Short Reports

Putative Determinants of Arterial Wall Compliance in NIDDM

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Aortoiliac arterial wall compliance was measured in apparently healthy subjects and in patients with non-insulin-dependent diabetes (NIDDM), on diet alone, who had no clinical evidence of peripheral arterial disease. Compliance was significantly lower in patients with diabetes. The two clinical groups were combined to provide as wide a range of blood glucose values as possible. After allowing for the influence of age, there were significant negative correlations between compliance and free fatty acid and insulin levels. These were almost completely accounted for by differences in blood glucose levels. Therefore, arterial compliance was best predicted on the basis of age and the area under the blood glucose curve. ***Diabetes Care*** **11:787–90, 1988**

Noninvasive techniques that use Doppler ultrasound to measure arterial wall compliance are harmless, simple to perform, and reproducible (1). We have shown that compliance is significantly lower in men with non-insulin-dependent diabetes mellitus (NIDDM) than in apparently healthy men of the same age (2). We found significant negative correlations between compliance and age, blood pressure, serum cholesterol and serum triglyceride levels, and a significant positive correlation between compliance and high-density lipoprotein (HDL) levels in apparently healthy men (3). Other studies have shown that age is an important factor associated with reduced arterial compliance in normal subjects (4–6) and that a low-salt diet in normotensive adult subjects resulted in a higher arterial compliance, independent of blood pressure (7).

The relationship between arterial compliance and other possible risk factors for arterial disease has not been reported. We describe a multivariate analysis of the relationship between compliance and glucose, plasma free fatty acid (FFA), insulin, and lipid levels in apparently normal and NIDDM subjects after controlling for the effect of age.

MATERIALS AND METHODS

The two groups consisted of 36 apparently healthy subjects (10 men, 26 women) and 27 NIDDM patients treated by diet alone (13 men, 14 women). The groups were matched for age, height, and weight. Patients with diabetes satisfied WHO criteria (8). None of the subjects smoked, and all were normotensive (diastolic pressure <95 mmHg). No subject had any symptoms or past history of arterial disease. None of the patients with diabetes had evidence of retinopathy, nephropathy, or neuropathy. All had normal ankle pressure indices at rest and after exercise, measured with Doppler ultrasound.

Each subject was rested supine for 10 min to allow

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TABLE 1
Characteristics of healthy and NIDDM subjects

Subjects	n	Age (yr)	Height (cm)	Weight (kg)	Body mass index (kg/m²)	Blood pressure*
Men						
Healthy	10	62 ± 13 (37–78)	171 ± 6 (159–180)	77 ± 12 (61–95)	26 ± 5 (18–38)	98 ± 9 (83–113)
Diabetic	13	60 ± 11 (36–74)	170 ± 7 (157–183)	79 ± 15 (58–109)	27 ± 5 (22–38)	98 ± 8 (86–118)
Women						
Healthy	26	69 ± 8 (57–93)	157 ± 7 (145–167)	66 ± 13 (43–96)	27 ± 4 (19–36)	95 ± 6 (87–111)
Diabetic	14	69 ± 9 (56–83)	157 ± 6 (147–168)	71 ± 11 (59–97)	29 ± 3 (24–36)	98 ± 5 (91–108)

Values are means ± SD with ranges in parentheses.
*Weighted mean blood pressure = systolic BP + 2(diastolic BP)/3.

blood pressure to stabilize. Two 4-MHz Sonicaid Doppler ultrasound units were used (Sonicaid, VA). The probes were placed over the left subclavian artery in the supraclavicular fossa and over each common femoral artery at the inguinal ligament in turn. The two signals obtained were passed through a Medishield Spectrum Analyser (London) and displayed on light-sensitive paper. The time delay between the start of the proximal and the distal pulse waves was calculated from the mean of 10 pulses from each side. The pulse-wave velocity (PWV) down the aortoiliac segments was calculated from the ratio of time delay (T) to the measured distance between the probes (L) as PWV = L/T m · s^{-1}. Gosling (9) has shown that compliance (AC) is calculated as AC = $66.7/\mathrm{PWV}^2$.

For each subject, fasting blood was collected, and a 75-g oral glucose load was then given, after which further blood samples were collected at 1 and 2 h. Blood glucose area is defined as the area under this 2-h curve. Each fasting blood sample was analyzed for glucose, glycosylated hemoglobin (HbA_{1c}), FFA, insulin, and lipid levels. Blood samples taken after the glucose load were analyzed for glucose, FFA, and insulin levels. A colorimetric method was used to estimate the FFA concentration (10). A radioimmunoassay method was used to determine the plasma insulin level (11).

Because glucose, insulin, FFA, HbA_{1c}, and triglycerides follow a log-normal distribution in nondiabetic subjects (12), with variability increasing with the mean level, these variables were all transformed by taking logarithms. Student's t test was used to compare the means of the transformed values for apparently healthy and NIDDM subjects of each sex. Means and 95% confidence intervals were calculated on the transformed values and then antilogged to give values in the original units. Multiple linear regression and partial correlation analyses were used to examine the relationships between arterial compliance and other variables.

RESULTS

The apparently healthy subjects and NIDDM patients were matched for age, height, body weight, and blood pressure (Table 1). FFA and insulin levels were significantly higher in the diabetic women compared with the apparently healthy women, both for the fasting levels and for the area under the 2-h curve after a glucose load (Table 2). Because the definition of diabetes is based on blood glucose, we have not shown a statistical analysis for difference in blood glucose in Table 2. Similar results were observed for men, except that the areas under the insulin curves were not significantly different. Arterial compliance was significantly lower in NIDDM patients than in apparently healthy subjects for both men and women (Table 3).

TABLE 2
Plasma free fatty acid, plasma insulin, and blood glucose levels of apparently healthy and NIDDM subjects

		Free fatty acid		Insulin		Glucose	
Subjects	n	Fasting level (mM)	Area (mM · h)	Fasting level (mU/ml)	Area (mU · ml⁻¹ · h)	Fasting level (mM)	Area (mM · h)
Men							
Healthy	10	310 (256,377)	334 (267,418)	9.2 (6.2,13.7)	104 (73,148)	5.2 (4.8,5.5)	12.8 (10.6,15.3)
Diabetic	13	405 (338,485)	625 (530,736)	18.2 (13.1,25.2)	110 (70,173)	9.8 (8.0,11.8)	29.3 (25.2,34.1)
P		<.05	<.0001	<.01	NS		
Women							
Healthy	26	342 (308,380)	401 (360,447)	8.3 (6.6,10.3)	93 (74,118)	5.3 (5.0,5.5)	15.3 (14.3,16.4)
Diabetic	14	444 (380,520)	657 (549,784)	20.8 (16.7,26.0)	138 (101,187)	9.6 (7.9,11.5)	32.8 (27.9,38.5)
P		<.005	<.0001	<.0001	<.05		

Values are means on log scale with 95% confidence intervals in parentheses (see MATERIALS AND METHODS).

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TABLE 3
Arterial compliance of apparently healthy and NIDDM subjects

	Men		Women	
Subjects	n	Arterial compliance	n	Arterial compliance
Healthy	10	1.02 ± 0.07	26	0.89 ± 0.05
Diabetic	13	0.55 ± 0.06	14	0.56 ± 0.03
P		<.0001 (.28,.67)		<.0001 (.20,.47)

Values are means ± SE with 95% confidence intervals for differences in means in parentheses.

Because the women were older than the men and arterial compliance decreases with age (3), compliance was adjusted for age by linear regression. The relationship between compliance and age was similar for both sexes, and after controlling for age, there was no significant difference between the arterial compliance of the two sexes ($t = 0.96$, $P = .34$, $n = 63$). After allowing for age, the partial correlations of compliance with blood glucose, FFA, fasting insulin, HbA_{1c}, serum cholesterol and triglycerides, and weight were statistically significant and negative (Table 4). There was no significant correlation with body mass index ($r = .21$). The strongest correlation was with area under the glucose curve [arterial compliance = 2.34 − 0.0061 (age) − 0.39 (glucose area)] (Fig. 1). After adjusting for glucose area, no significant correlation remained between compliance and any other variable either in the group as a whole or for each sex separately. Table 4 shows that all the other variables that were correlated with arterial compliance were also significantly positively correlated with area under the glucose curve. In contrast, when arterial compliance was adjusted for area under the FFA curve, it was still significantly negatively correlated with blood glucose (Table 4).

DISCUSSION

In this study, the effects of potential confounding factors, e.g., obesity, hypertension, and smoking, were controlled by matching or exclusion. Observations for healthy and NIDDM subjects were pooled to allow compliance to be related to a spectrum of glucose, FFA, and insulin values. We regard the two groups as coming from a continuum with respect to fasting blood glucose (Fig. 1). Sample size does not allow separate multivariate analysis of the two groups.

In previous studies with apparently healthy subjects, we found that arterial compliance correlated with blood pressure, total serum cholesterol, and HDL cholesterol (HDL-chol) (3). This was not shown in this study, maybe because when glucose metabolism is disturbed, as in diabetes, other potential determinants are less apparent. In addition, the healthy subjects in the previous study were accepted whatever their blood pressure, which was frequently elevated, whereas subjects with diastolic pressure >95 mmHg were excluded from this study, so that the range of blood pressures was smaller. A role for a wider range of blood pressures in determination of arterial compliance in diabetes is not precluded by this study. Also note that the correlation between arterial compliance and HDL-chol was .23 and fell to −.04 when glucose area was taken into account, because of the strong negative correlation between glucose area and HDL-chol (Table 4).

Wahlqvist et al. (13) showed that FFA can be incorporated into cholesterol ester in atheromas. Epidemiological evidence points to insulin as a risk factor for coronary artery disease (12,14,15), and experimental evidence shows that it influences atherogenesis (16). For these reasons, it was postulated that insulin and FFA could be determinants of arterial disease. Plasma FFA concentrations are elevated in diabetes.

After allowing for the effect of age, we found that arterial compliance was significantly negatively corre-

TABLE 4
Partial correlations

	Glucose		Free fatty acid		Insulin							
	Fasting level	Area	Fasting level	Area	Fasting level	Area	HbA_{1c}	Serum triglycerides	Weight	Blood pressure	Cholesterol	High-density lipoprotein
r_a	−.56*	−.63*	−.33‡	−.55*	−.46*	−.23	−.45*	−.32†	−.26†	−.14	.08	.23
r_{ag}	−.01	0	−.04	−.15	−.13	−.17	−.07	−.03	−.17	.03	.12	−.04
r_{af}	−.25†	−.30†	.15	0	−.18	−.16	−.18	−.08	−.25†	−.07	.13	.07
r_g	.91*	1	.47*	.69*	.57*	.15	.63*	.48*	.21	.25†	.02	−.41*

Partial correlations between arterial compliance and natural logarithm of blood glucose, plasma free fatty acid (FFA), and insulin levels; serum triglycerides; and weight for apparently healthy and NIDDM subjects combined ($n = 63$) after controlling for age (r_a), for age and area under glucose curve (r_{ag}), and for age and area under FFA curve (r_{af}). Correlations between glucose area (r_g) and putative determinants of compliance are also shown.
*$P < .001$, †$P < .05$, ‡$P < .01$.

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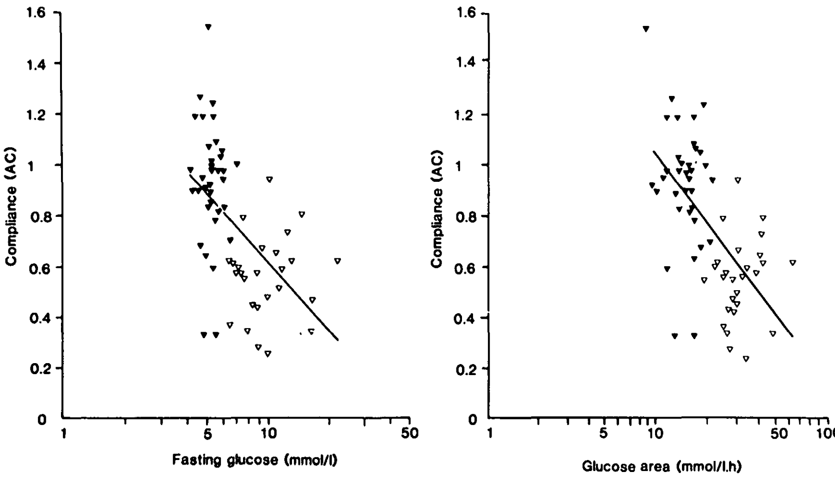

FIG. 1. Correlation between arterial compliance and log blood glucose levels between non-insulin-dependent diabetic (▽) and control (▼) subjects.

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lated with plasma insulin and FFA levels, serum triglyceride levels, and weight. However, these correlations could be almost completely accounted for by the strong positive correlations between blood glucose area and all of these variables. Blood glucose levels and age were the only significant determinants of changes in arterial wall compliance in the subjects studied. The changes in arterial wall compliance do not necessarily reflect the presence or severity of atherosclerosis. Nevertheless, a noninvasive measurement of arterial wall compliance, independently predicted by blood glucose status, is likely to be of clinical value when monitoring macrovascular disease in diabetes.

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