Endothelial Markers May Link Kidney Function to Cardiovascular Events in Type 2 Diabetes

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OBJECTIVE — The increased cardiovascular risk in diabetes has been linked to endothelial and renal dysfunction. The aim of this study was to investigate the role of stable fragments of the precursors of adrenomedullin, endothelin-1, vasopressin, and atrial natriuretic peptide in progression of cardiovascular disease in patients with diabetes.

RESEARCH DESIGN AND METHODS — This was a prospective, observational study design with a composite end point (death or unexpected admission to hospital due to a cardiovascular event) on 781 patients with type 2 diabetes (54 events, median duration of observation 15 months). The four stable precursor peptides midregional adrenomedullin (MR-proADM), midregional proatrial natriuretic peptide (MR-proANP), COOH-terminal proendothelin-1 (CT-proET-1), and COOH-terminal provasopressin or copeptin (CT-proAVP) were determined at baseline, and their association to renal function and cardiovascular events was studied using stepwise linear and Cox logistic regression analysis and receiver operating characteristic analysis, respectively.

RESULTS — MR-proADM, CT-proET-1, CT-proAVP, and MR-proANP were all elevated in patients with future cardiovascular events and independently correlated to serum creatinine. MR-proADM and MR-proANP were significant predictors of a future cardiovascular event, with MR-proANP being the stronger (area under the curve 0.802 ± 0.034, sensitivity 0.833, specificity 0.576, positive predictive value 0.132, and negative predictive value 0.978 with a cutoff value of 75 pmol/l).

CONCLUSIONS — The four serum markers of vasoactive and natriuretic peptides are related to both kidney function and cardiovascular events, thus linking two major complications of diabetes, diabetic nephropathy and cardiovascular disease.

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The main cause of death in patients with diabetes is cardiovascular disease: two of three diabetic patients develop heart failure or die from myocardial infarction or stroke, and diabetes is an established independent cardiovascular risk factor (1). There is clear evidence that hyperglycemia and hyperinsulinemia, both of which occur in type 2 diabetes, are linked to endothelial dysfunction resulting in atherosclerosis and, eventually, cardiovascular disease (2). On the other hand, in patients with diabetes, other risk factors such as hypertension, dyslipidemia, and central obesity are frequently present as well, clustered together in the metabolic syndrome. Several risk scores that take into account the above-mentioned factors have been developed to estimate cardiovascular risk in diabetes, and additional prognostic parameters including C-reactive protein and other inflammatory factors can help identify those with an excessive risk for events in the future (2).

One risk factor for cardiovascular events is diabetic nephropathy. The presence of nephropathy is a marker for endothelial damage, but neurohumoral factors are thought to contribute to the additional risk (3).

There are several vasoactive peptides with both cardiovascular and renal effects; among them are the natriuretic peptides atrial natriuretic peptide and brain natriuretic peptide, vasopressin, and the mainly endothelium-derived peptides adrenomedullin and endothelin-1, which also act as both vasoactive and natriuretic agents.

The main problem in measuring plasma concentrations of these peptides in a clinical setting is their rapid degradation and binding to receptors or binding proteins: ANP, for example, has a plasma half-life of 2–3 min. Therefore, assays have been developed to detect cleavage products of the preproproteins (4–7). These peptides are released in equimolar concentrations and serve as stable surrogate parameters for their active counterparts.

Recently, the following stable plasma markers of vasoactive peptides have been shown to predict outcome after myocardial infarction or in chronic heart failure: midregional adrenomedullin (MR-proADM) (8), COOH-terminal provasopressin or copeptin (CT-proAVP) (9,10), COOH-terminal proendothelin-1 (CT-proET-1) (11), and midregional proatrial natriuretic peptide (MR-proANP) (10, 12–14).

It has been shown in patients with type 2 diabetes that MR-proADM is associated with vascular function parameters and increased in those with elevated serum creatinine (15) and that it correlates to BMI in morbid obesity (16). Although CT-proET-1 has not been studied in the

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context of diabetes, endothelin-1 has been shown to be upregulated in diabetes (17) and to limit insulin action (18). Only little is known about the role of the two other peptides in diabetes: AVP is upregulated in the hypothalamus of diabetic rats (19), and ANP has been proposed to be involved in the hyperfiltration in hyperglycemia, contributing to the development of diabetic nephropathy (20). The aim of the current study was to study the relationship of the four plasma parameters with renal function and with future cardiovascular events in a prospective manner in a population of type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

— A total of 781 consecutive diabetic patients, mean ± SEM age 59 ± 0.5 years and diabetes duration 11.8 ± 0.4 years, treated at the diabetes outpatient clinic of the University Clinics of Vienna from 1 January 2006 to 17 February 2007 were studied. Upon entry in the study, a careful medical history with special focus on cardiovascular disease was taken, and history of ischemic heart disease (IHD) was recorded. All patients were asked to complete the Minnesota Living with Heart Failure questionnaire and the Dyspnoe score chart. Blood pressure, heart rate, electrocardiogram, and a blood sample for the determination of serum cholesterol, triglycerides, creatinine, A1C, blood glucose, and the markers were obtained from each patient, and New York Heart Association (NYHA) stage was assessed.

The study was conducted in accordance with the Declaration of Helsinki II and was approved by the local ethics committee. All participants gave written informed consent.

Laboratory procedures

Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, blood glucose, A1C, and serum creatinine were determined using standard laboratory procedures. Glomerular filtration rate (GFR) was calculated by the Cockroft-Gault and Modification of Diet in Renal Disease formulas, respectively. CT-proAVP, CT-proET-1, MR-proADM, and MR-proANP were determined from EDTA plasma of all patients at baseline with sandwich immunoluminometric assays (all from B.R.A.H.M.S., Hennigsdorf, Berlin, Germany), as described before (4–7).

End points

Based on the short observation period, a composite end point consisting of unplanned hospitalization for cardiovascular disease or death was chosen as the primary end point in this study. Unplanned cardiovascular events were defined as follows: hospitalization based on heart failure, myocardial infarction or unstable angina, symptomatic bradycardia, atrial fibrillation, ventricular tachycardia, peripheral and central arterial occlusive disease, transient ischemic attack, or stroke. All patients were traced through the national registry during 2007. Mortality data were obtained from the Austrian Central Office of Civil Registration (Zentrales Melderegister). If a patient had died, the date of death was recorded. Reports about hospitalization were obtained from the regional hospital data network (Krankenanstaltenverbund). Information about hospitalizations for cardiovascular disease was obtained from hospital files by a cardiologist, unaware of the results at index time.

Statistical analysis

Variables are expressed as means ± SEM or mean [95% CI], as stated. Sample size calculation was based on an expected log hazard ratio (HR) of 0.5 and an expected event rate of 10%. For $\alpha = 0.05$ and power >90%, a sample size of 600 patients was obtained.

For group comparisons of continuous variables, a two-tailed Student's *t* test was used. Categorical variables were evaluated with a χ^2 test. Associations of variables with NYHA stage were tested using Spearman's rank test.

Receiver operating characteristic analysis was performed to evaluate the predictive performance of MR-proADM, CT-proET-1, MR-proANP, and CT-proAVP. A forced-entry model was used to evaluate the role of creatinine and the four peptide markers MR-proADM, CT-proET-1, MR-proANP, and CT-proAVP as independent predictors of reaching the end point (unplanned hospitalization due to cardiovascular event and/or death). Variables, NYHA stage, IHD history, age, BMI, systolic blood pressure, A1C, LDL cholesterol, serum triglycerides, and serum creatinine were included in the models, with or without the addition of either one of the four peptide markers. Again, HRs are given as 1-SD increment. The results were retested in a stepwise Cox regression model.

Stepwise logistic regression models were calculated to identify independent variables to predict the reaching of the end point (unplanned hospitalization due to cardiovascular event and/or death). The *P* value for entering the stepwise model was set at 0.05 and for exclusion was set to 0.10. The stepwise approach was used to determine the most potent predictors independent of the number of events out of the variables as follows: NYHA stage, IHD history, age, BMI, systolic blood pressure, A1C, LDL cholesterol, serum triglycerides, serum creatinine, MR-proADM, CT-proET-1, MR-proANP, and CT-proAVP. All results of the regression model are presented using HRs Exp(*B*). HRs are given per 1-SD increment. In addition, 500 bootstrap repetitions were done for the Cox regression model, repeating the variable selection for each sample using the same entering and exclusion rules. This bootstrapping procedure is used as a test against overfitting the Cox regression model. We counted how often a variable was entered into the Cox regression models. The results were retested in a forced in model.

The proportional hazards assumption was assessed and satisfied for all variables based on time interaction test. To determine independent predictors of serum creatinine, stepwise linear regression was performed. Parameters included in the model were age (years), total and LDL cholesterol (milligrams per deciliter), A1C (percent), systolic and diastolic blood pressure RR (millimeters of mercury), heart rate (minute^{-1}), BMI (weight in kilograms divided by the square of height in meters), CT-proAVP (picomoles per liter), CT-proET-1 (picomoles per liter), MR-proADM (nanomoles per liter), and MR-proANP (picomoles per liter).

$P < 0.05$ was considered statistically significant. Statistical software SPSS for Windows (release 15.0; SPSS, Chicago, IL) was used for analysis.

RESULTS

Metabolic characterization and outcome

An overview of the demographic and metabolic parameters of the study group is given in Table 1. Of the entire study population 54 patients reached the composite end point during the observation period of up to 22 months (15 ± 6.9 months, median ± SD). They were significantly different from their event-free counter-

Table 1—*Baseline characteristics of the study population*

	Baseline
Age (years)	59.05 ± 0.5
Sex distribution (male/female) (%)	65.1/43.9
A1C (%)	7.82 ± 0.06
History of cardiovascular disease (%)	17.2
NYHA class distribution (I/II/III/IV) (%)	71.6/20.9/7.2/0.4
Serum creatinine (mg/dl)	1.05 ± 0.02
GFR (ml/min per 1.73 m^2)	91.17 ± 1.37
Serum cholesterol (mg/dl)	197.5 ± 1.8
LDL cholesterol (mg/dl)	110.3 ± 1.3
Systolic blood pressure RR (mmHg)	141.7 ± 0.8
Diastolic blood pressure RR (mmHg)	83.9 ± 0.5
MR-proANP (pmol/l)	96.63 ± 1.02
MR-proADM (nmol/l)	0.64 ± 0.01
CT-proET (pmol/l)	74.63 ± 1.02
CT-proAVP (pmol/l)	9.88 ± 0.43

parts regarding age ($P < 0.0001$), serum creatinine ($P = 0.002$), NYHA classification ($P < 0.0001$), but not A1C, total and LDL cholesterol, systolic and diastolic blood pressure, and Dyspnoe score.

Plasma markers

In contrast with A1C, glucose and serum lipids, MR-proADM (0.93 ± 0.07 vs. 0.62 ± 0.01 nmol/l, $P < 0.0001$), MR-proANP (220.0 ± 25.6 vs. 86.8 ± 2.6 pmol/l, $P < 0.0001$), CT-proET (197.6 ± 7.0 vs. 72.6 ± 0.9 pmol/l, $P = 0.001$), and CT-proAVP (16.0 ± 1.8 vs. 9.5 ± 0.5 pmol/l, $P = 0.001$) were all significantly higher in patients reaching the composite end point than in those who did not. With increasing NYHA stage, the serum levels of the four peptides also increased significantly ($P_{trend} < 0.001$ for all correlations, as assessed by Spearman's rank test).

In addition, age, serum triglycerides, A1C, systolic RR, serum creatinine, and GFR (calculated by both Cockroft-Gault and Modification of Diet in Renal Disease formulas) were significantly associated with NYHA stage ($P < 0.001$). In contrast, there was no significant correlation with serum cholesterol, LDL cholesterol, diastolic blood pressure, plasma glucose, or BMI.

Plasma markers and cardiovascular events and death

Receiver operating characteristic analysis was used to evaluate the ability of the four marker peptides MR-proADM, CT-proET-1, MR-proANP, and CT-proAVP to predict the primary end point. Areas under the curve (AUCs) of these models were 0.802 ± 0.034 (MR-proANP), 0.698 ± 0.04 (MR-proADM), 0.690 ± 0.038 (CT-proAVP), and 0.652 ± 0.048 (CT-proET) ($P < 0.001$ for all four markers). Using a cutoff value of 75 pmol/l, MR-proANP in this sample showed a sensitivity of 0.833, a specificity of 0.576, a positive predictive value (PPV) of 0.132, and a negative predictive value (NPV) of 0.978. The corresponding values for the three other markers are as follows: MR-proADM (cutoff 0.5 pmol/l): sensitivity 0.796, specificity 0.395, PPV 0.099, and NPV 0.960; CT-proAVP (cutoff 5 pmol/l): sensitivity 0.833, specificity 0.406, PPV 0.099, and NPV 0.972; and CT-proET (cutoff 60 pg/ml): sensitivity 0.722, specificity 0.325, PPV 0.078, and NPV 0.942.

Logistic Cox regression forced-entry analysis was used to identify independent predictors of reaching the composite end point. Creatinine was an independent predictor of cardiovascular events but became insignificant upon addition of any of the four markers. MR-proADM and MR-proANP but not CT-proET or CT-proAVP were significant predictors of an event (Table 2) (for a direct comparison of the five models, see supplementary Tables A1–A5, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-2168/DC1). In stepwise Cox regression models all four hormones remained significant markers of outcome (data not shown).

When stepwise regression analysis was performed including all four hormones beside all risk parameters (as mentioned in STATISTICAL ANALYSIS), only MR-proANP, together with NYHA stage and IHD history, remained a significant predictor of cardiovascular event occurrence; a 1-SD increment of MR-proANP was associated with a 1.564-fold risk (95% CI 1.360–1.798, $P = 0.000$) (supplementary Table A6, available in an online appendix). This result also held true if a forced-entry model was calculated (data not shown).

Bootstrap testing supported the importance and robustness of the model (supplementary Table A7). Of the bootstrap samples, 97.4% included MR-proANP.

Relation of plasma markers to renal parameters

Significant correlations were seen between serum creatinine (or GFR, as calculated by the Cockroft-Gault or MDRD formulas, respectively) and the plasma markers, as determined by linear regression analysis (R^2: MR-proADM 0.401, MR-proANP 0.341, CT-proET 0.319, and C-proAVP 0.443, $P < 0.001$ for all parameters). The plasma markers also correlated significantly with each other (not shown). In a stepwise linear regression analysis (Table 3), in which all hormones besides classic risk factors were included, all four plasma markers remained independent predictors of serum creatinine.

CONCLUSIONS

— There are three main findings in this study. *1*) In diabetic patients, progression to cardiovascular events is associated with the plasma levels of MR-proADM, CT-proAVP, CT-proET-1, and MR-proANP; *2*) MR-proANP and MR-proADM are significant independent predictors of cardiovascular events in this patient group; and *3*) all four markers are independent from each other predictor of serum levels of creatinine (and of GFR).

Plasma levels of all four markers were significantly higher in patients reaching the composite end point and significantly higher in patients with increasing severity of cardiac symptoms at baseline as assessed by NYHA stage. All four markers were useful as predictors of future cardiovascular events, with MR-proANP being the strongest. In this sample, the two markers MR-proADM and MR-proANP proved to be stronger predictors of an event than traditional risk markers. CT-pro-AVP and CT-proET only remained significant in a stepwise but not in a forced-entry Cox regression model. Of note, all four parameters showed a very good negative predictive quality, a property that would be very valuable were these parameters to be used in a clinical

Table 2—*Comparison of association of known risk factors and the four markers with cardiovascular events*

	NYHA	Age	Creatinine	
Model 1				
Significance	0.004	0.000	0.042	
Wald	8.275	13.025	4.116	
Exp(*B*) (95% CI)	1.689 (1.182–2.413)	1.833 (1.319–2.547)	1.125 (1.004–1.260)	
Model 2				CT-proAVP
Significance	0.004	0.000	NS	NS
Wald	8.253	12.434	—	—
Exp(*B*) (95% CI)	1.687 (1.181–2.411)	1.819 (1.304–2.537)	—	—
Model 3				CT-proET
Significance	0.022	0.001	NS	NS
Wald	5.208	11.187	—	—
Exp(*B*) (95% CI)	1.546 (1.063–2.247)	1.752 (1.261–2.434)	—	—
Model 4				MR-proADM
Significance	0.028	0.004	NS	0.018
Wald	4.810	8.278	—	5.553
Exp(*B*) (95% CI)	1.526 (1.046–2.226)	1.658 (1.175–2.341)	—	1.346 (1.051–1.724)
Model 5				MR-proANP
Significance	NS	NS	NS	0.000
Wald	—	—	—	31.191
Exp(*B*) (95% CI)	—	—	—	1.850 (1.491–2.297)

Logistic regression models using the following parameters (forced entry): NYHA, age, serum creatinine, LDL cholesterol, serum triglycerides, A1C, systolic RR, BMI (model 1) and the same parameters plus CT-proAVP (model 2), CT-proET (model 3), MR-proADM (model 4), or MR-proANP (model 5), respectively. Only parameters reaching significance are shown (see supplementary material for the full models). Exp(*B*) values are given per 1-SD increment with the exception of NYHA.

setting. The information that a patient currently has a lower risk for the occurrence of a cardiovascular event over the next year helps clinicians to better target aggressive management and close monitoring to those who really have a higher risk.

NH_2-terminal-pro brain natriuretic peptide, another natriuretic peptide marker, also showed a high NPV in a population comparable to the sample presented here. Again, NT-poBNP was superior to traditional risk factors in the prediction of cardiovascular events (21). MR-proANP, the strongest predictor in this sample, has been studied in comparison with NT-proBNP as the survival predictor in the setting of chronic heart failure (12) and acute cardiac failure and has been found to be noninferior to this established parameter.

It has been shown repeatedly that diabetic nephropathy is a main risk factor for future cardiovascular events (22). In confirmation of these observations, in this sample serum creatinine was significantly higher and glomerular filtration rate was significantly lower in those reaching the composite end point over the short time frame of a little more than 1 year. In addition, baseline serum creatinine was strongly associated with all four serum markers of vascular function, and all four remained independent predictors of serum creatinine in the stepwise linear regression model. Although creatinine was a highly significant predictor of outcome in a model including traditional risk markers, it became insignificant if any one of the four markers were added. Both adrenomedullin and endothelin may be produced by renal endothelial cells and have been studied in the context of nephropathy and renal failure (23); in this sample of diabetic patients the stable serum markers MR-proADM and CT-proET-1 also correlated with GFR and serum creatinine. In another sample of type 2 diabetic patients MR-proADM was increased in the presence of nephropathy and was related to insulin resistance (15). The markers MR-proANP and CT-proAVP have been studied in the context of sepsis and myocardial infarction (24) and have been used as outcome parameters regarding morbidity and mortality.

Table 3—*Association of variables with serum creatinine using stepwise linear regression analysis*

	Standardized coefficient	*T*	*P*
CT-proAVP (pmol/l)	0.443	13.335	<0.0001
MR-proADM (pmol/l)	0.177	4.005	<0.0001
MR-proANP (pmol/l)	0.163	4.102	<0.0001
CT-proET (pg/ml)	0.166	4.457	<0.0001
Heart rate (min^{-1})	−0.092	−3.390	0.001
Systolic blood pressure RR (mmHg)	−0.054	−1.987	0.047

Adjusted R^2 of the model was 0.611. Variables not included in the model were age, total and LDL cholesterol, triglycerides, A1C, fasting glucose, BMI, and diastolic RR.

These parameters, to our knowledge, have not been studied in patients with diabetes and in the context of diabetic nephropathy. However, CT-proAVP (copeptin) has been shown to correlate negatively with GFR in chronic heart failure (10), and MR-proANP was negatively correlated with serum creatinine in chronic heart failure (13). Thus, the close relationship of these parameters both with MR-proADM and CT-proET as well as with serum creatinine is noteworthy. It is not known how the precursor peptides of the vasoactive peptides are cleared

from the circulation, and decreased renal clearance is at least a partial explanation for the correlation of all four peptides with kidney function. Alternatively or in addition, the increase in the plasma levels of the four peptides could also be explained by increased production due to endothelial stress.

Although the vasoactive properties differ, all four peptides act as natriuretic agents. This natriuretic property is thought to be beneficial, and the fact that patients with heart failure do not have increased natriuresis but instead fluid retention and edema is thought to be due to (renal) resistance to the effect. Thus, the upregulation of natriuretic peptides in heart failure is thought to be physiological and cardio- and renoprotective. The higher levels of these peptides in patients progressing to an event would therefore represent an increased compensating effort of the body. Interestingly, in this study sample all four markers were independent predictors of serum creatinine in the multivariate linear regression analysis. This interesting finding underscores the complex regulation of kidney function with apparently each of the different peptide hormones (vasopressin, adrenomedullin, endothelin, and atrial natriuretic peptide) playing a distinct role in the diabetic kidney.

In the study sample presented here, the stable markers of all four peptides correlated strongly with each other (data not shown), despite their different origin, and all of them were higher in patients with a future event than in those who remained event free. To our knowledge, this is the first report of the four markers MR-proADM, CT-proET-1, MR-proANP, and CT-proAVP in a large sample of patients with diabetes. The data presented here describe a close relationship between renal function parameters and the four serum markers and a relationship of MR-proANP in particular and to a lesser extent the other three markers and the occurrence of cardiovascular events over a time frame of <1 year in a cohort of diabetic patients. Thus, these markers (or, rather, the active peptides for which they are surrogate markers) could be factors linking renal function to cardiovascular events.

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