The Behavior of the Plasma Homocysteine and Selenium Concentrations in Patients with Acute Myocardial Infarction

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Abstract

Background: Increased concentrations of plasma total homocysteine and decreased concentrations of plasma selenium are separately associated with cardiovascular disease.
Objective: Investigate the correlation between plasma total homocysteine and selenium in patients with acute myocardial infarction (AMI).
Methods: Patients of present study was thirty nine men with AMI admitted to Marburg Hospital in Marburg city, Germany on 2007. Plasma total homocysteine was determined using HPLC. Plasma selenium was determined using atomic absorption spectrometry**.**
Results: Plasma homocysteine of patients found to be increased, whereas plasma selenium found to be decreased when compared with reference range . The correlation between plasma homocysteine and selenium found to be negatively correlated.
Conclusion: The negative correlation between plasma tHcy and selenium may indicate that they have a significant impact on the process of atherogenesis. The change in the levels of plasma total homocysteine and plasma selenium might be result from oxidative stress associated with AMI.

سلوك مستويات الهوموسيستين و السلينيوم في بلازما دم المرضى المصابين باحتشاء العضلة القلبية الحاد

الخلاصة

الخلفية: إن الزيادة في تركيز الهوموسيستين والنقصان في تركيز السلينيوم في بلازما الدم عادة ما يقترن بأمراض الأوعية القلبية وبشكل منفصل.

الهدف: تقصي العلاقة المشتركة بين تركيز الهوموسيستين والسلينيوم في بلازما دم المرضى المصابين باحتشاء العضلة القلبية الحاد

الطرائق: المرضى الذين تم شمولهم بهذه الدراسة هم تسعة وثلاثون رجل أدخلوا إلى مستشفى ماربيرغ في مدينة ماربيرغ ، ألمانيا في عام ٢٠٠٧ يعانون الإصابة باحتشاء العضلة القلبية الحاد. تم قياس تركيز الهوموسيستين في بلازما الدم باستخدام تقنية الـ HPLC في حين تم قياس تركيز السلينيوم باستخدام تقنية مطيافية الامتصاص الذري.

النتائج: وجدت زيادة في تركيز الهوموسيستين، بينما سجل انخفاض في تركيز السلينيوم عند المرضى متى ما قورنت مع القيم المرجعية لكليهما. ووجد الارتباط بين تركيز الهوموسيستين والسلينيوم ارتباطا سلبيا.

الاستنتاج: إن الارتباط السلبي بين الهوموسيستين والسلينيوم قد يشير إلى إن لكل منهما تأثيرا هاما على عملية نشوء تصلب الشرايين ، وقد يكـــون الـــتغير في تركيزهما ناتج من زيادة الإجهاد التاكسي الناتج من المرض.

Introduction:

In the last of 1960s of past century, Kilmer S. McCully was suggests the hypothesis that elevated blood concentrations of homocysteine (tHcy) may be a risk factor for cardiovascular disease in by the observation that children with homozygous homocystinuria, a rare inborn error of metabolism causing markedly elevated blood tHcy concentrations, had a high incidence of premature occlusive vascular disease.[1,2] The initial epidemiological evidence in support of this hypothesis came from retrospective case-control studies.[3-5] More recently, however, contradictory results have been reported from prospective observational studies, including cohort and nested case-control studies, with some showing highly significant associations but others showing none.[6]

tHcy is a metabolic product of methyl group donation by the amino acid methionine; it is emerging as a risk factor for different type of diseases such as cardiovascular disease, Alzheimer's disease, and neural tube defects. Among the factors known to influence homocysteine metabolism are genetic and physiologic characteristics, and several nutrients such as folate, B-6, and riboflavin which are important cofactors for several enzymes involved in homocysteine metabolism [7-9], as well as, cobalamin (B-12) which is the final methyl-group donor in the conversion of tHcy to methionine [8].

Kilmer S. McCully was proposed an explanation to the role of tHcy in atherogenesis. He suggests that, LDL particles which are small and dense are associated with more rapid and severe atherogenesis, compared with LDL particles that are larger and less dense. LDL contains homocysteine bound by peptide bonds to the lysyl groups of apo-B protein to form homocysteinylated LDL [9]. Reaction of homocysteine thiolactone with normal human LDL produces LDL particles containing increased concentrations of homocysteine that are small, dense, and form aggregates that are phagocytosed by cultured monocytes. This process is believed to explain the uptake and deposition of homocysteinylated LDL within vascular macrophages during atherogenesis.[9,10]

A meta-analysis in 1995 by Boushey and colleagues suggested that for each 5 μmol/L increase in homocysteine there was a 70% higher risk of CAD, a 50% increase in cerebral vascular disease, and a strong association with peripheral vascular disease.[11] Based on these data, the authors suggested that 10% of the population's CVD risk is attributable to tHcy. Another meta-analysis done by Eikelboom and colleagues confirmed these data, namely that "there is a strong dose-dependent positive association between plasma homocysteine levels and risk for cardiovascular disease" that "is independent of other known risk factors."[12] While these and other studies revealed a strong epidemiological correlation, they also emphasized the need for randomized clinical trials to establish causation.[13,14] The first doubts about the causal role of tHcy were expressed after the reported lack of association

between CAD and a specific genetic polymorphism affecting ***MTHFR*** (677C→T).[15] Normally it would be expected that if a particular substance in blood causes a disease and its level is related to a genetic polymorphism, then that polymorphism would also be related to the disease. [16] While enzyme deficiencies caused by mutations in the ***CBS*** gene and the ***MTHFR*** gene are related to very high levels of tHcy with vascular consequences, [17]

Another study was based on a sample of 1960 men and women, aged 28–82 years, from the Framingham Offspring cohort. Relations were investigated between tHcy and its possible dietary determinants (estimated intake of B vitamins, protein, and methionine), some lifestyle factors (smoking status, alcohol use, and caffeine use), biochemical determinants (serum creatinine, plasma vitamin B-6, vitamin B- 12, and folate), and other factors (body mass index, blood pressure, and antihypertensive medication). Except for blood pressure, all the above-mentioned factors showed significant associations with tHcy. For example, the investigators found that tHcy was 1.5 μmol/L higher in heavy smokers than in nonsmokers. [18]

Low selenium levels in humans have been implicated with several pathologies; such as cardiovascular disease and cancer, however, an earlier animal investigation found a direct association between selenium intake and total plasma homocysteine (tHcy) concentrations.[7,19]

Recently, Uthus et al. [20] observed that tHcy decreases in rats fed a low-selenium diet and increases with selenium supplementation. Also, these authors recently reported an interactive effect of dietary selenium and folate in such a way that in selenium-deprived rats, some of the effects of folate deficiency seem to be ameliorated, probably by shunting the buildup of tHcy to glutathione. [21]

The increase in the levels of plasma tHcy and the decrease in the levels of plasma selenium are separately associated with cardiovascular disease, and both of them consider to be risk factor for such diseases, as shown in literatures above. In this study, we try to investigate the correlation between plasma selenium levels in association with tHcy in human patients with acute myocardial infarction (AMI) that has, to the best of our knowledge, never been tested.

Patients and Methods:

Patients:

Patients of present study was thirty nine men with AMI clinically diagnosed by ECG admitted to Marburg Hospital in Marburg city, Germany on 2007.

Methods:

Plasma tHcy was determined using reverse-phase HPLC with fluorimetric detection, as it had been described previously [22]

Plasma selenium was determined using flow-injection hydride generation atomic absorption spectrometry (AAS) (Perkin–Elmer Model 3100; Perkin Elmer Cetus Instruments, Norwark, CT) , as it had been described previously [23]

Statistical Analysis:

All values were expressed as mean ± standard deviation (SD) .

Results

Results of plasma tHcy and selenium of patients with AMI subject to present study are listed in table 1.

Table 1 Plasma tHcy and selenium of patients with AMI

	Mean	± SD	Upper value	Lower value	Reference range
tHcy (µmol/L)	24.90	11.81	57.93	9.88	5 - 15
Selenium (µmol/L)	0.451	0.13	0.75	0.21	0.58-1.81

The association between plasma tHcy and selenium was plotted and shows negative correlation (R^2=0.1277), as show in Figure 1.

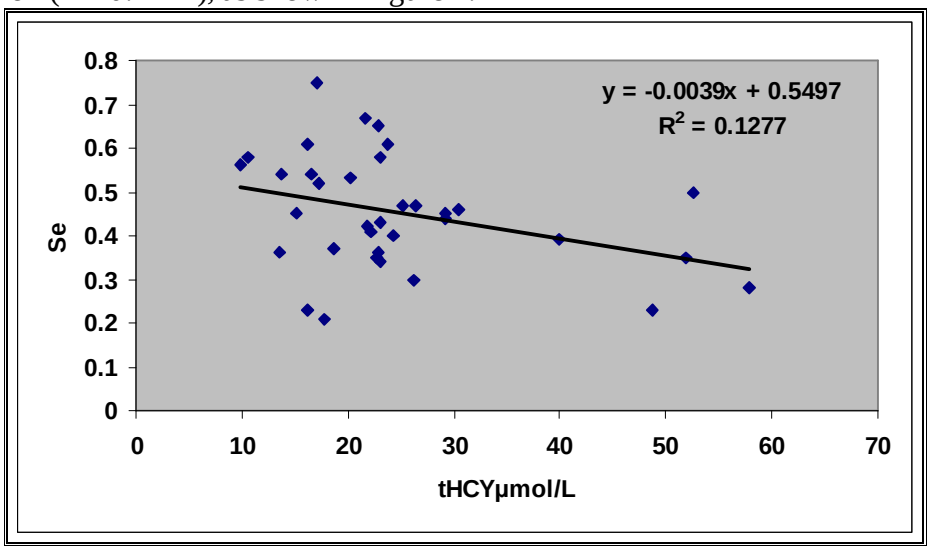

Figure 1 Correlation between plasma tHcy and selenium in patient with AMI

Hyperhomocysteinemia refers to elevated tHcy levels, and is frequently graded as mild (<30 µmol/L), intermediate (30–100 µmol/L), or severe (>100 µmol/L).[24]

Normal plasma homocysteine levels usually range from 5 to 15 µmol/L [25]. However, the definition of elevated homocysteine levels is not standardized, and substantial differences exist in the "normal" reference levels used in the literature. Higher fasting values are arbitrarily classified as mild and moderate hyperhomocyst(e)inemia (16 to 100 µmol/L) and severe hyperhomocyst(e)inemia (.100 µmol/L).[26]

Patients with AMI subject to present study could be categorized according to their tHcy levels into three group:

1. Group with tHcy levels like normal values.(5-15 µmol/L)
2. Group with mild tHcy levels (<30 µmol/L).
3. Group with intermediate tHcy levels (30–100 µmol/L), as shown in Figure 2.

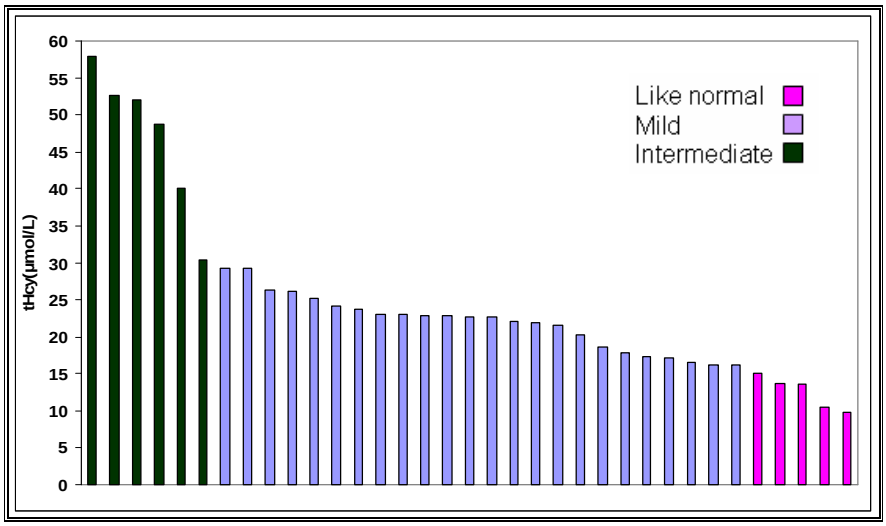

Figure 2 tHcy levels in patients with AMI

Discussion

Cardiovascular disease (CVD) remains the major cause of morbidity and death in developed countries.[26,27] Smoking cessation, and reductions of cholesterol levels and blood pressure have been shown to be useful strategies in the prevention of CVD [28]. However, these major, classic cardiovascular risk factors and such non modifiable risk factors as age, sex, and family history cannot fully explain why some persons develop myocardial infarction, stroke, and other CVD but other persons do not [29]. Other factors may also enhance the probability of developing CVD and contribute to atherogenesis. Pathologic and epidemiologic studies propose that only about one half to two thirds of the variation in anatomic extent of atherosclerosis and risk for atherosclerotic vascular disease can be explained by classic risk factors [26]. For that reason, many promising risk factors have been investigated. Among these, elevated plasma or serum levels of tHcy are of particular interest. Recent epidemiologic studies have shown that moderately elevated plasma homocysteine levels are highly prevalent in the general population and are associated with an increased risk for fatal and nonfatal CVD, independent of classic cardiovascular risk factors. [26]

Several studies had been done on a large number of patients and suggested that elevated plasma tHcy is an independent risk factor for cardiovascular-related as well as non-cardiovascular-related mortality.[30-32] In a prospective cohort study following 2,127 men and 2,639 women for over 4 years, increasing levels of plasma tHcy were directly related with increasing mortality. The population was divided into quantities based on initial plasma tHcy (5.1-8.9, 9.0-11.9, 12.0-14.9, 15.0-19.9, >20 µmol/L) and followed for survival. After adjusting for other cardiovascular risk factors, the overall mortality ratio was 1, 1.33, 2.02, 2.48, and 3.56 for the 5 quintiles. The authors were concluded that after multivariate adjustment, a 5 µmol/L increase in tHcy increased all-cause mortality by 49%, cardiovascular mortality 50%, cancer mortality 26%, and non-cancer, non-

cardiovascular mortality 104%. This data suggests that the level of tHcy likely to result in a low risk for mortality is below 9 and perhaps even lower. [32]

Other study investigates the effect of supplementation of selenium on plasma tHcy in a human population at risk for suboptimal selenium status.[33] The results of these study was show increase in glutathione peroxidase (Gpx) (selenium depending enzyme) activity in the selenium-supplemented group. They have shown that selenium supplementation at a dose of 200 g/d over 20 wk in human subjects does not change plasma tHcy concentration, despite a greater than twofold increase in plasma selenium [34]. Them findings are in contrast to a study in rats, in which supplementing rats with selenium raised plasma tHcy concentrations [28]. They explain their results by the lack of an effect of selenium supplements on plasma tHcy in humans may be attributable to a threshold effect. This threshold effect in rats may be related to plasma selenium concentrations required to maximize activity of Gpx.

In the present study, plasma tHcy of patients with AMI found to be increased, when compared with normal values. This result was agree with previous studies. [1-3]

Whereas plasma selenium of patients with AMI found to be decreased when compared with normal values. Also this result was agree with previous studies done by authors on patients with cancer [35] and AMI. [36] They attributed their finding to the acting of selenium as antioxidant by binding with vitamin E and as a constituent of glutathione peroxidase to scavenge free radical which acting to detoxify tissue peroxidation.

The major finding of the present study is the detection of a good negative correlation between tHcy and selenium in patients with AMI, i.e. when plasma tHcy was elevated plasma selenium was decreased and vise versa.

Also, we were found a graduation in the tHcy levels in the patients of present study, as shown in Figure 2. This may reflect the extension of infarction in cardiac muscle, and/ or rise in oxidative stress in some patients than other.

Other study explain the association between tHcy and CVD by suggestion that tHcy inhibits the agonist-induced nitric oxide radical $NO^{\cdot}$ increase but stimulates super oxide radical O^{-}_{2} production within endothelial cells due to endothelial injury associated with hyperhomocysteinemia .[37]

The depletion in selenium levels was reported in this study, this might be explain by consuming of selenium in the glutathione generation to reduce the toxic accumulation of tHcy. [13]

The correlation between tHcy and selenium might represents a new description to the patient status, and how the infarction affected cardiac muscle.

Conclusion

The negative correlation between plasma tHcy and selenium may indicate that they have a significant impact on the process of atherogenesis. The change in the levels of plasma total homocysteine and plasma selenium might be result from oxidative stress associated with AMI.

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