International Journal of Cardiology 167 (2013) 1354–1359

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

YKL-40 levels and atrial fibrillation in the general population ☆

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ARTICLE INFO

Article history:
Received 13 December 2011
Received in revised form 31 January 2012
Accepted 1 April 2012
Available online 21 April 2012

Keywords:
Cardiovascular diseases
Arrhythmia
Inflammation
Biomarkers
Epidemiology

ABSTRACT

Background: Atrial fibrillation is associated with inflammation. In contrast to inflammatory markers like C-reactive protein (CRP) and fibrinogen produced in the liver, YKL-40 is produced at the site of inflammation including in the myocardium. We hypothesized that elevated plasma YKL-40 levels associate with increased risk of atrial fibrillation.

Method and results: We measured plasma YKL-40 in 8731 participants from the prospective Copenhagen City Heart Study including 896 individuals who developed atrial fibrillation during up to 18 years of follow-up. Additionally, we measured YKL-40 in 6621 individuals from the cross-sectional Copenhagen General Population Study including 337 cases with atrial fibrillation. A YKL-40 level >95% percentile (>204 μg/L) versus <25% percentile (<36 μg/L) associated prospectively with a 2.10-fold (95%CI:1.43–3.09) increased risk of atrial fibrillation. Hazard ratios attenuated slightly after multifactorial adjustment to 2.01 (1.35–2.98), and further after additional adjustment for heart failure to 1.89 (1.27–2.80), for plasma CRP to 1.79 (1.20–2.67), and for fibrinogen levels to 1.89 (1.27–2.81). Adjusting multifactorially including both heart failure, CRP, and fibrinogen attenuated the risk of atrial fibrillation to 1.79 (1.20–2.67). These findings were supported in the cross-sectional study with an odds ratio of 2.73 (1.46–5.11) for a YKL-40 level >95% percentile versus <25% percentile, attenuating to an odds ratio of 2.13 (1.09–4.18) when adjusting multifactorially including heart failure, CRP, and fibrinogen.

Conclusions: Elevated plasma YKL-40 levels robustly associated with increased risk of atrial fibrillation originating from hospital admissions or visits to the emergency department, independent of heart failure, and CRP and fibrinogen levels. These findings need to be confirmed in other independent studies.

1. Introduction

YKL-40, also named chitinase-3-like-1 (CHI3L1) and human cartilage glycoprotein 39 (HC-gp39), is a novel inflammatory biomarker secreted by inflammatory cells [1,2]. The abbreviation YKL-40 is based on the 1-letter code for the first 3N-terminal amino acids: tyrosine (Y), lysine (K), and leucine (L), and its molecular weight of 40 kDa.

Atrial fibrillation is associated with inflammation and elevated levels of inflammatory markers such as C-reactive protein (CRP) and fibrinogen in large prospective studies [3–9]. While CRP and fibrinogen are produced centrally in the liver in response to cytokine production after an inflammatory stimulus, YKL-40 is produced by different cells in response to inflammation, including macrophages and neutrophils in the myocardium [10,11]. Since infiltrates of inflammatory cells have been observed in atrial biopsies from patients with atrial fibrillation [12], elevated YKL-40 levels might be a more distinct marker of atrial fibrillation than elevated levels of CRP and fibrinogen.

We tested the hypothesis that elevated plasma YKL-40 levels prospectively associate with increased risk of atrial fibrillation in the general population. Robustness of the association was examined by adjustment of risk estimates for gender and age; multifactorially for gender, age, body mass index, total cholesterol, high density lipoprotein (HDL) cholesterol, hypertension, hyperthyroidism, diabetes mellitus, statin use, heavy drinking, and current smoking; and multifactorially

☆ This work was supported by The Danish Heart Foundation; The Danish Agency for Science, Technology and Innovation (09-072074), The Danish Medical Research Council; Chief Physician Johan Boserup and Lise Boserup's Foundation; The Lundbeck Foundation; and Aase and Ejnar Danielsen's Foundation, all public or non-profit organizations with no right to approve or disapprove of the manuscript.

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doi:10.1016/j.ijcard.2012.04.006

as above including heart failure, or plasma levels of CRP or fibrinogen. Finally, we re-tested the hypothesis that elevated plasma YKL-40 levels associate with increased risk of atrial fibrillation in an independent cross-sectional study, adjusting risk estimates similarly as in the prospective study.

2. Methods

2.1. Study population

All participants in the Copenhagen City Heart Study and the Copenhagen General Population Study were white and of Danish descent, and follow-up was 100% complete, that is, we did not loose track of even a single participant. Studies were approved by Danish ethical committees (KF-100.2039/91 and H-KF-01-144/01) and conducted according to the Declaration of Helsinki. Informed consent was obtained from participants.

2.2. The Copenhagen City Heart Study

The Copenhagen City Heart Study is a prospective study of the Danish general population initiated in 1976–1978 (14,223 participants, participation rate 74%) with follow-up examinations in 1981–1983 (12,698 participants, participation rate 70%), 1991–1994 (10,135 participants, participation rate 61%), and 2001–2003 (6238 participants, participation rate 50%). Individuals were selected to reflect the adult Danish population aged 20-80+ years [13]. In the present study 8731 individuals participating in the 1991–1994 examination had plasma YKL-40 levels measured and results from this examination were considered baseline; the 167 individuals with atrial fibrillation at baseline were excluded. Individuals were followed for up to 18 years.

2.3. The Copenhagen General Population Study

The Copenhagen General Population Study is a cross-sectional study initiated in 2003 with ongoing inclusion [14]. Participants were ascertained exactly as in the Copenhagen City Heart Study. Plasma YKL-40 levels have been measured in 6621individuals including 337 cases of atrial fibrillation enrolled in the study from July 2004 through February 2005.

2.4. Atrial fibrillation

In both studies, atrial fibrillation was defined as a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of mechanical function. On the ECG, rapid oscillations, or fibrillatory waves that varied in amplitude, shape, and timing, replacing P waves, made the diagnosis and, in patients with intact atrio-ventricular conduction, the presence of an irregular, rapid ventricular response [15].

Information on a diagnosis of atrial fibrillation(World Health Organization; International Classification of Diseases, 8th edition: codes 427.93 and 427.94; 10th edition: I48.0-I48.9) was collected from 1976 and up until August 2010 by reviewing all hospital admissions and diagnoses entered in the national Danish Patient Registry, including visits to the emergency department from 1994. Alternatively, in the Copenhagen City Heart Study atrial fibrillation was diagnosed from electrocardiographic recordings obtained at the four study examinations and confirmed by two independent reviewers [16]. Of all atrial fibrillation events in the Copenhagen City Heart Study, 74% were identified through the national Danish Patient Registry alone, 26% through the national Danish Patient Registry and at one of the examinations, while none were diagnosed solely at an examination. Information about mortality was obtained from the national Danish Civil Registration System.

2.5. Biochemical analyses

Plasma YKL-40 levels were measured in duplicates by a commercial two-site sandwich-type enzyme-linked immunosorbent assay(Quidel Corporation, San Diego, CA), assessed daily for precision; coefficients of variations were 4–6% [17]. CRP levels were measured by a high-sensitivity turbidimetry assay (Dako, Glostrup; Denmark), assessed daily for precision and monthly for accuracy through a Scandinavian quality control program. Plasma fibrinogen, total cholesterol, and HDL cholesterol were measured using standard assays (Boehringer Mannheim, Konelab, or ILS Laboratories Scandinavia), assessed for precision and accuracy like CRP. Because plasma YKL-40 was measured again in 929 individuals attending both the 1991–94 and 2001–03 examinations of the Copenhagen City Heart Study, we were able to correct hazard and odds ratios for regression dilution bias [18].

2.6. Other covariates

Body mass index was calculated as body weight divided by height squared. Information on diagnoses of heart failure and hyperthyroidism were obtained from the national Danish Patient Registry and national Danish Causes of Death Registry(WHO International Classification of Diseases, 8th edition codes 427.09-11 and 242.0-99; 10th edition codes I50.0-9 and E05.0-9, respectively). Hypertension was self reported use of anti-hypertensive medication specifically prescribed as treatment for hypertension, and/or a systolic blood pressure ≥140 mmHg(≥135 mmHg for diabetics), and/or a diastolic blood pressure ≥90 mmHg(≥85 mmHg for diabetics). Diabetes mellitus was self-reported disease, treatment with anti-diabetic medication, and/or a non-fasting plasma glucose >11 mmol/L. Use of statin was self-reported. Alcohol consumption was self-reported in units per week (1 unit = 12 g) and heavy drinking defined as more than 14 and 21 units per week for women and men, respectively. Smokers were current smokers.

2.7. Statistical analyses

We used Stata 10.1. A two-sided P value <0.05 was considered significant. For trend tests by YKL-40 levels, the different groupings of subjects were coded 13(0–25 percentile), 38(25–50 percentile), 62(51–75 percentile), 83(76–90 percentile), 93(91–95 percentile), and 98(96–100 percentile), and ranked according to increasing YKL-40 levels; these groupings were done a priori to cover both quartiles and extreme phenotypes (top percentiles), similarly to that done previously [17]. Test for trend among ordered groups of continuous values was by a nonparametric test by Cuzick (because some of the variables were not normally distributed), and for categorical values by Cuzick's extension of the Wilcoxon rank-sum test [19]. All hazard and odds ratios were corrected for regression dilution bias [18], with a regression dilution ratio of 0.75 for YKL-40.

First, the relationship between plasma YKL-40 and risk of atrial fibrillation was studied prospectively in the Copenhagen City Heart Study using Cox regression models

Table 1
Baseline characteristics of individuals in the Copenhagen City Heart Study by plasma YKL-40 percentile groups.

	Percentile groups of plasma YKL-40						P-trend
	<25%	25–50%	51–75%	76–90%	91–95%	>95%	
	(<36 μg/L)	(36–55 μg/L)	(56–90 μg/L)	(91–152 μg/L)	(153–204 μg/L)	(>204 μg/L)	
Number of individuals	2159	2163	2185	1282	432	510	
Women	59%	57%	58%	57%	54%	43%	<0.001
Age, years	48 (35–58)	55 (44–66)	62 (54–72)	67 (60–75)	67 (60–75)	68 (61–75)	<0.001
Body mass index, kg/m^2	25 (22–27)	26 (22–28)	26 (23–28)	26 (23–29)	27 (24–29)	26 (24–29)	<0.001
CRP, mg/L	2.7 (0.9–3.7)	3.5 (1.3.–4.4)	4.1 (2.0.9–4.7)	4.6 (3.3–5.0)	4.4 (3.7–6.4)	4.8 (3.7–5.1)	<0.001
Fibrinogen, g/L	2.7 (2.3–3.2)	3.0 (2.5–3.5)	3.2 (2.6–3.6)	3.4 (2.8–3.8)	3.4 (2.7–3.9)	3.3 (2.7–3.9)	<0.001
Total cholesterol, mmol/L	5.7 (4.8–6.5)	6.2 (5.2–6.9)	6.4 (5.5–7.1)	6.4 (5.5–7.2)	6.3 (5.5–7.1)	6.2 (5.2–6.9)	<0.001
HDL cholesterol, mmol/L	1.6 (1.3–1.9)	1.6 (1.2–1.9)	1.6 (1.2–1.8)	1.6 (1.2–1.9)	1.6 (1.2–1.9)	1.6 (1.2–1.9)	0.4
Heart failure	5.1%	8.9%	13.0%	18.7%	20.4%	21.2%	<0.001
Hypertension	36%	49%	62%	70%	72%	71%	<0.001
Hyperthyroidism	2.0%	2.2%	2.6%	2.7%	1.6%	2.0%	0.57
Diabetes mellitus	2.0%	2.4%	4.6%	5.5%	9.0%	11.8%	<0.001
Statin use	0.5%	0.7%	1.3%	1.4%	1.6%	0.4%	0.006
Heavy drinkers	10%	11%	15%	20%	25%	38%	<0.001
Current smoking	43%	49%	49%	50%	53%	53%	<0.001

Values are from baseline at the 1991 to 1994 examination. Continuous values are summarized as mean and interquartile range. P values for trend among percentile groups of continuous values are by a nonparametric test by Cuzick. Categorical values are summarized in percent. P values for trend among percentile groups of categorical values are by Cuzick's extension of a Wilcoxon rank-sum test. CRP = C-reactive protein. HDL = high density lipoprotein.