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Low Plasma Level of Atrial Natriuretic Peptide Predicts Development of Diabetes: The Prospective Malmö Diet and Cancer Study

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Context: The cardiac natriuretic peptides are involved in blood pressure regulation, and large cross-sectional studies have shown lower plasma levels of N-terminal pro-natriuretic peptide levels [N-terminal atrial natriuretic peptide (N-ANP) and N-terminal brain natriuretic peptide (N-BNP)] in patients with insulin resistance, obesity, and diabetes.

Objective: In this study, we prospectively tested whether plasma levels of mid-regional ANP (MR-ANP) and N-BNP predict new-onset diabetes and long-term glucose progression.

Design, Setting, and Patients: MR-ANP and N-BNP were measured in 1828 nondiabetic individuals of the Malmö Diet and Cancer cohort (mean age 60 yr; 61% women) who subsequently underwent a follow-up exam including an oral glucose tolerance test after a median follow-up time of 16 yr. Logistic regression was used to adjust for covariates.

Results: During follow-up, 301 subjects developed new-onset diabetes. After full multivariate adjustment, MR-ANP was significantly inversely associated with incident diabetes (OR = 0.85; 95% CI = 0.73–0.99; $P = 0.034$) but not N-BNP (OR = 0.92; 95% CI = 0.80–1.06; $P = 0.262$). In fully adjusted linear regression models, the progression of fasting glucose during follow-up was significantly inversely related to baseline levels of MR-ANP ($P = 0.004$) but not N-BNP ($P = 0.129$). Quartile analyses revealed that the overall association was mainly accounted for by excess risk of incident diabetes in subjects belonging to the lowest quartile of MR-ANP. After full adjustment, the odds ratio for incident diabetes in the bottom compared with the top quartile of MR-ANP was 1.65 (OR = 1.08–2.51, $P = 0.019$) and 1.43 (OR = 1.04–1.96, $P = 0.027$) compared with all other subjects.

Conclusion: Low plasma levels of MR-ANP predict development of future diabetes and glucose progression over time, suggesting a causal role of ANP deficiency in diabetes development. **(*J Clin Endocrinol Metab* 97: 0000–0000, 2012)**

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Abbreviations: BMI, Body mass index; CI, confidence interval; FBG, fasting whole blood glucose; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; MDC, Malmö Diet and Cancer; MDC-CC, MDC study cardiovascular cohort; MR-ANP, mid-regional atrial NP; N-BNP, N-terminal pro-brain NP; NP, natriuretic peptide; OGTT, oral glucose tolerance test; OR, odds ratio; TG, triglyceride.

Whereas it is clear that diabetes patients are at increased risk of hypertension, cardiovascular disease, and heart failure, identification of drug-modifiable biological pathways causally related to both diabetes and hypertension has remained challenging. The natriuretic peptides (NP) are cardiac hormones, which are secreted from cardiomyocytes in response to cardiac wall stress and play a critical role in the regulation of blood pressure, intravascular volume, and cardiac remodeling (1, 2), and genetically determined low levels of atrial NP have been shown to be one contributor to higher risk of hypertension (3). Furthermore, it has been shown that a reduced level of NP is associated with obesity (4–6). Experimental studies have also shown that a reduced NP response is associated with activation of the renin-angiotensin system, which in turn could promote the development of insulin resistance (7–14).

Indeed, large cross-sectional studies have shown an inverse association with NP and the metabolic syndrome, fasting glucose, and insulin resistance (15–17). Recently, a Finnish study found that low levels of mid-regional atrial NP (MR-ANP) and N-terminal pro-brain NP (N-BNP) predicted diabetes (18). In this study, incident diabetes was retrieved through national registers on drug prescriptions of hypoglycemic agents, hospitalizations, and causes of death, and thus, a large proportion of diabetes patients, *i.e.* those with diet treatment, could not be identified. In addition, the majority of diabetic subjects in society are asymptomatic and will remain undiagnosed unless population screening of blood glucose levels is undertaken. For example, in the population-based Malmö Diet and Cancer (MDC) study cardiovascular cohort (MDC-CC), as many as 75% of those with diabetic fasting blood glucose values were unaware that they had diabetes (19).

Here, we tested the hypothesis that low NP levels (*i.e.* MR-ANP and N-BNP) lead to faster glucose progression over time and predicts diabetes development in healthy nondiabetic subjects who have been reexamined after 16 yr, including an oral glucose tolerance test (OGTT).

Materials and Methods

Study sample

The MDC study is a population-based study that enrolled 28,449 individuals between 1991 and 1996 (20). During the years 1991–1994, a random sample of the study subjects were selected to study the epidemiology of carotid artery disease (n = 6103), and this sample is referred to as the MDC-CC. Fasting plasma samples were obtained in 5405 subjects in the MDC-CC (21). Complete data on baseline covariates used in the present study, including MR-ANP and N-BNP, were available in 4742 individuals. Of these, we reexamined 2069 subjects between January 2007 and March 2010 using a protocol similar to that applied at the baseline exam but with addition of a 75-g OGTT with measurement of fasting plasma glucose at 0 min and after 120 min. We excluded subjects with cardiovascular disease or heart failure before the baseline exam (n = 48), resulting in 2021 subjects. In analysis of incident diabetes, 133 subjects with prevalent diabetes [fasting whole blood glucose (FBG) $\geq$ 6.1 mmol/liter or a history of physician-diagnosed diabetes mellitus or being on antidiabetic medication at the time of the baseline exam] were excluded, and in the remaining subjects, the OGTT was completed in 1828 subjects (n = 60 subjects did not perform the OGTT). The median (interquartile range, IQR) follow-up time was 16 (13–18) yr.

In cross-sectional analysis of associations between baseline values of MR-ANP and N-BNP with prevalent diabetes and FBG, patients with prevalent diabetes at baseline examination were included (n = 133 patients), resulting in a total number of subjects of 2021 in these analyses. In longitudinal analysis of change of fasting glucose from baseline to follow-up, the same 2021 subjects were used except 23 subjects who were excluded due to missing values of fasting glucose at the reexamination, resulting in 1998 subjects. All participants provided written informed consent, and the ethical committee at Lund University, Lund, Sweden, approved the study.

Clinical assessment

Clinical characteristics of the study population at the baseline exam are shown in Table 1. Participants underwent a standardized medical history with physical examination and laboratory assessment. Blood pressure was obtained after 10 min of rest in the supine position. We calculated the body mass index (BMI) as weight in kilograms divided by the square of the height in meters. Hypertension was defined as systolic blood pressure at least 140 mm Hg or diastolic blood pressure at least 90 mm Hg or use of antihypertensive therapy.

Laboratory assays

All analyses in plasma and whole blood were performed on samples drawn after an overnight fast. Analyses of fasting plasma lipids, serum insulin, FBG (baseline exam), and plasma glucose (reexamination) were carried out at the Department of Clinical Chemistry, Skåne University Hospital in Malmö, which is part of a national standardization and quality control system. High-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were analyzed using routine clinical chemistry methods on Cobas instruments (Roche Diagnostics Inc., Mannheim, Germany). N-BNP levels were determined using the Dimension RxL automated N-BNP method (Siemens Diagnostics, Nurnberg, Germany) (22). MR-ANP was measured using an immunoluminometric sandwich assay targeted against amino acids in the mid-region of the peptide (BRAHMS AG, Hennigsdorf, Germany) (23). This MR-ANP assay, which measures the mid-regional amino acids 53–90, has been shown to be equivalent to the N-terminal ANP assay, which is directed against amino acids 1–98 (23). Furthermore, MR-ANP has shown equal diagnostic and prognostic proprieties to that of N-BNP (24). Cystatin C was measured using a particle-enhanced immunonephelometric assay (25). Mean interassay coefficients of variation were less than or equal to 10% for MR-pro-ANP, 2.7% for N-BNP, and 4.3% for cystatin C. We used the homeostatic model assessment of insulin resistance (HOMA-IR) (26) to estimate insulin resistance and divided the population into quartiles.

TABLE 1. Baseline characteristics of study participants

	Subjects without diabetes[a]	Subjects with prevalent diabetes
n	1828	133
Age (yr)	56.9 ± 5.7	58.3 ± 5.5
Sex (% women)	60.9	46.6
Current smoker (%)	22.0	18.0
BMI (kg/m^2)	25.4 ± 3.5	28.8 ± 4.5
Systolic BP (mm Hg)	139.5 ± 18.2	147.3 ± 19.1
Diastolic BP(mm Hg)	86.2 ± 9.1	89.4 ± 9.5
High BP medication (%)	13.5	38.3
Hypertension (%)	60.1	75.9
FBG (mmol/liter)	4.9 ± 0.4	7.7 ± 2.7
Cystatin C (mg/liter)	0.76 ± 0.1	0.79 ± 0.1
TG (mmol/liter)	1.3 ± 0.7	1.9 ± 1.0
HDL-C (mmol/liter)	1.4 ± 0.4	1.2 ± 0.3
N-BNP (pg/ml)	60.0 (33.0–109.0)	50.8 ± (25.0–82.9)
MR-ANP (pmol/liter)	65.8 (51.3–84.9)	58.2 (43.4–79.2)
Insulin (mU/liter)	6.0 (4.0–9.0)	12.0 (7.0–18.0)
HOMA	1.6 ± 1.0	5.7 ± 9.1

Values are displayed as means ± SD, medians and 25–75% interquartile range, or frequency in percent. BP, Blood pressure.

[a] Subjects without OGTT data at reexamination (n = 60) not included.

Definition of incident diabetes

Incident diabetes was defined as fasting plasma glucose of at least 7.0 mmol/liter or a 2-h plasma glucose value of at least 11.0 mmol/liter during the OGTT at the reexamination or history of physician diagnosis of diabetes or initiation of antidiabetic medication any time after the baseline exam.

Statistical analysis

Variables that were not normally distributed (including MR-ANP and N-BNP) were log transformed before analysis. We used logistic regression models to calculate odds ratios (OR) for prevalent diabetes at baseline examination and OR for incident diabetes (patients with diabetes at baseline examination excluded) per 1 SD increment of log-transformed values of MR-ANP and N-BNP in models adjusted for age and sex (model 1) and adjusted for age, sex, waist circumference (waist), antihypertensive therapy, systolic blood pressure, TG, HDL-C, FBG, and cystatin C (model 2) with the exception that model 2 adjustment in cross-sectional analyses of prevalent diabetes and FBG did not include FBG. Furthermore, to explore whether any relationship between MR-ANP and N-BNP and diabetes was linear, MR-ANP and N-BNP levels were divided into quartiles and were related to prevalent diabetes at the baseline examination and incident diabetes after model 1 and model 2 adjustment. Multivariable linear regression analyses were performed to examine the relationship between log-transformed baseline plasma concentrations of MR-ANP and N-BNP and baseline values of FBG and glucose progression (difference between fasting glucose concentration at the reexamination and at the baseline exam divided by the follow-up time) adjusted using models 1 and 2. As for the analyses of the dichotomous phenotype of diabetes, we also related quartiles of MR-ANP and N-BNP to FBG levels at baseline examination and glucose progression. All analyses were performed using SPSS Windows version 16.0, and a two-tailed P value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study samples are listed in Table 1. In cross-sectional analyses at baseline, each 1 SD increment of MR-ANP [OR = 0.71; 95% confidence interval (CI) = 0.59–0.85; $P < 0.001$] and N-BNP (OR = 0.75; 95% CI = 0.62–0.90; $P = 0.002$) was associated with reduced odds of prevalent diabetes after model 1 adjustment and remained so after model 2 adjustment for both MR-ANP (OR = 0.77; 95% CI = 0.63–0.94; $P = 0.010$) and N-BNP (OR = 0.80; 95% CI = 0.66–0.97; $P = 0.021$). The odds of prevalent diabetes at baseline examination decreased significantly across quartiles of baseline values of MR-ANP and N-BNP (Table 2).

In cross-sectional linear regression analyses, crude analysis showed that FBG levels decreased across quartiles of baseline values of MR-ANP (Fig. 1). Furthermore, 1 SD increase of MR-ANP ($\beta = -0.107$; $P < 0.001$) and N-BNP ($\beta = -0.059$, $P = 0.018$) was significantly inversely associated with FBG after model 1 adjustment. However, after model 2 adjustment, only MR-ANP remained significantly inversely associated with FBG (MR-ANP: $\beta = -0.066$; $P = 0.008$; N-BNP: $\beta = -0.032$; $P = 0.183$). FBG levels decreased across quartiles of baseline values of MR-ANP (Table 3), whereas there were no significant associations for N-BNP (Table 3).

In the prospective analyses of nondiabetic subjects, each 1 SD increment of baseline values of MR-ANP (OR = 0.80; 95% CI = 0.70–0.91; $P = 0.001$) was significantly inversely related to incident diabetes in model 1, whereas N-BNP was nonsignificant (OR = 0.89; 95% CI = 0.78–1.01; $P = 0.078$). In model 2, which adjusted for renal function (cystatin C) as well as for clinical diabetes risk factors including fasting glucose at baseline, MR-ANP remained significantly inversely related to incident diabetes (OR = 0.85; 95% CI = 0.73–0.99; $P = 0.034$), but no significant association was seen for N-BNP (OR = 0.92;

TABLE 2. Logistic regression analysis examining biomarkers in quartiles in relation to prevalent diabetes at baseline

	Quartiles of MR-ANP		Quartiles of N-BNP	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1 with quartile group as categorical variables				
Group 1 (lowest values)	Referent		Referent	
Group 2	0.62 (0.38–0.99)	0.044	0.64 (0.39–1.05)	0.076
Group 3	0.49 (0.30–0.82)	0.006	0.88 (0.55–1.40)	0.583
Group 4 (highest values)	0.43 (0.26–0.73)	0.002	0.38 (0.21–0.68)	0.001
P for trend	0.75 (0.63–0.89)	0.001	0.79 (0.67–0.94)	0.007
1 SD change of peptides included as continuous variables	0.71 (0.59–0.85)	<0.001	0.75 (0.62–0.90)	0.002
Model 2 with quartile group as categorical variables				
Group 1 (lowest values)	Referent		Referent	
Group 2	0.63 (0.38–1.04)	0.073	0.78 (0.46–1.31)	0.343
Group 3	0.62 (0.36–1.06)	0.081	0.99 (0.60–1.63)	0.967
Group 4 (highest values)	0.51 (0.29–0.90)	0.019	0.42 (0.23–0.79)	0.007
P for trend	0.80 (0.67–0.97)	0.020	0.83 (0.69–0.99)	0.038
1 SD change of peptides included as continuous variables	0.77 (0.63–0.94)	0.010	0.80 (0.66–0.97)	0.021

Number of subjects was 2021. Model 1 was adjusted for age and sex at baseline. Model 2 was adjusted for age, sex, systolic blood pressure, antihypertensive treatment, waist circumference, and plasma levels of TG, HDL-C, and cystatin C at baseline. MR-ANP levels within quartiles are as follows [median (25–75% interquartile range)]: quartile 1, 42.4 (36.8–46.5) pmol/liter; quartile 2, 58.2 (54.5–61.9) pmol/liter; quartile 3, 74.0 (69.4–78.7) pmol/liter; quartile 4, 103.0 (91.7–122.0) pmol/liter. N-BNP levels within quartiles are as follows [median (25–75% interquartile range)]: quartile 1, 21.0 (13.4–27.0) pg/ml; quartile 2, 45.0 (38.0–51.0) pg/ml; quartile 3, 78.0 (67.9–91.7) pg/ml; quartile 4, 158.9 (130.0–226.8) pg/ml.

95% CI = 0.80–1.06; $P = 0.262$). Furthermore, MR-ANP remained significantly predictive of incident diabetes (OR = 0.86; 95% CI = 0.74–1.00; $P = 0.045$) even after additional adjustment for HOMA-IR at baseline, as a measure of insulin resistance, on top of model 2. In addition, MR-ANP remained significantly predictive of incident diabetes even after BMI, both separately and then simultaneously with measurements of waist circumference, was included on top of model 2. To examine whether or not the relationship between MR-ANP and new-onset diabetes was equal across the entire distribution of MR-ANP, analyses of quartiles were performed (Table 4). Although the linear trend with decreased diabetes risk across quartiles was significant, these analyses revealed that most of the difference in risk was seen between quartiles 2–4 and the reference quartile (quartile 1). Subjects belonging to quartile 1 of MR-ANP had markedly increased risk of incident diabetes (OR = 1.48; 95% CI = 1.09–2.01; $P = 0.013$ in model 1; and OR = 1.43; 95% CI = 1.04–1.96; $P = 0.027$ in model 2) when compared with all other subjects (quartiles 2–4) and when compared with quartile 4 (OR = 1.85; 95% CI = 1.28–2.68; $P = 0.001$ in model 1; and OR = 1.65; 95% CI = 1.08–2.51; $P = 0.019$ in model 2). No significant associations were seen for corresponding low N-BNP quartile group (data not shown). Analyses of baseline levels of MR-ANP and N-BNP in relation to long-term glucose progression, in which subjects with diabetes at baseline were included, showed that each 1 SD increment of baseline MR-ANP ($\beta = -0.004$; $P = 0.029$) but not N-BNP ($\beta = -0.002$; $P = 0.224$) was inversely related to glucose progression (millimoles increase of glucose per year) in model 1. Similarly, in model 2, only MR-ANP remained significantly inversely associated with glucose progression (MR-ANP: $\beta = -0.005$; $P = 0.004$; and N-BNP: $\beta = -0.003$; $P = 0.129$). The relationship between MR-ANP and glucose progression remained significant after additional adjustment for baseline insulin resistance on top of model 2 ($\beta = -0.005$; $P = 0.007$). As for analyses of incident diabetes, long-term glucose progression decreased across quartiles of MR-ANP (Table 5). However, in concordance with the analyses of new-onset diabetes, the greatest difference in glucose progression was observed between quartiles 2–4 and the reference quartile (quartile 1), supporting the conclusion that subjects with the 25% lowest MR-ANP are at risk of disadvantageous long-term glucose progression and diabetes

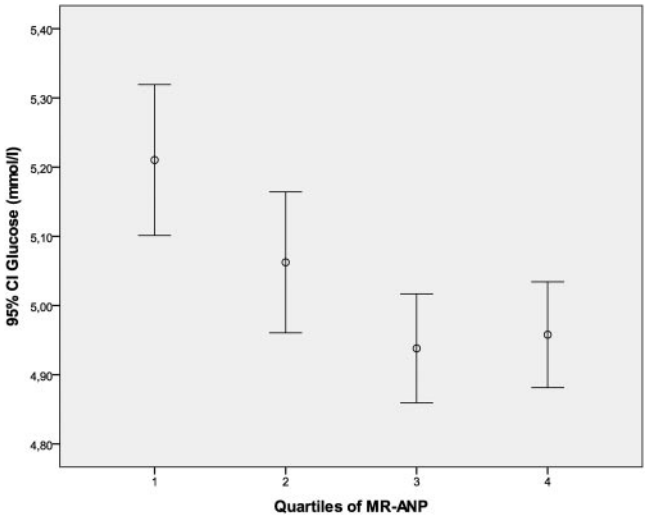

FIG. 1. Baseline glucose levels within quartiles of MR-ANP.

TABLE 3. Multivariable analysis of the relation of quartiles of baseline values of MR-ANP and BNP to fasting glucose levels at baseline

	Quartiles of MR-ANP		Quartiles of N-BNP	
	Regression coefficient (SE)	*P* value	Regression coefficient (SE)	*P* value
Model 1 with quartile group				
Group 1 (lowest baseline values)	Referent		Referent	
Group 2	−0.140 (0.067)	0.036	−0.113 (0.067)	0.094
Group 3	−0.264 (0.069)	<0.001	−0.045 (0.068)	0.509
Group 4 (highest baseline values)	−0.267 (0.071)	<0.001	−0.142 (0.070)	0.042
P for trend	−0.092 (0.023)	<0.001	−0.035 (0.022)	0.108
1 SD of change of peptides included as continuous variables	−0.107 (0.025)	<0.001	−0.059 (0.025)	0.018
Model 2 with quartile group				
Group 1 (lowest baseline values)	Referent		Referent	
Group 2	−0.094 (0.063)	0.135	−0.056 (0.064)	0.378
Group 3	−0.142 (0.065)	0.030	−0.004 (0.065)	0.955
Group 4 (highest baseline values)	−0.169 (0.069)	0.014	−0.067 (0.067)	0.317
P for trend	−0.055 (0.022)	0.011	−0.015 (0.021)	0.488
1 SD of change of peptides included as continuous variables	−0.066 (0.025)	0.008	−0.032 (0.024)	0.183

Number of subjects was 2021. β-Coefficient (regression coefficient) refers to increase (quartile or per 1 SD) of MR-ANP or N-BNP in relation to increase of glucose progression (millimoles glucose per year). Model 1 was adjusted for age and sex at baseline. Model 2 was adjusted for age, sex, systolic blood pressure, antihypertensive treatment, waist circumference, and plasma levels of TG, HDL-C, and cystatin C at baseline. MR-ANP levels within quartiles are as follows [median (25–75% interquartile range)]: quartile 1, 42.4 (36.8–46.5) pmol/liter; quartile 2, 58.2 (54.5–61.9) pmol/liter; quartile 3, 74.0 (69.4–78.7) pmol/liter; quartile 4, 103.0 (91.7–122.0) pmol/liter. N-BNP levels within quartiles are as follows [median (25–75% interquartile range)]: quartile 1, 21.0 (13.4–27.0) pg/ml; quartile 2, 45.0 (38.0–51.0) pg/ml; quartile 3, 78.0 (67.9–91.7) pg/ml; quartile 4, 158.9 (130.0–226.8) pg/ml.

development (Table 5). No significant associations were seen for N-BNP (Table 5).

Discussion

The key finding of our study is that reduced levels of circulating MR-ANP predict new-onset diabetes as well as degree of fasting glucose progression over time at the population level, independently of diabetes risk factors and renal function during 16 yr follow-up, suggesting that low ANP is causally related to diabetes development.

A role of ANP deficiency in hypertension is well established by genetic studies in both humans and animals (1, 3, 27) and in line with the physiological blood pressure-lowering actions of the hormone. In contrast, knowledge of physiological actions of ANP related to glucose metabolism is scarce. However, the present study and previous cross-sectional studies suggest that a natriuretic handicap might be one potential mechanism behind the frequent clustering of diabetes and hypertension (16, 17). Experimental data supports the notion that low ANP levels predisposes to development of diabetes and insulin resistance through an activation of the renin-angiotensin system causing increased oxidative stress (12), increased inflammatory response (8, 28), cross talk between the insulin and angiotensin signaling systems (13), and interference in glucose transporting (29). Indeed, earlier randomized studies have also suggested that therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers is associated with a reduced risk of diabetes (11, 30). However, a recent prospective trial with angiotensin II receptor blockers failed to show a significant reduction of glycemia (31). Importantly, it is unlikely that insulin resistance entirely explains the prospective relationship between MR-ANP and diabetes because it remained significant also after adjustment for insulin resistance. Interestingly, it has been shown that a direct infusion of ANP increases the circulating insulin levels in humans by 50% (32), and experimental studies have suggested an ANP-induced inhibition of glucagon secretion through its direct effect on pancreatic islets (33). Thus, it is possible that part of our results could be explained by beneficial effects of ANP on the β-cell. However, whatever is the cause of the relationship between reduced MR-ANP and long-term glucose deterioration and incident diabetes, our data support a primary role of ANP because we adjusted for all known clinical diabetes risk factors. Finally, the reason for low levels of MR-ANP in persons predisposed to diabetes could either be increased clearance (by the NPR-A receptor) or a decreased cardiac production of ANP (4). However, because the N-terminal fragments of ANP, such as MR-ANP, are not cleared by NPR-A (34), a decreased synthesis is the most plausible explanation.

Our data show that low levels of baseline MR-ANP predicts incident diabetes and steeper glucose progression better than low baseline levels of N-BNP. These findings

TABLE 4. Logistic regression analysis examining biomarkers in quartiles to incident diabetes excluding participants with prevalent diabetes at baseline

	Quartiles of MR-ANP		Quartiles of -BNP	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1 with quartile group as categorical variables				
Group 1 (lowest values)	Referent		Referent	
Group 2	0.59 (0.42–0.84)	0.003	0.65 (0.46–0.94)	0.020
Group 3	0.60 (0.42–0.86)	0.005	0.87 (0.61–1.23)	0.429
Group 4 (highest values)	0.54 (0.37–0.78)	0.001	0.77 (0.54–1.11)	0.161
P for trend	0.82 (0.73–0.93)	0.002	0.95 (0.84–1.07)	0.372
1 SD of change of peptides included as continuous variables	0.80 (0.70–0.91)	0.001	0.89 (0.78–1.01)	0.078
Model 2 with quartile group as categorical variables				
Group 1 (lowest values)	Referent		Referent	
Group 2	0.65 (0.45–0.96)	0.028	0.79 (0.53–1.17)	0.241
Group 3	0.86 (0.58–1.28)	0.460	0.98 (0.66–1.43)	0.899
Group 4 (highest values)	0.61 (0.40–0.92)	0.019	0.81 (0.54–1.20)	0.292
P for trend	0.88 (0.77–1.01)	0.061	0.95 (0.84–1.08)	0.469
1 SD of change of peptides included as continuous variables	0.85 (0.73–0.99)	0.034	0.92 (0.80–1.06)	0.262

Number of subjects was 1828. Model 1 was adjusted for age and sex at baseline. Model 2 was adjusted for age, sex, systolic blood pressure, antihypertensive treatment, waist circumference, and plasma levels of TG, HDL-C, and cystatin C at baseline. MR-ANP levels within quartiles are as follows [median (25–75% interquartile range): quartile 1, 42.9 (37.5–47.4) pmol/liter; quartile 2, 58.5 (54.9–62.2) pmol/liter; quartile 3, 74.4 (69.8–78.8) pmol/liter; quartile 4, 103.0 (92.3–122.0) pmol/liter. N-BNP levels within quartiles are as follows [median (25–75% interquartile range)]: quartile 1, 22.0 (14.0–28.0) pg/ml; quartile 2, 46.0 (39.7–52.0) pg/ml; quartile 3, 79.0 (69.0–92.5) pg/ml; quartile 4, 162.0 (131.2–227.6) pg/ml.

are in agreement with earlier cross-sectional studies (16, 17) and indicate that ANP and BNP may differently reflect propensity for diabetes and cardiovascular disease, respectively. ANP is considered to be mainly secreted by the cardiac atria, thus being less sensitive to increases in intraventricular pressure/hemodynamic stress than BNP, which in turn is mainly secreted by the cardiac ventricles (2, 35). Accordingly, N-BNP has also proven to be a more sensitive marker for the diagnosis of mild forms of left ventricular dysfunction compared with N-ANP (36, 37). Thus, although patients with prevalent cardiovascular disease and heart failure were excluded from our analyses, subclinical left ventricular systolic and/or diastolic dysfunction leading to relatively more BNP compared with ANP secretion could have attenuated the relationships between N-BNP and incident diabetes and glucose progression.

TABLE 5. Multivariable analysis of the relation of quartile group of baseline values of MR-ANP and BNP to Δ glucose values

	Quartiles of MR-ANP		Quartiles of N-BNP	
	Regression Coefficient (SE)	*P* value	Regression Coefficient (SE)	*P* value
Model 1 with quartile group				
Group 1 (lowest baseline values)	Referent		Referent	
Group 2	−0.010 (0.004)	0.043	−0.010 (0.005)	0.049
Group 3	−0.007 (0.005)	0.179	−0.006 (0.005)	0.247
Group 4 (highest baseline values)	−0.010 (0.005)	0.060	−0.006 (0.005)	0.273
P for trend	−0.003 (0.002)	0.115	−0.001 (0.002)	0.449
1 SD of change of peptides included as continuous variables	−0.004 (0.002)	0.029	−0.002 (0.002)	0.224
Model 2 with quartile group				
Group 1 (lowest baseline values)	Referent		Referent	
Group 2	−0.011 (0.005)	0.014	−0.009 (0.005)	0.052
Group 3	−0.007 (0.005)	0.121	−0.005 (0.005)	0.287
Group 4 (highest baseline values)	−0.013 (0.005)	0.012	−0.006 (0.005)	0.210
P for trend	−0.003 (0.002)	0.034	−0.001 (0.002)	0.371
1 SD of change of peptides included as continuous variables	−0.005 (0.002)	0.004	−0.003 (0.002)	0.129

Number of subjects was 1998. β-Coefficient (regression coefficient) refers to increase (quartile or per 1 SD) of MR-ANP or N-BNP in relation to increase of glucose progression (millimoles glucose per year). Model 1 was adjusted for age and sex at baseline. Model 2 was adjusted for age, sex, systolic blood pressure, antihypertensive treatment, waist circumference, and plasma levels of TG, HDL-C, and cystatin C at baseline. MR-ANP levels within quartiles are as follows [median (25–75% interquartile range): quartile 1, 42.5 (36.6–46.6) pmol/liter; quartile 2, 58.3 (54.6–61.9) pmol/liter; quartile 3, 74.0 (69.4–78.7 pmol/liter; quartile 4, 103.0 (91.8–122.0) pmol/liter. N-BNP levels within quartiles are as follows [median (25–75% interquartile range)]: quartile 1, 21.0 (13.5–27.0) pg/ml; quartile 2, 45.6 (39.0–52.0) pg/ml; quartile 3, 78.5 (68.7–92.0) pg/ml; quartile 4, 158.8 (130.0–226.5) pg/ml.

According to our data, subjects in the lowest quartile of MR-ANP had an approximately 60% increased risk of developing diabetes when compared with subjects in the top MR-ANP quartile and with a 40% increased risk compared with all other subjects (the three upper MR-ANP quartiles). These findings suggest a possible threshold effect of MR-ANP diabetes prediction, and the effect estimates may be of clinical significance because they were comparable to established diabetes risk factors. For example, within model 2, the OR for incident diabetes of more than 40% in the lowest MR-ANP quartile was similar in terms of effect size to 16 cm higher waist circumference. Measurements of MR-ANP levels might therefore serve as an additive tool together with classical diabetes risk factors for the early identification and prevention of patients at increased risk of developing diabetes. Furthermore, our findings together with the role of low ANP in hypertension (3) suggest that ANP deficiency may be a link between the huge clinical problem of shared propensity of both diabetes and hypertension and that lifestyle and drug interventions counteracting the primary cause of reduced ANP levels could be beneficial in preventing these disorders.

Our study has strengths and limitations. We studied a large population sample and based the definition of new-onset diabetes on results of an OGTT and a clinical reexamination. By performing an OGTT and clinical reexamination, we were able to retrieve the great majority of incident cases of diabetes including the large bulk of diabetes patients on nonpharmacological treatment as well as those unaware of having hyperglycemia. In addition, the reexamination enabled us to establish a strong independent relationship between baseline MR-ANP and glucose progression over time, a result that strengthens the reliability of the finding that MR-ANP predicts new-onset diabetes. On the other hand, we missed subjects who participated in the MDC-CC baseline exam but died during follow-up or did not participate in the reexamination for other reasons, which could lead to either over- or underestimation of our MR-ANP effect estimates on incident diabetes. Importantly, there was no significant difference between MR-ANP levels at baseline in participants compared with nonparticipants of the reexamination ($P = 0.73$), suggesting that such bias is of limited potential importance.

We did not measure mature ANP and BNP. However, the longer half-lives of MR-ANP and N-BNP compared with the mature hormones make them well suited for studies in ambulatory populations that have generally low resting levels. We cannot rule out that some of the incident cases of diabetes might be type 1 diabetes, because it can develop late in life; however, because the mean age of the study population was 60 yr at baseline examination, we assume that the majority are type 2 and thus drive our associations. Furthermore, both samples were comprised predominantly of individuals of European ancestry, and therefore, the results of this study may not be generalizable to other racial/ethnic groups.

Conclusions

In a large community-based cohort, followed prospectively for 16 yr, low plasma levels of MR-ANP were associated with the future development of diabetes and with longitudinal changes in fasting glycemia. These data suggest a primary role of low ANP level in diabetes development, which could have implications for both prediction and new ways to prevent diabetes and related disorders.

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