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Abnormal Exercise Test or CVD History on Weight Loss or Fitness: the Look AHEAD Trial

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Abstract

Purpose: Obesity and type 2 diabetes are associated with an increased risk of cardiovascular disease (CVD) and the combination of weight loss and increased physical exercise are commonly recommended to reduce CVD. This study examined whether people with obesity and type 2 diabetes with an abnormal graded exercise tolerance test (GXT) or a history of CVD would have less success in achieving weight loss and improved fitness, compared to adults without these conditions.

Methods: The Look AHEAD Study examined whether an intensive lifestyle intervention (ILI) compared with diabetes support and education (DSE) reduced cardiovascular events in adults with overweight/obesity and type 2 diabetes. Participants underwent a baseline maximal GXT and provided medical history data. Weight loss and fitness change were examined in 5011 participants over four years in those with or without an abnormal baseline GXT and/or history of CVD.

Results: After four years, weight loss in both ILI and DSE were significantly greater in those without a prior history of CVD than in those with a CVD history (6.69% vs 5.98%, $p=0.02$, in ILI and 0.73 vs -0.07% (weight gain), $p=0.01$, in DSE). Likewise, those without a prior history of CVD experienced greater improvements in fitness in both ILI and DSE relative to those with a history of CVD. Having an abnormal GXT at baseline did not affect weight loss or fitness.

Conclusions: A history of CVD at baseline modestly lessened weight loss and fitness changes at 4 years, whereas having any abnormality on the baseline GXT did not affect these outcomes. Thus, weight loss and improved fitness are achievable in adults with a history of CVD or ECG abnormalities.

Keywords

diabetes; obesity; cardiorespiratory fitness; cardiovascular disease; electrocardiography; weight loss

INTRODUCTION

The American Heart Association and the American College of Cardiology have recommended physical activity and weight management for prevention of CVD events (1, 2). Extensive data from cardiac rehabilitation studies have shown the possibility and benefits of improving fitness and losing weight in those with CVD (3). Jakicic et al. (4) showed that among the Look AHEAD cohort receiving a lifestyle intervention, those with a self-reported history of CVD improved cardiorespiratory fitness significantly less after one year than those without such history. However, beyond this early Look AHEAD report, no trials have assessed whether adults who are overweight or obese with diabetes and evidence or history of CVD can improve fitness that is similar to those without CVD. Moreover, it is unclear if similar weight loss can be achieved between individuals with and without a history of CVD, despite clinical recommendations to indicate weight loss may reduce CVD risk factors. Similarly, it is not known whether a pre-participation graded exercise tolerance test (GXT) that is abnormal by established criteria (5), but not severe enough to exclude participants from participation, will affect weight loss or improvement in cardiorespiratory fitness that occur during a lifestyle intervention program.

The Look AHEAD Study provides a unique opportunity to examine these questions. In Look AHEAD, overweight/obese participants were randomly assigned to an intensive lifestyle intervention (ILI) or a control group (Diabetes Support and Education, DSE) and followed over time. At 4 years, the ILI group had greater weight loss and larger improvements in fitness than DSE. However, the question of whether a history of CVD or an abnormal pre-participation GXT influences the change in weight or cardiorespiratory fitness achieved in response to a behavioral intervention focused on weight loss and physical activity has not previously been examined. These findings may provide insight into the characteristics of patients with type 2 diabetes that may influence response to a comprehensive behavioral weight management program. Moreover, these findings may be important for physicians and other healthcare providers when considering whether a lifestyle intervention focused on weight loss and physical activity is appropriate for individuals with a history of CVD or with the presence of abnormalities on a pre-participation GXT.

METHODS

Participants

Baseline data on Look AHEAD participants (6) and study methods (7) have been published previously. Look AHEAD is registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00017953) (NCT00017953). Briefly, Look AHEAD enrolled 5145 participants with type 2 diabetes, aged 45–76, with body mass index (BMI) ≥ 25 kg/m² (≥ 27 kg/m² if using insulin). Informed consent was obtained from each participant prior to screening. The study protocol was approved by the Institutional Review Board of each center and the National Institute of Diabetes and Digestive and Kidney Diseases.

Assessing Cardiorespiratory Fitness

All participants underwent a symptom-limited maximal GXT before randomization to assess baseline fitness and rule out contraindications to moderate intensity exercise. Participants also underwent submaximal GXTs after one and four years in the study. The maximal and submaximal GXTs have been described elsewhere (4, 8). To proceed from the baseline GXT to randomization the participant must have achieved at least 85% of predicted maximal heart rate ($HR_{max} = 220 - \text{age}$) and a calculated workload of at least 4 metabolic equivalents (METs). For participants taking a beta blocking medication, a rating of perceived exertion (RPE) of at least 18 on the Borg 15-category scale was required rather than the heart rate criteria. The pre-determined stopping point for each submaximal test conducted at one and four years was achieving at least 80% of predicted maximal heart rate if not taking a beta blocking medication or RPE of at least 16 on the Borg scale if taking a beta blocker. Cardiorespiratory fitness was defined as the estimated MET level based on the treadmill work load (i.e., speed and grade). As previously described, to compute the change in cardiorespiratory fitness, MET level at the point of test termination for the submaximal GXT (80% of predicted maximal heart rate if not taking a beta blocking medication or RPE of at least 16 on the Borg scale if taking a beta blocker) was compared to the MET level attained at the same submaximal point from the baseline GXT as previously described (4, 8) (see Slides, Supplemental Digital Content 1, which illustrate the of procedures for computing the change in fitness from baseline, using a maximal exercise test, to follow-up, using a submaximal exercise test). To evaluate heart rate and rhythm when determining an abnormal GXT, heart rate was determined from printed 12-lead electrocardiograms obtained during the last 10 seconds of every minute, immediately at test termination, and every two minutes during recovery.

Criteria for Abnormal GXT

An abnormal baseline GXT was defined by criteria associated with risk of acute exercise-related cardiovascular events or CVD mortality. Abnormal tests showed evidence of ischemia (ST segment depression of ≥ 1.0 mm), ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia, runs of at least three premature ventricular contractions, or exercise-induced bundle branch block), exercise-induced angina, abnormal hemodynamic response (heart rate recovery [HRR] <22 beats per minute two minutes post-exercise), or impaired exercise capacity (IEC; highest achieved workload of <5 METs) (9). Participants

with abnormal GXT results were excluded from the study or referred to their physician for evaluation following which some were subsequently cleared for study participation.

Defining History of CVD

At baseline, participants were asked about any prior history of myocardial infarction, stroke, transient ischemic attack, coronary artery bypass graft (CABG), coronary angioplasty/stent, carotid endarterectomy, lower extremity angioplasty, aortic aneurism repair, or heart failure (HF). If a participant reported a history of any of these events or conditions, he/she was deemed to have a history of CVD. If any CVD events occurred within 3 months prior to screening, the participant was offered the opportunity to rescreen in 3 months or was excluded before randomization.

Assessment of Body Weight

Weight was measured annually in duplicate on a digital scale, and change was follow-up weight minus baseline weight.

Interventions

The intervention has been described in detail elsewhere (10–12). Briefly, each ILI participant had contact weekly, in a combination of group and individual sessions, with a health coach for the first six months, three times per month for the next six months, and at least monthly through year 4. ILI participants were encouraged to adhere to a calorie restricted diet (1200–1800 kcal/day) with <30% of calories from fat, <10% from saturated fat, and 15% from protein and had a weight loss goal of 10%. They were also encouraged to exercise at least 175 minutes per week at the intensity of brisk walking and were given support in problem solving, goal setting, and self-monitoring to achieve these objectives.

The Diabetes Support and Education (DSE) group was given three educational sessions per year focused on diet, physical activity, and social support, but they were not given weight loss, nutrition, or physical activity goals, nor were they given specific support for behavior changes (13).

Statistical Methods

The distributions of selected baseline characteristics and GXT abnormalities for participants grouped by intervention assignment were compared using chi square tests and t-tests. Mixed effects models were fitted to the longitudinal changes in weight and fitness using maximum likelihood (14). This approach uses all data collected through the four years of follow-up and avoids the assumption that any data are missing completely at random (14). We used Wald tests to assess differences between participants grouped by intervention assignment with the presence of GXT abnormalities or history of CVD as predictors in models. Linear contrasts were used to estimate mean differences at Year 4 to summarized effect sizes from these models. Participants were grouped by intervention assignment in all analyses (i.e. intention-to-treat), regardless of adherence.

RESULTS

This analysis includes the 5,011 (97.4%) Look AHEAD participants for whom weight and fitness data were available at baseline and at least one annual follow-up visit. Baseline characteristics of the subset included in this analysis are shown in Table 1. All variables are balanced by intervention assignment. As shown in Table 1, 13.8% of patients reported a history of CVD and 19.3% experienced an abnormal baseline GXT test. ST depression and abnormal heart rate recovery were the most common abnormalities. At four years, 2009 (78.2%) participants in ILI and 1919 (74.5%) in DSE completed GXTs.

Weight Change

Compared to the DSE group, the ILI produced marked and statistically significant 4-year weight losses, overall and after stratification by every category of GXT abnormality and history of CVD, after adjusting for age and sex (Figure 1). After adjusting for age and sex, those with a self-reported history of CVD lost significantly less weight from baseline to year 4 in both DSE (-0.07% [weight gain] vs. 0.73% , $p=0.01$) and ILI (5.98% vs 6.69% , $p=0.02$) compared to those without a history of CVD. In contrast, weight loss in either ILI or DSE did not differ between those participants who had any GXT abnormality and those who did not. Specifically within the ILI, mean weight loss was significantly greater in participants with arrhythmia (12.35% vs 6.57% , $p=0.008$) angina (10.27% vs 6.56% , $p=0.01$), or abnormal HRR (7.87% vs 6.48% , $p=0.03$) compared with those without these abnormalities. However, the number of participants with each of these abnormalities was small, particularly ventricular arrhythmia ($n=6$), and angina ($n=14$). In DSE none of the abnormalities observed on the GXT were associated with differences in 4-year weight losses.

Change in Cardiorespiratory Fitness

The ILI had significantly greater improvements in fitness from baseline to Year 4 than DSE, overall and within all subgroups. Relative to those without a history of CVD, self-reported history of CVD was associated with poorer 4-year fitness changes in both the DSE (-0.12 METs vs 0.06 METs, $p=0.01$) and ILI (0.43 METs vs 0.61 METs, $p=0.004$) groups (Figure 2). Those who had any GXT abnormality at baseline did not experience different fitness outcomes than those with no GXT abnormalities (Figure 2). However, some specific GXT abnormalities at baseline did affect fitness change. In ILI ventricular arrhythmia was associated with greater fitness improvement (1.47 METs vs 0.58 METs, $p=0.04$). In both ILI and DSE, participants with IEC at baseline had smaller improvements in fitness than those who did not have IEC (DSE: -0.17 METs with IEC vs 0.03 METs without IEC, $p=0.01$; ILI: 0.25 METs with IEC vs 0.62 METs without IEC, $p=0.01$).

DISCUSSION

Participants in ILI had significantly greater weight loss and improved fitness at 4 years compared to those assigned to DSE, regardless of baseline history of CVD or GXT abnormalities, and this is consistent with the main findings from the Look AHEAD Study that demonstrated greater weight loss and improved fitness in ILI compared to DSE (10, 11).

However, the magnitude of the changes between those with and without a self-reported history of CVD, while statistically significant, are modest and may not be clinically meaningful. Moreover, magnitude of these changes between those with and without GXT abnormalities were not statistically or clinically meaningful. It has been suggested that a 3 percent difference in weight change (15) or a 2 MET difference in fitness (16) may be needed to impact cardiovascular disease risk, which may support that these be considered when determining clinical meaningfulness of these observed differences. Physicians and other healthcare providers should expect similar responses in weight loss and fitness to an ILI in patients with overweight/obesity and with type 2 diabetes regardless of the presence of a history of CVD or abnormalities observed on a pre-participation GXT.

The underlying cause for this statistically significant, but clinically modest, difference in weight loss by CVD history is not clear. One hypothesis to explain this finding is that participants' perception of the risk of participating in physical activity may be influenced by CVD history, which may have reduced energy expenditure and subsequent weight loss. For example, participants with a known history of CVD may have been reluctant to exercise as long, as often, or as vigorously as those without CVD. Jakicic et al. (17) found that at baseline, in the subset of Look AHEAD participants (n=2240) whose physical activity was monitored by accelerometry, there was no significant difference between those with and without a history of CVD in the number of bouts of physical activity per day, minutes per bout, or number of bouts with intensities of at least 6 or 10 METs. However, it is possible that physical activity in response to the intervention differed between participants with and without CVD, and this warrants investigation.

The above analyses were repeated excluding participants who underwent bariatric surgery, were diagnosed with cancer or heart failure, underwent a coronary artery bypass graft, or died prior to their year-4 exam (data not shown). The results did not change materially, suggesting that these conditions, which are commonly associated with weight loss, were not the cause of weight loss seen in the trial.

Although weight loss in ILI and DSE did not differ between those who had an abnormal GXT and those who had a normal test, some specific abnormalities were associated with greater weight loss in ILI. After adjustment for age and sex, Look AHEAD participants ILI and who experienced ventricular arrhythmia, angina pectoris, or impaired HRR during their baseline stress test lost more weight than their ILI counterparts without these conditions. These differences in weight loss were not associated with being referred for medical clearance on the basis of an abnormal GXT as those referred did not lose more weight than those not referred ($p=0.55$, data not shown). However, the small number of participants with these abnormalities limits any conclusions that can be drawn from these findings, and therefore should be interpreted with caution.

The association between angina pectoris on the baseline GXT and greater subsequent weight loss in the ILI group and a nonsignificant trend toward weight loss in the DSE group suggests a mechanism that is enhanced but not entirely created by the lifestyle intervention. This conclusion is supported by two observational studies that showed greater weight loss in those experiencing angina, either by self-report (18) or during a GXT (19), than in those

without angina. In the latter study, those with angina and weight loss had worse clinical outcomes. Again, such interpretations are limited by the fact that only 14 participants in ILI and 14 in DSE had angina on the baseline GXT, and therefore these findings warrant caution being interpreted for clinical meaningfulness.

Within each subgroup of GXT abnormality, and among those with a history of CVD, the ILI was associated with improved fitness, relative to DSE. DSE participants with an abnormal baseline GXT did not experience fitness change differently than those with normal GXTs, except that baseline IEC or history of CVD was associated with declining fitness over four years. An IEC at baseline or history of CVD was also associated with less improvement in fitness in the ILI group, compared with ILI participants without these characteristics. Morris et al (20) showed, in a large cohort referred for GXTs, that the expected rate of decline in fitness is greater in sedentary than in active men. Kokkinos and Myers (21), in their review of the fitness studies in CVD, observed a strong, consistent, inverse association between both fitness and change in fitness over time and CVD outcomes, with this association being at least as strong as any other described (e.g., smoking, hyperlipidemia). IEC is closely correlated with physical activity level (22) in what is likely a bi-directional relationship. Those with IEC may have been more sedentary prior to the study, which could explain the more rapid fitness decline in the DSE group. A likely explanation for these fitness changes is that those with IEC had a greater burden of CVD at baseline, whether previously diagnosed or not, and experienced decline (DSE) or less improvement (ILI) in fitness over the observed period due to their underlying CVD. Thus, patients with overweight/obesity and type 2 diabetes should be monitored for potential declines in fitness and should also be encouraged to engage in safe and effective interventions, which may need to be medically monitored, to sustain or potentially enhance fitness.

A self-reported history of CVD was associated with a decrease in fitness in the DSE group and a lesser improvement in fitness in the ILI group; however, the ILI resulted in significant improvement in fitness among those with and without a history of CVD. As with IEC, this history of CVD may be a marker of subsequent clinical decline (23).

One potential incongruity merits attention. ILI participants with IEC at baseline lost more weight but improved fitness less than those with normal exercise capacity; however, the modest differences may not be clinically meaningful and should be interpreted with caution. Given the strong correlation between weight loss and fitness gain, this divergence seems counter-intuitive. In this analysis the dietary aspect of the intervention, which has been shown by Wadden et al (24) to have had a strong impact on weight loss, was not considered. Determining long-term outcomes in these participants is beyond the scope of this paper; however, such evaluation may elucidate whether the weight loss seen in participants with IEC at baseline is a harbinger of overall clinical decline.

Strengths of this study include the size and diversity of the population included in the Look AHEAD trial and the high rate of participant retention. Look AHEAD also has also demonstrated the safety and effectiveness of the lifestyle intervention program in achieving both weight loss and fitness gain, which are commonly recommended for treating patients with type 2 diabetes to improve diabetes control and reduce its long-term complications.

This study also included limitations. Study participants included volunteers who met inclusion criteria expected to heighten adherence, which may result in these participants not reflecting the general population. While retention was high, the analyses included only participants for whom follow-up data are available. Individuals at highest risk for CVD events may not be represented given the inclusion criteria for this study. Since the independent variables (abnormal GXT and history of CVD) are risk factors for CVD, the underrepresentation of those at highest risk for CVD events may make the results inaccurate with regard to both weight loss and fitness change. An additional limitation of this study may be the use of a submaximal GXT to monitor change in fitness across the intervention period, and future studies should consider using a symptom-limited maximal GXT at all assessment periods to evaluate change in fitness.

CONCLUSIONS

In this large cohort of participants with obesity and type 2 diabetes, those participants without a history of CVD achieved significant, but modestly greater, improvements in weight losses and fitness in both ILI and DSE than those with a CVD history. Moreover, those with any GXT abnormality did not differ in weight loss or fitness changes from those with no abnormalities. However, in all subgroups, participants assigned to ILI had greater weight losses and improvements in fitness at Year 4 than those assigned to DSE regardless of CVD history or GXT abnormalities. Thus, overweight and obese adults with type 2 diabetes who have markers of CVD on a GXT or with a known history of CVD can lose weight and improve fitness with a lifestyle intervention. These findings provide insight into the characteristics of patients with type 2 diabetes that may influence response to a comprehensive behavioral weight management program. Moreover, these findings may be important for physicians and other healthcare providers, and suggest that a lifestyle intervention focused on weight loss and physical activity can be effective for treating overweight/obesity and improving fitness for individuals with a history of CVD or with the presence of abnormalities on a pre-participation GXT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A complete list of the Look AHEAD Study Group is provided (see Document, Supplemental Digital Content 2, which provides a complete list of the Look AHEAD Study Group). Results of the present study do not constitute endorsement by ACSM.

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Figure 1:

4-year weight loss by group assignment and GXT abnormality or CVD history[‡]

White bars = DSE; Black bars = ILI.

Adjusted for age and sex.

[‡]Defined as self-report of myocardial infarction, stroke, transient ischemic attack, coronary artery bypass graft, angioplasty/stent, carotid endarterectomy, angioplasty of lower extremity, aortic aneurysm repair, or heart failure.

All between-group (ILI vs DSE) differences are significant at $p < 0.001$.

* Difference between YES/NO in ILI, $P = 0.01$

[†] Difference between YES/NO in ILI and DSE, $P = 0.01$

Abbreviations: GXT: graded exercise tolerance test; CVD: cardiovascular disease; ST Dep: ST segment depression; Arrhyth: arrhythmia; Abn HRR: abnormal heart rate recovery; IEC: impaired exercise capacity; Any GXT abn: any GXT abnormality; H/O CVD: history of cardiovascular disease.

Figure 2:

4-year fitness change by group assignment and GXT abnormality or CVD history[‡]

White bars = DSE; Black bars = ILI.

Adjusted for age, sex, and baseline fitness (METs).

[‡]Defined as self-report of myocardial infarction, stroke, transient ischemic attack, coronary artery bypass graft, angioplasty/stent, carotid endarterectomy, angioplasty of lower extremity, aortic aneurysm repair, or heart failure.

All between-group differences are significant at $p < 0.001$ except those with angina, where $p = 0.02$.

* Difference between YES/NO in ILI, $P = 0.01$

† Difference between YES/NO in ILI and DSE, $P = 0.01$

Abbreviations: GXT: graded exercise tolerance test; CVD: cardiovascular disease; ST Dep: ST segment depression; Arrhyth: arrhythmia; Abn HRR: abnormal heart rate recovery; IEC: impaired exercise capacity; Any GXT abn: any GXT abnormality; H/O CVD: history of cardiovascular disease.

Table 1.

Baseline description of participants, prevalence of baseline GXT abnormalities, and self-reported prior cardiovascular disease * at baseline for participants grouped by intervention assignment. Data are limited to participants with at least one post-randomization annual weight measurement.

	DSE (N = 2497)	ILI (N = 2514)	p-value
Age (mean, SD)	58.8 (6.9)	58.6 (6.8)	0.19
Sex (#, % female)	1493 (59.8%)	1492 (59.4%)	0.75
Race/Ethnicity (#, %)			
Latino			
African American	2 (0.1%)	3 (0.2%)	
American Indian	2 (0.1%)	5 (0.3%)	
White	85 (5.1%)	84 (4.9%)	
Other/multiracial/unknown	50 (3.0%)	48 (2.8%)	
Not Latino			0.94
African American	285 (17.1%)	299 (17.5%)	
American Indian	102 (6.1%)	101 (5.9%)	
White	1108 (66.4%)	1126 (65.9%)	
Other/multiracial/unknown	34 (2.0%)	42 (2.5%)	
BMI (mean, SD)	36.0 (5.8)	35.9 (6.0)	0.44
HbA1c (mean, SD)	7.30 (1.19)	7.25 (1.15)	0.15
Insulin Use (# using, %)	391 (15.7%)	368 (14.6%)	0.31
ST depression	165 (6.6%)	183 (7.3%)	0.35
Arrhythmia	14 (0.6%)	6 (0.2%)	0.07
Angina	14 (0.6%)	14 (0.6%)	0.99
HR recovery	86 (4.8%)	72 (4.1%)	0.29
Impaired exercise capacity (IEC)	234 (9.4%)	247 (9.8%)	0.58
Any GXT abnormality	475 (19.0%)	491 (19.5%)	0.65
Self-reported prior CVD	333 (13.3%)	356 (14.2%)	0.40
GXT abnormality and/or prior CVD	720 (28.8%)	765 (30.4%)	0.22
GXT referral and/or prior CVD	582 (23.3%)	611 (24.3%)	0.41
GXT referral	299 (12.8%)	317 (13.4%)	0.58

* Defined as self-report of myocardial infarction, stroke, transient ischemic attack, coronary artery bypass graft, angioplasty/stent, carotid endarterectomy, angioplasty of lower extremity, aortic aneurysm repair, or heart failure.