; the type I error rate was fixed at 0.05.

3. Results

3.1. Baseline Characteristics. At baseline, none of the demographic variables were significantly different when comparing ILI with DSE and these demographics have been published previously [10] on a larger sample ($n = 5145$); however, the data for this paper are only on those for whom we could calculate HRR at Year 1 ($n = 4503$). The reasons for missing data have been explained in an earlier report by Jakicic et al. [14]. These included scheduling issues, refusal to participate, medical reasons, and other reasons not specified.

3.2. Heart Rate Recovery Variables at Baseline and Year 1. The data at baseline and at Year 1 are presented for the heart rate variables in Table 1. Separate analyses were done for those with and without β-blocker usage. At baseline, none of the heart rate variables were significantly different between ILI versus DSE; this was true for both those with and without β-blocker usage. As expected, all resting, exercise, and recovery heart rate variables were lower for those on β-blockers and therefore subsequent bivariate and multivariate analyses were done only on those individuals who were not on β-blocker since the groups could not be combined in further HRR analyses.

At the Year 1 fitness assessment, which used a submaximal test [14], all heart rate variables improved more ($P < 0.0001$) in ILI versus DSE (Table 1), that is, resting heart rate was lower (72.8 ± 11.4 versus 77.7 ± 11.7 b/min), heart rate range increased (57.7 ± 12.1 versus 53.1 ± 12.4 b/min), heart rate at 2 minutes of recovery was lower (89.3 ± 21.8 versus 93.0 ± 12.1 b/min), and heart rate recovery was greater (41.25 ± 22.0 versus 37.8 ± 12.5 b/min) for ILI versus DSE, respectively. Nevertheless, ILI and DSE reached the same peak heart rate (130.5 ± 6.2 versus 130.8 ± 6.6 b/min for ILI versus DSE, resp.) confirming that both groups exercised to the same peak level during the exercise test. A similar trend was observed at Year 1 for those on β-blockers with ILI exhibiting greater improvement in all heart rate variables yet still reaching the same peak heart rate during exercise.

3.3. Correlates of Heart Rate Recovery at Year 1. Table 2 lists the Spearman correlation coefficients of 1-year Heart Rate Recovery with selected baseline measures, including age, duration of diabetes, waist circumference, BMI, HbA1c, and Triglycerides, and 1-year changes in weight and fitness. In this analysis, only those participants without β-blocker usage were included, and we used this analysis to determine which variables to include in the model used in Table 4. Not surprisingly, age was the strongest predictor of HRR ($r = -0.22$; $P < .0001$) since the key heart rate variables influencing the HRR also are lower with greater age, that is, lower peak HR with exercise and slower recovery after exercise with greater age. The second strongest predictor of faster HRR was the percentage of weight change ($r = -0.18$; $P < .0001$). Other variables that were associated with HRR were self-reported duration of diabetes ($r = -0.11$; $P < .0001$); hemoglobin A1c ($r = -0.10$; $P < .0001$); waist circumference ($r = -0.10$; $P < .0001$); percent fitness change ($r = -0.09$; $P < .0001$).

Once these HRR predictor variables were identified, all participants (ILI and DSE) were divided into groups based upon (1) treatment group (Table 3(a)); (2) age, gender, diabetes medication usage, CVD history, hypertension, waist circumference (Table 3(b)); and (3) weight losses and/or fitness gains (Table 3(c)). In every comparison, significant, or borderline significant relationships were demonstrated.

3.4. Influence of Weight Change and Fitness Change Gain upon Heart Rate Recovery at Year 1. Based on their one-year weight loss and fitness changes, participants who were not on a β-blocker were divided into four separate weight loss groups and four separate fitness gain groups, revealing that HRR improved with greater weight losses as well as with greater fitness gains (Table 3(c)). Next, to examine the combined influences of weight loss and fitness gain on HRR, the participants were divided into 16 paired subgroups, based upon their combined weight and fitness losses and or gains (pairings noted in footnote in Table 3(c)). These groupings were used to form five separate groups, ranging from "Low" success in which participants either gained

Table 1: Heart rate variables at baseline (a) and Year 1 (b) for participants with and without β-blocker use. Values are mean (SD).

Variable		No β-blocker use			β-blocker use		
		ILI ($N = 1786$ baseline, 1743 Y1)	DSE ($N = 1751$ baseline, 1712 Y1)	P value (DSE versus ILI)	ILI ($N = 520$ baseline, 562 Y1)	DSE ($N = 446$ baseline, 485 Y1)	P value (DSE versus ILI)
(a) Baseline*	Resting heart rate (b/min)	79.35 (11.85)	79.42 (11.75)	0.8683	70.12 (10.96)	69.66 (11.18)	0.5228
	Peak heart rate (b/min)	154.2 (12.78)	154.2 (13.13)	0.8702	130.8 (18.73)	130.8 (19.40)	0.9557
	Heart rate range (b/min)	74.93 (14.90)	74.67 (15.20)	0.6125	60.73 (15.70)	61.01 (16.54)	0.7895
	Heart rate at 2 minutes recovery (b/min)	112.1 (14.59)	112.5 (20.40)	0.5539	95.72 (16.16)	94.80 (16.40)	0.3832
	Heart rate recovery (b/min)	42.16 (12.67)	41.62 (19.15)	0.3300	35.15 (11.95)	35.62 (12.22)	0.5449
(b) Year 1*	Resting heart rate (b/min)	72.77 (11.35)	77.68 (11.73)	<.0001	65.89 (11.59)	68.80 (11.12)	<.0001
	Peak heart rate (b/min)	130.5 (6.24)	130.8 (6.60)	0.1355	117.7 (17.87)	118.7 (17.99)	0.3539
	Heart rate range (b/min)	57.69 (12.06)	53.11 (12.35)	<.0001	51.80 (15.34)	49.83 (15.34)	0.0396
	Heart rate at 2 minutes Recovery (b/min)	89.30 (21.75)	92.96 (12.14)	<.0001	82.97 (15.43)	85.89 (15.15)	0.0021
	Heart Rate Recovery (b/min)	41.17 (22.02)	37.84 (12.47)	<.0001	34.71 (12.16)	32.82 (11.54)	0.0105

*Note that the baseline (a) was a maximal test while the Year 1 (b) test was submaximal.

Table 2: Correlations with Year 1 heart rate recovery[a].

Variable	N	Spearman correlation	P value
Age	3371	−0.2220	<.0001
Self-reported duration of diabetes (yrs)	3348	−0.1018	<.0001
Waist circumference	3367	−0.0999	<.0001
BMI	3371	−0.0464	0.0071
Hemoglobin A1c%	3371	−0.1026	<.0001
Triglycerides (mgdL)	3371	−0.0863	<.0001
Percent weight change	3371	−0.1837	<.0001
Percent fitness change	3289	0.0849	<.0001

[a]Results at Year 1 for 3371 participants never on β-blocker, where HRR could be calculated.

weight, lost fitness, or both to "High" success in which the participants achieved a 10% weight loss and 15% fitness gain at Year 1. This combined fitness/weight loss variable was significantly related to HRR at Year 1 and is illustrated in Figure 1, where there is a marked improvement in those in the "High Success" group compared to all other groups with lesser weight loss and/or fitness gain.

3.5. Multiple Regression Analysis for Heart Rate Recovery at Year 1. As a consequence of the intervention, ILI achieved a greater HRR than did DSE at Year 1 (Figure 1). Even after adjusting for significant influencing variables (i.e., age, gender, duration of diabetes, HbA1c, BMI, waist circumference, etc.), the treatment group effect remained highly significant. Results for the multiple linear regression models are presented in Table 4(a). The least square means for HRR were 41.48 for the ILI and 37.94 for the DSE, resulting in a highly significant between group difference ($P < .0001$) (Figure 1). A separate multiple linear regression model was fit to examine the differences in HRR among the five success groups (low, moderate low, moderate, moderate high, and high success). (Table 4(b)). The least square means for HRR were 44.92, and 40.60 for the high and moderate high success groups, and 38.64, 38.34, and 37.79 for the moderate, moderate low, and low success groups, respectively. Adjusted pairwise group comparisons revealed that HRR for the high success and moderate high success groups were significantly higher than all lower success groups ($P < .05$). The moderate, moderate low, and low groups were not significantly different from each other.

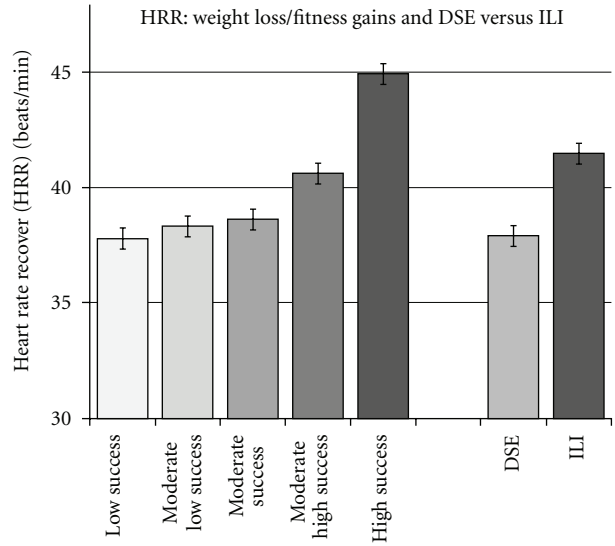

Figure 1: Combined influence of weight loss and fitness gain on Heart Rate Recovery (left) and Comparison of DSE versus ILI (right). (Levels of success were determined by combinations of weight loss and fitness gain in the 8 subgroups as described in Table 3(c)).

4. Discussion

The key findings are that an intensive lifestyle program of weight loss through diet and exercise resulted in greater improvement in HRR than a diabetes support education program at one year ($P < 0.001$) and furthermore, the magnitude of the improvement was influenced by the combined effects of weight loss and fitness gain. Though some studies have evaluated the effects of weight loss and/or physical activity on HRR in overweight and obese individuals and also those with T2DM, to our knowledge, the Look AHEAD trial is the first study to examine the effects of an extended (1 year) intensive lifestyle intervention upon HRR in a large cohort of overweight and obese individuals with type 2 DM.

4.1. Baseline Characteristics and 1 Year Changes with Intervention in Look AHEAD. The characteristics of the individuals randomized to ILI and DSE were essentially equal at baseline and none were found to be statistically different. While it was not the aim of this paper to analyze all of the changes in these variables after 1 year of intervention in the Look AHEAD study group, another publication [10] has reported greater benefits for weight loss (8.6 versus 0.7%; $P < 0.0001$), fitness gain (20.9 versus 5.7%; $P < 0.0001$), and lowered hemoglobin A1c (7.3 to 6.6% versus 7.3 to 7.2%) in ILI versus DSE, respectively. Systolic and diastolic pressure, triglycerides, HDL cholesterol, and urine albumin-to-creatinine ratio improved more in ILI than DSE participants (all $P < 0.01$) and the prevalence of the metabolic syndrome declined from 93.6 to 78.9% in the

Table 3: HRR according to treatment, select variables, weight loss, fitness gain, and combined effects of weight loss/fitness gain.

(a) Influence of treatment upon HRR at Year 1

Variable	Subgroup	*N*	Mean ± SD	*P* value
Treatment	Diabetes support and education	1665	37.92 ± 12.42	<.0001
	Weight loss intervention	1706	41.59 ± 12.41	

(b) Influence of select variables upon HRR at Year 1

Variable	Subgroup	*N*	Mean ± SD	*P* value
Age	45–55	1239	42.26 ± 12.47	<.0001
	56–65	1723	39.15 ± 12.21	
	66–76	409	34.88 ± 12.45	
Gender	Male	1310	39.26 ± 12.17	0.0540
	Female	2061	40.11 ± 12.77	
Diabetes severity	No diabetic meds, no insulin	435	42.36 ± 12.68	<.0001
	Diabetic meds only	2290	39.73 ± 12.43	
	Insulin only	128	37.54 ± 12.74	
	Insulin and diabetic meds	469	38.17 ± 12.52	
History of CVD	No	3124	39.92 ± 12.60	0.0160
	Yes	247	37.93 ± 11.75	
Hypertension	No	729	42.72 ± 12.53	<0.0001
	Yes	2642	38.97 ± 12.43	
Waist circumference group (adjusted for gender)	1	676	41.71 ± 12.72	0.0062
	2	695	40.01 ± 12.24	
	3	799	39.61 ± 12.56	
	4	516	38.51 ± 12.13	
	5	681	38.73 ± 12.76	

(c) Influence of weight losses and fitness gains upon HRR at Year 1

Variable	Subgroup	*N*	Mean ± SD	*P* value
Weight group	Weight gain (1)*	839	37.69 ± 12.48	<.0001
	4.9% weight loss to 0% weight gain (2)	1154	38.36 ± 11.88	
	5% weight loss to 9.9% weight loss (3)	706	40.21 ± 12.28	
	10% weight loss and greater (4)	741	43.92 ± 12.88	
Fitness group	Fitness loss (5)	764	38.98 ± 12.82	0.0001
	0% to 7.49% fitness gain (6)	781	39.96 ± 12.48	
	7.5% fitness gain to 14.9% fitness gain (7)	526	40.25 ± 12.06	
	15% fitness gain and greater (8)	1284	40.78 ± 12.49	
Combined weight and fitness group*	Low success	818	38.11 ± 12.57	<0.0001
	Moderate low success	537	38.68 ± 12.60	
	Moderate success	595	38.62 ± 11.71	
	Moderate high success	925	40.61 ± 12.31	
	High success	480	44.29 ± 12.72	

* Groupings: The five combined weight and fitness groups were determined by combining the four weight groups with the 4 fitness groups, based upon relatives success in both weight loss and fitness gain. Low success (1 and 5; 2 and 5; 1 and 6); moderate low success (3 and 5; 1 and 7; 2 and 6); moderate success (3 and 6; 2 and 7; 4 and 5; 1 and 8); moderate high success (2 and 8; 4 and 6; 4 and 7; 3 and 6; 3 and 8); high success (4 and 8).

ILI group compared with a decline of 94.4 to 87.3% in the DSE group.

4.2. Heart Rate Recovery and β-blocker Usage. In response to the intervention, ILI participants exhibited improved HRR compared with DSE. This was true in those participants without β-blocker usage as well as those taking β-blockers (Tables 1(a) and 1(b)). This latter finding is consistent with the results of Maeder et al. [16] who found that β-blocker use did not influence the interpretation of HRR despite the lower absolute values due to the β-blocker effect. Two other studies have found similar results. Arena et al. [17] studied

Table 4: (a) Association of Year 1 Heart Rate Recovery with treatment group. (b) Association of Year 1 Heart Rate Recovery with combined weight and fitness changes.

(a)

	HRR at Year 1			
Model*	*B*	SE	*P* value	R^2
Model A				
ILI versus DSE	3.544	0.379	<0.0001	0.255
	Least square means			
	LSMEAN	SE	*P* value for testing equality of LSMEANs	
ILI	41.48	0.27	<0.0001 (ILI versus DSE)	
DSE	37.94	0.27		

(b)

	HRR at Year 1			
Model*	*B*	SE	*P* value	R^2
Model B				
Moderate high success versus high success	−4.32	0.62	<0.0001	0.27
Moderate success versus high success	−6.28	0.68	<0.0001	
Moderate low success versus high success	−6.58	0.70	<0.0001	
Low success versus high success	−7.13	0.64	<0.0001	
	Least square means^			
	LSMEAN	SE		
Low success[a]	37.79	0.39		
Moderate low success[b]	38.34	0.48		
Moderate success[c]	38.64	0.45		
Moderate high success[a,b,c,d]	40.60	0.36		
High success[a,b,c,d]	44.92	0.51		

^ Same superscripts indicate groups are significantly different from each other.
*Models were adjusted for baseline covariates, including age, gender, clinical site, diabetes duration, diabetes medication use, history of cardiovascular disease, hypertension, BMI, waist circumference, HbA1c, and triglycerides.

520 individuals with heart failure (HF) and found that HRR maintains its prognostic value in HR irrespective of β-blocker use. Karnik et al. [18] conducted a retrospective study of 334 patients who underwent exercise stress echocardiography and compared those with and without β-blocker therapy. They found that HRR was not affected by β-blocker use in patients without stress-induced ECG abnormalities; however, in those with a positive stress echocardiogram result, HRR improved in the presence of β-blocker therapy.

During exercise, there is an increase in heart rate due to increased sympathetic and reduced vagal (parasympathetic) activity. However, when the exercise bout is stopped, the rapid decrease in heart rate is predominantly accomplished by vagal reactivation, making HRR a marker of parasympathetic control of the heart. Therefore, a delay in HRR after exercise is an indicator of impaired autonomic nervous system functioning, specifically reduced parasympathetic activity. These results suggest that the ILI intervention, which produced weight loss and improved physical fitness, also had a beneficial effect upon autonomic nervous system function as reflected in the improved HRR.

4.3. Relationship of Weight Loss and Fitness Gain on HRR. We found that both greater weight loss and fitness gains were associated with greater improvements in HRR ($P < 0.001$). While there is a paucity of published work that addresses the issue of whether weight loss influences HRR, a recent study by Brinkworth et al. [19] measured HRR in 42 overweight and obese males (body mass index $33.8 \pm 0.6\,kg/m^2$, mean age 46.5 + 1.3 years) before and after a 12-week weight loss program based upon an energy restricted diet while physical activity was kept at baseline level. These individuals had neither T2DM nor symptoms of cardiovascular disease, but rather had components of the metabolic syndrome. Although peak heart rate remained unchanged, HRR at 1 minute improved significantly from 33.1 + 1.4 to 36.9 + 1.3 beats/min ($P < .001$) after weight loss. There was neither a change in physical activity levels ($P = .67$) nor cardiorespiratory fitness ($P = .30$) and thus these benefits were attributed directly to the weight loss.

In 373 postmenopausal women, similar in age (45–75 y) and ethnic diversity to our population, Earnest et al. [20] studied autonomic nervous system balance as measured by heart rate variability (HRV) after a six-month moderate

exercise training program in which participants exercised at 50%, 100%, and 150% of the NIH Consensus Development Panel's recommended minimal physical activity level [21]. They found significant ($P < 0.0001$) improvement in all parasympathetically derived time and frequency domain measurements associated with HRV in a dose-dependent pattern across all groups, with only the 100% and 150% groups experiencing improvements in HRV, revealing that moderate intensity exercise is sufficient to improve autonomic nervous system function as measured by HRV.

When we examined the combined groups of weight loss and fitness gain in our participants, we found a combined influence. The group that achieved the highest success, a 10% weight loss and a 15% fitness gain at the end of Year 1 achieved the greatest improvement in HRR. Overall, the present data support a dose-response relationship such that those participants that met more of the goals, as we rated from "Low" to "High" success, attained greater improvements in HRR. Thus, it seems important that clinicians encourage both weight loss and exercise in the treatment of overweight/obese and sedentary patients with diabetes.

4.4. Heart Rate Recovery, Autonomic Dysfunction, and T2DM. Heart Rate Recovery (HRR) appears to be an established prognostic indicator for cardiovascular disease and all-cause mortality in healthy individuals as well as those with T2DM. Cheng et al. [15] examined the association of HRR to CVD-related and all-cause mortality in 2,333 men with documented diabetes (mean age 49.4 years) that had baseline HRR measurement following maximal exercise; however, HRR was measured as heart rate peak—heart rate at 5 min of recovery. During a median of 14.9 years followup, men in the highest quartile of HRR (i.e., healthiest group), had fewer cardiovascular deaths compared with those in the other quartiles illustrating that a decreased HRR, even measured as long as 5 min after recovery, was independently predictive of cardiovascular and all-cause death in men with T2DM.

Carnethon et al. [22] measured heart rate variability (HRV) and QT duration at baseline and annually over 3.2 years in 2,980 participants in the Diabetes Prevention Program (DPP). HRV and QT duration reflect fitness and autonomic nervous system function; DPP was a randomized clinical trial using lifestyle intervention in adults at risk for diabetes development. They found that higher resting heart rate at baseline, representing both poor fitness and impaired autonomic function, was associated with a modestly increased incidence of diabetes. Further, improved fitness and/or autonomic function, as indicated by lowered heart rate and increased HRV, was associated with a reduced risk of development of diabetes, even after adjustment for changes in weight and physical activity levels.

Yamada et al. [23] examined the relationship between silent myocardial ischemia (SMI) and HRR in type 2 diabetes and found that HRR was significantly associated with SMI (odds ratio 0.83 [95% CI 0.75–0.92]; $P = 0.0006$), even after adjustment for maximal exercise workload, resting heart rate, maximum heart rate, rate pressure product, HbA1c, use of sulfonamides, and a history of cardiovascular disease, leading the investigators to conclude that HRR can predict SMI in patients with type 2 diabetes.

4.5. Long-Term Impact of the Look AHEAD Study on Cardiovascular Outcomes. The Look AHEAD (Action for Health in Diabetes) study is designed to assess the long-term health consequences of intentional weight loss in individuals with type 2 diabetes [11]. The primary outcomes, which are CVD morbidity and mortality parameters. These data are now being analyzed and have not yet been reported. However, the present study shows that HRR, an important surrogate marker of CVD, can be improved with greater weight loss and gains in fitness. This observation is supported by a recent study by Georgoulias et al. [24] in which 285 patients underwent SPECT myocardial perfusion imaging combined with exercise testing. Cardiovascular death and nonfatal myocardial infarction were considered as hard cardiac events, while late revascularization procedures as soft events. During the mean follow-up period of 31 months, hard cardiac events occurred in 21 (8%) patients, 15 of whom had abnormal HRR value, while 35 (14%) patients underwent revascularization, 31 of whom had abnormal HRR values. HRR was a strong predictor for both hard cardiac (coefficient = −0.41, SE = 0.052, $P < 0.001$) and soft cardiac events (coefficient = −0.63, SE = 0.058, $P < 0.001$). Thus, the change in HRR variable herein is a favorable outcome and suggests a reduction in CVD risk.

5. Conclusions

A lifestyle intervention to promote weight loss through diet and physical activity improved Heart Rate Recovery following exercise, a variable associated with autonomic dysfunction and cardiovascular risk in adults with T2DM. While weight loss and fitness gains each have separate beneficial influences on HRR, those participants who achieved both the greatest amount of weight loss and the greatest gains in fitness showed the most amount of improvement in Heart Rate Recovery, an important marker of cardiovascular risk.

Appendix

A. Look AHEAD Research Group at Year 1

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Diet Assessment Center, University of South Carolina, Arnold School of Public Health, Center for Research in Nutrition and Health Disparities. Elizabeth J. Mayer-Davis, Ph.D. (principal investigator); Robert Moran, Ph.D.

Hall-Foushee Communications, Inc. Richard Foushee, Ph.D.; Nancy J. Hall, MA.

A.4. Federal Sponsors

National Institute of Diabetes and Digestive and Kidney Diseases. Barbara Harrison, MS; Van S. Hubbard, M.D. Ph.D.; Susan Z.Yanovski, M.D.

National Heart, Lung, and Blood Institute. Lawton S. Cooper, M.D., MPH; Jeffrey Cutler, M.D., MPH; Eva Obarzanek, Ph.D., MPH, RD.

Centers for Disease Control and Prevention. Edward W. Gregg, Ph.D.; David F. Williamson, Ph.D.; Ping Zhang, Ph.D.

Acknowledgments

This study is supported by the Department of Health and Human Services through the following cooperative agreements from the National Institutes of Health: DK57136, DK57149, DK56990, DK57177, DK57171, DK57151, DK57182, DK57131, DK57002, DK57078, DK57154, DK57178, DK57219, DK57008, DK57135, and DK56992. The following federal agencies have contributed support: National Institute of Diabetes and Digestive and Kidney Diseases; National Heart, Lung, and Blood Institute; National Institute of Nursing Research; National Center on Minority Health and Health Disparities; Office of Research on Women's Health; and the Centers for Disease Control and Prevention. This research was supported in part by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases. The Indian Health Service (I.H.S.) provided personnel, medical oversight, and use of facilities. The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the I.H.S. or other funding sources. Additional support was received from The Johns Hopkins Medical Institutions Bayview General Clinical Research Center (M01RR02719); the Massachusetts General Hospital Mallinckrodt General Clinical Research Center (M01RR01066); the University of Colorado Health Sciences Center General Clinical Research Center (M01RR00051) and Clinical Nutrition Research Unit (P30 DK48520); the University of Tennessee at Memphis General Clinical Research Center (M01RR0021140); the University of Pittsburgh General Clinical Research Center (M01RR000056 44) and NIH grant (DK 046204); the VA Puget Sound Health Care System Medical Research Service, Department of Veterans Affairs; and the Frederic C. Bartter General Clinical Research Center (M01RR01346). Members of the look AHEAD Research Group participated in this work. The following organizations have committed to make major contributions to Look AHEAD: Federal Express; Health Management Resources; Johnson & Johnson, LifeScan Inc.; Optifast-Novartis Nutrition; Roche Pharmaceuticals; Ross Product Division of Abbott Laboratories; Slim-Fast Foods Company; and Unilever.

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