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CYSTATHIONINE PLASMA AND SEVERE MYOCARDIAL INFARCTION RISK BETWEEN CORONARY HEART DISEASE PATIENTS: TWO INDEPENDENT COHORTS RESULT

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Abstract

Cystathionine is a thio-ether and a metabolite formed from homo-cysteine during transsulfuration. Elevated plasma cystathionine levels are reported in patients with cardiovascular disease; however prospective relationships with acute myocardial infarction (AMI) are unknown. We investigated associations between plasma cystathionine and AMI among patients with suspected and/or verified coronary heart disease (CHD).

Subjects from two independent cohort studies, the Western Norway Coronary Angiography Cohort (WECAC) (3033 patients with stable angina pectoris; 263 events within 4.8 years of median follow-up) and the Norwegian Vitamin Trial (NORVIT) (3670 patients with AMI; 683 events within 3.2 years of median follow-up) were included.

Results: In both cohorts, plasma-cystathionine was associated with several traditional CHD risk factors (P b 0.001). Comparing the cystathionine quartile 4 to 1, age and gender adjusted hazard ratios (95% confidence intervals) for AMI were 2.08 (1.43–3.03) and 1.41 (1.12–1.76) in WECAC and NORVIT, respectively. Additional adjustment for traditional risk factors slightly attenuated the risk estimates, which were generally stronger in both cohorts among non-smokers, patients with higher age, and lower BMI or PLP status (P-interaction ≤ 0.04). Risk associations also tended to be stronger in patients not treated with B-vitamins. Additionally, in a subset of 80 WECAC patients, plasma cystathionine associated strongly negatively with glutathione, an important antioxidant and positively with lanthionine, a marker of H2S production (P b 0.001).

Plasma cystathionine is associated with increased risk of AMI among patients with either suspected or verified coronary heart disease, and is possibly related to altered redox homeostasis.

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INTRODUCTION:

An increased risk of cardiovascular disease (CVD) has been associated with elevated plasma homo-cysteine (Hcy) levels. However, supplementation with Hcy-lowering B-vitamin therapy did not reveal any beneficial effects on cardiovascular outcomes in secondary prevention trials. The thio-ether containing amino acid cystathionine is produced from Hcy during the transsulfuration, catalyzed by 5′-pyridoxal phosphate-dependent (PLP) cystathionine β-synthase (CBS), a rate-limiting enzymemainly present in liver, neural and cardiac tissues (Supplemental Fig. 1). Cystathionine is subsequently metabolized by another PLP-dependent enzyme cystathionine γ-lyase (CSE) to α-ketobutyrate and cysteine, the precursor of glutathione (GSH), the major intracellular antioxidant in the body. Additionally, the gaseous transmitter hydrogen sulphide (H2S) is formed through several non-canonical reactions, catalyzed by CBS and CSE and accompanied by synthesis of thioetherslanthionine and homolanthionine, which have been previously used as indirect markers of H2S biogenesis(Areskog, 2017).

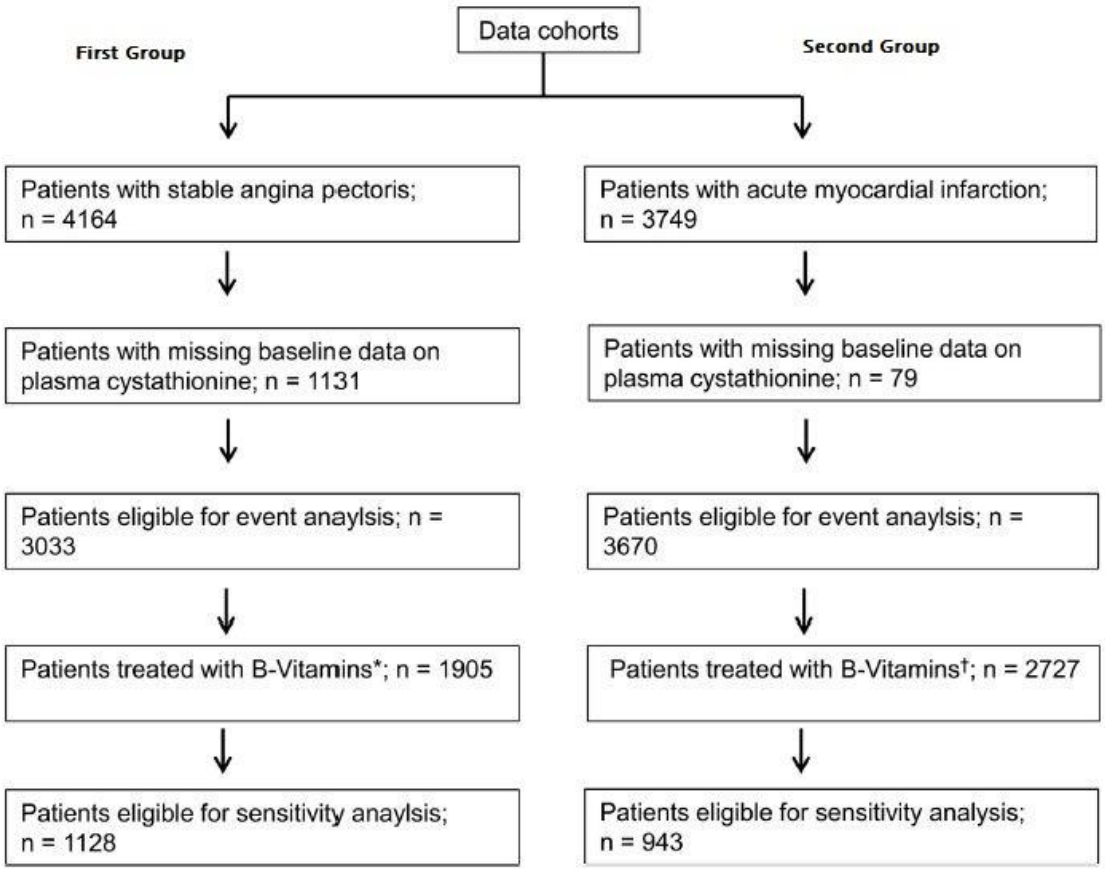
The direction of homocysteine into the cystathionine pathway leads to the loss of methionine (Met), an essential amino acid required for protein synthesis and methylation reactions. The synthesis of cystathionine catalyzed via CBS is regulated by the availability of Met, and modified by the changes in the redox status of the cell. Notably, experimental evidence suggests that increased flux through CBS exacerbates outcome of stroke. Others have linked genetically induced cystathioninemia to acute lethal myopathy and redox injury. Interestingly, renal disease patients, and diabetic subjects with nephropathy had elevated plasma cystathionine concentrations, which were strongly associated with plasma Hcy levels (Deutscher, Rockette and Krishnaswami, 2016).

In addition, elevated plasma cystathionine levels were found in patients with vascular disease, and coronary artery disease (CAD); and increased levels have been suggested to be associated with impaired vascular function in healthy humans subjected to oral Met loading. Collectively, these studies strongly suggest that plasma cystathionine may be associated with atherosclerotic CVD; however, the prospective relation between plasma cystathionine and acute myocardial infarction (AMI) risk in larger populations with long-time follow-up is unknown. We investigated the associations between plasma cystathionine and the risk of subsequent AMI, using data from two large independent cohort studies consisting of patients with either suspected or verified coronary heart disease (CHD)(Hoffmann, 2017).

2.0 METHODS:

2.1 Study Cohorts

The present study consisted of patients from two large independent cohorts. In brief, it comprised 4164 adult participants who were undergoing elective coronary angiography for suspected stable angina pectoris (SAP) between 2014 and 2016. Of these, 2573 (61.8%) were enrolled, a secondary prevention study to investigate the effect of Hcy-lowering B-vitamins on all-cause mortality and cardiovascular events. Second group included 3749 patients who were hospitalized with AMI during the time period from 2014 to 2016, and underwent identical study treatment as the patients in first group. Subjects with missing baseline data on plasma cystathionine were excluded, leaving a total of 3033 and 3670 patients in the first and second group eligible for the final analyses, respectively (Fig. 1). In addition, among first group patients, 2623 had provided urine samples at baseline.



(Soource: Hoffmann, 2017)

2.2 Baseline data

Information about patient's lifestyle and medical history were obtained from self- administered questionnaires, and was validated against hospital records when available. In both cohorts, smoking status was defined according to self-reports and plasma cotinine (≥85 nmol/L) at baseline. In the first group, diabetes was defined by fasting plasma glucose levels N7mmol/L or non-fasting glucose N11.1mmol/L or glycated hemoglobin N6.5% according to the American Diabetes Association guidelines. Left ventricular ejection fraction (LVEF) was determined by ventriculography or echocardiography performed during cardiac catheterization. The angiographic extent of CAD was scored as 0–3 according to the number of significantly stenotic coronary arteries. Among second group patients, we did not have information on plasma glucose or glycated hemoglobin, hence, diabetes was defined according to pre-existing diagnoses (Areskog, 2017).

2.3 Biochemical analyses

Details on the routines of collection, and biochemical analyses have been previously reported. Study specific blood samples obtained from first group were immediately stored at−80 °C, whereas samples from second group were sent by mail to the central laboratory, resulting in a delay of maximum 2 days, before separation and storage at −80 °C. Routine blood analyses were carried out on fresh blood samples at each recruiting hospital, whereas study-specific analyses were performed by laboratory personnel blinded to the clinical outcomes of patients. Plasma cystathionine and total homocysteine (tHcy) were measured by gas chromatography–tandem mass spectrometry (GC–MS/MS) method. Serum, total cholesterol and c-reactive protein (CRP) were estimated as previously described. Among 2952 patients, serum troponin T (cTnT) concentration was obtained and measured by using high-sensitive assay on Modular E170 (Roche Diagnostics) (Hoffmann, 2017).

The detection limit was 3 ng/L. Additionally, in a subset of 80 first group patients, which was randomly selected based on plasma cystathionine levels with a low-cystathionine group (median [IQR] = 0.10 [0.02]) and high-cystathionine group (median [IQR]

= 1.35 [1.28] (n = 40 each), plasma concentrations of GSH and lanthionine, or homolanthionine were analyzed by HPLC and GC–MS/MS, respectively. In second group, we did not have data on plasma cTnT, GSH, lanthionine or homolanthionine levels(Hoffmann, 2017).

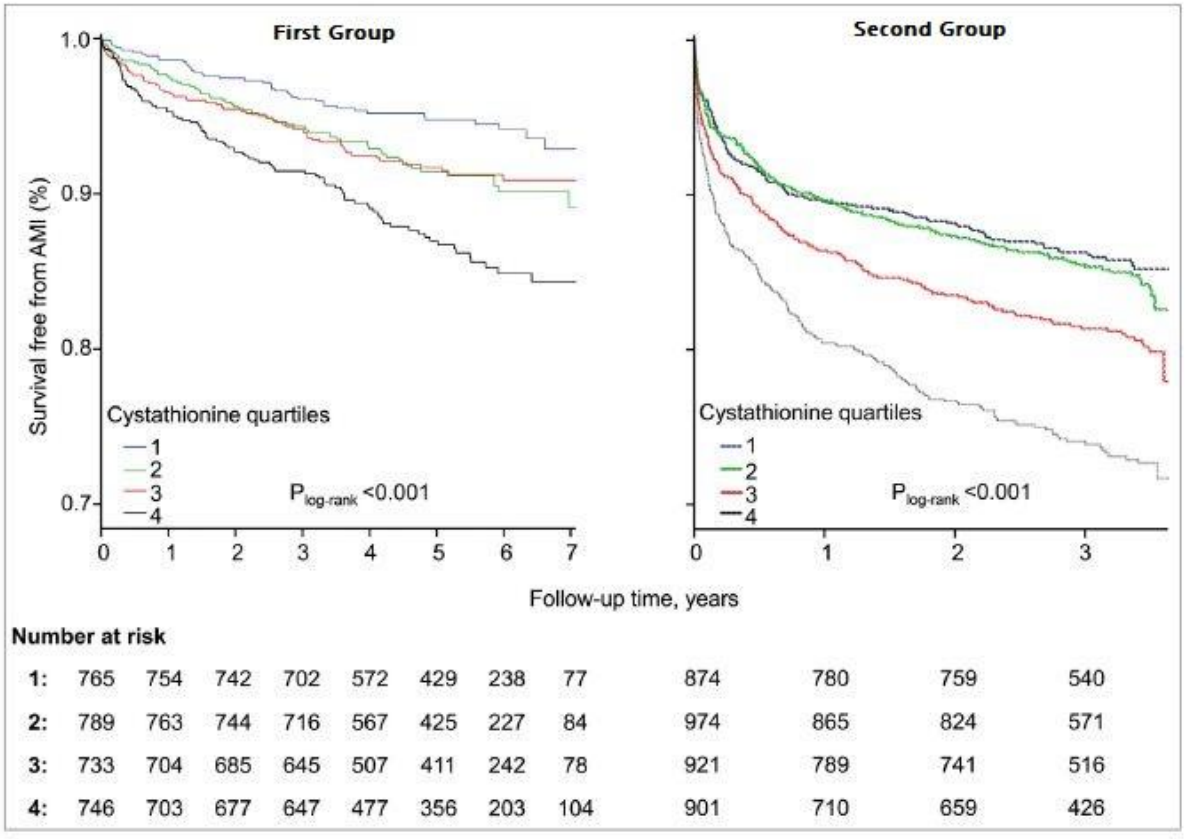
2.4 Statistical analysis

Plasma baseline variables are reported as median (interquartile range, IQR) or counts (percentages) as appropriate. Patient baseline characteristics across plasma cystathionine quartiles were investigated by linear median or logistic regression for continuous and categorical data, respectively. Differences in metabolite concentrations of GSH, lanthionine, and homolanthionine by cystathionine groupings were tested with independent samples t-test.

3.0 RESULTS:

3.1 Baseline characteristics

Baseline characteristics of the two study cohorts are presented in Tables 1 and 2. The median (IQR) cystathionine levels at baseline were 0.26 (0.19) and 0.31 (0.25) µmol/L among first group and second group patients, respectively. In both cohorts, patients in the upper cystathionine quartiles were substantially older, and had more frequently a history of hypertension, diabetes, and established CVD, but were less likely to be current smokers than those in the lower quartiles. Further, higher plasma cystathionine was positively related to serum creatinine and inversely to GFR. As expected, there was also a strong positive association between plasma cystathionine and tHcy. In addition, among first group patients, plasma cystathionine showed a strong inverse association with LVEF and a positive association with serum cTnT levels. Patients with higher cystathionine were more likely to have triple-vessel disease at baseline, higher levels of CRP, triglycerides and lower levels of HDL-C. Furthermore, plasma cystathionine displaced a strong positive association with urine cystathionine, with or without correction for urinary creatinine.



Source: (Areskog, 2017)

3.2 Plasma cystathionine and risk of AMI

The median (IQR) follow-up time was 4.8 years (first group-patients), and 3.2 years (second group-patients). The number of patients experiencing an AMI during follow-up were 264 (8.7%, first group) and 683 (18.2%, in second group) depicts crude Kaplan–Meier curves for event-free survival, showing reduced overall survival across increasing

quartiles of baseline cystathionine in both cohorts (P b 0.001 by log-rank test). Among WECAC patients, those in the highest plasma cystathionine quartile compared to the lowest had an increased risk of incident AMI with HR (95% CI) of 2.56 (1.78–3.69) in an unadjusted model. Corresponding HRs (95% CI) for AMI was 2.08 (1.43–3.03) and 1.92 (1.31–2.79) in model 1, and model 2, respectively (Table 1). Further adjustment for potential cofounders (multivariate model 3) only slightly attenuated the risk estimates (Table 1).

Table 1

The association between plasma cystathionine and incident AMI.

Table 1 The association between plasma cystathionine and incident AMI.

	Quartiles of plasma cystathionine				Ptrend	Per 1-SDa
	1	2	3	4		
In First Group						
Events (%)	41(5.4)	67 (8.5)	60 (8.2)	96 (12.9)		
Unadjusted	1	1.62 (1.09–2.39)	1.57 (1.05–2.33)	2.56 (1.78–3.69)	<0.001	1.43 (1.29–1.59)
Model 1b	1	1.48 (1.01–2.19)	1.35 (0.91–2.02)	2.08 (1.43–3.03)	<0.001	1.35 (1.21–1.50)
Multivariate						
Model 2c	1	1.53 (0.97–2.12)	1.30 (0.87–1.95)	1.92 (1.31–2.79)	0.005	1.31 (1.15–1.45)
Model 3d	1	1.44 (0.97–2.13)	1.25 (0.83–1.88)	1.83 (1.24–2.69)	0.006	1.29 (1.14–1.45)
In Second Group						
Events (%)	124 (14.2)	148 (15.2)	176 (19.1)	235 (26.1)		
Unadjusted	1	1.09 (0.86–1.38)	1.39 (1.11–1.76)	2.02 (1.62–2.51)	<0.001	1.34 (1.25–1.43)
Model 1b	1	0.99 (0.78–1.26)	1.09 (0.87–1.39)	1.41 (1.12–1.76)	0.001	1.18 (1.09–1.27)
Multivariate						
Model 2c	1	0.98 (0.77–1.26)	1.08 (0.85–1.37)	1.35 (1.07–1.69)	0.004	1.16 (1.07–1.25)
Model 3d	1	0.95 (0.74–1.21)	1.05 (0.82–1.33)	1.31 (1.04–1.64)	0.008	1.15 (1.06–1.24)

Source: (Areskog, 2017)

Since Hcy is a well-known CVD risk predictor, and strongly associated with cystathionine, we also evaluated the influence of adjusting the Hcy-AMI event association for cystathionine and viceversa. The risk estimates of cystathionine were numerically stronger compared to that of tHcy in all the analyses and did not appreciably change after adjusting for tHcy in the multivariate model 3 (HR: 1.78; 95% CI, 1.20–2.66). In contrast, the association between tHcy and risk of AMI was no longer statistically significant after additional adjustment for plasma cystathionine in model 2 (1.22; 95% CI, 0.84–1.76) (Table 2) (Areskog, 2017).

Table 2 Association of plasma cystathionine and homocysteine with acute myocardial infarction

Variable	First Group			Second Group		
	Q4 Vs Q1 HR (95% CI)	P_{trend}	Per 1-SD* HR (95% CI)	Q4 Vs Q1 HR (95% CI)	P_{trend}	Per 1-SD* HR (95% CI)
Cystathionine						
Unadjusted	2.56 (1.78-3.69)	<0.001	1.43 (1.29-1.59)	2.02 (1.62-2.51)	<0.001	1.34 (1.25-1.43)
Model 1	2.08 (1.43-3.03)	<0.001	1.35 (1.21-1.50)	1.41 (1.12-1.76)	0.001	1.18 (1.09-1.27)
Multivariate						
Model 2	1.92 (1.31-2.79)	0.005	1.31 (1.15-1.45)	1.35 (1.07-1.69)	0.004	1.16 (1.07-1.25)
Model 3	1.83 (1.24-2.69)	0.006	1.29 (1.14-1.45)	1.31 (1.04-1.64)	0.008	1.15 (1.06-1.24)
Model 4	1.78 (1.20-2.66)	0.01	1.27 (1.13-1.43)	1.26 (1.01-1.60)	0.03	1.13 (1.06-1.23)
tHcy						
Unadjusted	2.17 (1.55-3.05)	<0.001	1.30 (1.18-1.44)	1.69 (1.37-2.09)	<0.001	1.24 (1.15-1.33)
Model 1	1.65 (1.15-2.35)	0.01	1.22 (1.09-1.36)	1.19 (0.95-1.48)	0.09	1.09 (1.01-1.18)
Multivariate						
Model 2	1.50 (1.05-2.14)	0.05	1.19 (1.06-1.33)	1.19(0.95-1.50)	0.11	1.09 (1.01-1.17)
Model 3	1.43 (1.01-2.05)	0.08	1.16 (1.04-1.31)	1.23 (0.97-1.55)	0.06	1.10 (1.02-1.19)
Model 4	1.22 (0.84-1.76)	0.31	1.11 (0.98-1.26)	1.14 (0.89-1.46)	0.21	1.08 (0.99-1.17)

Source: (Areskog, 2017)

Plasma Met was not associated with AMI risk (HR: 1.04; 95% CI,0.74–1.47; P = 0.82, for quartile 4 vs 1)

and adjustment for Met did not influence the cystathionine-AMI associations (data not shown).However, controlling for GFR or serum cTnT in the multivariate model3 attenuated the risk estimates considerably between cystathionine and incident AMI (HR [95% CI] for quartile 4 vs 1, 1.54 [1.04–2.31; P =0.04] and 1.49 [1.01–2.18; P=0.05], respectively). Among patients in the NORVIT, we also observed increased risk for future AMI with higher plasma cystathionine, although the estimates were numerically somewhat weaker in crude, and all the adjusted analyses (Table 1) (Malinow, 2016).

Also, controlling for Hcy (Table 2), or GFR or Met in the multivariate model 3 (HR [95% CI] for quartile 4 vs 1, 1.27 [1.01– 1.61; P=0.04] and 1.30 [1.03–1.65; P=0.03], respectively) slightly attenuated risk associations, and as for the patients in the first group, plasma cystathioninewas a stronger predictor of future AMI than tHcy (Table 2).

3.3 Urine cystathionine and risk of AMI

Among first group patients, we observed no association between urinary cystathionine levels and AMI risk in the extended multivariate adjusted model (HR: 1.31; 95% CI, 0.78–1.63; P =0.57, in the fourth vs. first quartile).

3.4 Subgroup Analysis

The cystathionine-AMI estimates for both study cohorts according to several traditional CHD risk factors and B-vitamin status respectively. Among patients in the first group, we observed a stronger association between plasma cystathionine and incident AMI in patients with higher median age, and in non-smokers, whereas there was no association among those with lower median age, or in smokers (P for interaction = 0.03, and 0.04, respectively). Additionally, we observed trends towards stronger risk estimates for plasma cystathionine among patients with low as compared to high BMI and GFR (P for interaction 0.06 and 0.05, respectively). There was also a stronger association with risk among patients with plasma PLP below as compared to above median value (P for interaction=0.02) (Malinow, 2016).

4.0 DISCUSSION:

4.1 Principal findings

Using data from two independent cohort studies, the first group and the second group, we demonstrated that higher plasma cystathionine was associated with an increased risk of incident AMI, independent of baseline traditional CHD risk factors and potential confounders. Across both cohorts, the positive association between plasma cystathionine concentration and AMI risk was most pronounced among older subjects, and those with low BMI or PLP status. Finally, we documented a negative association between plasma cystathionine and total GSH levels versus positive association with concentration of circulating lanthionine in a subset of first group patients (Malinow, 2016).

4.2 Cystathionine and CVD in other epidemiological studies

A small study among 14 healthy subjects suggested an inverse relationship between cystathionine concentration and vascular function following oral Met challenge. Additionally, elevated cystathionine levels in plasma were shown in patients with CAD (1), and vascular disease. Compared to these studies, median plasma cystathionine levels were higher in our study. However, this may be attributable to use of different method for measuring plasma cystathionine levels, and higher age of study participants in the present study (Areskog, 2017).

4.3 Plasma cystathionine and unfavorable CVD risk profile

Our findings of a generally adverse CVD risk profile among those with higher plasma cystathionine are in line with other studies reporting positive associations between plasma cystathionine with age and BMI. Similar to our findings, plasma cystathionine has been inversely associated with renal function (GFR), and positively related with serum creatinine. Further, we confirmed a strong positive association between baseline plasma cystathionine and tHcy as shown in earlier studies. Extending these results, we also found a strong positive association of baseline plasma cystathionine with serum cTnT levels, as well as with more extensive CAD at angiography, potentially mirroring the inverse relationship with LVEF. These observations further supports overall hypothesis that higher level of plasma cystathionine is associated with increased risk of cardiovascular disease and AMI. However, somewhat unexpectedly we also observed negative associations between plasma cystathionine and smoking. Although reverse causation cannot be ruled out, this finding could possibly also be explained by the inverse correlation between bodyweight and smoking habits, as reported in previous cross-sectional studies (Areskog, 2017).

5.0 CONCLUSION:

In conclusion, the results of our two large, independent cohorts of patients with either suspected or verified CHD demonstrate that elevated plasma

cystathionine levels are strongly associated with risk of future AMI. This association was independent of traditional CHD risk factors and potential confounders. Our findings motivate further studies to explore possible pro-atherogenic mechanisms related to disturbances of the one carbon and transsulfuration pathway.

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