

Diabetes, Glucose, Insulin, and Heart Rate Variability

The Atherosclerosis Risk in Communities (ARIC) study

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OBJECTIVE — To describe the progression of autonomic impairment among individuals with diabetes and pre-diabetic metabolic impairments.

RESEARCH DESIGN AND METHODS — We investigated the consequence of diabetes and pre-diabetic metabolic impairments on the 9-year change in heart rate variability (HRV) in a population-based cohort of 6,245 individuals aged 45–64 years at baseline and cross-sectional associations among 9,940 individuals.

RESULTS — Diabetic subjects had a more rapid temporal decrease in HRV conditional on baseline HRV than nondiabetic subjects. Adjusted mean annual changes (95% CI) (ms/year) in the SD of all normal-to-normal R-R intervals were -0.65 (-0.69 to -0.61) for those with normal fasting glucose vs. -0.95 (-1.09 to -0.81) for diabetic subjects, in root mean square of successive differences in normal-to-normal R-R intervals -0.35 (-0.39 to -0.30) vs. -0.66 (-0.82 to -0.51), and in R-R interval 6.70 (6.37 – 7.04) vs. 3.89 (2.72 – 5.05). While we found cross-sectional associations between decreased HRV and diabetes and nondiabetic hyperinsulinemia and a weak inverse association with fasting glucose, neither impaired fasting glucose nor nondiabetic hyperinsulinemia was associated with a measurably more rapid decline in HRV than normal.

CONCLUSIONS — Cardiac autonomic impairment appears to be present at early stages of diabetic metabolic impairment, and progressive worsening of autonomic cardiac function over 9 years was observed in diabetic subjects. The degree to which pre-diabetic metabolic impairments in insulin and glucose metabolism contribute to decreases in cardiac autonomic function remains to be determined.

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; HF, high-frequency power; HRV, heart rate variability; IFG, impaired fasting glucose; LF, low-frequency power; NFG, normal fasting glucose; rMSSD, root mean square of successive differences in normal-to-normal R-R intervals; SDNN, SD of all normal-to-normal R-R intervals.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Diabetic autonomic neuropathy is a frequent cause of morbidity and mortality among diabetic individuals (1–5) and is characterized by widespread neurological degeneration affecting the small nerve fibers of the parasympathetic and sympathetic branches of the autonomic nervous system (1). Autonomic nervous system abnormalities may occur quite early in the course of diabetes, followed by a continued gradual decline (1,6–9). Early detection of subclinical autonomic dysfunction in diabetic individuals is important for risk stratification and subsequent management, possibly including pharmacologic and lifestyle interventions (10).

Heart rate variability (HRV) can detect cardiac autonomic impairment in diabetic individuals before traditional cardiovascular autonomic function tests such as the Ewing battery (11–13). Although the natural history of the Ewing battery performance has been described (11,14–19), little is known about the progression of autonomic neuropathy as measured by HRV. While several large population-based cohorts have reported associations between low HRV and prevalent diabetes (20–23), the longitudinal effect of diabetes on HRV has not been examined. Furthermore, the influence of insulin resistance and glucose tolerance on HRV among nondiabetic subjects has not been determined.

This study describes the natural history of HRV in diabetes in the Atherosclerosis Risk in Communities (ARIC) cohort. Over 9 years of follow-up, we examined HRV in individuals with normal fasting glucose (NFG), impaired fasting glucose (IFG), diabetes, and nondiabetic hyperinsulinemia.

RESEARCH DESIGN AND METHODS

The ARIC study is a multicenter prospective study of the natural history and etiology of atherosclerotic and cardiovascular disease event rates in four U.S. communities. The study population was selected as a probability

sample of 15,792 men and women aged 45–64 years from Forsyth County, NC (12% black); Jackson, MS (100% black); selected suburbs of Minneapolis, MN; and Washington County, MD (24). The ARIC study has been described elsewhere (24,25). Eligible participants were interviewed at home and then invited to a baseline clinical examination (1987–1989) and three triennial follow-up clinical examinations. HRV was measured at the baseline and final follow-up exams. Diabetes status was assessed at each exam.

Assessment of cardiac autonomic control

HRV was assessed via 2- and 6-min beat-to-beat heart rate recordings taken ~9 years apart. The use of short-term HRV recordings is supported by a 1996 consensus statement (10). The baseline 2-min and follow-up 6-min beat-to-beat R-R interval data were collected while resting and supine, according to similar standardized protocols (26–29). Data processing, artifact identification and imputation, and quality control exclusions have been described, as well as a comparison of measurement properties of the 2- and 6-min records (25,30). We only examined time domain measures (the mean normal-to-normal R-R interval length [ms], the SD of all normal-to-normal R-R intervals [SDNN (ms)], and the root mean square of successive differences in normal-to-normal R-R intervals [rMSSD (ms)]) because our method for dealing with the different length recordings was suboptimal for frequency domain measures (25). SDNN reflects total variability, while rMSSD estimates high frequency variations in heart rate and primarily reflects parasympathetic activity (10). While SDNN and rMSSD measure fluctuations in autonomic nervous system activity, the mean R-R interval length measures the sum of parasympathetic and sympathetic influences.

After a 12-h fast, blood was drawn from the antecubital vein of seated participants and shipped to the central clinical chemistry laboratory in Minneapolis, MN (31). Glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method on a Coulter DACOS device (Beckman Coulter, Fullerton, CA). Insulin was measured by radioimmunoassay (¹²⁵I insulin kit; Cambridge Medical Diagnosis, Bilerica, MA), with a 7 pmol/l lower limit of sensitivity and 33% cross-

reactivity with proinsulin (32). Individuals who had not fasted for at least 8 h were considered nonfasting.

Diabetes was defined as fasting glucose ≥ 7.0 mmol/l, nonfasting glucose ≥ 11.1 mmol/l, self-reported physician diagnosis, or pharmacologic hypoglycemic treatment. Nondiabetic subjects had either IFG (fasting glucose between 5.6 and 7.0 mmol/l) or NFG (fasting glucose < 5.6 mmol/l) (33). Hyperinsulinemia was fasting insulin ≥ 115 pmol/l (the 80th percentile). Insulin was not treated as a continuous variable because of the insensitivity of the assay at low values.

Statistical analysis: cross-sectional

For the baseline cross-sectional analysis, we excluded individuals with missing HRV records ($n = 816$) or invalid HRV data ($n = 2,340$); those with extreme HRV values ($n = 254$); those aged < 45 years ($n = 32$); those with missing diabetes information ($n = 100$); those whose race was other than white or black ($n = 35$) or blacks living in Maryland or Minnesota ($n = 42$); individuals with prevalent or unknown coronary heart disease ($n = 763$); those with missing information on hypertension, smoking, education, or BMI ($n = 55$); those taking specified drugs (β -blockers, antiarrhythmics, antianginals, peripheral vasodilators, or digoxin) ($n = 1,240$); or nondiabetic subjects without fasting insulin or glucose information ($n = 175$) for a sample size of 9,940 (the “cross-sectional” sample).

We examined the cross-sectional associations between HRV and measures of metabolic impairment. We calculated adjusted means for the HRV measures by diabetes and fasting glucose status and used linear regression to determine the association between HRV and fasting glucose among nondiabetic subjects, adjusting for age, sex, race, study center, hypertension, smoking, education, and BMI. To verify the linear nature of the relation, we examined the relationship between quintiles of fasting glucose and HRV and also fit restricted quadratic splines (34). We used similar methods to study the relationship at baseline between fasting insulin or hyperinsulinemia and HRV among nondiabetic subjects.

Statistical analysis: longitudinal

For the longitudinal analysis of the effect of diabetes, fasting glucose, and insulin

resistance on the subsequent change in HRV, we further excluded individuals who did not attend the third follow-up exam ($n = 2,355$); with missing ($n = 312$) or invalid ($n = 678$) HRV data; with extreme HRV values ($n = 112$); with missing diabetes information ($n = 63$); or who were taking specified drugs ($n = 175$) for a sample size of 6,245 (the “longitudinal” sample).

Change in HRV was the outcome, and various metabolic impairments were the exposures. We defined the mean annual change between baseline and follow-up as HRV at follow-up minus HRV at baseline divided by the number of years between baseline and follow-up. We present the mean annual change in HRV by diabetes, fasting glucose, and insulin resistance status, adjusted for baseline age, sex, race, study center, hypertension, smoking, education, and BMI. We also calculated the mean annual change adjusted for baseline HRV, correcting for measurement error in continuous baseline covariates (25).

We examined potential interaction by hypertension and obesity, using models with interaction terms and stratified models. No evidence of interaction by hypertension or obesity was found. SAS (version 8; SAS Institute, Cary, NC) was used.

RESULTS

Diabetes and HRV at baseline

Compared with the full ARIC baseline cohort, the 9,940 individuals in these analyses did not differ greatly in age, race, smoking status, education, and blood pressure (data not shown). Members of the full cohort were more likely to be diabetic (12 vs. 10%) or hypertensive (35 vs. 27%). Of the 969 diabetic individuals, 47% reported taking diabetes medications in the past 2 weeks, and 62% reported having been diagnosed with diabetes (Table 1).

Diabetic subjects had lower SDNN, rMSSD, and R-R interval than nondiabetic subjects, both without (Table 1) and with (Table 2) adjustment. The IFG group had a smaller mean R-R interval and slighter smaller mean rMSSD than the NFG group, but there was little difference in SDNN (Table 2). Among nondiabetic subjects, however, there was a weak dose response between quintiles of fasting glucose and HRV (Table 2). Linear regression

Table 1—Selected baseline characteristics adjusted for age, race, and sex: the ARIC study

Baseline characteristics	Cross-sectional sample				Longitudinal sample			
	Nondiabetic subjects	NFG	IFG	Diabetic subjects	Nondiabetic subjects	NFG	IFG	Diabetic subjects
n	8,971	5,410	3,561	969	5,788	3,567	2,221	457
Age (years)*	54	53	54	55	53	53	54	55
Race (% black)*	23	22	25	46	20	18	22	37
Sex (% men)*	42	36	52	41	41	34	51	40
Smoking (%)								
Current smoker	25	26	24	23	20	22	19	19
Former smoker	31	30	34	32	33	30	36	30
Never smoker	43	44	42	46	47	48	46	51
Education (%)								
<High school	21	20	22	30	16	15	18	24
High school	22	32	34	33	34	33	35	34
>High school	46	48	44	36	50	52	47	42
Hypertension (%)†	25	21	32	45	22	18	28	40
BMI (kg/m ²)	27	26	28	30	27	26	28	30
Glucose (mmol/l)‡	5	5	6	10	5	5	6	9
Insulin (pmol/l)‡	75	62	93	170	72	61	90	167
Systolic blood pressure (mmHg)	119	118	122	125	118	116	120	123
Diastolic blood pressure (mmHg)	125	72	74	73	72	72	74	73
Diabetes diagnosis (%)*	—	—	—	62	—	—	—	58
Diabetes treatment (%)*								
Insulin	—	—	—	20	—	—	—	15
Sulfonylureas	—	—	—	25	—	—	—	23
Other/unknown	—	—	—	2	—	—	—	1
Total treated	—	—	—	46	—	—	—	48
HRV (ms)								
SDNN	37	38	37	32	38	38	37	34
rMSSD	28	29	28	24	28	29	28	25
R-R interval	906	920	886	844	910	923	890	852

*Unadjusted. †Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported use of antihypertensive medications during the 2 weeks preceding the clinic examination. ‡Among fasting individuals only.

models demonstrated an inverse cross-sectional association between fasting glucose and HRV in nondiabetic subjects, with higher glucose values corresponding to lower HRV values. For each 0.5-mmol/l increase in fasting glucose, the difference in SDNN was -0.26 (95% CI -0.60 to 0.08), in rMSSD -0.63 (-1.00 to -0.26), and in R-R interval -16.41 (-19.13 to -13.69).

Diabetes and HRV over time

SDNN and rMSSD decreased between the baseline and follow-up exams, while R-R interval increased (Table 3). At both the baseline and follow-up exams, diabetic subjects had lower HRV than nondiabetic subjects. Sixty-seven percent of the cohort had an overall decline in SDNN during the 9-year follow-up, 61% a decline in rMSSD, and 70% an increase in R-R interval. These percentages were the same for

nondiabetic and diabetic subjects. There was no difference between nondiabetic and diabetic subjects in the 9-year change in HRV. After adjusting for baseline HRV, however, diabetic subjects had a greater decrease in SDNN and rMSSD by factors of 1.4 and 1.9 and a smaller increase in R-R interval by a factor of 0.6. While the IFG group had a slightly greater mean increase in R-R interval than the NFG group without adjustment for baseline R-R interval, there was no difference among the groups in the rate of change in R-R interval after adjustment for baseline R-R interval, and there were no other differences among the groups in the rate of change in HRV (Table 3).

Hyperinsulinemia

Among nondiabetic subjects at baseline, individuals with hyperinsulinemia had lower HRV than subjects without (Table

2). This difference remained after stratification by fasting glucose status (data not shown). The relationship between insulin and HRV was present in a dose-response manner throughout the insulin distribution (Table 2).

Surprisingly, nondiabetic individuals with hyperinsulinemia at baseline had a smaller annual decrease in SDNN and rMSSD and a greater annual increase in R-R interval than nondiabetic subjects without hyperinsulinemia (Table 4). Consequently, at follow-up there was no difference in SDNN and rMSSD between those with and without hyperinsulinemia at baseline, and the difference in R-R interval had decreased. After adjusting for baseline HRV, there was no difference in the mean annual change in HRV between those with and without hyperinsulinemia. These findings were the same in the NFG and IFG groups (data not shown).

Table 2—Adjusted* means (95% CI) for baseline HRV measures (ms) by baseline diabetes, glucose, or insulin status: the ARIC study

	SDNN	rMSSD	R-R interval
Diabetes/glucose status (n = 9,940)			
NFG	37.31 (36.88–37.74)	28.99 (28.52–29.45)†	916.99 (913.54–920.43)†
IFG	36.80 (36.27–37.33)	27.74 (27.17–28.31)‡	887.96 (883.75–892.16)‡
Diabetes	32.75 (31.71–33.78)†‡	23.87 (22.75–24.98)†‡	852.69 (844.45–860.94)†‡
Glucose quintile (n = 8,971)§			
I	37.66 (36.96–38.36)	29.82 (29.07–30.57)	927.24 (921.68–932.79)
II	37.30 (36.56–38.04)	28.42 (27.63–29.22)	915.49 (909.63–921.36)
III	37.08 (36.41–37.75)	28.19 (27.47–28.91)	905.87 (900.56–911.18)
IV	37.04 (36.32–37.77)	27.58 (26.80–28.36)	895.04 (889.29–900.79)
V	36.74 (35.81–37.67)	27.73 (26.73–28.73)	872.18 (864.78–879.58)
Hyperinsulinemia status (n = 8,971)§			
Absent	37.71 (37.35–38.08)	28.95 (28.56–29.34)	914.16 (911.29–917.03)
Present	34.47 (33.57–35.37)¶	25.61 (24.64–26.58)¶	862.95 (855.81–870.10)¶
Insulin quintile (n = 8,971)§			
I	38.91 (38.19–39.63)	30.95 (30.17–31.72)	944.81 (939.12–950.49)
II	38.43 (37.66–39.19)	29.40 (28.58–39.22)	924.58 (918.59–930.57)
III	37.07 (36.38–37.77)	28.14 (27.39–28.89)	908.15 (902.69–913.61)
IV	36.66 (35.92–37.40)	27.52 (26.73–28.32)	883.10 (877.28–888.91)
V	34.12 (33.21–35.03)	25.11 (24.13–26.09)	853.91 (846.75–861.08)

*Adjusted for age, sex, race, study center, hypertension, smoking, education, and BMI. †P < 0.05 compared with IFG. ‡P < 0.05 compared with NFG. §Among nondiabetic subjects only. Hyperinsulinemia is defined as fasting insulin ≥ 115 pmol/l (the 80th percentile). ||P < 0.05 compared with the lowest quintile (I) of glucose or insulin. ¶P < 0.05 compared with no hyperinsulinemia. Lower cut points for the glucose quintiles: 5.0, 5.3, 5.6, and 6.0 mmol/l. Lower cut points for the insulin quintiles: 43, 57, 79, and 115 pmol/l.

CONCLUSIONS— Our examination of the HRV changes in diabetes suggests that decreases in autonomic function are present early in the development of diabetes and that diabetes leads to a progressive decline in autonomic function. Diabetic subjects experienced a more rapid decline for SDNN or rMSSD and a less rapid increase for R-R interval, conditional on baseline HRV over 9 years of follow-up. There were no sizable differences in HRV between those with NFG or IFG, although there was a weak, approximately linear association between fasting glucose and HRV among nondiabetic subjects, suggesting that the association between fasting glucose and HRV is relatively weak and without a detectable threshold at 5.6 mmol/l. Nondiabetic individuals with hyperinsulinemia had lower HRV in a cross-sectional analysis. However, by the end of follow-up, we could detect no significant difference in SDNN and rMSSD between participants with and without hyperinsulinemia at baseline.

Our cross-sectional findings essentially agree with reports from the Hoorn Study (20), the Framingham Study (21,23), and a previously analyzed subset of the ARIC study (22). In the Hoorn study of 631 individuals aged 50–75

years, HRV, as measured using R-R interval, SDNN, low-frequency power (LF), and high-frequency power (HF) from 3-min records, was lower among diabetic subjects compared with those with NFG, after adjusting for age and sex (20). Although these measures were lower among those with IFG compared with those with NFG, only SDNN was statistically significantly decreased (20). In the Framingham Study of 1,919 individuals, HRV, as measured using SDNN, LF, HF, and LF/HF from 2-h records, was lower among diabetic subjects than in those with NFG (23). Individuals with IFG had decreased SDNN, HF, and LF compared with those with NFG (23). In a subset of 1,933 individuals from the ARIC study, HF from 2-min records was lower among diabetic than nondiabetic subjects, and there was an inverse association between HF and fasting insulin (22). The Insulin Resistance Atherosclerosis Study (35) found a direct association between heart rate and fasting insulin. In a study using the full ARIC cohort, individuals with increased heart rate or decreased LF were at an increased risk of developing diabetes, with no association observed for SDNN or HF (36).

Our findings are generally consistent with a pathophysiological model linking

hyperglycemia or its related metabolic consequences to the pathogenesis of autonomic neuropathy in diabetes (22,37–39). Diabetic subjects had lower HRV in the cross-sectional analysis and a greater mean annual decrease in HRV conditional on baseline HRV. As expected, the majority of nondiabetic and diabetic subjects experienced an overall decrease in HRV over the 9-year follow-up. This proportion did not differ between nondiabetic and diabetic subjects, and, without adjustment for baseline HRV, diabetic subjects did not experience a greater mean annual decrease in HRV. This reflects the greatly reduced HRV at baseline in diabetic subjects. After adjustment for baseline HRV, diabetic subjects clearly had a greater decrease in HRV, consistent with their increased risk for neuropathy.

However, we found only a weak cross-sectional relationship between fasting glucose and HRV and little difference between those with NFG or IFG. Furthermore, our results for fasting insulin and hyperinsulinemia among nondiabetic subjects are difficult to interpret. There is evidence that acute increases in insulin are associated with sympathetic neural activation, as reflected by norepinephrine levels and muscle sympathetic nerve activity (40–42). Although we found

Table 3—Adjusted* means (95% CI) at baseline and follow-up and annual mean changes over 9 years of follow-up (95% CI) of HRV measures by baseline diabetes status: the ARIC study

	NFG	IFG	Diabetes
<i>n</i>	3,567	2,221	457
SDNN			
Baseline (ms)	37.57 (37.05–38.09)	37.39 (36.74–38.05)	34.60 (33.14–36.05)†
Follow-up (ms)	31.46 (31.00–31.92)	31.42 (30.85–32.00)	27.95 (26.67–29.23)†
Mean annual change (ms/year)	−0.69 (−0.75 to −0.62)	−0.67 (−0.75 to −0.58)	−0.74 (−0.92 to −0.56)
Mean annual change adjusted for baseline SDNN (ms/year)‡	−0.66 (−0.71 to −0.61)	−0.66 (−0.72 to −0.60)	−0.95 (−1.08 to −0.81)‡
rMSSD			
Baseline (ms)	28.48 (27.95–29.02)	27.74 (27.06–28.41)	25.20 (23.70–26.70)†
Follow-up (ms)	24.98 (24.45–25.50)	24.83 (24.16–25.49)	21.09 (19.62–22.57)†
Mean annual change (ms/year)	−0.39 (−0.46 to −0.32)	−0.32 (−0.41 to −0.24)	−0.46 (−0.65 to −0.26)
Mean annual change adjusted for baseline rMSSD (ms/year)‡	−0.36 (−0.41 to −0.30)	−0.34 (−0.41 to −0.27)	−0.66 (−0.82 to −0.50)‡
R-R interval			
Baseline (ms)	920.54 (916.46–924.62)	892.18 (887.03–897.32)†	859.42 (847.98–870.85)†
Follow-up (ms)	976.21 (971.73–980.70)	955.26 (949.60–960.92)†	908.43 (895.85–921.01)†
Mean annual change (ms/year)	6.24 (5.79–6.68)	7.09 (6.52–7.65)†	5.49 (4.24–6.74)
Mean annual change adjusted for baseline R-R interval (ms/year)‡	6.74 (6.33–7.16)	6.61 (6.09–7.13)	3.88 (2.72–5.04)‡

*Adjusted for age, sex, race, study center, hypertension, smoking, education, and BMI. † $P < 0.05$ compared with NFG. ‡Corrected for measurement error in the baseline covariates.

decreased HRV among those with hyperinsulinemia, individuals with hyperinsulinemia at baseline did not experience a more rapid decrease in HRV over the course of follow-up. While the experimental evidence persuasively indicates that physiologic levels of insulin stimulate sympathetic activity, these effects may not

apply to the effects of insulin under conditions of sustained insulin resistance or chronic hyperinsulinemia. It must also be mentioned that the single measure of fasting insulin available on our cohort members at baseline represents a suboptimal characterization of their habitual levels of fasting insulin. A temporal decline in HRV

could exist among the cohort members with hyperinsulinemia as originally hypothesized, but we are unable to rule out the possibility that this association was not detected in our study as a result of misclassification of individuals with sustained hyperinsulinemia.

In addition, we only observed HRV at

Table 4—Adjusted* means (95% CI) at baseline and follow-up and annual mean changes over 9 years of follow-up (95% CI) of HRV measures by hyperinsulinemia status at baseline among 5,788 baseline nondiabetic subjects in the ARIC study

	Hyperinsulinemia†	
	Absent	Present
SDNN		
Baseline (ms)	37.99 (37.55–38.42)	35.17 (34.04–36.30)§
Follow-up (ms)	31.55 (31.17–31.94)	31.17 (30.17–32.17)
Mean annual change (ms/year)	−0.72 (−0.78 to −0.67)	−0.44 (−0.58 to −0.30)§
Mean annual change adjusted for baseline SDNN (ms/year)‡	−0.69 (−0.73 to −0.65)	−0.62 (−0.73 to −0.52)
rMSSD		
Baseline (ms)	28.58 (28.13–29.03)	25.90 (24.74–27.07)§
Follow-up (ms)	24.87 (24.43–25.31)	24.89 (23.74–26.03)
Mean annual change (ms/year)	−0.42 (−0.47 to −0.36)	−0.11 (−0.26 to 0.04)§
Mean annual change adjusted for baseline rMSSD (ms/year)‡	−0.39 (−0.43 to −0.34)	−0.28 (−0.40 to −0.16)
R-R interval		
Baseline (ms)	916.78 (913.35–920.21)	870.85 (861.92–879.77)§
Follow-up (ms)	973.40 (969.61–977.19)	943.33 (933.47–953.19)§
Mean annual change (ms/year)	6.35 (5.97–6.73)	8.12 (7.15–9.10)§
Mean annual change adjusted for baseline R-R interval (ms/year)‡	6.58 (6.23–6.93)	6.78 (5.87–7.69)

*Adjusted for age, sex, race, study center hypertension, smoking, education, and BMI. †Hyperinsulinemia is defined as fasting insulin ≥ 115 pmol/l (the 80th percentile). ‡Corrected for measurement error in the baseline covariates. § $P < 0.05$ compared with no hyperinsulinemia.

rest and were unable to examine frequency domain measures. Consequently, we are unable to attribute HRV changes to parasympathetic or sympathetic activity changes, and our ability to definitely attribute the HRV changes to cardiac autonomic function changes is limited. In particular, the observed change in HRV could be due to other intrinsic regulatory mechanisms of HRV, such as subclinical cardiomyopathy.

This is the first study to examine the change in HRV over 9 years among individuals with diabetes and pre-diabetic metabolic impairment in a large, biracial, population-based cohort. This is an epidemiologic investigation, and as such we used one measure of autonomic function that has commonly been used at the population level to describe differences in autonomic function. Future studies should investigate the type and extent of autonomic dysfunction in relation to the development of diabetes and/or insulin resistance. While we were unable to measure insulin resistance, fasting insulin levels have been shown to correlate well with rates of whole-body glucose uptake as measured by glucose clamps (43). A sizable proportion of the diabetic subjects were taking hypoglycemic medications, such as insulin or sulfonylureas. Studies such as ours are unable to separate the effects of the medications on HRV from the effects of the underlying disease on HRV.

While there was a sizable amount of missing HRV information, the differences in cardiovascular risk factors between those with HRV information and the full cohort were small. The individuals in the longitudinal analysis of the change in HRV were, on average, healthier than the original baseline cohort and than the general population, which could have biased our estimates of the influence of baseline characteristics on the subsequent change in HRV.

Many of our findings suggest that decreases in autonomic function are present at early stages of metabolic impairment and that diabetic metabolic impairment is associated with a progressive worsening of autonomic function. By contrast, the cross-sectional association between fasting glucose and HRV was weak and neither baseline fasting glucose status nor insulin resistance status at baseline led to a measurably more rapid 9-year decline in HRV. Consequently, more work is needed

to determine to what degree nondiabetic levels of metabolic impairments in insulin and glucose metabolism contribute to decreases in autonomic function.

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