Atherosclerosis 210 (2010) 649–655

Contents lists available at ScienceDirect

Atherosclerosis

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

Gamma-glutamyltransferase and prognosis in patients with stable coronary heart disease followed over 8 years

L.P. Breitling[a,*], N.C. Grandi[a], H. Hahmann[b], B. Wüsten[c], D. Rothenbacher[a], H. Brenner[a]

[a] Division of Clinical Epidemiology and Aging Research C070, German Cancer Research Center, Bergheimer Str 20, 69115 Heidelberg, Germany
[b] Schwabenland-Klinik, Isny-Neutrauchburg, Germany
[c] Klinik am Südpark, Bad Nauheim, Germany

ARTICLE INFO

Article history:
Received 18 November 2009
Received in revised form
14 December 2009
Accepted 28 December 2009
Available online 11 January 2010

Keywords:
Coronary heart diseases
Prospective cohort study
Gamma-glutamyltransferase
Prognosis
Secondary cardiovascular disease

ABSTRACT

Objectives: Serum gamma-glutamyltransferase (γ-GT) predicts incident cardiovascular disease and mortality. The present study examined whether γ-GT also is associated with prognosis in patients with stable coronary heart disease.
Methods and results: This study included 1152 participants (aged 30–70 years at baseline) of an in-patient rehabilitation programme after acute coronary syndrome, recruited in two rehabilitation clinics in Germany in the years 1999–2000 (KAROLA study). Until year 8 follow-up, 147 participants had experienced a non-fatal or fatal secondary cardiovascular disease event. Confounder-adjusted Cox proportional hazards models revealed an increase in risk for secondary events over ascending γ-GT quartiles, with hazard ratios (95% confidence interval) of 1.21 (0.72–2.03), 1.32 (0.80–2.16) and 1.75 (1.08–2.83) for the 2nd, 3rd and 4th in reference to the lowest quartile (P_{trend} = 0.024). The association with all-cause mortality examined as a secondary outcome was slightly stronger (hazard ratio of 4th quartile: 1.97 [1.15–3.36]; P_{trend} = 0.017).
Conclusions: In patients with stable coronary heart disease, serum γ-GT was associated with prognosis independent of a variety of established risk markers. The association appeared similar to that reported for primary cardiovascular disease, which should motivate additional studies of its clinical utility in cardiovascular patient care.

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1. Introduction

In recent years, serum γ-glutamyltransferase (γ-GT) has been found to be consistently associated with incident coronary heart disease and cardiovascular mortality [1–6]. Similarly, γ-GT concentrations are predictive for incident diabetes mellitus [7,8], one of the most important risk factors not only for primary, but also for secondary cardiovascular disease events.

More detailed investigations of γ-GT in cardiovascular disease are scarce. In a purely cross-sectional analysis in patients referred for elective coronary angiography, patients with significant coronary artery disease had somewhat higher γ-GT concentrations than those without, but no statistically significant independent association was found [9]. In contrast, γ-GT measured 4 weeks after a "very small or unconfirmed acute myocardial infarction" was strongly associated with 10-year mortality in another study [10]. A somewhat smaller study of diagnostic angiography patients also reported a more than doubled risk of adverse outcome in subjects with previous myocardial infarction and high γ-GT [11]. In subjects with heart failure symptoms [12], γ-GT was found to be positively associated not only with disease severity, but also with the probability of death or heart transplantation.

Given the convenient availability of γ-GT measurements in standard clinical settings, an evaluation of the prognostic value of this marker in heart disease patients is of high interest. We therefore investigated the association of baseline serum levels of γ-GT with the risk of secondary cardiovascular disease events (CVD) in patients with stable coronary heart disease during long-term follow-up.

2. Methods

2.1. Study design

Eligible subjects for the KAROLA prospective cohort study were patients aged 30–70 years and admitted from January 1999 to May 2000 to one of two participating rehabilitation clinics for in-hospital rehabilitation within 3 months (average: 6 weeks) after acute myocardial infarction or coronary artery revascularization.

* Corresponding author. Tel.: +49 6221 5481 52; fax: +49 6221 5481 42.
E-mail addresses: L.Breitling@dkfz-heidelberg.de, lutz.breitling@gmail.com (L.P. Breitling).

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doi:10.1016/j.atherosclerosis.2009.12.037

The two specialized clinics located in the south and middle of Germany receive referrals from a large geographic area, since each person experiencing an acute coronary syndrome is entitled to participate in a specialized in-patient rehabilitation programme. The study was conceived to allow detailed analyses of prognostic factors in patients with stable coronary heart disease, i.e. relating to long-term prognosis after the potentially distorting occurrence of early mortality. Written informed consent was obtained from all participants, and the study protocol was approved by the ethics boards of the physicians' chambers of Hessen and Baden-Württemberg, and of the Universities of Ulm and Heidelberg. Detailed descriptions of the KAROLA study, which complied with the Declaration of Helsinki, have been published elsewhere [13,14].

2.2. Baseline and follow-up examinations

Baseline information was collected by standardized self-administered questionnaires at the beginning of the rehabilitation programme and included basic sociodemographic, medical/anamnestic and health-related behavior information. Data on alcohol consumption during the hospital stay were collected in another standardized self-administered questionnaire before discharge. Additionally, relevant data were obtained from hospital records, including secondary diagnoses, drug prescriptions at discharge and results of routine blood parameter measurements including serum γ-GT at the end of rehabilitation.

Active follow-up was conducted 1, 3, 4.5, 6 and 8 years after baseline. Participants were mailed standardized questionnaires asking for updated information on incident disease and health-related behaviors. Information on secondary CVD events since last follow-up, respectively, baseline was provided by the patients' general practitioners. In the case of deceased participants, death certificates indicating the cause of death were obtained from Public Health authorities.

2.3. Exposure definitions

Measurements of serum γ-GT concentrations at 25 °C were part of routine laboratory assessments during rehabilitation and pertinent data were obtained from hospital records. As sex-specific reference ranges are commonly used in the study of γ-GT, the exposure was primarily defined by sex-specific quartiles, i.e. subjects were assigned to quartiles using as cut-offs the 25th, 50th and 75th percentiles of serum γ-GT in either males or females depending on the sex of the individual. For trend testing, the category indicator assuming values of 0 (lowest quartile) through 3 (highest quartile) was treated as a continuous variable. To capture potentially stronger effects particularly in the upper concentration range, we also fitted 'higher resolution' models with the fourth γ-GT quartile further divided at the 90th and 95th percentiles. Models including γ-GT concentrations after natural logarithmic (*ln*) transformation were also analyzed.

2.4. Outcome definitions

The primary outcome of interest for the present analyses was the occurrence of a non-fatal or fatal secondary cardiovascular disease event. Non-fatal events included physician-reported incident myocardial infarction or stroke. Fatal events were cases with CVD as the main cause of death according to the official death certificate (ICD-9, 390–459, or ICD-10, I00–I99 and one case of R57.0 [cardiogenic shock]). All-cause mortality was examined as a secondary outcome. Subjects without any physician-based follow-up information or ascertained death were excluded from the primary outcome analysis.

2.5. Statistical analysis

The study population was described according to major baseline characteristics. Correlations between γ-GT and other markers were quantified by Spearman correlation coefficients, controlling for age and sex using the PARTIAL statement of the CORR procedure in SAS [15]. Subsequently, the association between serum γ-GT categories or *ln*(γ-GT) and prognosis was examined by Kaplan–Meier plots and/or Cox proportional hazards models [16]. The survival time was defined as the time from study inclusion to the occurrence of the first outcome event as described above, censoring at the date of last physician-based follow-up information (primary outcome) or at the date of last sign of life (all-cause mortality). The proportional hazards assumption was assessed by visual inspection of Kaplan–Meier and log–log survival plots. Basic Cox models were adjusted for age and sex, full models additionally controlled for potentially confounding variables known to be strongly associated with both γ-GT and CVD from the literature [7], in particular body mass index (BMI; $\leq$25, >25–30, >30 kg/m^2), elevated serum LDL cholesterol ($\geq$100 mg/dL), history of diabetes, hypertension and myocardial infarction, and smoking status (never, former, current smoking), and for covariables generally indicating the disease severity at baseline, namely extent of coronary artery involvement (0–1, 2, 3–4 vessels affected), and discharge prescription of angiotensin-converting enzyme-inhibiting drugs and of diuretics. We furthermore explored the possibility of heterogeneity of associations by age in the fully adjusted models of *ln*-transformed γ-GT, including interaction terms with age, which was categorized in these models for ease of interpretability (30–49, 50–59, 60+ years).

The stability of the statistical associations was assessed by excluding subjects with extreme γ-GT concentrations (>95th sex-specific percentiles), and furthermore by examining the impact of additionally including alcohol consumption intensity (during in-patient time or during the previous 12 months) or serum markers correlated with γ-GT in the Cox proportional hazards models. To explore the role of manifest heart failure in this context, we examined the Spearman correlations of γ-GT with angiographically determined ejection fraction (available for 514 subjects) and with the concentration of amino-terminal pro-brain natriuretic peptide (NT-proBNP; available for 1128 subjects) determined as reported previously [14]. We examined the impact of adjusting for heart failure by adding *ln*-transformed NT-proBNP to the fully adjusted models, or by adjusting for an indicator of moderately-to-severely impaired left ventricular function formed based on available semi-quantitative angio- or echocardiographic data (impaired function prevalent at baseline in 230 of 1053 subjects with sufficient data).

All significance tests were two-tailed and p-values with a level of <0.05 were considered statistically significant. The software package SAS 9.2 was used for all statistical analyses [15].

3. Results

3.1. Baseline characteristics

Of 1206 subjects recruited at baseline, follow-up information for secondary CVD events and serum γ-GT values were complete for 1049 (87.0%). In addition, 103 more subjects with follow-up information about vital status could be included into the all-cause mortality analyses (total 1152 [95.5%]). The median age (interquartile range [IQR]) of the overall population of n = 1152 was 60 (54–65) years. In the 178 females, median (IQR; range) γ-GT concentrations were 14.5 (10–24; 6–265) IU/L. The corresponding values describing the distribution in the 974 males were 18 (13–29; 5–730) IU/L. The median (IQR) time between the acute event preceding study inclusion and the assessment of γ-GT was 41 (34–49) days. The

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