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The inflammatory biomarker YKL-40 as a new prognostic marker for all-cause mortality in patients with heart failure

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ABSTRACT

Background: Despite progress in management of patients with heart failure (HF) these patients still have a poor prognosis. We tested the hypothesis whether the inflammatory biomarker YKL-40 alone or in combination with high-sensitivity C-reactive protein (hs-CRP) and/or N-terminal-pro-B natriuretic peptide (NT-proBNP) could be a new prognostic biomarker for all-cause mortality in patients with HF.
Methods and results: A total of 717 of the 1000 patients with severe left ventricular systolic dysfunction included in the EchoCardiography and Heart Outcome Study were included in Denmark and had blood sample available for serum YKL-40 determination. Mean age of patients was 70 years, and 73% were male. During the 7 years follow-up period 458 patients died. Patients were categorised according to serum YKL-40 at entry into four quartiles: quartile I with median serum YKL-40 = 60 μg/L (5–95% Confidence interval (CI): 30–82), quartile II: YKL-40 = 107 μg/L (CI: 86–132), quartile III: YKL-40 = 169 μg/L (CI: 142–221), and quartile IV: YKL-40 = 286 μg/L (CI: 230–770). Hazard ratios for all-cause mortality were with quartile I as reference 1.33 (CI: 0.99–1.80), 1.35 (CI: 0.99–1.82), and 1.54 (CI: 1.14–2.08) for serum YKL-40 II to IV quartiles, respectively following multivariable adjustment for cardiovascular risk factors (age, left ventricular ejection fraction, gender, history of heart failure, ischemic heart disease, chronic pulmonary disease, diabetes mellitus, stroke, hypertension, NT-proBNP, hs-CRP, and renal function).
Conclusion: Serum YKL-40 is significantly associated with all-cause mortality in patients with HF and could potentially be a new prognostic biomarker in these patients.

Introduction

Heart failure (HF) is a consequence of cardiac overload and injury, and characterized by clinical symptoms due to cardiac impairment. Despite progress in management, patientswith HF have a poor prognosis, and the morbidity and mortality in these patients remain high. The biomarkers N-terminal-pro-B natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein (hs-CRP) have been the focus for monitoring and risk assessment in patients with HF (Hammerer-Lercher et al. 2006; Scirica et al. 2009; Tang et al. 2008).

Since inflammatory pathways may promote extracellular matrix (ECM) remodelling and HF progression (Radauceanu et al. 2008), recent research has focused on new inflammatory biomarkers as YKL-40.

YKL-40 is a highly conserved heparin-, chitin-, and collagen-binding glycoprotein and mainly produced by macrophages, neutrophils and cancer cells (Johansen et al. 2009; Lee et al. 2011). YKL-40 regulates vascular endothelial growth factor (Francescone et al. 2011) and has a role in inflammation, angiogenesis, cell proliferation and differentiation, and remodelling of the ECM (Francescone et al. 2011; Gratchev et al. 2008; Johansen et al. 2009; Kzhyshkowska et al. 2006, 2007; Lee et al. 2011; Rathcke et al. 2009). Hypoxia and interleukin 6 stimulates YKL-40 production (Junker et al. 2005).

Abbreviations: HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal-pro-B natriuretic peptide; CI, confidence interval; ECM, extracellular matrix; IHD, ischemic heart disease; STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction; ECHOS, EchoCardiography and Heart Outcome Study; NYHA, New York Heart Association; CV, coefficient of variations; eGFR, estimated glomerular filtration rate; WMI, wall motion index; MI, myocardial infarction; HT, hypertension; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; TIA, transient ischemic attack; BetaBL, beta-blocker; ACE-I, angiotensin converting enzyme inhibitors; AT-II-BL, AT-II antagonists; CaBL, calcium blockers.

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Serum levels of YKL-40 is suggested to be a novel biomarker of diseases characterized by inflammation and ongoing tissue remodelling (Francescone et al. 2011; Johansen et al. 2009; Kzhyshkowska et al. 2007; Lee et al. 2011; Rathcke et al. 2009). Macrophages in atherosclerotic plaques express YKL-40, particularly those that have infiltrated deeper into the lesion. The highest YKL-40 mRNA expression is found in macrophages in the early atherosclerotic lesion (Boot et al. 1999). There is evidence of a strong relationship between serum YKL-40 and ischemic heart disease (IHD) (Kastrup 2011; Mathiasen et al. 2010), since it is elevated in patients with IHD (Kastrup et al. 2009; Kucur et al. 2007; Mathiasen et al. 2011; Thomsen et al. 2010), and is a strong independent biomarker for cardiovascular an all-cause death in these patients (Kastrup et al. 2009). It has also been demonstrated that serum YKL-40 levels are significantly elevated at admission in patients with acute ST-elevation myocardial infarction (STEMI) (Hedegaard et al. 2010; Nojgaard et al. 2008; Wang et al. 2008) and then decreased slowly thereafter towards normal levels. Furthermore, YKL-40 may be an indirect biomarker of poor left ventricular ejection fraction (LVEF) recovery after a STEMI (Hedegaard et al. 2010). A recent study of 194 patients with HF found elevated serum YKL-40 levels in the patients compared to healthy subjects, but serum YKL-40 was not predictive of overall mortality or incident of cardiovascular events in this small study (Rathcke et al. 2010).

The aim of the present study was to evaluate whether serum YKL-40 alone or in combination with hs-CRP and/or NT-proBNP could be a prognostic biomarker for all-cause mortality in a larger cohort of patients with HF.

Materials and methods

Patients

A total of 717 of the 1000 patients included in the EchoCardigraphy and Heart Outcome Study (ECHOS) were included in Denmark, and had serum samples for the present sub-study. The ECHOS included patients with HF and left ventricular systolic dysfunction in the prospective, multicentre, double-blind, randomised, placebo-controlled study evaluating the effect of Nolomirole 5 mg twice daily, over a treatment period of at least 12 months (Torp-Pedersen et al. 2008). The first patient was enrolled on 23 April 2001, and the last patient on 23 January 2004. To be eligible for inclusion in the ECHOS, patients were required to be admitted to hospital with a clinical diagnosis of HF. Patients should have had a history of dyspnoea or fatigue at rest or on slight exercise, corresponding to New York Heart Association (NYHA) class III–IV within the last month and left ventricular function <35%. Patients were also required to be on diuretic treatment. The original design and organisation of the study has been describes in details previously (Torp-Pedersen et al. 2008). Written informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Controls

For comparing plasma YKL-40 levels from our patients to healthy controls, we used plasma YKL-40 levels from 3130 healthy subjects (1837 women, 1293 men) aged 21–84 years from Danish general population, the Copenhagen City Heart Study (Bojesen et al. 2011). These subjects had no known disease at the time of blood sampling in 1991–1994 and remained healthy and alive during the 16 years follow-up period. The median plasma YKL-40 in these 3130 healthy subjects was 40 μg/L (25–75% percentile range: 29–58 μg/L).

Measurements

Serum concentrations of YKL-40 were determined in duplicates, in samples stored frozen for up to 9 years at −80°C, by a commercial ELISA (Quidel, San Clara, CA, USA) using streptavidin-coated microplate wells, a biotinylated-Fab monoclonal capture antibody, and a alkaline phosphatise-labelled polyclonal detection antibody. The recovery is 102%, detection limit 20 μ/L. The intra-assay coefficient of variations (CVs) were 5.0% (at 40 μg/L), 4% (at 104 μg/L), and 4% (at 155 μg/L). The inter-assay CV was <6%.

hs-CRP was determined using an immunoturbidimetric assay (ITA, Roche/Hitachi Modular Analytics SWA Model M1 and M2, Germany). The intra- and inter-assay CV was for both 6%.

NT-proBNP was measured using a double antibody sandwich technique with ElectroChemiLuminescense as signal (Elecsys NT-proBNP, Roche/Modular Analytics SWA Diagnostics). Measuring range of the assay was 10.1–87.1 pmol/L. Assay sensitivity was <5.9 pmol/L with intra- and inter-assay coefficients of variation 6% and 5% respectively.

The estimated glomerular filtration rate (eGFR) was calculated as previously described (Levey et al. 1999).

All patients had left ventricular systolic function evaluated in a core laboratory based on videotaped echocardiograms. Wall motion index (WMI) was calculated using a 16 segment reverse scoring system, as previously described (Kober et al. 1994). WMI can be used as an estimation of LVEF by multiplying WMI by 30.

Follow-up

The patients had a 6.8 years follow-up period (mean ± 0.8 year). Information about death was collected at November 2008. In the present study we examined time from randomisation to death from any cause. Information about death came from the Danish Central Civil Register, which records the vital status of all inhabitants in Denmark. Registration is 100% in these registers.

Ethics and organisation

The local Scientific Ethical Committee approved the study and it was conducted in accordance with the Declaration of Helsinki III and Guidelines for Good Clinical Practice in the European Union. All participants signed a written consent after oral and written information.

Statistical analysis

All statistical analysis was performed using the Statistical Analysis System (SAS) version 9.1 (SAS Institute, Cary, NC, USA). Nolomirole had no effect on mortality or any of the parameters measured. Thus, the placebo and the Nolomirole group were analyzed together.

Continuous variables are presented as median and 5th to 95th percentiles as confidence intervals (CI). Categorical variables are shown as frequency and percentages.

Patients were categorised according to serum YKL-40 at entry into four quartiles: quartile I (range: 0–83 μg/L), quartile II (range: 84–136 μg/L), quartile III (range: 137–224 μg/L), and quartile IV (range: 224–1499 μg/L). For continuous variables, univariate association between the YKL-40 groups were done by the Kruskal–Wallis test (eGFR, hs-CRP, age, LVEF, haemoglobin, NT-proBNP). Comparative analysis for categorical patient characteristics was done by the Cochran-Armitage Trend test (gender, smoking status, history of HF, IHD, previous myocardial infarction (MI), hypertension (HT), and chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), NYHA class II–IV, hyperlipidaemia, stroke/transient ischemic attack (TIA), treatment (at