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Brief Report

Gamma-glutamyltransferase and Future Risk of Pneumonia: A Long-Term Prospective Cohort Study

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Abstract Serum gamma-glutamyltransferase (GGT) has been linked with the risk of adverse health outcomes. We aimed to assess the prospective association of GGT activity with pneumonia risk. Serum GGT was measured at baseline in 2,400 middle-aged men. Within-person variability in GGT values was corrected for using data from repeat measurements. During a median follow-up of 25.3 years, 409 pneumonia cases were recorded. The age-adjusted regression dilution ratio of GGT was 0.68 (95% CI: 0.63-0.73). Gamma-glutamyltransferase was approximately log-linearly associated with pneumonia risk. In analysis adjusted for several major pneumonia risk factors, the hazard ratio (95% CI) for pneumonia per 1 standard deviation increase in GGT was 1.14 (1.02-1.28). The association was however attenuated on additional adjustment for high sensitivity C-reactive protein (hsCRP) 1.08 (0.96-1.22). There is an approximately log-linear positive association between GGT activity and future risk of pneumonia in a middle-aged male population, which is partly dependent on hsCRP.

Keywords gamma-glutamyltransferase; pneumonia; cohort study

Abbreviations

CI Confidence interval

COPD Chronic obstructive pulmonary disease

GGT Gamma-glutamyltransferase

HR Hazard ratio

hsCRP High sensitivity C-reactive protein

IQR Interquartile range

KIHD Kuopio Ischemic Heart Disease

SD Standard deviation

Introduction

Pneumonia affects about 450 million people worldwide and causes approximately 4 million deaths annually.[1] It is a common cause of death among the young, elderly, and people with comorbid conditions.[1] Despite the advent of new effective antimicrobial strategies within the last few decades, mortality from pneumonia continues to increase.[2] Pneumonia is also associated with substantial morbidity, reduced quality of life, and high healthcare costs.[2] Major risk factors which predispose to pneumonia include smoking, excessive alcohol consumption, respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), and other chronic conditions such as kidney and liver disease.[2] Pneumonia constitutes a substantial public health burden and is a preventable health condition.

Gamma-glutamyltransferase (GGT), commonly used as a marker for excessive alcohol consumption [3] and an index of liver injury, has been consistently shown to be positively and independently linked with the future risk of adverse vascular and non-vascular outcomes. [4,5] Gamma-glutamyltransferase is a marker of oxidative stress[6] and has pro-inflammatory properties[7] and has been suggested to be involved in the pathogenesis of these adverse outcomes via pro-oxidant and inflammatory pathways. Emerging evidence suggests that high GGT activity is associated with an increased risk of pulmonary dysfunction and COPD.[8] Since inflammatory processes as well as oxidative stress are involved in the pathogenesis of pneumonia, we hypothesized that GGT may be linked to the risk of pneumonia. However, the relationship between GGT and the risk of pneumonia has not been previously investigated. In this context, we aimed to assess the prospective association of serum GGT with risk of pneumonia, using a study which comprised a population-based cohort of 2,400 Caucasian men.

Methods

Participants in the current analysis comprised a general population-based sample of 2,422 middle-aged men aged 42-61 years who were recruited into the Kuopio Ischemic Heart Disease (KIHD) risk factor study. The local ethics committee of the University of Eastern Finland approved the study protocol and all study procedures were conducted according to the Declaration of Helsinki. Study design, recruitment methods and assessment of risk markers have been described in previous reports.[9-11] Participants of the KIHD study constituted a representative sample of men who were living in the city of Kuopio and its surrounding rural communities in eastern Finland. Baseline examinations were conducted between March 1984 and December 1989. Of 3,433 potentially eligible and randomly selected men who were invited to participate in the study, 3,235 were found to be eligible. Of this number, 553 did not respond to the invitation or declined to give informed consent, leaving 2,682 men who volunteered to participate in the study. The current dataset analyzed comprised of 2,400 men who had complete information on GGT, relevant covariates, and pneumonia outcomes. Serum GGT activity was measured using the kinetic method (Thermo Fisher Scientific, Vantaa, Finland) with repeat measurements performed 4 years and 11 years after the baseline measurements in a random subset of participants.[9,10] Incident cases of pneumonia that occurred from study entry to 2014 were included in this analysis. The diagnoses of pneumonia cases were made by qualified physicians based on the International Classification of Diseases codes used in clinical practice and were collected by linkage to the National Hospital Discharge Register and a comprehensive review of hospital records. All skewed variables (GGT, high sensitivity C-reactive protein (hsCRP), and triglycerides) underwent log transformation to approximate normal distributions. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

Results

Baseline characteristics of study participants and cross-sectional correlates of GGT are reported in **Table 1.** The mean [standard deviation (SD)] age of study subjects at study entry was 53 (5) years. The mean (SD) of $\log_e$ GGT was 3.13 (0.65) U/L. Serum GGT values were significantly and positively correlated with alcohol consumption, physical measures [body mass index (BMI) and blood pressure], lipids, fasting plasma glucose, and inflammation as measured by hsCRP.

During a median (IQR) follow-up of 25.3 (16.8-27.8) years, 409 hospital diagnosed pneumonia cases were recorded (incident rate of 7.84 per 1000 person-years at risk; 95% CI 7.12 to 8.64)**.** Repeat measurements of GGT taken 4 and 11 years after baseline were available in a random sample of 730 men. The overall age-adjusted regression dilution ratio of GGT was 0.68 (95% CI: 0.63 to 0.73), which suggests that using baseline measurements of GGT could underestimate the association between GGT and pneumonia risk by [(1/0.68)-1]*100 = 47%. On adjustment for risk factors for pneumonia (age, BMI, smoking status, history of diabetes, prevalent histories of coronary heart disease, asthma, chronic bronchitis, tuberculosis and cancer, alcohol consumption, socioeconomic status, and physical activity), GGT was positively associated with the risk of pneumonia in an approximately log-linear fashion (**Figure**). In an age-adjusted analysis, the HR for pneumonia per 1 SD increase in GGT was 1.17 (95% CI: 1.05 to 1.29), which was minimally attenuated on further adjustment for several risk factors for pneumonia 1.14 (95% CI: 1.02 to 1.28). The association was attenuated on additional adjustment for hsCRP 1.08 (95% CI: 0.96 to 1.22). The associations were stronger after correction for within-person variability in GGT values (**Table**). In an age-adjusted analysis, the initial association 1.17 (95% CI: 1.05 to 1.29) was attenuated after single additional adjustment for hsCRP 1.06 (95% CI, 0.95 to 1.18).

Discussion

In this general population-based cohort of middle-aged approximately healthy Caucasian men, we observed an increase in the risk of pneumonia with increasing GGT activity. The association between

GGT activity and pneumonia remained independent after adjustment for several established risk factors, but was attenuated on further adjustment for hsCRP. Additionally, in an age-adjusted analysis, the GGT-pneumonia association was attenuated on single additional adjustment for hsCRP; which suggest that the association between GGT and pneumonia is dependent on inflammation. Pneumonia is a well-known inflammatory condition of the lung tissue,[12] oxidative stress is a common pathogenic mechanism underlying the development of inflammatory lung diseases such as pneumonia,[13] and high GGT activity signifies a state of oxidative stress.[14] Elevated GGT activity may also reflect chronic subclinical inflammation, a state characterised by elevated levels of CRP, which is also secreted by the liver and directly and strongly correlated with GGT activity.[15] Taking the evidence together suggests that inflammatory processes and oxidative stress may underlie the aetiology between GGT and pneumonia. However, it is unlikely that high GGT activity can be considered a direct cause of pneumonia on the basis of current evidence, but rather GGT is a risk marker of pneumonia. It can also be argued that high GGT activity is a marker of underlying health status such as poor general health due to a disease condition, which may predispose to pneumonia. Furthermore, increased GGT activity is a biomarker of exposure to smoking and various environmental pollutants,[16,17] which may play direct roles in the aetiogenesis of pneumonia. Despite the likelihood that GGT could only be a risk marker for pneumonia, assays for GGT may have the potential to aid in the identification of individuals at high risk of developing pneumonia. There is already accumulating evidence that elevated GGT activity (even below the upper limits of normal) is associated with an increased risk of several chronic disease conditions.[4] Assays for GGT are commonly measured as part of routine liver function panels and are sensitive, well standardized, inexpensive, and simple tests. Further investigation into the biological pathways involved in the relationship between GGT and pneumonia and whether information on GGT can be used in risk assessment of pneumonia is warranted.

This is the first evaluation of the association between serum GGT activity and the risk of prospectively collected pneumonia cases using a general population-based prospective cohort study. Other strengths

include the large sample size, long-term and complete follow-up of participants, and detailed analyses which include adjustment for a comprehensive panel of major confounders, assessment of the shape of the relationship between GGT and pneumonia risk, as well as correction for within-person variability in GGT values. A number of limitations deserve mention and which include (i) the inability to generalize the findings to women and other races; (ii) lack of data on other liver enzymes, hence the inability to assess for confounding or interaction; (iii) the possibility of residual confounding due to errors in measurements of some covariates and/or unmeasured relevant confounders such as underlying health conditions (eg. autoimmune diseases, viral hepatitis, cholelithiasis), influenza immunisation status, lung function, and other health modifying behaviours; and (iv) biases due to lack of data on specific types of pneumonia and possibility of excluding potential cases of pneumonia that were not captured at healthcare facilities.

In conclusion, there is an approximately log-linear positive association between GGT activity and future risk of pneumonia in a middle-aged population, which is partly dependent on inflammation as measured by hsCRP. Further research is needed to evaluate if measurements of GGT will have any role in the prevention and risk assessment of pneumonia in the general population.

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Compliance with Ethical Standards:

Funding This study was funded by The Finnish Foundation for Cardiovascular Research, Helsinki, Finland.

Conflict of Interest None

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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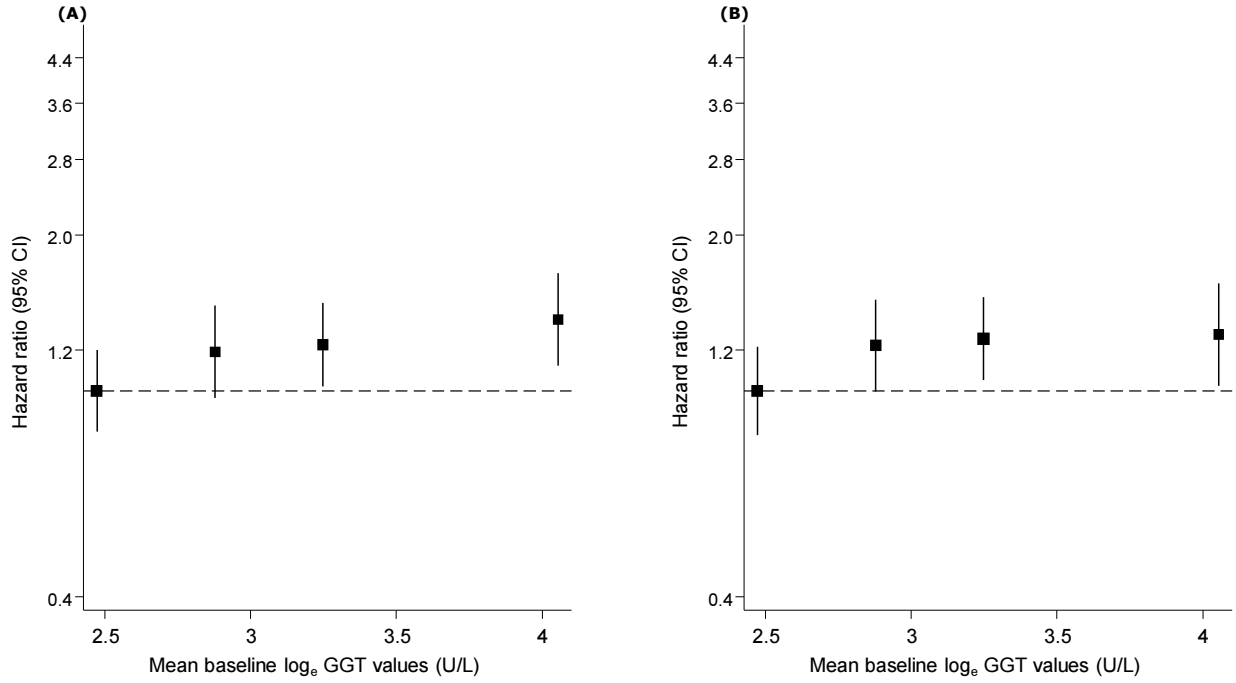
Figure legend

Figure. Hazard ratios for pneumonia, by quartiles of baseline levels of gamma-glutamyltransferase



A, adjusted for age; **B**, adjusted for age, body mass index, smoking status, history of diabetes, prevalent coronary heart disease, history of asthma, history of chronic bronchitis, history of tuberculosis, history of cancer, alcohol consumption, socioeconomic status, and physical activity

Table 1. Baseline characteristics and cross-sectional correlates of gamma-glutamyltransferase

	Mean (SD) or median (IQR) or n (%)	Pearson correlation r (95% CI)†
GGT (U/L)	20 (15-33)	-
Questionnaire/Prevalent conditions		
Age at survey (years)	53 (5)	-0.03 (-0.07, 0.01)
Alcohol consumption (g/week)	75.1 (134.3)	0.29 (0.25, 0.32)***
History of type 2 diabetes	98 (4.1)	-
Current smoker	764 (31.8)	-
History of CHD	615 (25.6)	-
History of asthma	84 (3.5)	-
History of chronic bronchitis	181 (7.5)	-
History of tuberculosis	93 (3.9)	-
History of cancer	41 (1.7)	-
Physical measurements		
BMI (kg/m^2)	26.9 (3.6)	0.34 (0.31, 0.38)***
SBP (mmHg)	134 (17)	0.22 (0.18, 0.26)***
DBP (mmHg)	89 (11)	0.23 (0.19, 0.26)***
Physical activity (KJ/day)	1538 (1483)	0.03 (-0.01, 0.07)
Socio-economic status	8.57 (4.22)	0.01 (-0.03, 0.05)
Lipid markers		
Total cholesterol (mmol/l)	5.91 (1.09)	0.10 (0.06, 0.14)***
HDL-C (mmol/l)	1.30 (0.30)	-0.03 (-0.07, 0.01)
Triglycerides (mmol/l)	1.10 (0.80-1.56)	0.26 (0.23, 0.30)***
Metabolic, renal, and inflammatory markers		
Fasting plasma glucose (mmol/l)	5.36 (1.28)	0.20 (0.16, 0.24)***
Serum creatinine (μmol/l)	89.6 (20.8)	0.00 (-0.04, 0.04)
Estimated GFR (ml/min/1.73 m^2)	87.0 (17.2)	-0.00 (-0.04, 0.04)
C-reactive protein (mg/l)	1.30 (0.71-2.49)	0.26 (0.23, 0.30)***

BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure; asterisks indicate the level of statistical significance: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$,

†Pearson correlation coefficients between $\log_e$ GGT and the row variables adjusted for age

Table 2. Association between gamma-glutamyltransferase and risk of pneumonia

GGT (U/L)	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Baseline GGT	1.17 (1.05 to 1.29)	0.004	1.14 (1.02 to 1.28)	0.026	1.08 (0.96 to 1.22)	0.175
Usual GGT*	1.25 (1.08 to 1.46)	0.004	1.21 (1.02 to 1.44)	0.026	1.13 (0.95 to 1.34)	0.175

HRs are reported per SD increase in GGT values

CI, confidence interval; GGT, gamma-glutamyltransferase; HR, hazard ratio; SD, standard deviation;

*, indicates correction for within-person variability in values of GGT, that is, the extent to which an individual's GGT measurements vary around a long-term average value ("usual GGT values")

Model 1: Adjusted for age

Model 2: Model 1 plus body mass index, smoking status, history of diabetes, prevalent coronary heart disease, history of asthma, history of chronic bronchitis, history of tuberculosis, history of cancer, alcohol consumption, socioeconomic status, and physical activity

Model 3: Model 2 plus high sensitivity C-reactive protein