

# Association of Fasting Plasma Glucose With Heart Rate Recovery in Healthy Adults

## A Population-Based Study

Claudia Panzer,<sup>1</sup> Michael S. Lauer,<sup>2</sup> Andreas Brieke,<sup>1</sup> Eugene Blackstone,<sup>3,4</sup> and Byron Hoogwerf<sup>5</sup>

**Diabetes is associated with abnormal autonomic function and increased mortality. Abnormal heart rate recovery after exercise, a measure of autonomic dysfunction, is also associated with increased mortality. The objective of this study was to determine the association of fasting plasma glucose with abnormal heart rate recovery and its prognostic importance in healthy adults. We studied 5,190 healthy adults who did not have medically treated diabetes (mean age 45 years, 39% women), were enrolled in the Lipid Research Clinics' Prevalence Study, and underwent exercise testing. Heart rate recovery was defined as the change from peak heart rate to that after 2 min of recovery; an abnormal value was  $\leq 42$  bpm. All-cause mortality was assessed over 12 years. A total of 504 participants (10%) had impaired fasting glucose, and 131 (3%) had untreated diabetes. An abnormal heart rate recovery was found in 1,699 (33%). Compared with participants who had normal fasting plasma glucose, abnormal heart rate recovery was more common among those with impaired fasting glucose (42 vs. 31%; relative risk, 1.34; 95% confidence interval [CI], 1.20–1.50;  $P < 0.0001$ ) and those with diabetes (50 vs. 31%; relative risk, 1.61; 95% CI, 1.35–1.92;  $P < 0.0001$ ). Fasting plasma glucose remained an independent predictor of abnormal heart rate recovery even after adjustment for age, sex, and other confounders ( $P = 0.0003$ ). An abnormal heart rate recovery added to impaired fasting plasma glucose for the prediction of death. Fasting plasma glucose is strongly and independently associated with abnormal heart rate recovery, even at nondiabetic levels. *Diabetes* 51:803–807, 2002**

From the <sup>1</sup>Department of Internal Medicine, Cleveland Clinic Foundation, Cleveland, Ohio; the <sup>2</sup>Department of Cardiology, Cleveland Clinic Foundation, Cleveland, Ohio; the <sup>3</sup>Department of Cardiothoracic Surgery, Cleveland Clinic Foundation, Cleveland, Ohio; the <sup>4</sup>Department of Biostatistics and Epidemiology, Cleveland Clinic Foundation, Cleveland, Ohio; and the <sup>5</sup>Department of Endocrinology, Cleveland Clinic Foundation, Cleveland, Ohio.

Address correspondence and reprint requests to Michael S. Lauer, MD, FACC, Director of Clinical Research and Stress Laboratory, Department of Cardiology, Desk F-25, Cleveland Clinic Foundation, Cleveland, OH 44195. E-mail lauerm@ccf.org

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<sup>1</sup>Formula in SI Units was derived from the original model in which a decrease of (500/glucose) by one corresponded to an increase in plasma glucose of  $\sim 25$  mg/dl at a level of 100 mg/dl.

**D**iabetes and impaired fasting glucose are associated with increased mortality, particularly from cardiovascular causes (1–3). Diabetes is frequently complicated by an autonomic neuropathy (4), which can be detected by noting reduced heart rate variability (5,6). The Framingham Heart Study demonstrated a reduction of heart rate variability, along with a sympathetic-parasympathetic imbalance, not only in patients with diabetes but also in individuals with impaired fasting glucose (7).

Abnormal heart rate recovery after exercise is an easy-to-measure marker of reduced parasympathetic activity (8,9) and has been found to be an independent predictor of mortality in submaximal as well as in symptom-limited exercise stress testing (10–12). Given the known associations among diabetes, impaired fasting glucose, and autonomic dysfunction, we hypothesized that increasing levels of fasting glucose would be associated with higher rates of abnormal heart rate recovery and that this association would be of prognostic importance. We tested these hypotheses in a healthy, population-based cohort of adults who did not have medically treated diabetes.

### RESEARCH DESIGN AND METHODS

**Population sample.** The study population, derived from the Lipid Research Clinics Prevalence Study, a cross-sectional survey among North Americans assembled to determine the prevalence of dyslipidemia and its association with diet and coronary artery disease, has been described in detail elsewhere (13,14). Between 1972 and 1976, fasting plasma cholesterol and triglyceride levels of 48,431 white men and women were measured at a baseline visit at 10 participating centers in the U.S. and Canada. Participants were invited for a second visit if they were part of a 15% randomly selected sample or if lipid abnormalities were present. At this second visit, 13,852 participants underwent a detailed evaluation that included exercise testing and various blood tests, including fasting plasma glucose. A detailed medical, family, and drug history was obtained, and information regarding smoking, alcohol use, exercise habits, and educational status was elicited. Systolic and diastolic blood pressure, height, weight, and lipid profiles were measured.

The study cohort for this analysis included adults who were  $>30$  years of age and who underwent an exercise test. People with medically treated diabetes were excluded. We also excluded people with known cardiovascular disease, symptomatic peripheral vascular disease, and a history of cardiac arrhythmias.

**Exercise testing.** Eligible participants underwent exercise testing according to the modified Bruce protocol with seven 3-min stages in which the speed and inclination were increased in a stepwise manner (stage 1: 2.7 km/h and 10% inclination; stage 2: 4 km/h and 12% inclination; stage 3: 5.5 km/h and 14% inclination) (13). Electrocardiogram and heart rate were monitored continuously, whereas blood pressure was assessed at the end of each stage. Stress testing was continued until participants reached and maintained 90% of their age-predicted maximum heart rate for 1 min; participants aborted before the

TABLE 1  
Baseline characteristics according to fasting plasma glucose groups

Characteristic	<6.1 mmol/l (n = 4,555)	6.1–6.9 mmol/l (n = 504)	≥7.0 mmol/l (n = 131)	P
Age (years)	44 ± 10	48 ± 10	50 ± 9	<0.0001
Female sex [n (%)]	1,882 (41)	107 (21)	34 (26)	0.001
White ethnicity [n (%)]	4,373 (96)	485 (96)	121 (92)	0.108
BMI (kg/m <sup>2</sup> )	26 ± 4	27 ± 4	30 ± 4	<0.0001
Resting heart rate (bpm)	80 ± 13	81 ± 14	85 ± 14	0.0034
Resting systolic blood pressure (mmHg)	125 ± 17	135 ± 18	141 ± 20	<0.0001
Antihypertensive treatment [n (%)]	222 (5)	58 (12)	16 (12)	0.001
Fasting plasma glucose (mmol/l)	5.2 ± 0.4	6.3 ± 0.2	9.1 ± 3.3	<0.0001
Cholesterol level (mmol/l)	5.7 ± 1.1	6.0 ± 1.2	6.4 ± 1.5	<0.0001
HDL cholesterol	1.3 ± 0.4	1.2 ± 0.4	1.1 ± 0.4	<0.0001
LDL cholesterol	3.8 ± 1.1	3.9 ± 1.1	3.8 ± 1.1	<0.0033
Triglycerides	1.6 ± 1.1	2.3 ± 2.0	4.0 ± 3.8	<0.0001
Current smoker [n (%)]	1,663 (37)	163 (32)	41 (31)	0.095
Alcohol (g/week)	12 ± 17	19 ± 23	16 ± 21	<0.0001
Exercise at least three times a week [n (%)]	899 (20)	106 (21)	25 (19)	0.768
Regularly engage in strenuous exercise [n (%)]	1,109 (24)	125 (25)	31 (24)	0.957
Education level [at least some college; n (%)]	2,186 (48)	282 (56)	50 (38)	0.001

Continuous variables are presented as the means ± SD; categorical variables are presented as n (%) of patients.

attainment of the target heart rate because of chest pain, fatigue, dyspnea, leg pain, or electrocardiogram abnormalities (≥1 mm horizontal ST-segment change, major arrhythmia, conduction defects); a decrease in systolic blood pressure; technical difficulties occurred; or participants requested to stop. Immediately after exercise, participants were seated. Heart rate and blood pressure were measured immediately after exercise and again 2 min into recovery.

**Determination of heart rate recovery and physical fitness.** Heart rate recovery was defined as the change from peak heart rate to that measured after 2 min of recovery. A cutoff value of ≤42 bpm was considered abnormal; as we have previously described in a very similar population, this cutoff value yielded the highest log-rank statistic of all those tested between the 10th and 90th percentiles (10). Physical fitness was assessed by noting the heart rate measured at stage 2 of the exercise test, with low physical fitness defined as being in the highest quartile of heart rate at stage 2 of the exercise test for sex and decade of age (13).

**Determination of fasting plasma glucose.** At the second visit, clinical plasma chemistry values for glucose, AST, alkaline phosphatase, thyroxine, total bilirubin, total globulin, uric acid, and creatinine were obtained. Participants reported to the Lipid Research Center after an overnight fast of at least 12 h. Serum and plasma samples were, after centrifugation, frozen at –20°C and shipped either to the Central Clinical Chemistry, Laboratory Procedures Division of the Upjohn Company (King of Prussia, PA) or to the BioScience Laboratories (Van Nuys, CA). At Laboratory Procedures, plasma glucose was measured by the ferricyanide method in a single channel AutoAnalyzer. At BioScience Laboratories, plasma glucose was measured on the ABA-100 by a hexokinase method (15).

**Follow-up.** In 1977, the Lipid Research Clinics' mortality follow-up study of all participants who were examined at visit 2 and who were ≥30 years of age was begun to assess subsequent overall and specific cause mortality. The surveillance was carried out annually by mail and telephone. In the case of death, death certificates were reviewed and the cause of death was evaluated by interviewing physicians or next of kin. Mean follow-up was 12 years with 99% completeness for assessment of vital status.

**Statistical analysis.** For descriptive purposes, we divided the study population into three groups according to fasting glucose levels of <6.1 mmol/l, 6.1–6.9 mmol/l, and ≥7.0 mmol/l (16). Differences in baseline and exercise characteristics were tested using Kruskal-Wallis and  $\chi^2$  tests, as appropriate. Prevalence ratios and confidence intervals relating the frequency of an abnormal heart rate recovery to fasting glucose level were calculated. Participants were then divided into prespecified fasting glucose strata of 3.9–4.4, 4.4–4.9, 5.0–5.5, 5.6–6.1, 6.1–6.9, and ≥7.0 mmol/l. Within each stratum, the prevalences of an abnormal heart rate and low physical fitness were calculated; the Mantel-Haenszel extension test was used to test for trends (17). Logistic regression modeling (18) was used to assess the impact of potential confounders on the association between blood glucose levels and an abnormal heart rate recovery. Prespecified confounding and/or interacting variables included age, sex, BMI, resting heart rate, resting systolic blood pressure, antihypertensive treatment, HDL and LDL cholesterol, triglycerides,

alcohol consumption, and education level. We carefully tested for possible interactions and used transformations of blood glucose levels, considered as a continuous variable, in our analyses. Goodness of fit was assessed by the Hosmer-Lemeshow statistic, a statistical method to assess how well an applied model fits the actual data. A large P value in the Hosmer-Lemeshow statistic suggests that the model is well-calibrated and fits the data well (18). We evaluated the association of fasting plasma glucose and mortality, stratified for the presence or absence of an abnormal heart rate recovery, using the Kaplan-Meier curves (19) and Cox proportional hazards analyses. All analyses were performed using the SAS system (Versions 6.12 and 8.1; SAS, Cary, NC).

## RESULTS

**Baseline and exercise characteristics.** Of the 2,023 women and 3,167 men who were eligible for analysis, 504 adults (10%) met the criteria for impaired fasting plasma glucose, and 131 (3%) were classified as having untreated diabetes. Baseline characteristics according to fasting plasma glucose are shown in Table 1. Participants with impaired and diabetic fasting plasma glucose levels were older; were less likely to have some college education or to be female; drank more alcohol; and had higher BMI, resting heart rates, and resting systolic blood pressures. They were more likely to be taking antihypertensive treatment and to have higher triglycerides and total cholesterol levels with decreased HDL-cholesterol levels.

Exercise findings according to fasting plasma glucose are summarized in Tables 2 and 3. Compared with men with normal glucose levels, male participants with elevated fasting plasma glucose had lower peak workloads and higher heart rates at stage 2. Peak heart rates and heart rate recovery values were lower, whereas peak systolic blood pressures were higher with higher levels of fasting glucose. Ischemic ST-segment response was not significantly different in the three groups. The same findings were true for women, with the exception of heart rate at stage 2 (Table 3).

**Fasting plasma glucose, heart rate recovery, and physical fitness.** Compared with subjects with normal fasting plasma glucose, an abnormal heart rate recovery was more frequent among individuals with an impaired

TABLE 2  
Exercise characteristics of men ( $n = 3,167$ ) according to fasting plasma glucose groups

Characteristic	<6.1 mmol/l ( $n = 2,673$ )	6.1–6.9 mmol/l ( $n = 397$ )	$\geq 7.0$ mmol/l ( $n = 97$ )	<i>P</i>
Peak workload (MET)	11.1 $\pm$ 2.2	10.1 $\pm$ 2.3	9.9 $\pm$ 2.4	<0.0001
Heart rate recovery (bpm)	49 $\pm$ 14	46 $\pm$ 14	43 $\pm$ 13	<0.0001
Heart rate at stage 2 (bpm)	133 $\pm$ 18	137 $\pm$ 16	138 $\pm$ 15	<0.0001
Peak heart rate (bpm)	162 $\pm$ 15	160 $\pm$ 15	157 $\pm$ 15	<0.0001
Peak systolic blood pressure (mmHg)	172 $\pm$ 27	182 $\pm$ 30	193 $\pm$ 32	<0.0001
Low physical fitness [ $n$ (%)]	625(23)	123(31)	27(28)	0.003
Abnormal heart rate recovery [ $n$ (%)]	873(33)	167(42)	48(50)	0.001
Ischemic ST-segment response	74(3)	19(5)	3(3)	0.10

\* Continuous variables are presented as the means  $\pm$  SD; categorical variables are presented as  $n$  (%) of patients.

fasting glucose (42 vs. 31%; prevalence ratio, 1.34; 95% confidence interval [CI], 1.20–1.50;  $P < 0.0001$ ). This finding was even more frequent among participants with frank diabetes (50 vs. 31%; prevalence ratio, 1.61; 95% CI, 1.35–1.92;  $P < 0.0001$ ).

Figure 1 depicts the prevalence of abnormal heart rate recovery and low physical fitness as a function of plasma glucose. The prevalence of an abnormal heart rate recovery increased with rising plasma glucose levels, even at glucose levels <6.1 mmol/l ( $\chi^2$  trend 107,  $P = 0.001$ ). There was also an association between increasing levels of plasma glucose and low physical fitness, but this association was weaker ( $\chi^2$  trend 9,  $P = 0.003$ ).

We tested the association of plasma glucose and abnormal heart rate recovery for possible interactions with the prespecified variables of age, sex, race, BMI, resting systolic blood pressure, HDL cholesterol, smoking, regular physical activity, and resting heart rate. We found a strong interaction between plasma glucose and resting heart rate for prediction of abnormal heart rate recovery ( $P$  for interaction = 0.0008). As shown in Fig. 2, we found a minimal association between plasma glucose and heart rate recovery among participants with resting heart rates below the median value of 80 bpm, whereas a strong association was present among participants with resting heart rates  $\geq 80$  bpm.

When fasting plasma glucose was analyzed as a continuous variable, we again noted a strong correlation of fasting plasma glucose levels and impaired heart rate recovery. An increase of plasma glucose of 1.4 mmol/l was associated with a 1.34-fold risk of the odds of impaired heart rate recovery (95% CI, 1.24–1.46;  $\chi^2 = 51$ ;  $P < 0.0001$ ; Hosmer-Lemeshow statistic 30<sub>8</sub>,  $P = 0.0002$ ). We tested three different transformations of plasma glucose in other

unadjusted models: logarithmic, exponential, and inverse. We found a strong association of plasma glucose with abnormal heart rate recovery for all models, but by far the best model fit was seen with inverse transformation of glucose. A decrease of (27.8/glucose) by 1, corresponding to an increase in plasma glucose of 1.4 mmol/l at a level of 5.6 mmol/l, was associated with an odds ratio (OR) of 1.63 (95% CI, 1.48–1.79;  $\chi^2 = 105$ ;  $P < 0.0001$ ; Hosmer-Lemeshow statistic 5.6<sub>8</sub>,  $P = 0.69$ ) for prediction of an abnormal heart rate recovery<sup>(1)</sup>.

**Fasting plasma glucose, heart rate recovery, and all-cause mortality.** During the 12-year follow-up period, there were 238, 54, and 23 deaths in the normal plasma glucose, impaired fasting plasma glucose, and diabetic group, respectively. When participants with normal plasma glucose and impaired plasma glucose were classified by the presence or absence of an abnormal heart rate recovery, those with both an abnormal heart rate recovery and impaired fasting glucose had markedly greater mortality (Fig. 3). In age- and sex-adjusted analysis, participants with an abnormal heart rate recovery in the normal plasma and impaired fasting plasma glucose group had similar mortality ratios (hazard ratio, 1.8; 95% CI, 1.4–2.3;  $P < 0.0001$ ; and 1.7; 95% CI, 1.0–2.9;  $P < 0.0001$ , respectively). An abnormal heart rate recovery added to impaired fasting plasma glucose for the prediction of death (age- and sex-adjusted hazard ratio for both abnormalities: 2.4, 95% CI, 1.6–3.5;  $P < 0.0001$ ).

**Multivariable analysis.** Fasting plasma glucose remained an independent predictor of abnormal heart rate recovery after adjustment for age, sex, BMI, resting heart rate, resting systolic blood pressure, antihypertensive treatment, HDL and LDL cholesterol, triglycerides, alcohol consumption, and education level (adjusted OR for de-

TABLE 3  
Exercise characteristics of women ( $n = 2,023$ ) according to fasting plasma glucose groups

Characteristic	<6.1 mmol/l ( $n = 1882$ )	6.1–6.9 mmol/l ( $n = 107$ )	$\geq 7.0$ mmol/l ( $n = 34$ )	<i>P</i>
Peak workload (MET)	8.9 $\pm$ 2.1	8.3 $\pm$ 1.6	8.0 $\pm$ 1.9	<0.0006
Heart rate recovery (bpm)	50 $\pm$ 15	45 $\pm$ 16	45 $\pm$ 15	<0.0001
Heart rate at stage 2 (bpm)	148 $\pm$ 17	147 $\pm$ 17	149 $\pm$ 16	0.8734
Peak heart rate (bpm)	160 $\pm$ 16	153 $\pm$ 19	156 $\pm$ 18	<0.0001
Peak systolic blood pressure (mmHg)	163 $\pm$ 26	171 $\pm$ 26	186 $\pm$ 35	<0.0001
Low physical fitness [ $n$ (%)]	401(21)	10(9)	10(29)	0.006
Abnormal heart rate recovery [ $n$ (%)]	549(29)	44(41)	18(53)	0.001
Ischemic ST-segment response	78(4)	8(8)	2(2)	0.14

\* Continuous variables are presented as the means  $\pm$  SD; categorical variables are presented as  $n$  (%) of patients.

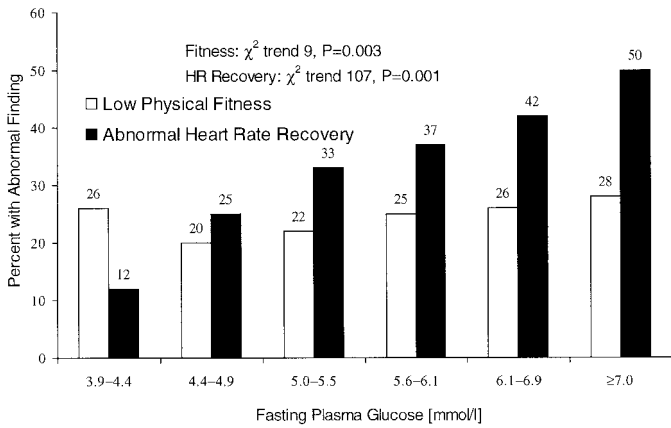


FIG. 1. Fitness variables according to fasting plasma glucose groups.

crease of glucose of (27.8/glucose) by 1, 1.17; 95% CI, 1.05-1.30;  $\chi^2 = 9$ ;  $P = 0.003$ )<sup>(1)</sup>. Among patients with a resting heart rate of at least the median value of 80 bpm, the association between fasting plasma glucose and heart rate recovery was stronger (adjusted OR, 1.35; 95% CI, 1.17-1.55;  $\chi^2 = 17$ ;  $P < 0.0001$ ), whereas no significant association was noted among those with a resting heart rate  $< 80$  bpm. After similar adjustments, fasting plasma glucose was no longer an independent predictor of low physical fitness.

DISCUSSION

In a population-based cohort of healthy adults, fasting plasma glucose was strongly associated with an abnormal heart rate recovery, even after adjusting for confounding factors. The association between fasting plasma glucose and heart rate recovery was particularly evident among those with resting heart rates  $\geq 80$  bpm. An abnormal heart rate recovery was of the same predictive significance in participants with normal plasma glucose and with impaired fasting glucose and acted additively to impaired fasting plasma glucose for the prediction of death. The weaker association between fasting plasma glucose and low physical fitness was no longer present after adjustment for confounding variables.

This report is, to our knowledge, the first to evaluate the

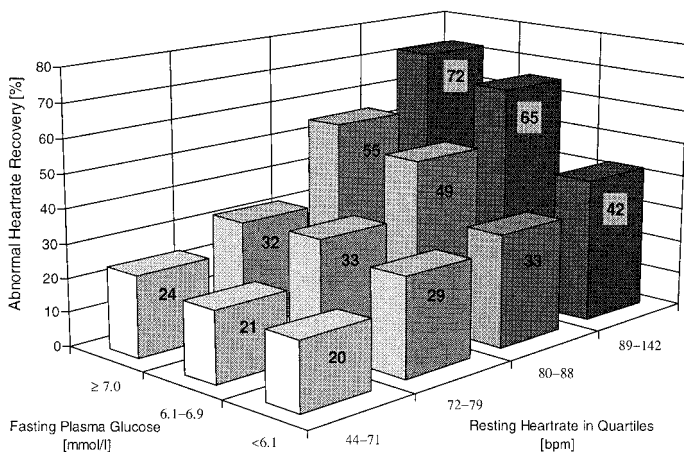
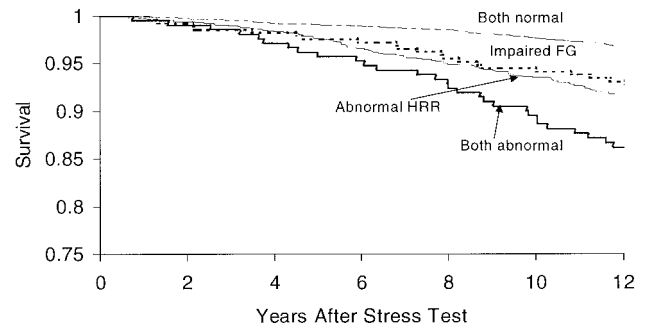


FIG. 2. Interaction between plasma glucose and resting heart rate for prediction of abnormal heart rate recovery.



No at Risk	3,131	3,127	3,120	3,111	3,106	3,101	3,092	3,089	3,075	3,061	3,049	3,037	3,023
Both normal	293	291	289	288	286	285	283	280	277	276	275	273	271
Impaired FG	1,422	1,417	1,411	1,403	1,393	1,378	1,365	1,354	1,346	1,335	1,322	1,310	1,299
Abnl HRR	211	210	209	206	203	202	200	197	193	190	186	183	180
Both abnl													

FIG. 3. Kaplan-Meier survival curves of the effects of abnormal heart rate recovery and impaired fasting glucose on all-cause mortality.

relationship between fasting plasma glucose and an abnormal heart rate recovery. In previous studies, the association of autonomic dysfunction with diabetes was evaluated by power spectral analysis of heart rate variability (20). The frequency components of heart rate variability can partially distinguish parasympathetic from sympathetic influences on the heart (5,20). The Framingham Heart Study evaluated heart rate variability across the spectrum of fasting plasma glucose (7) and found a reduction in heart rate variability in participants with diabetes as well as in participants with impaired fasting glucose.

Our current study adds to these findings in several important respects. First, fasting plasma glucose was strongly associated with an easily measured marker of autonomic dysfunction, namely abnormal heart rate recovery, which in previous studies was shown to be a powerful and independent predictor of all-cause mortality (10-12). Second, the strong and independent association between fasting plasma glucose and abnormal heart rate recovery extended below diabetic and even impaired fasting glucose levels. Third, heart rate recovery further risk-stratified participants with impaired fasting glucose. An abnormal heart rate recovery added to impaired fasting glucose for the prediction of death.

The mechanism by which fasting plasma glucose is associated with abnormal heart rate recovery is unclear. During recovery from exercise, vagal reactivation is primarily responsible for the acute reduction in heart rate (9). Impaired heart rate recovery is therefore indicative of parasympathetic dysfunction. The recent report from the Framingham Heart Study noted that increasing levels of fasting plasma glucose were associated with a progressive decrease in vagal tone (7). Thus, our results may well reflect subtle changes of sympathetic and parasympathetic balance that occur with even minimal abnormalities of glucose metabolism. Whether these changes in autonomic function are due to elevated glucose levels themselves is not clear (21). Some groups have suggested that plasma insulin levels are more closely correlated with autonomic neuropathy (22-24). A recent report showed that reduced insulin levels resulting from weight loss were associated with improvements of autonomic function; this group also noted that increases in plasma insulin levels correlated with decreased vagal tone, increased sympathetic tone, and impaired baroreflex activity (25).

The clinical and therapeutic implications of our findings are unclear. Early cardiac autonomic neuropathy in patients with type 1 diabetes, evaluated by heart rate variability, was favorably altered by improved glycemic control (26). The results of our current study, along with our previous observations about the prognostic importance of an abnormal heart rate recovery, suggest that exercise testing could be useful for risk stratification among patients with impaired fasting glucose, diabetes, and maybe even high normal glucose levels. Additional research will be needed to test this hypothesis. Furthermore, it is not clear whether therapy specifically designed to improve either glycemic control or autonomic function (e.g., with beta blockers) in such patients will improve long-term outcome.

Our study has several limitations. First, the exercise tests in the Lipid Research Clinics Prevalence Study were submaximal, not symptom-limited. Thus, our ability to assess the association between physical fitness and fasting blood glucose was limited. In addition, we could not reliably analyze the association of maximum heart rate with heart rate recovery. Second, recovery heart rate was measured at 2 min rather than at 1 min, which is most reflective of the parasympathetic influence on heart rate control (8). Third, even though the study cohort was population-based, it may not reflect the general population, as its main purpose was to assess the relation of lipid abnormalities to subsequent mortality. Fourth, we have no information on insulin levels, insulin resistance, or other measures of glycemia (e.g., meal- or glucose-stimulated glucose or glycated hemoglobin), as these parameters were not obtained or available in the Lipid Research Clinics Prevalence Study. Future research will be needed to determine whether the autonomic abnormalities noted during exercise testing among patients with elevated blood glucose are due to hyperglycemia itself, hyperinsulinemia, or any of a number of the well-known metabolic abnormalities associated with hyperinsulinemia. Fifth, we did not perform formal gas exchange measurement or obtain lactic acid levels, so we could not determine whether anaerobic threshold was reached. Finally, we did not measure serum catecholamines, which may have influenced heart rate dynamics during late exercise and early recovery.

Despite these limitations, we found that fasting plasma glucose was a strong and independent predictor of abnormal heart rate recovery, an easy-to-measure exercise laboratory parameter for assessment of autonomic dysfunction. Future research is needed to determine how best to incorporate heart rate recovery into the risk stratification of patients with impaired fasting glucose and diabetes.

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