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Serum gamma-glutamyl transferase activity: A new marker for stent restenosis?☆

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Abstract

Stent restenosis remains the main limitation of percutaneous coronary intervention. Elevated serum gamma-glutamyl transferase (GGT) level is associated with an inflammatory response. We aimed to determine the correlation of stent restenosis with the serums level of GGT. One hundred and twenty patients (age 58.56 ± 10.46 years, 66% male) with a history of coronary stent implantation and had undergone control coronary angiography (60 with restenosis and 60 without) were included. All had baseline serum GGT activity and were free of systemic and hepatobiliary disease. Median baseline serum GGT activity was significantly higher in patients with restenosis (34.00 U/L (24.00–47.75)) than in those without restenosis (21.00 U/L (17.25–26.7500)) ($P < 0.0001$). Stent restenosis was identified in 38% of the patients with a serum GGT value >40 U/L and in 5% of patients with a serum GGT value ≤40 U/L ($P < 0.001$). Serum C-reactive protein (CRP) and total bilirubin levels were significantly higher ($P = 0.011$ and 0.037, respectively) and alkaline phosphatase levels were significantly lower in patients with restenosis ($P = 0.029$). Levels of GGT, CRP, and alkaline phosphatase were independent predictors of restenosis ($P = 0.001$, 0.019 and 0.004, respectively). In conclusion, the serum level of GGT may be an independent marker for stent restenosis.

Keywords: Percutaneous coronary intervention; Stent; Restenosis; Gamma-glutamyl transferase

1. Introduction

The use of coronary artery stenting has produced a major improvement in the treatment of patients with coronary artery disease (CAD). However, despite the major advances in stent technology and antiplatelet therapy, restenosis remains the major limitation of intracoronary stent implantation. The estimated overall clinical restenosis rate is 15–25% [1]. Neointimal proliferation is the main mechanism involved in stent restenosis. In the last decade, several studies have shown that inflammatory mechanisms play a vital role in neointimal proliferation and stent restenosis [2].

Gamma-glutamyl transferase (GGT) is a plasma membrane enzyme that breaks down extracellular glutathione, which is an important antioxidant involved in the resynthesis of intracellular glutathione [3]. It has been shown that in rat lung epithelial cells, GGT expression is increased by oxidants; this suggests that an increase in GGT activity may be a marker for oxidative stress in the murine model [4]. Other research indicates that increased serum GGT activity could be used as a marker for increased oxidative stress in humans [5]. It has been shown that GGT promotes LDL oxidation and generates reactive oxygen species in the presence of iron ions [6,7] and that oxidative stress has an important role in inflammation [3,8].

Serum GGT activity is used as a marker for hepatobiliary disease and alcohol consumption [9]. However, in the CARDIA study, serum GGT values were strongly and positively correlated with determinants of oxidative stress such as the

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levels of C-reactive protein (CRP), uric acid, and fibrinogen [10]. In addition, in patients with a history of myocardial infarction and documented CAD, it has been found that the level of GGT has an independent predictive value for the mortality and the incidence of non-fatal myocardial infarction [11]. In a large study of middle-aged men, the level of GGT had a prognostic significance for overall and cardiac-related mortality [12].

We therefore investigated the correlation of stent restenosis with the serum GGT level and attempted to determine whether that association depends on the presence of diabetes mellitus or alcohol consumption. We also investigated the associations between the serum level of GGT with cardiac risk factors, stent restenosis, and the levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and CRP.

2. Materials and methods

We retrospectively evaluated 1500 adult patients who had undergone coronary stent implantation between 1996 and 2002 at the Baskent University Hospital in Ankara, Turkey. Every patient was treated routinely with thienopyridine for at least 6 months after stent deployment. Serum GGT activity was determined before stent deployment. Control coronary angiography was performed in patients ($n = 215$) with either chest pain or a positive treadmill test result during initial examination. Of the 215 patients, those who exhibited either residual stenosis after coronary stent implantation or severe systemic or active hepatobiliary disease were excluded from the study. Among the remaining, we randomly selected 120 patients (60 with stent restenosis and 60 without restenosis).

We noted the subjects' clinical and demographic characteristics, which included coronary risk factors, age, sex, history of arterial hypertension, diabetes mellitus, overweight (body mass index >25 kg/m^2), menopausal status, tobacco smoking, family history of premature CAD, alcohol consumption, and medications. Serum levels of CRP, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, ALT, AST, alkaline phosphatase, total bilirubin, and direct bilirubin were recorded, as was the site of the lesion in which the stent had been deployed.

Control coronary cineangiograms were interpreted by two independent interventional cardiologists who were blinded to each patient's clinical characteristics and laboratory test results. As defined by Gaspardone et al. [13], stent restenosis was accepted as narrowing in over 50% according to the results of control coronary angiography.

Serum GGT levels were measured by the enzymatic calorimetric test at 37 °C, and L-gamma-glutamyl-3-carboxy-4-nitroanilide was used as substrate [14]. To perform that evaluation, the Roche/Hitachi analyzer (Mannheim, Germany) was used. In our laboratory the normal reference value of the GGT level for a healthy individual was 8–61 U/L. Serum CRP levels were measured by the immunoturbidimetric method (Roche Diagnostics, GmbH, Mannheim, Germany) with a normal reference value of less than 10 mg/L. Serum GGT activity and all other hematochemical data were based on the analysis of antecubital vein blood samples after an overnight fasting before the stent implantation, according to our usual clinical laboratory procedures.

The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and the local committee approved the study.

2.1. Statistical analysis

All computations were performed using the Statistical Program for the Social Services version 10.0 for Windows (SPSS Inc., Chicago, Ill, USA). The distribution of continuous variables for normality was tested with One-Sample Kolmogorov–Smirnov test and data are presented as mean ± standard deviation (S.D.) or median and interquartile ranges, as appropriate. Categorical variables are reported as frequencies and group percentages. Differences between patients with and without stent restenosis in normally and non-normally distributed variables were evaluated by the unpaired t-test and the Mann–Whitney U-test, respectively. Categorical variables were analyzed by the χ^2-test. Multiple logistic regression analysis was used to determine the independent predictors related to stent restenosis. Significant univariate variables with $P < 0.05$ were included in the multiple logistic regression analysis for the calculation of odds ratios and 95% confidence intervals. All P values are 2-sided, and a P value of <0.05 was considered significant.

3. Results

The mean age of the patients was 58.56 ± 10.46 years (range, 33–84 years), and 80 (66.6%) subjects were men. Twenty-eight (23.3%) of the patients had diabetes mellitus, and 61 (50.8%) had hypertension. In addition, 71 (59.2%) were overweight, 64 (53.3%) were tobacco smokers, 17 (14.2%) consumed alcohol, and 48 (40%) had a family history of premature CAD. Of the 40 women participants, 31 (77.5%) were postmenopausal. The history of statin use was noted in 69 (57.5%) patients. The sites of lesions in which stents were implanted are shown in Table 1. The median time to assesment of restenosis was 12.0 months (range: 6–45) following the stent deployment. The clinical characteristics and laboratory values of the study population are shown in Table 2.

Age and sex and the prevalences of hypertension, diabetes mellitus, overweight, tobacco smoking, a family history of premature CAD, menopause were similar in patients with or without restenosis. Medications including statins and thienopiridines did not differ between the groups ($P > 0.05$). Only alcohol consumption was significantly higher in patients with restenosis ($P = 0.018$) (Table 2). The median serum GGT level was significantly higher in patients who