Clinical Biochemistry xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Clinical Biochemistry

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

Myeloperoxidase, asymmetric dimethyl-arginine and the renin-angiotensin-aldosterone-system in cardiovascular risk patients: Cross-sectional findings from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study

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ARTICLE INFO

Article history:
Received 15 December 2016
Received in revised form 15 March 2017
Accepted 17 March 2017
Available online xxxx

Keywords:
Myeloperoxidase
Asymmetric dimethyl-arginine
Renin-angiotensin-aldosterone-system
Cardiovascular disease

ABSTRACT

Objectives: The leukocyte-derived myeloperoxidase (MPO), the nitric oxidase synthase (NOS) inhibitor asymmetrical dimethyl-arginine (ADMA) and the renin-angiotensin-aldosterone-system (RAAS) are associated with cardiovascular diseases (CVD). This study aimed to investigate potential interactions between the RAAS, ADMA and MPO in cardiovascular risk patients.

Design and methods: All in all, 1446 patients, who were referred to coronary angiography, were included in this prospective study. MPO, ADMA and circulating serum markers of the RAAS system were measured. Additionally, all-cause and CVD mortality, cardiovascular risk factors, inflammatory and endothelial markers, and medication use were investigated.

Results: MPO concentrations were significantly associated with ADMA ($P = 0.002$), renin ($P = 0.001$) and angiotensin II levels ($P = 0.015$), whereas ADMA was in tendency associated with renin ($P = 0.059$) and significantly with angiotensin II ($P = 0.001$). Both, ADMA and MPO were inversely correlated with angiotensinogen, angiotensin I and the angiotensin I/angiotensin II ratio. ADMA and angiotensin II were found stronger independent risk factors for all-cause and CVD mortality compared to MPO.

Conclusions: MPO concentrations were significantly associated with higher ADMA levels and an up-regulated circulating RAAS in patients with CVD. Moreover, serum levels of ADMA and angiotensin II were shown to be more predictive for all-cause and CVD mortality compared to MPO.

Abbreviations: CVD, cardiovascular disease; CAD, coronary artery disease; CRP, C-reactive protein; MPO, myeloperoxidase; HOCL, hypochlorus acid; NO, nitric oxide; NOS, nitric oxide synthase; ADMA, asymmetrical dimethyl-arginine; ROS, reactive oxygen species; DDAH, dimethyl-arginine dimethyl-amino-hydrolase; RAAS, renin-angiotensin-aldosterone-system; LURIC study, Ludwigshafen Risk and Cardiovascular Health study; ELISA, enzyme-linked immunosorbent assay; CV, coefficient of variation; HPLC, high pressure liquid chromatography; hsCRP high-sensitive C-reactive protein, IL-6, interleukin-6; VCAM-1, vascular cellular adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; LC-MS/MS, liquid chromatography tandem-mass spectrometry; IDMS, isotope dilution mass spectrometry; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index; HR, hazard ratio; CI, confidence interval; AT_1-R, angiotensin II type-1 receptor; NADPH, nicotinamide-adenine-dinucleotide phosphate.

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http://dx.doi.org/10.1016/j.clinbiochem.2017.03.013
0009-9120/

1. Introduction

Cardiovascular diseases (CVDs), including coronary artery disease (CAD), hypertension, congestive heart failure, peripheral vascular disease and stroke, continue to raise medical and public health problems worldwide and constitute the leading cause of death and disability in the Western world [1]. Inflammation has been established as a key component of atherosclerosis and vascular disease. In support of this fact, several independent epidemiological studies have confirmed that inflammatory markers, including the C-reactive protein (CRP), cytokines and endothelial adhesion molecules are clinically useful markers in predicting the risk of CVD [2]. Previous investigations suggest pathogenic links between myeloperoxidase (MPO) and inflammation as well as CVD [3–5]. The leukocyte-derived MPO is well known to produce a cascade of reactive oxidative species, including the hypochlorous acid (HOCl), which may ultimately lead to lipid peroxidation, direct scavenging of nitric oxide (NO), and nitric oxide synthase (NOS) inhibition [6].

MPO and MPO-derived reactive oxidants have been identified in human atherosclerotic lesions [7,8]. Leitner et al. reported a key role of MPO in the regulation of the endogenous NOS inhibitor asymmetrical dimethyl-arginine (ADMA) under inflammatory conditions [9]. Plasma concentrations of ADMA have been elevated in patients with CVD [10] and emerged as an independent predictor of all-cause and CVD mortality [11,12]. In addition, several studies have demonstrated that increased plasma concentrations of ADMA are associated with an increased reactive oxygen species (ROS) production [13,14]. Oxidative stress can decrease the activity of the dimethyl-arginine dimethylamino-hydrolase (DDAH), which degrades ADMA in the liver, leading to elevated plasma levels of ADMA [14,15]. In cell experiments, MPO-derived reactive oxidants inhibited the DDAH [9]. This leads to inhibition of the NO synthesis with subsequent vasoconstriction and endothelial dysfunction [9,16]. The interplay between MPO and ADMA is further linked to the renin-angiotensin-aldosterone-system (RAAS), which itself contributes to the development of endothelial dysfunction and atherosclerosis. NO, which is synthesized by NOS in the kidneys, is considered to be implicated in the control of renin secretion from the macula densa into the peripheral blood circulation [17,18]. The RAAS with its key-marker angiotensin II is well known to play an essential part in the pathogenesis of atherosclerotic lesions [19].

This study was conducted to elucidate potential associations between the leukocyte-derived MPO, the endogenous NOS inhibitor ADMA and the circulating RAAS in a large cohort of patients with cardiovascular risk referred to coronary angiography (Ludwigshafen Risk and Cardiovascular Health [LURIC] study [20]).

2. Materials and methods

2.1. Study design and participants

The LURIC study is a prospective cohort study designed to evaluate the effect of genetic and plasma biomarkers of cardiovascular health. In total, 3316 study participants referred to coronary angiography were recruited between 1997 and 2000. Data for all the markers reported were available for 1446 subjects (43.6%). A detailed flow diagram on patient recruitment is illustrated in Fig. 1. A detailed description of the baseline examination has been published previously [20]. In brief, inclusion criteria were Caucasian origin, clinical stability except for acute coronary syndromes, and the availability of a coronary angiogram. The indications for coronary angiography in individuals with clinically stable condition were chest pain and/or non-invasive test results consistent with myocardial ischemia. Individuals with any acute illness other than acute coronary syndrome, chronic non-cardiac diseases (i.e.

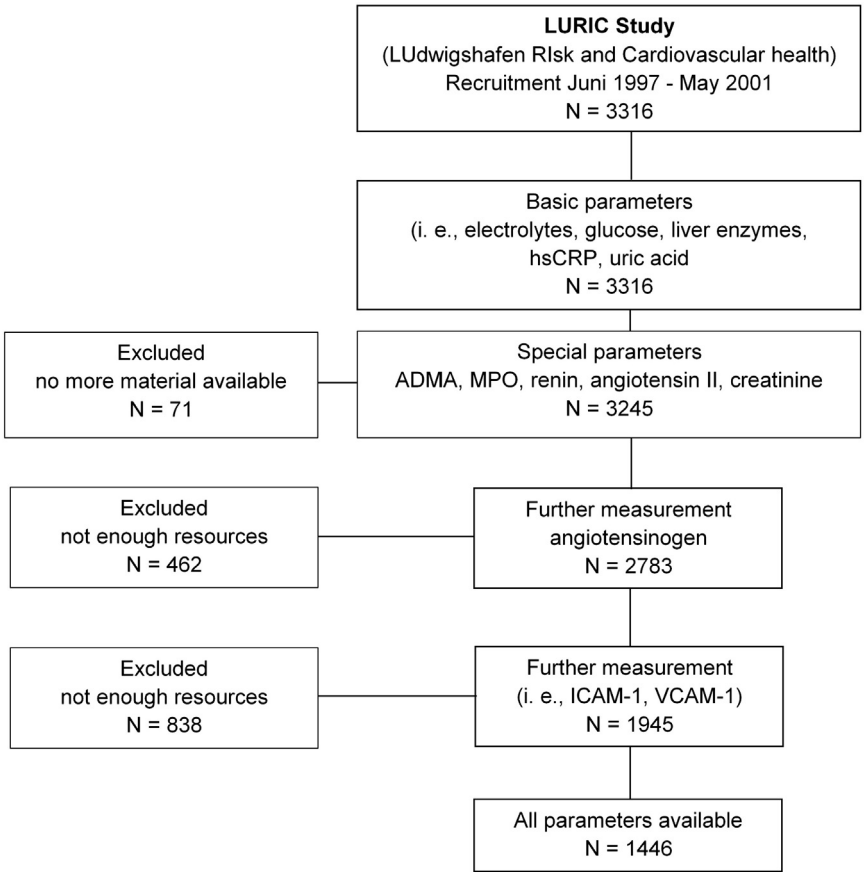

Fig. 1. Flow diagram on patient recruitment. Abbreviations: hsCRP = high-sensitive C-reactive protein, ADMA = asymmetric dimethyl-arginine, MPO = myeloperoxidase, ICAM-1 = intercellular adhesion molecule-1, VCAM-1 = vascular cell adhesion molecule-1.

Please cite this article as: S. Zelzer, et al., Myeloperoxidase, asymmetric dimethyl-arginine and the renin-angiotensin-aldosterone-system in cardiovascular risk patients: Cross-..., Clin Biochem (2017), http://dx.doi.org/10.1016/j.clinbiochem.2017.03.013