Atherosclerosis 240 (2015) 21–25

Contents lists available at ScienceDirect

Atherosclerosis

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

Is albuminuria a myocardial infarction risk equivalent for atherothrombotic events?

Philipp Rein [a, b, c], Christoph H. Saely [a, b, c], Alexander Vonbank [a, b, c], Peter Fraunberger [d], Heinz Drexel [a, b, c, e, *]

[a] Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Feldkirch, Austria
[b] Department of Medicine and Cardiology, Academic Teaching Hospital Feldkirch, Austria
[c] Private University of the Principality of Liechtenstein, Triesen, Liechtenstein
[d] Medical Central Laboratories, Feldkirch, Austria
[e] Drexel University College of Medicine, Philadelphia, PA, USA

ARTICLE INFO

Article history:
Received 18 November 2014
Received in revised form
25 January 2015
Accepted 18 February 2015
Available online 24 February 2015

Keywords:
Albuminuria
Albumin to creatinine ratio
Myocardial infarction
Coronary artery disease
Coronary angiography
Prospective

ABSTRACT

Objective: People with chronic kidney disease frequently experience cardiovascular events. This study sought to investigate whether the presence of albuminuria displays a vascular risk equivalent to that in patients with prior myocardial infarction.
Methods: Albuminuria was defined as a urinary albumin to creatinine ratio of 30 μg/mg or greater in 852 consecutive patients undergoing coronary angiography. Prospectively, we recorded vascular events over 3.2 ± 1.2 years.
Results: From our patients, 513 (60.2%) had neither albuminuria nor a history of MI, 126 (14.8%) had albuminuria without prior MI, 137 (16.1%) did not have albuminuria but had a history of MI, and 76 (8.9%) had both, albuminuria and prior MI. Compared with the incidence of the composite endpoint among normoalbuminuric patients with no prior MI (11.9%), event rates nearly doubled both in patients with albuminuria without prior MI (24.6%; $p = 0.003$) and in normoalbuminuric patients with a history of prior MI (21.2%; $p = 0.004$) and were highest in patients with both, albuminuria and prior MI (36.8%; $p < 0.001$). Importantly, event rates were not significantly different between patients with albuminuria and no prior history of MI and those with normoalbuminuria but prior MI ($p = 0.972$). Moreover, the event rate in patients with both, albuminuria and history of MI, was significantly higher ($p < 0.05$) than in the two groups exhibiting only one of the two conditions.
Conclusion: This is the first study demonstrating that albuminuria is a CAD risk equivalent. Thus, cardiovascular risk factors in albuminuric patients should be treated as aggressively as in patients with prior MI.

1. Introduction

Chronic kidney disease (CKD) is well known to increase the risk of cardiovascular morbidity and mortality. Among the many reasons therefor, impaired kidney function is associated with an excess of traditional risk factors, e.g. an adverse lipid profile [1,2] and enhanced coagulability and inflammatory activity [3]. With the background of large cohort studies [4,5], KDIGO recommends all people with CKD (defined by an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or the presence of albuminuria) to be considered at increased risk for cardiovascular disease [6], and the European Society of Cardiology recommends patients with an eGFR <60 ml/min/1.73 m^2 to be considered at very high risk for cardiovascular disease – like patients with previous myocardial infarction (MI) [7].

As with the eGFR [4], many studies have confirmed that albuminuria is an independent predictor of cardiovascular events [8,9]. However, in contrast to the aspect of eGFR [5], no study has prospectively assessed whether the risk of cardiovascular disease in patients with albuminuria is as high as in those with a prior history of MI. To examine this issue, we investigated the rates of vascular

* Corresponding author. Department of Medicine and Cardiology and VIVIT Institute, Academic Teaching Hospital Feldkirch, Carinagasse 47, A-6800 Feldkirch, Austria.
E-mail address: vivit@lkhf.at (H. Drexel).

http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.037
0021-9150/

events in a well-characterized high risk cohort with: 1) albuminuria and no history of prior MI; and 2) no albuminuria but a history of prior MI.

2. Methods

2.1. Study subjects

From August 2005 through December 2007 we enrolled 898 consecutive white patients who were referred to coronary angiography for the evaluation of established or suspected stable coronary artery disease (CAD) on the basis of current guidelines [10] and for whom information on albuminuria and prior history of MI was available. Patients who had suffered myocardial infarction or acute coronary syndrome within three months prior to the baseline angiography were not enrolled. Also, five patients with type 1 diabetes were excluded from the analyses.

Information on history of MI and conventional cardiovascular risk factors was obtained by a systematic standardized interview; systolic/diastolic blood pressure was measured by the Riva-Rocci method under resting conditions in a sitting position at the day of hospital entry at least 5 h after hospitalization. Hypertension was defined according to the 2013 European Society of Cardiology/European Society of Hypertension guidelines [11], and T2DM was diagnosed according to World Health Organization criteria [12]. With respect to antihypertensive medication, patients were asked for the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, diuretics, beta-blockers, calcium antagonists, alpha-receptor blockers, centrally active agents, direct vasodilators, aldosterone antagonists, and renin inhibitors. Height and weight were recorded, and body mass index (BMI) was calculated as body weight (kg)/height $(m)^2$.

Overall, 70.8% of our patients were on aspirin, 46.8% on statins, 31.0% on angiotensin converting enzyme (ace) inhibitors, and 11.2% on angiotensin II receptor blocking agents. Among patients with T2DM, 39.6 were not receiving any antidiabetic medication, and 20.3%, 24.8%, 38.1%, and 2.0% were receiving – alone or in combination – insulin, sulfonylurea, metformin, and glitazones, respectively.

The present study complies with the Declaration of Helsinki, and was approved by the Ethics Committee of the University of Innsbruck. All participants gave written informed consent.

2.2. Laboratory analyses

Venous blood samples were collected after an overnight fast of 12 h before angiography was performed, and laboratory measurements were performed from fresh serum samples, as described previously [13]. The serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were determined on Roche Cobas 6000 and 8000 clinical chemistry platform. All patients without known diabetes underwent an oral glucose tolerance test (OGTT) with 75 g glucose.

Urinary albumin excretion was expressed as the albumin/creatinine concentration ratio in a second morning urine specimen. Urinary albumin concentration was determined by immunoturbidometry (Tina-quant Albumin Gen.2 Assay, Roche Diagnostics). Both serum and urinary creatinine concentrations were measured with a modified Jaffé method (Creatinine Jaffé Gen.2 Assay, Roche Diagnostics), the analytical imprecision for albumin and creatinine in urin were below 3%. Albuminuria was defined as an urinary albumin to creatinine ratio (ACR) of 30 μg/mg or greater in a single-spot urine sample. The eGFR was assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which in patients with nearly normal renal function has been shown to give more accurate estimates of GFR than the MDRD-equation [14].

2.3. Prospective study

During an average follow-up time of 3.2 ± 1.2 years we recorded fatal and nonfatal cardiovascular end points, including vascular death (fatal myocardial infarction, sudden cardiac death, fatal ischemic stroke, and mortality from congestive heart failure due to CAD), nonfatal myocardial infarction, nonfatal ischemic stroke, need for coronary artery bypass grafting and percutaneous coronary intervention, or for non-coronary revascularizations. A major coronary event was defined as the occurrence of cardiac death or a definite fatal or nonfatal myocardial infarction. Follow-up data were available for 852 patients (95.4%). Patients underwent follow-up visits at our institution, where information on cardiovascular endpoints was obtained by a standardized interview. Study endpoints reported by the patients were cross-checked against medical records. Further, follow-up data were collected by telephone contacts with patients and family physicians, and mortality was ascertained through a national registry of death.

2.4. Statistical analysis

Differences in patient characteristics were tested for statistical significance with the Chi square test for categorical variables; the Mann–Whitney-U test was used for continuous variables, as appropriate. The Wilcoxon–Gehan statistic was used to compare differences in the cumulative incidence rates of vascular events. Adjusted hazard ratios (HR) for the incidence of vascular events were derived from Cox proportional hazards models. For these analyses, continuous variables were z-transformed [15]. Results are given as mean ± standard deviation if not denoted otherwise. Statistical significance was defined as two-tailed p-value <0.05 and analyses were performed with the software package SPSS 11.0 for Windows (SPSS, Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

At baseline, median ± interquartile range of the ACR was 13.1 ± 21.3 μg/mg and albuminuria was present in 202 (23.7%) of our patients. Prior to inclusion in the study, 213 patients (25.0%) had experienced MI. The prevalence of a history of MI was higher in patients with albuminuria than in normoalbuminuric patients (37.6 vs. 21.1%; $p < 0.001$). From our patients, 513 (60.2%) had neither albuminuria nor a history of MI, 126 (14.8%) had albuminuria but no prior MI, 137 (16.1%) did not have albuminuria but had a history of MI, and 76 (8.9%) had both, albuminuria and prior MI.

Table 1 summarizes the baseline characteristics of the patient groups: those with albuminuria and those with normoalbuminuria, both with and without a history of MI. When risk factors were compared, patients without albuminuria but with prior MI in comparison to the group of patients with albuminuria and no history of prior MI had a higher prevalence of smoking ($p = 0.040$) and were more likely to receive cardiovascular medication ($p < 0.001$ for aspirin and statins, respectively; and $p = 0.003$ for beta blockers), whereas BMI ($p = 0.032$), HbA1c ($p = 0.037$), total cholesterol ($p = 0.005$) and LDL-C ($p = 0.012$) were higher among those with albuminuria but no prior MI. With respect to the presence of albuminuria, the prevalence of significant stenoses at baseline angiography did not differ in patients with a prior history of MI ($p = 0.152$) nor in those without previous MI ($p = 0.072$). In