# Arterial Stiffness Is Inversely Related to Plasma Adiponectin Levels in Young Normotensive Patients With Type 1 Diabetes

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**OBJECTIVE**—This study investigated the association between arterial stiffness and plasma adiponectin in patients with type 1 diabetes.

**RESEARCH DESIGN AND METHODS**—Participants were normotensive patients with type 1 diabetes who were up to age 40 years. Subjects on statins with macrovascular disease or overt nephropathy were excluded. Large artery stiffness was assessed by measurement of carotid-femoral pulse wave velocity (PWV), whereas plasma adiponectin was measured by radioimmunoassay.

**RESULTS**—Data from 80 patients (age 27.1 ± 6.1 years, BMI 24.2 ± 3.1 kg/m$^2$, $HbA_{1c}$ 7.5 ± 1.6%, 39 men, adiponectin 13.9 ± 6.7 μg/mL, and PWV 5.6 ± 0.9 m/s) were analyzed. Log adiponectin inversely correlated with age-adjusted PWV ($r = -0.291$, $P = 0.009$) and waist circumference ($r = -0.427$, $P < 0.001$). In a fully adjusted model, age, expiration/inspiration index, and log adiponectin were independently associated with PWV, explaining 39.6% of its variance.

**CONCLUSIONS**—Arterial stiffness is inversely related to adiponectin concentration in young patients with type 1 diabetes without major complications.

*Diabetes Care* 36:734–736, 2013

Arterial stiffness, an independent predictor of total and cardiovascular mortality, can be assessed noninvasively by measurement of pulse wave velocity (PWV) (1), which is increased at early stages of type 1 diabetes (2,3). Plasma adiponectin, an adipocytokine with insulin-sensitizing, antiatherogenic, and anti-inflammatory properties (4), is high in patients with type 1 diabetes (5,6). Although adiponectin is inversely related to arterial stiffness in subjects with essential hypertension (7,8), no adiponectin-PWV relationship has been shown in children/adolescents with type 1 diabetes (9). This study investigated the association between adiponectin and PWV in young adults with type 1 diabetes.

## RESEARCH DESIGN AND METHODS

This was a cross-sectional study enrolling outpatients with type 1 diabetes aged 18–40 years. Subjects with cardiovascular disease, overt nephropathy, hypertension, and dyslipidemia (including those on statins) were excluded. Carotid-femoral PWV was measured with automatic computerized technique (SphygmoCor; AtCor Medical, West Ryde, Australia). Cardiac autonomic function was assessed as proposed by Ewing et al. (10) using the computer-aided system VariaCardio TF4 (Medical Research Limited, Leeds, U.K.) via *1*) heart rate response to slow deep breathing (expiration/inspiration index), *2*) heart rate response to standing up (30:15 ratio), *3*) heart rate response to Valsalva maneuver, and *4*) blood pressure response to standing up. Each normal, borderline, or abnormal test was graded as 0, 1, or 2, respectively. Cardiac autonomic neuropathy (CAN) score was the sum of partial scores (range 0–8). Adiponectin was measured by radioimmunoassay (Linco Research, St. Charles, MO). Adiponectin was log transformed because it showed positively skewed distribution. Partial correlation coefficients were calculated, and independent predictors of PWV were identified by multivariate linear regression via the Statistical Package for Social Sciences software (release 17.0; SPSS, Chicago, IL).

## RESULTS

Participants ($n = 80$, 49% male) were young (27.1 ± 6.1 years), predominantly (66%) nonsmokers, and normotensive (systolic/diastolic blood pressure 119.9 ± 12.7/76.8 ± 12.4 mmHg) adults with normal BMI (24.2 ± 3.1 kg/m$^2$) and lipids (LDL 102.3 ± 26 mg/dL, HDL 58.8 ± 13.2 mg/dL, and triglyceride 68 ± 35.7 mg/dL), moderate duration of diabetes (12.3 ± 7.7 years), low rates of early complications (retinopathy 20%, microalbuminuria 7.5%, and CAN 8.8%), and suboptimal metabolic control ($HbA_{1c}$ 7.5 ± 1.6%). The majority (78.7%) of patients were insulin treated via multiple daily injections and the rest with continuous subcutaneous infusion. Patients with microalbuminuria were treated with ACE inhibitors.

Adiponectin (population mean 13.9 ± 6.7 μg/mL) was higher in females (16.8 ± 6.7 μg/mL) than in males (10.9 ± 5.2 μg/mL; $P < 0.001$). Log adiponectin was inversely associated with waist circumference ($r = -0.427$, $P < 0.001$) and total insulin units/day ($r = -0.227$; $P = 0.043$). PWV (mean 5.6 ± 0.9 m/s) correlated strongly with age ($r = 0.452$, $P < 0.001$) and was

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Received 27 February 2012 and accepted 8 August 2012.
DOI: 10.2337/dc12-0387

similar in males (5.8 ± 0.8 m/s) and females (5.4 ± 0.9 m/s; $P = 0.086$). After adjustment for age (including all CAN tests), PWV correlated with waist circumference ($r = 0.279$; $P = 0.01$), systolic ($r = 0.250$; $P = 0.03$) and diastolic ($r = 0.303$; $P = 0.007$) blood pressure, expiration/inspiration index ($r = -0.308$; $P = 0.006$), total insulin units/day ($r = 0.247$; $P = 0.028$), and log adiponectin ($r = -0.291$; $P = 0.009$). PWV did not differ with respect to current smoking status, microalbuminuria, retinopathy, or drug therapy. Patients with CAN had higher PWV (6.5 ± 1.2 m/s) than patients without CAN (5.5 ± 0.8 m/s; $P = 0.008$), but PWV did not correlate with total CAN score ($r = 0.175$; $P = 0.12$).

Three multivariate linear regression models were created to further examine the PWV–log adiponectin association (Table 1). In the first model, log adiponectin was inversely associated with PWV, independently of age, diabetes duration, blood pressure, and expiration/inspiration index, whereas this relationship remained virtually unchanged after the addition of sex in the second model. In the fully adjusted third model, where measures of adiposity were also included, age, expiration/inspiration index, and log adiponectin were independently associated with PWV, explaining 39.6% of the variance of PWV. Adjustment for total insulin units/day and smoking did not affect the PWV–log adiponectin association and the β-coefficients of model 3. Hence, according to the latter model, due to the log transformation of the adiponectin values, a twofold increase in adiponectin will result in a 0.322 m/s decrease in PWV.

**CONCLUSIONS**—This is the first report on the relationship of adiponectin with arterial stiffness in young patients with type 1 diabetes, while the emergence of age and expiration/inspiration index as independent predictors of arterial elasticity corroborates previous findings (1,11). Adiponectin may act as an endogenous modulator of vascular remodeling and decrease PWV by reducing inflammatory mediators, neointimal thickening, and vascular smooth muscle cell proliferation (4). The increased adiponectin in patients with type 1 diabetes is attributed to compensatory response to vascular injury, decreased renal clearance, subcutaneous insulin treatment, and posttranslational modifications (glycosylation) (4,12,13).

The significant PWV-adiponectin association in multivariate analysis after adjustment for insulin units renders unlikely the possibility of confounding or mediation by insulin. In line with our previous findings, PWV showed an inverse relation with parasympathetic activity expressed as expiration/inspiration index (11). The apparently paradoxical lack of a relationship between PWV and $HbA_{1c}$, which corroborates two related reports (14,15), could be explained by the cross-sectional design and by speculating that the effects of hyperglycemia on the vasculature may not be detected with measures such as PWV and/or may reach a measurable extent only after decades from diagnosis of diabetes.

While insulin resistance is usually a late, secondary phenomenon in type 1 diabetes, we cannot exclude the possibility that in participants with insulin resistance and low adiponectin, the effect of the latter on PWV was exerted to some extent via hyperinsulinemia, inasmuch as adiponectin enhances insulin sensitivity through stimulation of adenosine monophosphate–activated protein kinase (4). The lack of association between smoking and arterial stiffness could be attributed to participants' young age and the fact that smoking status was assessed dichotomously because no detailed data such as pack/years were available. The fact that our population consisted exclusively of young, normotensive patients with no cardiovascular disease may account for the absence of a blood pressure–PWV association.

Study limitations include the relatively small sample size and the cross-sectional design. Therefore, a causative adiponectin-arterial stiffness relationship cannot be established. Hence, the decrease in PWV with lifestyle/pharmacologic interventions that increase adiponectin may be attributed rather to the intervention itself than to adiponectin elevation. Future studies may assess adiponectin at diagnosis of diabetes and after cardiovascular events, while randomized trials could target increasing adiponectin in patients with type 1 diabetes and low adiponectin.

**Table 1**—*Multivariate analysis with PWV as dependent variable*

| | β-Coefficient | SE | Standardized β-coefficient | *P* |
|---|---|---|---|---|
| Model 1. Independent variables: age, SBP or DBP, E/I index, diabetes duration, and log adiponectin ($R^2 = 0.395$) | | | | |
| Age | 0.040 | 0.017 | 0.268 | 0.021 |
| E/I index | −1.312 | 0.602 | −0.235 | 0.032 |
| Log adiponectin | −1.236 | 0.411 | −0.282 | 0.004 |
| DBP* | 0.014 | 0.007 | 0.184 | 0.065 |
| Diabetes duration | 0.019 | 0.013 | 0.160 | 0.153 |
| Model 2: Model 1 plus sex ($R^2 = 0.395$) | | | | |
| Age | 0.040 | 0.017 | 0.264 | 0.023 |
| E/I index | −1.367 | 0.609 | −0.245 | 0.028 |
| Log adiponectin | −1.088 | 0.463 | −0.248 | 0.022 |
| DBP | 0.012 | 0.007 | 0.168 | 0.101 |
| Diabetes duration | 0.019 | 0.013 | 0.158 | 0.157 |
| Sex | −0.135 | 0.192 | −0.074 | 0.458 |
| Model 3: Model 2 plus BMI or waist circumference ($R^2 = 0.396$) | | | | |
| Age | 0.039 | 0.017 | 0.262 | 0.026 |
| E/I index | −1.364 | 0.614 | −0.244 | 0.029 |
| Log adiponectin | −1.070 | 0.495 | −0.244 | 0.034 |
| DBP | 0.012 | 0.008 | 0.165 | 0.124 |
| Diabetes duration | 0.019 | 0.013 | 0.160 | 0.159 |
| Sex | −0.133 | 0.195 | −0.073 | 0.498 |
| BMI | 0.004 | 0.032 | 0.012 | 0.913 |

DBP, diastolic blood pressure; E/I index, expiration/inspiration index; SBP, systolic blood pressure. *SBP has virtually the same impact in the model ($R^2 = 0.40$, β = 0.013, standardized β = 0.176, $P = 0.067$).

**Acknowledgments**—No potential conflicts of interest relevant to this article were reported.

A.T. acquired the majority of data, performed statistical analysis, interpreted results, wrote the first draft of the manuscript, and is responsible for the final version of the manuscript. S.L. conceived the idea for this investigation, designed the research project, performed statistical analysis, interpreted results, drafted the manuscript, and made critical revisions of the final version of the manuscript for important intellectual content. K.A., E.D., and K.M. gathered data, interpreted results, and drafted the final version of the manuscript. N.T. gathered data, interpreted results, drafted the manuscript, and made critical revisions of the final version of the manuscript for important intellectual content. D.K. analyzed data, interpreted results, and drafted the final version of the manuscript. N.K. handled funding and supervision, drafted the manuscript, and made critical revisions of the final version of the manuscript for important intellectual content. A.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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