

Prevalence and Predictors of Abnormal Cardiovascular Responses to Exercise Testing Among Individuals With Type 2 Diabetes

The Look AHEAD (Action for Health in Diabetes) study

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OBJECTIVE — We examined maximal graded exercise test (GXT) results in 5,783 overweight/obese men and women, aged 45–76 years, with type 2 diabetes, who were entering the Look AHEAD (Action for Health in Diabetes) study, to determine the prevalence and correlates of exercise-induced cardiac abnormalities.

RESEARCH DESIGN AND METHODS — Participants underwent symptom-limited maximal GXTs. Questionnaires and physical examinations were used to determine demographic, anthropometric, metabolic, and health status predictors of abnormal GXT results, which were defined as an ST segment depression ≥ 1.0 mm, ventricular arrhythmia, angina pectoris, poor postexercise heart rate recovery (< 22 bpm reduction 2 min after exercise), or maximal exercise capacity less than 5.0 METs. Systolic blood pressure response to exercise was examined as a continuous variable, without a threshold to define abnormality.

RESULTS — Exercise-induced abnormalities were present in 1,303 (22.5%) participants, of which 693 (12.0%) consisted of impaired exercise capacity. ST segment depression occurred in 440 (7.6%), abnormal heart rate recovery in 206 (5.0%), angina in 63 (1.1%), and arrhythmia in 41 (0.7%). Of potential predictors, only greater age was associated with increased prevalence of all abnormalities. Other predictors were associated with some, but not all, abnormalities. Systolic blood pressure response decreased with greater age, duration of diabetes, and history of cardiovascular disease.

CONCLUSIONS — We found a high rate of abnormal GXT results despite careful screening for cardiovascular disease symptoms. In this cohort of overweight and obese individuals with type 2 diabetes, greater age most consistently predicted abnormal GXT. Long-term follow-up of these participants will show whether these abnormalities are clinically significant.

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Cardiovascular disease (CVD) risk factors improve with exercise in individuals with diabetes (1). Similarly, individuals with diabetes who are physically active or have higher fitness levels have reduced CVD incidence and mortality (2,3). Nevertheless, participation in exercise may involve risks for individuals with diabetes because of their high prevalence of CVD, including silent ischemia, and other comorbid conditions (4).

Knowledge about the typical cardiovascular responses to exercise in individuals with type 2 diabetes has come mainly from small clinic-based studies (5) and a few larger studies in the general population (4,6,7). The Look AHEAD (Action for Health in Diabetes) study is a multicenter randomized clinical trial designed to evaluate the long-term effects of an intensive lifestyle intervention program of weight loss and physical activity on morbidity and mortality from CVD in overweight and obese individuals with type 2 diabetes (8). Graded exercise tests (GXTs) with electrocardiographic monitoring were conducted at baseline in 5,783 individuals, providing the largest sample of systematic stress testing ever conducted in individuals with type 2 diabetes. The aims of this analysis are to examine the range of abnormal exercise responses and to examine the degree to which demographic factors, health characteristics, and medication use associate with abnormal exercise responses. Identifying predictors from readily available demographic and clinical data may assist risk stratification before exercise testing or exercise prescription for individuals with diabetes.

RESEARCH DESIGN AND METHODS

This was a cross-sectional analysis of GXTs among individuals screened for participation in the Look AHEAD clinical trial (8). Individuals with previously diagnosed diabetes, aged

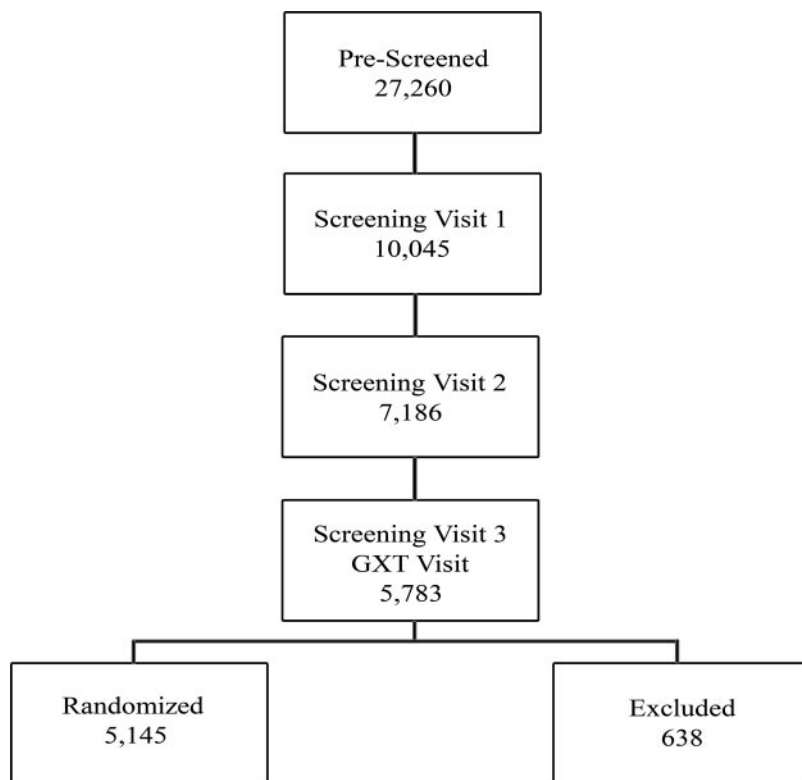


Figure 1—Study entry flow diagram. Participants included in the present analysis were the 5,783 individuals seen in screening visit 3.

45–76 years, with BMI ≥ 25 kg/m² (≥ 27 kg/m² if using insulin) were recruited. Informed consent was obtained from all participants before screening, consistent with the Declaration of Helsinki and each center's institutional review board guidelines. Participants were excluded if they had baseline A1C $\geq 11\%$, resting blood pressure $\geq 160/100$ mmHg, fasting triglycerides ≥ 600 mg/dl, or factors that might limit their successful participation in an intensive lifestyle intervention focused on weight loss.

Eligibility was determined by a series of clinical visits (Fig. 1). Individuals with a history of recent or significant cardiovascular disease or symptoms (defined in ref. 8) were excluded before exercise testing. Eligible participants underwent a maximal GXT within 3 months of the initial examination.

Immediately before the GXT, a brief physical examination was conducted to assess contraindications to exercise which, if present, disqualified volunteers from further participation. The use of β -blockers was not a study exclusion criterion. However, because heart rate data from participants using β -blockers were not considered informative, these heart rate data are not included in this

report. Other data from participants taking β -blockers (e.g., ST segment changes) are included. All GXTs were done before randomization, and the analyses herein include the 5,783 individuals who underwent the GXT, regardless of whether they were ultimately randomized.

Demographic and health status predictors

Full details of the Look AHEAD design and methods (8) and participants (9) are reported elsewhere. Height and weight were measured using standard protocols and were used to calculate BMI (weight in kilograms divided by the square of height in meters). Seated heart rate and blood pressure measurements were obtained after a 5-min rest using an automated Dinamap Monitor Pro 100. Two measurements were obtained and averaged.

GXT

The GXT protocol was designed such that most participants would achieve maximal voluntary exertion over ~ 8 –12 min, in accordance with American College of Sports Medicine recommendations (10). A supine resting 12-lead electrocardiogram (ECG) was first obtained. Each par-

ticipant started walking on the treadmill at 1.5 mph on a level (0%) grade, and speed was increased gradually by 0.5 mph units until the participant reached a brisk but comfortable self-selected walking speed or 4.0 mph. This self-selected treadmill speed was used for the GXT.

After a brief rest, the GXT was initiated at 0% grade. The speed remained constant while the grade was increased by 1% every minute until voluntary exhaustion or until the participant exhibited or reported signs or symptoms of exercise intolerance, using American College of Sports Medicine criteria (10). During the last 10 s of each exercise stage and at the point of test termination, heart rate was measured from a 12-lead ECG, and rating of perceived exertion (RPE) was obtained using the Borg 15-category scale (10). Under this RPE scale, the participant reports exertion levels along a scale from 6 (no exertion) to 20 (maximal exertion).

Blood pressure was measured during the last 45 s of each even minute exercise stage (i.e., stages 2, 4, and 6) and at the point of test termination. Peak exercise capacity expressed as METs was estimated from treadmill speed and elevation (10). At test termination, the participant was placed in a supine position with heart rate and blood pressure monitored at 2-min intervals for at least 8 min or until the supervising physician indicated that sufficient recovery had occurred. The supervising physician was asked to record any significant ST segment changes, type and frequency of arrhythmias, ECG-determined heart rate, and blood pressure at rest and at specified times during each test.

Definition of abnormal exercise tests

Abnormal GXT results were defined by criteria related to risk of acute exercise-related cardiovascular events or CVD mortality: electrocardiographic changes suggestive of coronary ischemia (ST segment depression of ≥ 1.0 mm) or 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 < 22 bpm over 2 min after exercise [11,12]), and impaired exercise capacity (highest achieved workload of < 5 METs [3,7]). Because of the lack of a consensus threshold for defining an abnormal systolic blood pressure (SBP)

response, this was analyzed as a continuous variable.

Statistical analysis

Logistic regression was used to assess relationships between the prevalence of each abnormality and individual risk factors. The relationships between mean SBP during exercise and risk factors were assessed with ANOVA.

RESULTS — Look AHEAD screened 27,260 potential participants, of whom 5,783 underwent a GXT (Fig. 1) and are described in Table 1. Their mean achieved RPE was 19.3, and the 25th percentile was 19, according to the Borg scale, which indicates that most participants reported being at or very near maximal voluntary effort. Overall, 1,303 (22.5%) tests were abnormal (Fig. 2), and 638 subjects were not randomly assigned into the Look AHEAD trial because of safety concerns due to GXT abnormalities. The most frequent abnormality was impaired exercise capacity (12.0%), followed by ST segment depression (7.6%), heart rate recovery abnormalities (5.0%), exercise-induced angina (1.1%), and ventricular arrhythmias (0.7%).

The bivariate associations between each category of abnormality and predictor variables are shown in Fig. 2 and supplementary Table A1 (available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc09-1787/DC1>). Age is the only significant predictor of all types of abnormal response. A1C was not associated with any GXT abnormalities.

Greater mean SBP responses were observed for participants who were male, younger, non-Latino, or African American; did not use antihypertensive medications or insulin; and had midrange resting SBP or higher resting diastolic blood pressure (DBP), shorter duration of diabetes, no history of CVD, or BMI <40 kg/m² (Table 2).

Higher workload was attained by participants who were male, younger, or Latino; were not taking blood pressure medications; had lower baseline SBP, higher baseline DBP, shorter durations of diabetes, no history of CVD, or lower BMI; or did not use insulin (Table 2).

CONCLUSIONS — More than one in five (22.5%) Look AHEAD participants had an abnormal GXT despite a pre-screening process that excluded anyone who reported CVD symptoms during the previous 3 months or those with any his-

Table 1—Characteristics of cohort receiving baseline GXT

	Frequency
Sex and age	
Female	3,441 (59.5)
45–54 years	903 (26.2)
55–64 years	1,907 (55.4)
65–76 years	631 (18.3)
Male	2,342 (40.5)
45–54 years	404 (17.2)
55–64 years	1,301 (55.6)
65–76 years	637 (27.2)
Race and ethnicity*	
Latino	731 (12.6)
African American	6 (0.8)
American Indian	2 (0.3)
White	214 (29.3)
Other/multiracial/unknown	509 (69.6)
Not Latino	4,994 (86.4)
African American	914 (18.3)
American Indian	308 (6.2)
White	3,569 (71.5)
Other/multiracial/unknown	203 (4.1)
BMI (kg/m ²)†	
25 to <30	821 (14.2)
30 to <35	2,008 (34.8)
35 to <40	1,618 (28.1)
≥40	1,319 (22.9)
A1C (%)‡	
<7.0	3,118 (54.1)
7.0–8.9	2,133 (37.0)
9.0–10.9	513 (8.9)
Insulin use	
No	4,839 (83.7)
Yes	944 (16.3)
Time with diabetes (years)§	
<5	2,545 (44.4)
5 to <10	1,558 (27.2)
≥10	1,634 (28.5)
CVD history	
No	5,013 (86.7)
Yes	770 (13.3)
SBP (mmHg)	
<120	1,632 (28.2)
120 to <130	1,198 (20.7)
130 to <140	1,264 (21.9)
140 to <150	1,026 (17.7)
150 to <160	663 (11.5)
DBP (mmHg)	
<70	2,762 (47.8)
70–84	2,618 (45.3)
≥85	403 (7.0)
Use of blood pressure medication	
No	1,969 (34.0)
Yes	3,814 (66.0)
Randomized	
No	638 (11.0)
Yes	5,145 (89.0)

Data are n (%). *Ethnicity is missing for 58 participants because of a change in how it was recorded. †BMI is missing for 17 participants. ‡Mean ± SD A1C is 7.10 ± 1.32% (missing from 17 participants). §Self-report (missing from one participant). ||Self-report of prior heart attack, stroke, transient ischemia attack, bypass surgery, angioplasty, endarterectomy, congestive heart failure, or stent.

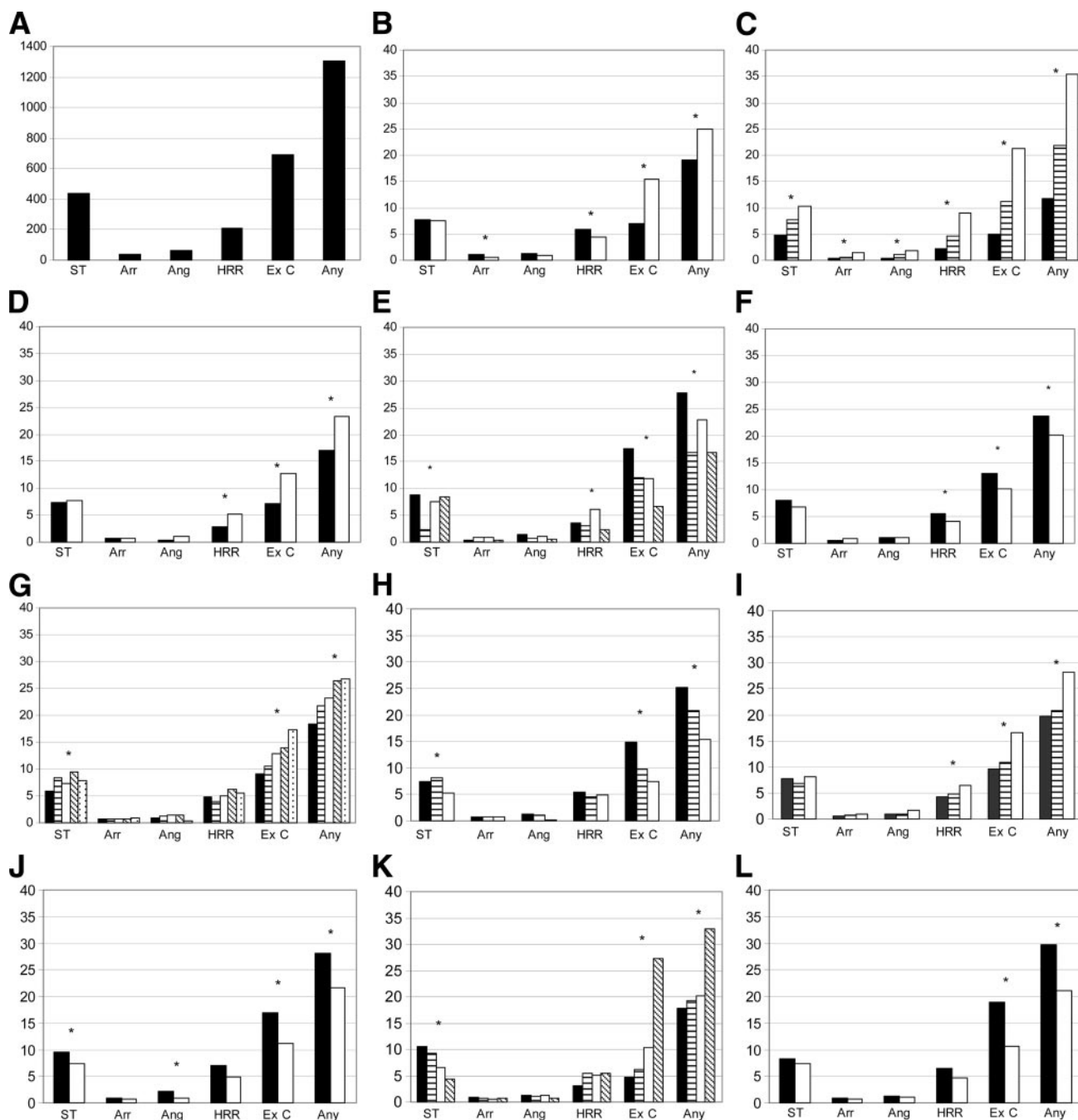


Figure 2—Number or prevalence (%) of abnormal test prevalence by predictor variables. A: Number of abnormal tests. B: Abnormal test prevalence (%) by sex: ■, men; □, women. C: Abnormal test prevalence (%) by age: ■, 45–54 years; ▨, 55–64 years; □, 65–75 years. D: Abnormal test prevalence (%) by ethnicity: ■, Latino; □, not Latino. E: Abnormal test prevalence (%) by race: ■, African American; ▨, American Indian; □, white; ▩, other/multiracial/unknown. F: Abnormal test prevalence (%) by use of blood pressure medicines: ■, yes; □, no. G: Abnormal test prevalence (%) by systolic blood pressure: ■, <120 mmHg; ▨, 120–129 mmHg; □, 130–139 mmHg; ▩, 140–149 mmHg; ▪, 150–159 mmHg. H: Abnormal test prevalence (%) by diastolic blood pressure: ■, <70 mmHg; ▨, 70–84 mmHg; □, at least 85 mmHg. I: Abnormal test prevalence (%) by years with diabetes: ■, <5 years; ▨, 5 to <10 years; □, at least 10 years. J: Abnormal test prevalence (%) by cardiovascular disease history: ■, yes; □, no. K: Abnormal test prevalence (%) by BMI: ■, 25 to <30 kg/m²; ▨, 30 to <35 kg/m²; □, 35 to <40 kg/m²; ▩, at least 40 kg/m². L: Abnormal test prevalence (%) by use of insulin: ■, yes; □, no. *P < 0.05. Ang, Exercise-induced angina; Arr, ventricular arrhythmia (ventricular fibrillation, ventricular tachycardia, runs of at least three premature ventricular beats, or exercise-induced bundle branch block); Any, any abnormality from among those listed; Ex C, impaired exercise capacity (highest achieved workload of <5.0 METs); HRR, heart rate recovery of <22 bpm over 2 min after exercise; ST, ST segment depression of at least 1.0 mm.

tory of several CVD abnormalities. Other studies have sought to determine the prevalence of CVD in individuals with di-

abetes, using various markers for CVD. In the Milan Study on Atherosclerosis in Diabetes (MiSAD) (4,5), all participants had

diabetes and were aged 40–65 years at study entry, and only ST segment changes constituted an abnormal GXT. In MiSAD,

Table 2—Systolic blood pressure response (maximum minus pretest resting) and maximum METs among risk factor subgroups

	SBP response	P	Maximum METs	P
Sex				
Female	55.1 ± 23.5	<0.001	6.7 ± 1.9	<0.001
Male	58.9 ± 23.6		7.9 ± 2.2	
Age (years)				
45 to <55	58.1 ± 22.4	<0.001	7.9 ± 2.1	<0.001
55 to <65	57.6 ± 23.9		7.3 ± 2.1	
65 to <76	52.6 ± 23.6		6.4 ± 1.9	
Ethnicity				
Latino	54.2 ± 22.6	0.003	7.9 ± 2.1	<0.001
Not Latino	57.0 ± 23.7		7.1 ± 2.1	
Race				
African American	59.8 ± 24.2	<0.001	6.7 ± 2.0	<0.001
American Indian	43.9 ± 18.8		7.0 ± 2.1	
White	56.9 ± 23.6		7.2 ± 2.1	
Other/multiracial/unknown	56.9 ± 22.8		8.1 ± 2.2	
Use of blood pressure medications				
Yes	55.9 ± 23.8	0.002	7.0 ± 2.0	<0.001
No	57.9 ± 23.2		7.6 ± 2.3	
SBP (mmHg)				
<120	56.0 ± 22.7	0.01	7.5 ± 2.1	<0.001
120–129	58.3 ± 23.5		7.3 ± 2.1	
130–139	57.3 ± 24.0		7.1 ± 2.1	
140–149	55.6 ± 23.6		7.0 ± 2.1	
150–159	55.1 ± 25.2		6.8 ± 2.0	
DBP (mmHg)				
<70	55.3 ± 24.1	<0.001	6.9 ± 2.0	<0.001
70–84	57.5 ± 23.1		7.4 ± 2.1	
≥85	60.0 ± 23.2		7.8 ± 2.2	
Years with diabetes				
<5	57.8 ± 22.8	<0.001	7.4 ± 2.1	<0.001
5–9	57.3 ± 23.7		7.2 ± 2.1	
≥10	54.0 ± 24.5		6.8 ± 2.1	
CVD history				
Yes	50.9 ± 24.2	<0.001	6.7 ± 2.0	<0.001
No	57.5 ± 23.4		7.3 ± 2.1	
BMI (kg/m ²)				
25 to <30	57.2 ± 22.9	<0.001	8.4 ± 2.4	<0.001
30 to <35	57.6 ± 23.1		7.8 ± 2.0	
35 to <40	57.5 ± 23.4		6.9 ± 1.8	
≥40	53.8 ± 24.8		5.9 ± 1.5	
Insulin use				
Yes	54.4 ± 24.9	0.002	6.6 ± 2.0	<0.001
No	57.0 ± 23.3		7.3 ± 2.1	
A1C (%)				
<7.0	57.0 ± 22.9	0.39	7.2 ± 2.1	0.35
7.0–8.9	56.3 ± 24.5		7.2 ± 2.1	
9.0–10.9	55.8 ± 23.9		7.2 ± 2.0	

Data are means ± SD. No covariate adjustments have been made.

13.2% of the 735 participants had abnormal tests. Although this overall abnormal rate is lower than what we observed, MiSAD had a higher rate of ST segment changes than our population did (7.6%). The Detection of Ischemia in Asymptom-

atic Diabetics (DIAD) (13) study, which evaluated 522 individuals with type 2 diabetes, who were aged 50–75 years and had no history of CVD, found that 113 (22%) had abnormal adenosine perfusion stress tests. To the extent that these mark-

ers approximate true CVD, the prevalence of CVD in middle-aged asymptomatic diabetic adults is likely between 13 and 22%. Our overall rates are consistent with this observation.

Age was the only predictor that showed a consistent association with abnormal tests. Although this is the first description of such a large group of diabetic participants to undergo stress testing, in nondiabetic populations, the association of greater age with GXT abnormalities has been known for several decades (14).

Impaired exercise capacity

Of the participants, 12% were not able to attain a workload of at least 5 METs, with 58% of the abnormal tests due to impaired exercise capacity. Of those who did not achieve at least 5 METs, 73.6% reported a Borg score of at least 19, compared with 83.6% of those who did reach at least 5 METs ($P < 0.001$). Therefore, motivation may have been a factor in poor exercise capacity for some participants.

Ribisl et al. (15) found that among the 5,145 randomized Look AHEAD participants, greater age, higher BMI, and higher A1C predicted lower exercise capacity. The present analysis, which includes participants not randomized and thus may represent a broader and potentially more generalizable cross-section of the diabetic population, also adds analysis of ECG and blood pressure variables. In contrast to the report of Ribisl et al., the association between A1C and impaired exercise capacity is not present in this larger sample.

Myers et al. (2) showed that in 6,213 men referred for a clinical exercise test, 25.5% failed to achieved a maximal exercise capacity of 5 METs, and those with diabetes had an age-adjusted relative mortality risk from any cause of ~2.3 (95% CI 1.5–3.5) compared with those who achieved >8 METs. In our study, the lower prevalence (12%) of impaired exercise capacity may be explained in part by population differences. Participants in the study of Myers et al. underwent exercise testing for clinical reasons, which included symptomatic CVD or other conditions for which potential participants in Look AHEAD were excluded before stress testing.

This analysis showed divergent directions of association between SBP and DBP and impaired exercise capacity. These bivariate associations persist in regression models in which SBP and DBP are controlled for each other. Elevated SBP is a well-recognized risk factor for CVD and

has been associated with decreased exercise endurance (16). Sufficiently elevated DBP is also a diagnostic criterion for hypertension and is associated with adverse CVD events (17) and ischemia (4). However, in older populations, lower DBP is associated with CVD (18) and is believed to result from decreased compliance of the aorta and its large branches due to atherosclerotic disease (19). Wider pulse pressure has been shown to be a strong predictor of CVD events in older individuals with type 2 diabetes (20). Some younger Look AHEAD participants may be expected to have less central atherosclerotic burden and, hence, better arterial compliance, on the basis of age alone. However, all participants had type 2 diabetes. The clear association of lower DBP with abnormal GXTs in this population suggests that decreased arterial compliance may originate at an earlier age in individuals with diabetes.

ECG changes

ST segment depression of at least 1.0 mm is a recognized threshold for an abnormal ECG response to exercise. This definition provides a sensitivity of 45% and a specificity of 85% for coronary artery disease diagnosed by angiography (21). Factors associated with an increased risk of ST segment depression and ventricular arrhythmia included greater age and lower BMI. Greater age is a known CVD risk factor. The association of lower BMI with ECG changes may be explained by the increased rate of impaired exercise capacity with higher BMI. Those with a lower BMI exercised to a higher level (Table 2), creating a greater cardiac stress, which increased the chance of detecting ST segment changes or arrhythmias.

Angina

The recent acknowledgment that diabetes imparts risk of CVD events equivalent to a known history of CVD (22) makes our observed rate of angina seem low (1.1%) for a cohort of individuals with diabetes aged >45 years. However, before the GXT, we excluded potential participants who reported recent angina. The expected rate of angina in this population is unknown. Nevertheless, our data show that even in asymptomatic overweight or obese adults with diabetes who have been carefully screened for cardiovascular symptoms, angina still occurs with maximal stress testing, albeit at a rate of 1.1%.

Hemodynamic response

Abnormal heart rate recovery occurred in 5.0% of participants undergoing stress testing. Many of the predictors of abnormal heart rate recovery we found are known risk factors for CVD (22). Abnormal heart rate recovery was associated with higher BMI. As discussed, those with lower BMI exercised to higher MET levels than those with higher BMI. However, those with higher BMI routinely demonstrate higher workloads for more routine tasks. This higher inherent workload leads to a higher catecholamine state, which causes less difference between baseline and peak exercise heart rate and a slower heart rate recovery after exercise. In fact, our data confirm our conclusion. Higher BMI was associated with a higher resting and first-stage exercise heart rate and a smaller increase in heart rate from resting to peak exercise ($P < 0.001$ in each case, data not shown).

Others have proposed that either an exaggerated (23) or a low (7,24) SBP response may reflect underlying cardiovascular abnormalities. The cross-sectional data presented here do not settle the question of whether a larger or smaller SBP response to exercise increases CVD risk. However, because greater age was associated with every category of established abnormality that we examined and greater age was associated with lower SBP response, it is conceivable that a lower SBP response is associated with higher risk of adverse CVD outcomes.

Implications of results on future Look AHEAD study outcomes

Look AHEAD GXT eligibility criteria were adopted for participant safety, given that unsupervised exercise training was part of the study intervention. These tests eliminated 638 potential participants: 11.1% of those reaching the final stage of screening and 49% of those who had abnormal GXT results. These criteria may reduce the rate of the trial's primary end point and the generalizability of the findings.

Limitations

For the first year of testing, data forms included text fields for "significant ST segment changes" and angina; however, these responses were not required. This approach was changed thereafter to require physicians to indicate the degree of ST depression. Independent reviews by an experienced exercise physiologist and a clinician experienced in GXT were conducted for all tests that included at least

1.0 mm of ST depression and the 405 instances when physicians noted ST depression but did not quantify it. The 180 instances for which these two reviewers disagreed were resolved by a cardiologist independent of Look AHEAD, whose decision was final. We did not have sufficient data to comment on ST segment slope. Full data were not available for the 638 participants who were deemed ineligible for randomization into Look AHEAD by physicians who supervised their GXTs, but whose results are included in this analysis, which may have led to an underestimation of abnormality rates.

Because the present analysis is concerned with baseline data in Look AHEAD, follow-up outcome data on the participants are not available for this report. Those with clinically significant abnormalities were referred to their physicians.

Some clinicians may argue that our definition of abnormal GXT results may more accurately be termed predictors of CVD events or CVD mortality. Whether heart rate recovery and maximal achieved workload should be used to define abnormality or simply be included among a list of risk criteria is certainly open for debate; however, for simplicity, we included these factors in what we termed abnormal.

Summary

Among a large cohort of overweight and obese individuals with type 2 diabetes, 22.5% had abnormal stress tests by ECG, angina, heart rate recovery, or exercise capacity criteria despite thorough pretest screening. Diminished exercise capacity is the most common abnormality in this cohort, occurring at nearly twice the rate of any other abnormality. The most consistent risk factor for any type of abnormality is older age, which is even a more consistent risk factor than duration of diabetes or history of CVD. These results support heightened vigilance for CVD in older patients with diabetes. Continued follow-up in these individuals as part of the Look AHEAD study will determine whether any of these abnormalities during exercise testing are accurate predictors of subsequent cardiovascular events.

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