Copeptin is an independent predictor of diabetic heart disease and death

Sofia Enhörning, MD, PhD,[a,b] Bo Hedblad, MD, PhD,[a,b] Peter M. Nilsson, MD, PhD,[a,b] Gunnar Engström, MD, PhD,[a] and Olle Melander, MD, PhD[a,b] ***Malmö, Sweden***

Background We previously discovered that high copeptin is associated with incidence of diabetes mellitus (diabetes), abdominal obesity, and albuminuria. Furthermore, copeptin predicts cardiovascular events after myocardial infarction in diabetic patients, but whether it is associated with heart disease and death in individuals without diabetes and prevalent cardiovascular disease is unknown. In this study, we aim to test whether plasma copeptin (copeptin), the C-terminal fragment of arginine vasopressin prohormone, predicts heart disease and death differentially in diabetic and nondiabetic individuals.

Methods We related plasma copeptin to a combined end point composed of coronary artery disease (CAD), heart failure (HF), and death in diabetes (n = 895) and nondiabetes (n = 4187) individuals of the Malmö Diet and Cancer Study–Cardiovascular cohort.

Results Copeptin significantly interacted with diabetes regarding the combined end point (P = .006). In diabetic individuals, copeptin predicted the combined end point (hazard ratio [HR] 1.32 per SD, 95% CI 1.10-1.58, P = .003) after adjustment for conventional risk factors, prevalent HF and CAD, and remained significant after additional adjustment for either fasting glucose (P = .02) or hemoglobin A1c (P = .02). Furthermore, in diabetic individuals, copeptin predicted CAD (HR 1.33 per SD, 95% CI 1.04-1.69, P = .02), HF (HR 1.62 per SD, 95% CI 1.09-2.41, P = .02), and death (HR 1.32 per SD, 95% CI 1.04-1.68, P = .02). Interestingly, among nondiabetic individuals, copeptin was not associated with any of the end points.

Conclusions Copeptin predicted heart disease and death, specifically in diabetes patients, suggesting copeptin and the vasopressin system as a prognostic marker and therapeutic target for diabetic heart disease and death. (Am Heart J 2015;169:549-556.e1.)

Introduction

Vasopressin (AVP), also called antidiuretic hormone, is a peptide involved in diverse physiological functions and released from the posterior pituitary gland in conditions of decreased blood volume or high plasma osmolality. Vasopressin exerts its antidiuretic effects through the AVP 2 receptor in the kidney.[1] The AVP 1a receptor is involved in blood platelet aggregation and vasoconstriction in the vessels and gluconeogenesis and glycogenolysis in the liver,[2-5] whereas the AVP 1b receptor is found in the anterior hypophysis and the Langerhans islets of the pancreas, where it mediate secretion of adrenocorticotrophic hormone, insulin, and glucagon.[6,7] Thus, AVP may affect glucose metabolism through several different mechanisms.

Vasopressin is a small, short-lived peptide, and most assays measuring AVP have relatively limited sensitivity. An assay has been developed to measure plasma copeptin (copeptin), the C-terminal portion of the AVP precursor. Copeptin is considered to be a stable, reliable, and clinically useful surrogate marker for AVP.[8] In the Swedish population-based Malmö Diet and Cancer study Cardiovascular Cohort (MDC-CC), we recently found elevated copeptin to be associated with incident diabetes mellitus (diabetes) independently of a range of different clinically used diabetes risk factors including plasma glucose and insulin,[9,10] as well as independently associated with incident abdominal obesity.[10] Furthermore, copeptin is proposed as a useful biomarker in cardiovascular and renal disease,[11] and is suggested to contribute to the progression and predict prognosis in heart failure (HF)[12,13] and to predict prognosis in stroke[14,15] and myocardial infarction.[16] In the acute setting, copeptin can rule out myocardial infarction.[17-19] In addition, elevated copeptin has previously been associated with cardiovascular events after acute myocardial infarction in diabetes

From the [a]Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden, and [b]Department of Internal Medicine, Skåne University Hospital, Malmö, Sweden.

Conflict of interest: None declared.

Submitted June 10, 2014; accepted November 21, 2014.

Reprint requests: Sofia Enhörning, MD, PhD, Department of Clinical Sciences, Lund University, Clinical Research Center (CRC), Jan Waldenströms gata 35, Bldg 91, Floor 12, Skåne University Hospital, SE 205 02 Malmö, Sweden.

E-mail: sofia.enhorning@med.lu.se

0002-8703

http://dx.doi.org/10.1016/j.ahj.2014.11.020

patients,[20] and with cardiovascular morbidity and mortality in hemodialysis patients with diabetes.[21] However, it is not known whether copeptin predicts heart disease or death in unselected diabetic and nondiabetic individuals in the population. Based on our previous findings that copeptin predicts diabetes,[9,10] and its predictive role in diabetes patients with hemodialysis[21] and myocardial infarction,[20] we hypothesized that elevated copeptin predicts coronary artery disease (CAD), HF, and death differentially in individuals with diabetes and individuals without diabetes.

Methods

The MDC is a population-based prospective cohort consisting of 30,447 individuals born between 1923 and 1950 and surveyed at a baseline examination in 1991 to 1996.[22] The study complies with the Declaration of Helsinki. The study protocols were approved by the ethics committee of Lund University. All participants provided written informed consent. From the MDC cohort, 6,103 subjects were randomly selected to be studied for the epidemiology of carotid artery disease. This sample is referred to as the MDC-CC and was examined in 1991 to 1994.[23] At the MDC-CC baseline investigation, fasting plasma samples were available in 5,405 individuals and copeptin was measured. Complete data on covariates, including potential confounders and copeptin, were available in 5,082 individuals (Figure 1). Blood pressure was measured using a mercury-column sphygmomanometer after 10 minutes of rest in the supine position. Data on current smoking and use of antihypertensive treatment were ascertained from a baseline questionnaire.

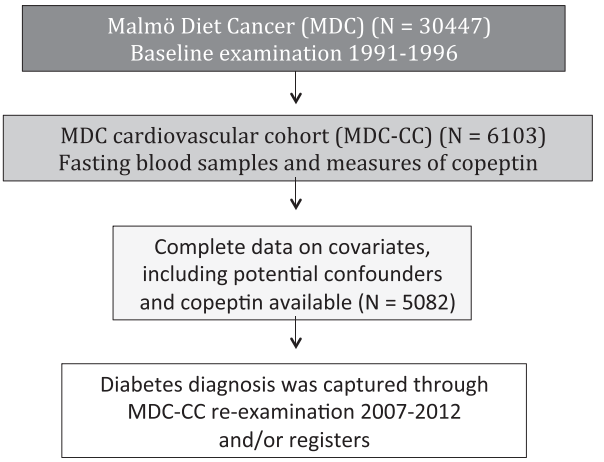
Furthermore, the MDC-CC was reexamined between 2007 and 2012 (67% participation rate) (Figure 1) with fasting plasma samples and additional measurement of an oral glucose tolerance test.[10]

Ascertainment of diabetes diagnosis

Diabetes cases were defined based on 6 different national and regional diabetes registers as detailed in online Supplementary Appendix. In addition, diabetes cases at the baseline examination of MDC-CC were obtained by self-report of a physician diagnosis or use of diabetes medication according to a baseline questionnaire, or fasting whole blood glucose of ≥6.1 mmol/L (corresponding to fasting plasma glucose concentration of ≥7.0 mmol/L). Furthermore, a diabetes diagnosis could be captured at the MDC-CC reinvestigation by self-report of a physician diagnosis or use of diabetes medication according to a questionnaire or fasting plasma glucose of ≥7.0 mmol/L or a 120-minute value post–oral glucose tolerance test plasma glucose >11.0 mmol/L.

Participants were classified as diabetic individuals regardless of whether diabetes was established before or at the baseline examination or during a follow-up period of 15.6 ± 2.8 years after the baseline examination. In subanalyses, diabetes cases were divided into those who had diabetes before or at the baseline examination (prevalent diabetes) (Table III) and those who developed diabetes during follow-up (incident diabetes) (Table IV).

Figure 1



Population description.

Ascertainment of end points

Cases of CAD, HF, and death were identified by the Swedish National Patient Register, which is a principal source of data for numerous research projects and covers more than 99% of all somatic and psychiatric hospital discharges and Swedish Hospital-based outpatient care[24]; the Swedish Cause-of-Death Register, which comprises all deaths among Swedish residents occurring in Sweden or abroad[25,26]; and the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).[27] The registers have previously been validated for classification of outcomes for HF[28] and myocardial infarction.[24,29,30] *Coronary artery disease* was defined as fatal or nonfatal myocardial infarction, death due to ischemic heart disease, percutaneous coronary intervention, or coronary artery bypass grafting, whichever came first, on the basis of *International Classification of Diseases, 9th and 10th Revisions* codes 410 and I21, respectively, in the Swedish National Patient Register or the Swedish Cause-of-Death Register, codes 412 and 414 (*International Classification of Diseases, 9th Revision*) or I22, I23, and I25 (*International Classification of Diseases, 10th Revision*) of the Swedish Cause-of-Death Register. Coronary artery bypass grafting was identified from national classification of surgical procedures, KKÅ from 1963 until 1989 and