Plasma Adiponectin, Body Mass Index, and Mortality in Patients With Chronic Heart Failure

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Background—Recent studies have suggested that higher body mass index (BMI) is associated with improved prognosis in chronic heart failure (CHF). The adipocytokine adiponectin is inversely associated with BMI, and in healthy subjects, low adiponectin is a predictor of mortality. In a prospective study, we therefore evaluated the association between plasma adiponectin levels and mortality among patients with CHF.

Methods and Results—In 195 CHF patients (age 69.3±10.2 years, BMI 27.3±5.2 kg/m², left ventricular ejection fraction 30±8.9%, mean±SD), plasma adiponectin and N-terminal pro brain natriuretic peptide (NT-proBNP) were measured at baseline. Adiponectin was positively associated with NT-proBNP (β=0.47, P<0.001), and both biomarkers were negatively associated with BMI (β=−0.43, P<0.001 for adiponectin and β=−0.38, P<0.001 for NT-proBNP, respectively) During a median follow-up of 2.6 years, 46 (23.5%) of the patients died. After adjustment for clinical variables associated with CHF severity (age, systolic blood pressure, left ventricular ejection fraction <25%, duration of CHF, and creatinine clearance) and for NT-proBNP, the hazard ratio of mortality for values in the 2 upper tertiles relative to the lowest tertile of adiponectin was 3.23 (P=0.032). BMI predicted mortality independently of clinical parameters of CHF severity (hazard ratio=0.63, P=0.012), but this association became insignificant after additional adjustment for NT-proBNP (hazard ratio=0.74, P=0.13).

Conclusions—A high adiponectin level was a predictor of mortality, independent of risk markers of CHF severity, presumably because of its role as a marker for wasting. BMI was also associated with mortality, but a part of this relation may be mediated by adiponectin and NT-proBNP levels. (Circulation. 2005;112:1756-1762.)

Key Words: adiponectin ■ body mass index ■ natriuretic peptides ■ heart failure

Obesity is a known risk factor for cardiovascular disease and for the development of chronic heart failure (CHF).1 However, recent data suggest that high body mass index (BMI) is associated with a more favorable prognosis in patients with established CHF.2-5 The mechanisms underlying this finding remain unexplained, but negative energy balance and subsequent weight loss may be of importance.6 Adipose tissue has been demonstrated to secrete a number of cytokines that are important regulators of energy balance.7

Adiponectin is a recently discovered adipocyte-specific cytokine that is abundant in plasma but decreased in conditions such as obesity8 and type 2 diabetes mellitus.9 Furthermore, in healthy individuals, low plasma adiponectin levels have been connected with increased risk of cardiovascular events.10 Adiponectin is suggested to be a modulator rather than a marker of insulin sensitivity, and administration of adiponectin has been observed to decrease body weight in experimental animals.11-13 Hence, adiponectin may be involved in the mechanisms by which body mass and body composition affect the prognosis in CHF. To date, adiponectin has not been studied in patients with CHF, and consequently, the possible role of adiponectin in relation to CHF severity and mortality is unknown.

Plasma brain natriuretic peptide (BNP) and the N-terminal of the prohormone (NT-proBNP) are well-established powerful risk markers in CHF.14-18 and plasma levels of these cardiac peptides appear to be inversely associated with BMI.17 Plasma adiponectin levels are downregulated in obese subjects, and therefore, we hypothesized that a relationship between plasma levels of adiponectin and NT-proBNP exists. Furthermore, we speculated that plasma adiponectin levels, as well as BMI, might be associated with the prognosis in CHF. To test these hypotheses, we evaluated in a prospective population of patients with documented systolic CHF (1) the relationship between plasma adiponectin concentrations and plasma NT-proBNP levels and (2) a possible association between baseline plasma adiponectin, BMI, and mortality.
Study Population
All patients in the present study were included from our specialized heart failure clinic at Frederiksberg University Hospital, Copenhagen, Denmark. The clinic has been operating since 1999; the original design of the clinic has been described in detail previously. Additionally, patients with known or suspected systolic CHF are referred to the clinic, either directly by general practitioners or by the departments of internal medicine or cardiology of the hospital, on an open-access basis. If systolic CHF is confirmed, the patients are offered admission to the clinic. A total of 195 consecutive CHF patients with confirmed chronic systolic heart failure were included in the present study. This population from the heart failure clinic has been described in detail previously.19 Systolic CHF was defined as left ventricular ejection fraction (LVEF) ≤45% by echocardiography or ventriculography. Diabetes mellitus was defined as history of diabetes and, according to the recommended diagnostic criteria of the World Health Organization, as fasting blood glucose >6.1 mmol/L measured on 2 occasions on 2 different days.19 At the baseline visit, all patients were examined by a physician, and the following information was obtained: medical history, including medications used; physical examination; New York Heart Association (NYHA) classification based on patient information; echocardiography (supplemented by isotopic ventriculography if echocardiography was technically insufficient); measurements of height and weight; resting blood pressure; and heart rate. Patients were followed up for a median of 2.6 years (range 0.5 to 3.9 years). None of the participants were lost to follow-up. The patients with CHF included in the present study have been followed up with respect to mortality status on a regular basis since baseline. All deaths were confirmed by the Danish Personal Register, which records all deaths in Denmark within 2 weeks. The investigations conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the central local ethics committee of Copenhagen, and all patients provided written informed consent.

Laboratory Measurements
After a minimum 8-hour overnight fast and 20 minutes of supine rest, venous blood was drawn into EDTA tubes and promptly centrifuged at 4°C, and plasma was frozen at −80°C in aliquots until analyses of adiponectin, NT-proBNP, and insulin were performed. Plasma adiponectin was determined by a validated, novel, in-house, time-resolved immunofluorometric assay based on commercially available antibodies and recombinant human adiponectin (R&D Systems), as previously described by the adapted method.18 The adiponectin molecule is known to form a wide range of polymers, of which the predominant polymers include trimers, hexamers, and highly aggregated multimers.21 Previous experiments, according to Laemmli’s method,22 have demonstrated that both monoclonal antibodies used are able to detect several adiponectin polymers in serum, including the 3 major molecular forms. Standards and unknown samples were analyzed in duplicate, nonspecific binding in quadruplicate. The assay is sensitive (detection limit <1.5 μg/L) and precise (within-assay coefficient of variation of standards and unknown samples averaged <5%). Finally, the assay yielded an average adiponectin level of 14 mg/L (range 6 to 27 mg/L) in a population of healthy, nonobese subjects of both genders (n=25, mean age 40 years, mean BMI 24 kg/m²), which is in line with the originally reported values.8 NT-proBNP was measured by a double-antibody sandwich technique with electrochemiluminescence as signal (Elecsys 2010, Roche Diagnostics). The sensitivity of the assay is <49.8 ng/L, and the intra-assay and interassay coefficients of variation are <5.0%.23 Fasting plasma insulin was measured by a double-antibody sandwich immunosassay (Elecsys 2010, Roche Diagnostics). The intra-assay and interassay coefficients of variation were <5%, with a lower detection limit of 1.39 pmol/L. Insulin resistance was assessed by determining the homeostasis model, as the homeostasis model assessment of insulin resistance index (defined as fasting plasma glucose [mmol/L]×fasting plasma insulin [pmol/L]/22.5). Creatinine clearance was calculated by the Cockcroft-Gault equation: (140−age)×weight (kg)/serum creatinine (μmol/L).24

Statistical Analysis
Patients were divided in tertiles according to their baseline adiponectin levels. Comparisons between the groups were performed by 1-way ANOVA or Kruskal-Wallis test for continuous variables, according to whether or not their distribution was gaussian. The χ² test was used for categorical data. Adiponectin, NT-proBNP, and fasting insulin were logarithmically transformed in all analyses. Multivariable linear regression analyses, examining the correlates of log-transformed adiponectin levels, included baseline variables that were associated with adiponectin at the P<0.10 level in univariate analyses. The relationship between plasma log NT-proBNP levels and BMI was examined in multivariable linear regression analyses, which included variables after the same criterion. There was no effect modification by gender, and thus, all linear regression analyses were sex-pooled. The standardized coefficient (β) with standard errors (SE) is shown for the linear regression analyses; standardized coefficients are interpretable as adjusted correlation coefficients.

Levels of adiponectin, BMI, and NT-proBNP were compared for subjects who died versus subjects who were alive at the time of follow-up, using the Mann-Whitney test. Cumulative survival according to increasing tertiles of adiponectin, fasting insulin, and NT-proBNP, as well as BMI categories (by the World Health Organization classification,25 ie, normal weight: BMI <25 kg/m², overweight: BMI 25.0 to 29.9 kg/m², and obese: BMI ≥30 kg/m²) was estimated by Kaplan-Meier curves followed by a trend test.

In multivariable Cox proportional hazard analyses, the association between plasma adiponectin, BMI, and mortality was examined. Adiponectin was treated both as a continuous and as a categorical variable. The main models were adjusted for variables that were considered to reflect severity of heart failure at baseline and that were associated with mortality in univariate analyses at the P<0.10 level (age, LVEF <25%, systolic blood pressure, and creatinine clearance). Duration of heart failure was also included in the models, because this variable was considered to be a potential confounder of BMI and adiponectin as predictors of survival. In addition, the influence of plasma NT-proBNP levels on the predictive value of adiponectin and of BMI was examined in analyses with and without adjustment for this biomarker. In secondary analyses, the retention criterion used in the Cox models was expanded to include parameters that were associated with mortality at the P<0.20 level, with the inclusion of NYHA class. These analyses yielded similar results as the main models, and consequently, NYHA class was excluded from the analysis. The multivariable Cox proportional hazard analyses were performed as stepwise regressions with backward elimination. For the Cox regression analyses, the assumption of deviation from linearity was explored by comparison of models with nonlinear transformation of the respective variables (square root terms) with models that contained linear terms of the covariates. The assumption of proportionality with regard to adiponectin, BMI, and NT-proBNP was met. When we used formal interaction analyses with log-transformed adiponectin levels and age (<65 years), sex, impaired renal function (creatinine clearance <70 mL/min), and BMI <25 kg/m², no interactions were found. All values are 2-tailed, and a probability value <0.05 was considered statistically significant. The statistical software package SPSS version 11.5 (SPSS Inc) was used for all analyses.

Results
Clinical Characteristics
At total of 195 patients (55 women and 140 men) were enrolled in the study. The mean (±SD) age was 69.3 (±10.3) years (range 36 to 91 years). Mean LVEF was 30% (±8.3%). The majority of patients (88%) were either NYHA functional class II or III, 11% were NYHA I, and 1 patient (0.5%) was NYHA class IV. Mean BMI was 27.3 (±5.2) kg/m². The
The median duration of CHF was 6 months (range 1 to 186 months). Sixty-six percent of the patients were treated with an ACE inhibitor, 12% were treated with an angiotensin II antagonist, and only 31% received an /H9252-blocker at the time of referral (/H9252-blocker dose was uptitrated in the heart failure clinic for most of these patients during follow-up; data not shown). A total of 48 (24.6%) of the population had a confirmed diagnosis of diabetes mellitus; of these, 96% had type 2 diabetes mellitus. Ischemic heart disease was the most prevalent cause of CHF (55%), followed by idiopathic cardiomyopathy (14%) and hypertension (10%).

Plasma Adiponectin Levels and Baseline Variables
Clinical characteristics according to tertiles of baseline adiponectin levels are presented in Table 1. The demographic data demonstrated that patients in the high tertiles were older and more often female. Furthermore, the prevalence of diabetes mellitus was lower in the high adiponectin tertiles (P=0.005), whereas there were no significant differences in the prevalence of ischemic heart disease (P=0.14) between tertiles. Higher levels of adiponectin were associated with low insulin resistance (ie, high insulin sensitivity), as evaluated by the inverse association with fasting plasma insulin (β=−0.58, P<0.001), the homeostasis model assessment of insulin resistance (β=−0.22, P=0.003), and BMI (β=−0.43, P<0.001) for the association with log-transformed adiponectin. Plasma adiponectin levels were positively associated with NT-proBNP levels (β=0.47, P<0.001; Figure 1A) and negatively associated with creatinine clearance (β=−0.42, P<0.001), whereas no association with LVEF or functional capacity, as assessed by NYHA class, was observed.

Multivariable linear regression analyses demonstrated that plasma NT-proBNP was independently associated with adiponectin levels (log transformed for both biomarkers), although the relationship was attenuated after adjustment, β being 0.23

| TABLE 1. Baseline Characteristics According to Tertiles of Plasma Adiponectin Levels |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Characteristics                              | Tertiles of Adiponectin, mg/L |
| Demographics                                  | ≤11.6 (n=64) | 11.7 to 19.8 (n=66) | >19.8 (n=64) |
| Age, y†                                       | 64.5 (10.5) | 70.5 (8.9) | 73.0 (9.6) | <0.0001 |
| Female/male, %                                | 20/80 | 23/77 | 43/57 | 0.008 |
| BMI, kg/m²†                                    | 29.7 (5.5) | 27.3 (4.4) | 24.6 (4.2) | <0.0001 |
| Concomitant diseases, % (n)                   | Ischemic heart disease | 60 (38) | 63 (41) | 47 (28) | 0.14 |
|                                              | Diabetes mellitus | 30 (19) | 24 (16) | 22 (13) | 0.005 |
|                                              | Hypertension | 3.7 (2) | 11.1 (6) | 16.4 (9) | 0.095 |
| Heart failure measurements                    | LVEF, %† | 30.1 (8.7) | 30.5 (7.2) | 29.6 (9.0) | 0.80 |
|                                              | NYHA class III/IV, % (n) | 28.6 (18) | 21.2 (14) | 29.0 (18) | 0.53 |
|                                              | NT-proBNP, ng/L‡ | 557 (258–1333) | 1169 (410–3271) | 2231 (1120–4680) | <0.0001 |
|                                              | Creatinine clearance, mL/min† | 93 (39) | 71 (27) | 58 (20) | <0.0001 |
|                                              | SBP, mm Hg† | 136.4 (25.6) | 138.7 (20.9) | 140.8 (25.2) | 0.62 |
|                                              | Duration of CHF, mo† | 5 (2–26) | 8 (2–48) | 6 (3–36) | 0.31 |
|                                              | Use of ACE inhibitors/AT-II antagonists, % (n) | 71.9 (46) | 81.8 (54) | 73.0 (46) | 0.35 |
|                                              | Use of β-blockers, % (n) | 34.3 (22) | 28.7 (19) | 29.6 (19) | 0.27 |
| Metabolic status                              | Fasting insulin, pmol/L‡ | 97 (72–142) | 57 (38–99) | 38 (21–55) | <0.0001 |
|                                              | Fasting blood glucose, mmol/L‡ | 5.4 (4.9–6.3) | 5.0 (4.7–5.6) | 4.9 (4.4–5.6) | 0.04 |
|                                              | HOMA-IR‡ | 4.2 (2.8–6.5) | 2.1 (1.4–3.9) | 1.3 (0.8–2.1) | <0.0001 |
|                                              | HbA1c (%)† | 6.5 (1.5) | 5.9 (0.6) | 6.3 (1.4) | 0.010 |
|                                              | Urinary A/C ratio, mg/g‡ | 14 (6–32) | 15 (6–24) | 19 (6–63) | 0.25 |
| Lipid status, mmol/L†                         | Total cholesterol | 5.1 (1.1) | 4.9 (1.1) | 5.5 (1.6) | 0.04 |
|                                              | LDL cholesterol | 2.9 (0.9) | 3.0 (0.9) | 3.4 (1.4) | 0.03 |
|                                              | HDL cholesterol | 1.1 (0.3) | 1.4 (0.4) | 1.7 (0.4) | <0.0001 |
|                                              | Triglycerides | 2.3 (1.5) | 1.4 (0.7) | 1.1 (0.4) | <0.0001 |

SBP indicates systolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; AT-II, angiotensin II; and A/C, albumin/creatinine.

* Differences between tertiles of adiponectin by ANOVA, Kruskal-Wallis test, or χ² test.
† Values are mean (SD).
‡ Values are median (interquartile range).
In addition, HDL cholesterol and fasting blood glucose levels were both associated with plasma adiponectin levels, whereas fasting plasma insulin was independently negatively correlated. The model explained 62% of the variance of plasma adiponectin levels.

Subsequently, the relation between plasma levels of NT-proBNP and BMI was examined. There was an inverse association between log-transformed NT-proBNP and BMI ($\beta=-0.38$, $P<0.001$; Figure 1B). A multivariable linear regression analysis demonstrated that BMI had an independent impact on plasma NT-proBNP levels, $\beta$ being $-0.36$ ($P<0.001$) after adjustment (Table 2). Increasing age and decreasing LVEF also independently correlated with plasma NT-proBNP levels, whereas there was only weak evidence of an association with NYHA class ($\beta=0.13$, $P=0.092$).

**Survival Analyses**

During the 2.5 years of follow-up, 46 (23.5%) of the patients died. In subjects who died compared with those who were alive at follow-up, baseline median (interquartile range) plasma adiponectin and NT-proBNP levels were higher (18.7 [13.1 to 29.0] versus 14.4 [9.3 to 22.0] mg/L, $P=0.011$, and 2508 [875 to 5041] versus 1021 [333 to 2322] ng/L, $P<0.001$, respectively) and BMI was lower (25.6 [22.3 to 28.3] versus 27.4 [24.2 to 30.7] kg/m$^2$, $P=0.018$).

The unadjusted overall mortality risk was markedly elevated in the 2 upper tertiles of adiponectin, corresponding to mortality rates of 30% and 32% compared with 12% in the lowest tertile ($P=0.018$ for trend; Figure 2A). This observation was in accordance with the markedly reduced mortality risk in obese patients (11%) compared with 27% and 32% in overweight and normal weight heart failure patients, respectively ($P=0.024$ for trend; Figure 2B). There was no relation between fasting plasma insulin levels and mortality ($P=0.29$ for trend; data not shown), and exclusion of diabetic patients did not change this observation. Finally, unadjusted overall mortality risk was clearly associated with increasing tertiles of plasma NT-proBNP ($P=0.0015$ for trend; Figure 2C).

In multivariable Cox proportional hazard analyses, the association between adiponectin, BMI, and mortality was examined. After adjustment for the clinical variables of age, systolic blood pressure, LVEF, creatinine clearance, and duration of CHF, the model of log adiponectin also included triglycerides and LDL cholesterol. The model of log NT-proBNP also included ischemic heart disease and systolic blood pressure.

Both models included the following additional parameters: sex, diabetes, use of ACE inhibitors/angiotensin II antagonists, use of $\beta$-blockers, creatinine clearance, and duration of CHF. The model of log adiponectin also included triglycerides and LDL cholesterol. The model of log NT-proBNP also included ischemic heart disease and systolic blood pressure.

The regression coefficients reflect changes in outcome relative to a 1-SD difference in the predictors.
because BMI no longer was significantly associated with mortality \((P=0.13; \text{analysis 4})\). There was no independent association between age, creatinine clearance, duration of CHF, and mortality in multivariable analyses. Finally, we analyzed adiponectin as a categorical variable, comparing the hazard of patients in the 2 upper tertiles with those in the lowest tertile. This analysis demonstrated that high levels of adiponectin were associated with a 3-fold increased risk of mortality \((P=0.032)\), independent of clinical variables and of baseline plasma NT-proBNP levels (analysis 5).

**Discussion**

Several new observations were made in this prospective study of CHF patients with documented systolic dysfunction. Plasma adiponectin levels were clearly and positively related with NT-proBNP concentrations. Furthermore, high baseline adiponectin levels were associated with an increased risk of mortality, independent of clinical parameters of CHF severity and even independent of plasma NT-proBNP levels. BMI was also associated with outcome; however, BMI was not an independent predictor of mortality in analyses that included measurements of plasma adiponectin or NT-proBNP levels.

Plasma adiponectin levels were related to several of the clinical baseline variables. Hence, the adiponectin level was inversely associated with fasting plasma insulin and BMI, which is in accordance with previous studies in obese subjects and patients with type 2 diabetes mellitus.\(^9\) The present study extends these findings to include patients with CHF.

To the best of our knowledge, the present study is the first to examine the association between adiponectin and BNP levels. We found a strong positive relation between plasma adiponectin levels and NT-proBNP concentrations, which was explained in part by differences in BMI. However, even after adjustment for BMI, age, gender, fasting insulin, LVEF, kidney function, and other parameters that had an impact on plasma levels of these 2 proteins, a modest but independent and statistically significant relation between adiponectin and NT-proBNP was observed. The present study does not provide any explanation for this relationship. However, intravenous infusion of natriuretic peptide increases glycerol concentrations in human subcutaneous adipose tissue,\(^{26}\) which suggests a direct lipid-mobilizing effect. Furthermore, adiponectin levels are reduced in subjects with increased fat

**TABLE 3. Multivariable Cox Proportional Hazard Analyses of Mortality**

<table>
<thead>
<tr>
<th>Analysis/Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariable analysis 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin, mg/L*</td>
<td>1.62 (1.19–2.19)</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI, kg/m(^2)†</td>
<td>0.83 (0.55–1.28)</td>
<td>0.41</td>
</tr>
<tr>
<td>Multivariable analysis 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin, mg/L*</td>
<td>1.27 (0.91–1.79)</td>
<td>0.17</td>
</tr>
<tr>
<td>BMI, kg/m(^2)†</td>
<td>0.84 (0.56–1.28)</td>
<td>0.43</td>
</tr>
<tr>
<td>NT-proBNP, ng/L*</td>
<td>2.01 (1.44–3.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable analysis 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m(^2)†</td>
<td>0.63 (0.45–0.89)</td>
<td>0.12</td>
</tr>
<tr>
<td>Multivariable analysis 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m(^2)†</td>
<td>0.74 (0.51–1.07)</td>
<td>0.13</td>
</tr>
<tr>
<td>NT-proBNP, ng/L*</td>
<td>2.02 (1.37–2.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable analysis 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin, mg/L‡</td>
<td>3.23 (1.11–9.69)</td>
<td>0.032</td>
</tr>
<tr>
<td>BMI, kg/m(^2)†</td>
<td>0.81 (0.53–1.22)</td>
<td>0.31</td>
</tr>
<tr>
<td>NT-proBNP, ng/L*</td>
<td>1.62 (1.09–2.39)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Adiponectin is modeled as a continuous variable in analyses 1 and 2 and as tertiles in analysis 5. Analyses 1 through 5 included adjustment for age, LVEF \(<25\%\), systolic blood pressure, creatinine clearance, and duration of CHF.

*Hazard ratios per 1 SD increment of log-transformed marker: adiponectin, 1 SD = 0.26 mg/L; NT-proBNP, 1 SD = 0.58 ng/L.
†Hazard ratios per 1 SD (5.2 kg/m\(^2\)) increment in BMI.
‡Hazard ratios for patients with values in the 2 upper tertiles relative to the lowest tertile, corresponding to values \(\geq 11.6\) mg/L.

**Figure 2.** Kaplan-Meier survival curves according to tertiles of plasma adiponectin (A), categories of BMI (B), and tertiles of plasma NT-proBNP levels (C). Probability values for trend between the respective tertiles and categories were as follows: adiponectin, \(P=0.018\); BMI, \(P=0.024\); and NT-proBNP, \(P=0.0015\).
mass. Thus, it could be hypothesized that natriuretic peptides, through an increased lipid mobilization, indirectly stimulate adiponectin levels. NT-proBNP is, however, contrary to BNP, believed to be physiologically inactive, and therefore, future studies including measurements of both BNP and NT-proBNP in relation to adiponectin, BMI, and body composition are needed to address this issue.

We found a clear and inverse association between plasma levels of NT-proBNP and BMI, independent of possible confounders such as age, gender, systolic function of the left ventricle, and kidney function. This finding is in accordance with previous reports on BNP and BMI in healthy individuals, hypertensive obese patients, and CHF patients. The present study extends the findings using BNP to NT-proBNP. There are several potential mechanisms responsible for this association. First, a natriuretic peptide clearance receptor, NPR-C, has been isolated in adipose tissue in humans. Furthermore, elevated NPR-C gene expression has been demonstrated in patients with hypertension and obesity. These findings suggest that the clearance of natriuretic peptides is increased in obese CHF patients, due to an upregulation of the gene expression of the NPR-C receptor in adipose tissue, which could explain in part the impact of BMI on plasma levels of the B-type natriuretic peptides. However, the peripheral elimination of NT-proBNP is not well understood, and consequently, impaired synthesis and release from the myocytes of the natriuretic peptides in obese subjects may also be part of the mechanisms underlying the reduced plasma natriuretic peptide levels. Recently, a novel lipolytic and potential lipid-mobilization effect of these peptides has been identified. The lipolytic effect of the natriuretic peptides is independent of the catecholamine pathway and of insulin and is mediated by a specific adipocyte plasma membrane receptor (NPR-A), which operates via a cGMP-dependent pathway. This recent research in natriuretic peptides raises the interesting possibility that the relation between natriuretic peptides and BMI could be bidirectional.

Survival analyses demonstrated that high adiponectin levels were associated with an increased mortality risk, because patients with circulating adiponectin levels in the 2 upper tertiles had a 3-fold increased risk of mortality compared with those in the lowest tertile. This finding could be counterintuitive, because adiponectin has been described to have antiinflammatory and antiatherogenic properties. Furthermore, high circulating adiponectin levels are related to a reduced risk of cardiovascular disease in healthy individuals. On the other hand, it is now generally accepted that several traditional risk factors cannot readily be applied to patients with CHF. Hence, higher serum cholesterol is suggested to be beneficial in these patients. Increased resting energy expenditure in CHF has been reported, and this may play a role in the unexplained weight loss that is part of wasting in CHF. Adiponectin has recently been suggested to increase energy expenditure and induce weight loss through a direct effect on the brain. Therefore, it could be hypothesized that high plasma adiponectin levels, in connection with increased energy expenditure, might not be beneficial in patients with established CHF. Conversely, weight loss increases plasma adiponectin levels, and thus, high plasma adiponectin levels in CHF patients could be a marker of the wasting process and may be one explanation of the association between high adiponectin levels and increased mortality risk in the present CHF population. We did not measure changes in weight in the present study, and future studies in populations with established CHF are needed to address this issue.

High BMI was related to a reduced mortality risk; however, this association was not independent of baseline levels of adiponectin. This observation indicates that increased energy expenditure may be more important than the actual BMI level in relation to prognosis. Previous studies have addressed the relationship between BMI and prognosis in CHF, and it appears that the presence of obesity is associated with improved survival. However, these studies included neither measurements of adiponectin nor of BNP or NT-proBNP. Thus, the role of the B-type natriuretic peptides in relation to weight and weight loss in CHF remains unclear. Patients with a high BMI are likely to experience heart failure symptoms at an earlier and less severe stage of heart failure. However, the prognostic impact of BMI was not affected by adjustment for duration of heart failure or the other possible confounders, such as systolic blood pressure and age; primarily, adjustment for NT-proBNP attenuated the predictive value of BMI. In CHF patients, weight loss is associated with a markedly increased risk of death. High levels of the B-type natriuretic peptides could, through their lipolytic effect, be expected to exaggerate the wasting process, which implies that a reduced NT-proBNP level in obese CHF patients may be related to a decreased level of wasting and thus a more favorable prognosis.

Additional limitations of the present study should be mentioned. The only cytokine measured was adiponectin; other important adipokines, such as tumor necrosis factor-α, may have a stronger association with survival in patients with CHF. We did not measure changes in weight nor NT-proBNP or adiponectin during follow-up, and hence, no causality of the interrelationship between these parameters can be determined from the present study. The relatively small number of deaths requires that caution be exercised in the interpretation of the present results, especially considering the complex interaction between adiponectin, BMI, and NT-proBNP. Furthermore, the cutoff point used for adiponectin in the present study population may be not be applicable in other heart failure populations. Finally, because this is the first study to examine adiponectin in relation to prognosis in heart failure, the present findings should be confirmed in other studies.

The present study shows for the first time that high adiponec- tin levels are associated with an increased risk of mortality in patients with CHF. A high BMI was also related with improved survival; however, part of this association may be mediated by adiponectin and NT-proBNP. Furthermore, the current data suggest that plasma levels of adiponectin and the BNPs are associated. Finally, the present findings confirm that plasma adiponectin levels are inversely associated with BMI and fasting plasma insulin, and we have demonstrated that BNP and NT-proBNP are negatively related to BMI.

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References


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