The Influence of Diabetes Mellitus on Midregional Proadrenomedullin Concentrations and Prognostic Value in Heart Failure Outpatients

PERNILLE HOLMAGER, MD,[1] MORTEN SCHOU, MD, PhD,[2] MICHAEL EGSTRUP, MD, PhD,[3] IDA GUSTAFSSON, MD, PhD,[4] JENS PETER GOETZE, MD, DMSci,[5] FINN GUSTAFSSON, MD, DMSci,[6] TOBIAS WIRENFELDT KLAUSEN,[7] JENS FABER, MD, DMSci,[1,8] AND CAROLINE KISTORP, MD, PhD[1,8]

Herlev, Copenhagen, Hvidovre, Denmark

ABSTRACT

Background: Diabetes mellitus (DM) is associated with an adverse outcome in heart failure (HF). Increased concentrations of midregional proadrenomedullin (MR-proADM) have been associated with DM and are predictors of mortality in HF patients. The aim of this study was to elucidate the impact of DM on MR-proADM concentrations and the prognostic value regarding all-cause mortality and hospitalization among HF patients.

Methods and Results: We included 366 patients from an HF clinic; 69 (19%) had a history of DM and 40 (11%) had newly diagnosed DM (Hb_{A1c} ≥48 mmol/mol). The median MR-proADM concentration was unaffected by DM status ($P = .20$) but increased in HF patients with impaired renal function ($P < .001$). During a median follow-up of 55 months, 189 died, and 292 either died or were hospitalized. After adjustment for clinically relevant parameters, MR-proADM was associated with all-cause mortality (hazard ratio [HR] 1.3, 95% confidence interval [CI] 1.1−1.4; $P = .01$) and the combined end point of death and hospitalization (HR 1.2, 95% CI 1.1−1.4; $P = .02$) per 1 SD increment of ln-transformed variable. No interaction between DM and MR-proADM was found regarding mortality or hospitalization.

Conclusions: Diabetes status had no impact on MR-proADM concentrations or in the predictive ability of MR-proADM in HF patients. (*J Cardiac Fail 2015;21:250−257*)

Key Words: Diabetes, heart failure, adrenomedullin, outcome.

The coexistence of diabetes mellitus (DM) and heart failure (HF) is associated with a markedly adverse prognosis that is independent from traditional parameters reflecting severity of HF, including left ventricular ejection fraction (LVEF).[1] The mechanism behind this finding remains to be fully elucidated, but increased inflammation, endothelial dysfunction, and diabetic nephropathy may play a role.[2,3]

Adrenomedullin (ADM) is a vasoactive peptide hormone which is activated in heart failure (HF) in response to neurohormonal stimulation, cytokines, and shear stress in myocytes and vascular endothelium and released from endothelial cells and vascular smooth muscle cells. Adrenomedullin exerts its effects through a G-protein−linked calcitonin receptor−like receptor, which has been identified in the heart, kidney, and vasculature.[4,5] In HF nonhuman animal models, ADM mediates protective effects by activation of nitric oxide−mediated vasodilation and by stimulating glomerular filtration rate (GFR), leading to increased natriuresis and increased cardiac output.[6] Adrenomedullin has a short half-life and is partially bound to a protein in circulation, which challenges direct measurement in plasma.[7,8] Recently, a stable fragment of the prohormone, midregional proadrenomedullin (MR-proADM) has been found and validated in clinical settings.[9] In humans, the concentrations of MR-proADM in plasma increase in various diseases, including renal failure and

From the [1]Endocrine Unit, Department of Medicine, Herlev University Hospital, Herlev, Denmark; [2]Department of Cardiology, Herlev University Hospital, Herlev, Denmark; [3]Department of Cardiology, Bispebjerg University Hospital, Copenhagen, Denmark; [4]Department of Cardiology, Hvidovre University Hospital, Hvidovre, Denmark; [5]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [6]Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [7]Department of Hematology, Herlev University Hospital, Herlev, Denmark and [8]Faculty of Health Sciences, Copenhagen University, Copenhagen, Denmark.

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Reprint requests: Pernille Holmager, MD, Department of Endocrinology, Herlev Hospital, Herlev, Denmark. Tel: +0045 3868 4308. E-mail: pernille.holmager@regionh.dk

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type 2 DM, and in patients with HF.[10−14] The predictive ability of MR-proADM measurement has predominantly been reported in earlier HF studies, suggesting that measurement of this biomarker provides prognostic information regarding overall mortality.[12,14−21]

In patients with DM, MR-proADM has been related to vascular injury, and increased plasma concentrations have been reported in diabetes patients with nephropathy.[11,22] Furthermore, high MR-proADM concentrations have been found in poorly regulated DM patients compared with healthy subjects, indicating a relationship with glucose metabolism.[23]

Thus, MR-proADM is a potential biomarker in HF patients with DM and could be associated with prognosis. To our knowledge, no earlier studies have evaluated the effect of DM on MR-proADM concentrations and the prognostic effect in outpatients with HF.

The aims of the present study were (a) to examine whether MR-proADM concentrations are affected by DM status in HF, (b) to evaluate if the presence of DM has an effect on the prognostic value of MR-proADM, and (c) to address its potential additional prognostic information to N-terminal pro−B-type natriuretic peptide (NT-proBNP) regarding overall mortality and hospitalization in outpatients with systolic HF.

Materials and Methods

Study Population

All HF patients in the present study were recruited from April 2000 to January 2009 from the specialized HF clinic at Frederiksberg University Hospital, Copenhagen, Denmark, and this population has previously been described.[24−26] Patients with known or suspected systolic HF were referred to the clinic, either directly from the general practitioners or from the departments of internal medicine or cardiology of the hospital. If systolic HF was confirmed, the patient was offered referral to the clinic. Patients enrolled in the present study were required to have left ventricular dysfunction defined as LVEF ≤45% by means of echocardiography and available baseline measurements of MR-proADM and NT-proBNP. No other exclusion criteria were applied. At baseline, patients were examined by a senior physician with training in cardiology at a specialist level and a specialized HF nurse and were evaluated by means of the following: medical history including medication, physical examination, New York Heart Association (NYHA) functional classification based on patient information, body mass index (BMI), resting blood pressure, heart rate, and standard transthoracic echocardiography. History of DM was confirmed by medical records or by receiving antidiabetic treatment. In patients without a history of DM, hemoglobin A1c (Hb_{A1c}) at baseline ≥48 mmol/mol was used as diagnostic criterion for newly diagnosed DM, in accordance with current guidelines from the World Health Organization and the American Diabetes Association.[27] At the initial visit, the cardiologist planned initiation and uptitration of the anticongestive treatment. The treatment plan was then executed by the HF nurse who also ensured HF education and arranged follow-up visits as clinically indicated. The study was approved by the local Ethics Committee of Copenhagen, and all patients provided written informed consents.

Laboratory Measurements

After a minimum 8-hour overnight fast and 20 minutes of supine rest, venous blood was obtained. Blood was drawn into EDTA tubes, promptly centrifuged at 4°C, and plasma frozen at −80°C in aliquots until laboratory analyses. MR-proADM was measured by means of a chemiluminescence immunoassay on the automated Kryptor platform (Thermo Fisher, Henningsdorf, Germany).[4] The lower detection limit is reported to be 0.08 nmol/L, the intraassay coefficient of variation (CV) <5%, and the interassay CV at 0.4 nmol/L is 10%.[9] Hb_{A1c} was measured with the use of an immunoturbidimetric assay, using alkaline hematin D-575, on a Cobas Integra analyzer (Roche Diagnostics, Basel, Switzerland). NT-proBNP levels were measured with the use of a double-antibody sandwich assay with electrochemiluminescence as a signal (Elecsys 2010; Roche Diagnostics).[10] Estimated glomerular filtration rate (eGFR) was calculated with the use of the Modification of Diet in Renal Disease (MDRD) formula.[28]

Outcome Data

The prespecified study end points consisted of all-cause mortality and the combined end point of hospitalization for ≥24 hours due to any cause and all-cause mortality. The median follow-up period was 55 (range 9−91) months. Information on end points was obtained from The Danish National Patient Registry, which records all hospital admissions and deaths in Denmark within 2 weeks. The validity of the end points obtained from The Danish National Patient Registry has been documented previously.[29]

Statistical Analysis

Patients were divided into tertiles according to MR-proADM levels. Values are expressed as mean ± SD, or as median with interquartile range (IQR). Comparisons between groups were performed by means of 1-way analysis of variance or Kruskall-Wallis test for continuous variables, according to whether or not their distribution were gaussian. The chi-square test was used for categoric data. Univariable and multivariable linear regression analyses were used to assess the association between MR-proADM concentrations and the potential variables: DM status, age, sex, NYHA functional class, Hb_{A1c}, BMI, total cholesterol, LVEF, NT-proBNP, and eGFR. Logarithmic transformation of MR-proADM and NT-proBNP was used in all of the linear regressions and in the Cox proportional hazard regression analyses to meet the assumptions of linearity. Owing to a limited number of patients in NYHA functional class IV, the patients were divided into 2 groups: NYHA functional classes I/II and III/IV.

Time-to-event analyses were performed with the use of the Kaplan Meier plots, and log rank test was used to compare these plots. Multivariable Cox regression analyses were performed as stepwise regression with backward elimination. The association between MR-proADM levels and outcome was evaluated in Cox models entering MR-proADM as a continuous and as a categoric variable. In the multivariable Cox models, covariables were included based on their documented clinical relevance: model 1: age and sex; model 2: age, sex, ischemic heart disease (IHD), eGFR, LVEF <30% vs ≥30%, NYHA functional class III/IV vs I/II, systolic blood pressure, heart rate, and presence of DM; and model 3: model 2 plus NT-proBNP levels. Regarding all-cause mortality and the combined end point, patients with MR-proADM concentrations in the highest tertile were compared