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ORIGINAL ARTICLE

Are There Differences in Plasma Homocysteine Levels between Patients with Asthma and the Healthy Population? An Initial Study in Slovakia

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ABSTRACT

Background: Homocysteine can affect the expression of genes that are closely linked to oxidative stress and inflammatory processes, suggesting a link between plasma homocysteine (P-Hcy) level and chronic airway inflammation in asthmatic patients. This study investigated the differences in P-Hcy level in asthmatic patients compared to a healthy population.

Methods: A total of 76 patients were enrolled in the study on the basis of absence of any diagnosis for any diseases other than asthma that was compared with the control healthy group having no diagnosis for any other diseases. We compared the obtained P-Hcy levels between the asthma and control groups by taking into account biochemical parameters serum C-reactive protein (S-CRP) level, serum aspartate transferase (S-AST) level or the patient's body mass index (BMI).

Results: The patients with asthma showed an increased level of P-Hcy. Also, the S-AST level slightly increased in the asthma group and on the contrary, the S-CRP level increased in the control group.

Conclusion: Our research demonstrated that patients with asthma had an elevated P-Hcy level when compared to the healthy population.

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Introduction

Homocysteine (Hcy) is a sulphur amino acid that appears in the body as an intermediate in the biochemical conversion of methionine to cysteine-transulfation (1). This amino acid is not found in naturally occurring proteins, but is produced in organisms through the metabolism of methionine in the methylation cycle. Homocysteine is also present in plasma (1.00%) in its freely reduced form. Reduced homocysteine has a highly reactive free thiol group which is involved in redox reactions and is susceptible to auto-oxidation at the physiological pH. Subsequently, a disulfide bond is formed between the two homocysteine molecules or a mixed disulfide with cysteine. Homocysteine on reduction can form bonds with proteins up to 70.00% of homocysteine in plasma is bound to albumins (2-5).

"Normal" homocysteine levels have long been a subject of much debate. The authors Smith and Refsum concluded that homocysteine levels ≤10 µmol/L are probably "safe", but higher levels may have negative health effects (6). Fan *et al.* based on meta-analyses from multiple databases demonstrated

an increased risk of death to be closely associated with elevated homocysteine levels above 5 µmol/L. In recent years, increased attention has been paid to the importance of homocysteine levels and its association with various diseases and health problems (1, 6, 7-10).

"Normal" plasma homocysteine concentrations are in the range of 5-16 µmol/L. Reaching a level of 10 µmol/L is considered a desirable upper limit, and this level is achievable through an optimal diet that contains sufficient levels of vitamins B_6, B_9, and B_{12} (11-13). Homocysteine metabolism can be affected by various physiological factors (gender, advanced age, obesity, etc.), lifestyle factors (vitamin intake, alcohol, smoking, excessive coffee, physical activity, etc.), genetic factors [protein kinase C-β (PKC-β), methylenetetrahydrofolate reductase (MTHFR), methionine synthesis, etc.], nutritional factors (folate, vitamin B_6 and vitamin B_{12} deficiency), pharmaceuticals (phosphate, vitamin B_{12} and vitamin B_6 antagonists), and diseases (14).

Plasma homocysteine (P-Hcy) levels are closely correlated with demographic, genetic, and physiological factors. Patients' habits (e.g., smoking), lifestyle (e.g., diet), diseases, use of certain medications, and transplantations can also contribute to increased or decreased levels (15). It is thought that elevated plasma homocysteine levels may stimulate endothelial dysfunction, increasing the production of reactive oxygen species and reduce endothelial nitric oxide as a precursor of atherosclerosis. Activation of the immune system could have a key function in the development and progression of cardiovascular diseases too (16). In this situation, many immune system cells and inflammatory factors are stimulated. In addition, other elements including adhesion molecules, metalloproteins and C-reactive protein (CRP) have been found to be positively correlated with P-Hcy levels (17-19).

The pathogenic mechanism of homocysteine is involved in mediating the expression of inflammatory substances and cytokines, increased inflammatory cell numbers, and enhanced response to oxidative stress, which represents an important factor in the pathogenesis of asthma. Through increased production of free radicals, oxidative stress can cause bronchospasm in asthmatic patients. When toxic homocysteine is incompletely converted to non-toxic methionine, there is an accumulation of homocysteine in the blood as hyperhomocysteinemia that results in increased levels of oxidative stress. Homocysteine can affect the expression of genes that are closely linked to oxidative stress and inflammatory processes, suggesting a link between P-Hcy and chronic airway inflammation in asthmatic patients (20, 21).

Through the reduction of homocysteine levels, immune and antioxidant therapies may have a therapeutic role. When peptide drugs are used to replenish N-acetylcysteine, repair of the damaged endothelium of the cell and restoration of alveolar epithelial cells can occur (22). Several studies have suggested an association between folate levels and the risk of respiratory diseases such as including asthma (23-25). Lin *et al.* demonstrated a correlation between folate levels and the risk of atopy, a respiratory disease in children and adults. They confirmed the association between immunoglobulin E (IgE) levels and blood serum folate levels in patients with asthma. The research included spirometry and the results of a questionnaire survey that examined patients' symptoms (26).

Low folate levels are associated with less allergic inflammation, but the reasons for this are not clear, but there are biologically plausible mechanisms that could explain this observation (27). Folate is critical for optimal lymphocyte function, so it is possible that a certain level of folate in the blood serum is required to trigger and maintain inflammatory responses which would mean that those with the lowest folate levels are protected from allergic inflammation. Folate may influence markers of allergic inflammation through epigenetic mechanisms. Individuals with the lowest folate levels are protected from developing an allergic phenotype (28-30). However, given that regulatory T-cell function will be optimal, but with higher folate levels and concomitant methylation of immunoregulatory genes, regulatory T-cell function may be compromised, increasing the risk of an allergic phenotype. This claim was already confirmed during research on folate exposure in utero, where it was associated with an increased risk of allergic respiratory disease in children (31). This study investigated the differences in P-Hcy level in asthmatic patients compared to a healthy population.

Materials and Methods

The research was conducted from January 2023 to September 2023 and was approved by the Ethics Committee of the University of Prešov under the number ECUP082023PO, and IRB (Institutional Review Board) approval was not necessary. The entire research was in accordance with the current rules of the World Medical Association and our institution ethics committee approved this research based on principles for medical researches involving human subjects. The research sample consisted of deliberately selected probands/patients who were divided into two main groups and selected on the basis of medical history.

The research group was patients with asthma (without diagnosis of any other diseases) in whom P-Hcy, serum C-reactive protein (S-CRP, related

to chronic inflammation in asthma patients) and serum aspartate transferase (S-AST, related to accumulation in the body when toxic homocysteine is imperfectly converted to non-toxic methionine) were determined by biochemical examination, and the control group as probands without diagnosis of any other diseases in whom the same biochemical parameters were examined. At the same time, we divided the values of the P-Hcy parameter (plasma homocysteine) according to the Medirex reference intervals into 3 basic groups, namely the resulting value of below 5.0 µmol/L=below normal, 5-15 µmol/L=normal and above 15.00 µmol/L=above normal. The patients were 30 subjects with asthma and the control group were 46 probands. After the baseline distribution of parameters, we proceeded to test hypothesis 5 using a MANOVA test to be appropriate when the independent variable (P-Hcy) was qualitative in nature (reference value intervals) and the dependent variables were quantitative in nature (serum ferritin, serum vitamin B12, serum vitamin D, serum folic acid).

The age range was 11-67 years from both sexes (26.32% men and 73.68% women) and study groups were from the territory of eastern Slovakia. To obtain the necessary data, including informed consents, we collaborated with the Nutriadapt Clinic in Prešov, Slovakia. Blood collection was performed by a nurse and the blood samples were evaluated in the laboratory. The recorded data were tabulated and subsequently analysed and evaluated. The research was carried out through the obtained medical histories, measured personal data and blood tests. The obtained values were recorded in a spread sheet using MS Excel.

To analyse the body mass index (BMI), we chose Chi-Square test among the statistical methods. The correlation between the P-Hcy parameter and the research/control group was verified using the Mann-Whitney U test. We verified the relationship between P-Hcy and S-CRP; P-Hcy and S-AST variables by Wilcoxon test. Finally, we used multivariate analysis of variance (MANOVA)/multivariate analysis of covariance to compare the means of multivariate samples and to verify the relationship between BMI and each parameter. SPSS software (Version 20, Chicago, IL, USA) was used for statistical analysis and a p value less than 0.05 was considered statistically significant.

Results

Baseline characteristics of research and control groups were presented in Table 1. Our findings revealed a reduction in plasma homocysteine level in relation to lifestyle and dietary modification (higher amounts of B vitamins, vitamin D and folic acid). Table 2 shows that the mean value (N=63) of serum folic acid level was 54.82±66.85 ug/L (within normal range), vitamin B12 level was 258.24±815.6 ug/L (within normal range), vitamin D level was 75.29±26.22 ug/L (high concentration) and serum folic acid was 26.59±19.95 ug/L (within normal range).

At the same time, we have provided the basic descriptive statistics of the values of the P-Hcy parameter (plasma homocysteine) according to the Medirex reference intervals in Table 2. Based on the MANOVA test, it was shown that the parameter λ (0.59) had taken value revealing the mean of the factors differed less and the test was meaningful (p=0.0002) that was lower than the established significance level (α). Figure 1 compares plasma homocysteine level (P-Hcy) in the study and control groups. We rejected the null hypothesis and accepted the alternative hypothesis in which we hypothesized that "it was possible to demonstrate a statistical association between homocysteine (P-Hcy) levels and ferritin, folic acid, and vitamin D and B12 levels".

A direct correlation was visible between the measured P-Hcy values and the other monitored parameters. Using correlation analysis, the greatest dependence was demonstrated between the parameter P-Hcy and folic acid (Table 3). Figure 2a and Figure 2b and Figure 3a and Figure 3b by using Wilcoxon test compared plasma homocysteine level (P-Hcy) and serum C-reactive protein (S-CRP) level in the research and the control groups. It was shown that the most pronounced negative relationship (r=-0.53; significant tightness) was between P-Hcy and

Table 1: Baseline descriptive comparison of research and control groups.

Group	Item	Abundance (N)	Min	Max	Average	SD
Research	Age-Man	5	31.00	61.00	47.80	11.21
Control	Age-Man	15	21.00	54.00	36.20	7.34
Research	Age-Woman	25	26.00	67.00	47.64	11.48
Control	Age-Woman	31	11.00	55.00	38.65	11.26
Research	BMI-man	5	22.16	32.79	27.13	3.92
Control	BMI-man	15	25.52	41.80	32.69	4.83
Research	BMI-woman	25	21.78	44.99	31.15	5.79
Control	BMI-woman	31	22.08	36.44	28.24	3.42

BMI: Body mass index; max: Maximum; min: Minimum; N: Abundance; SD: Standard deviation.

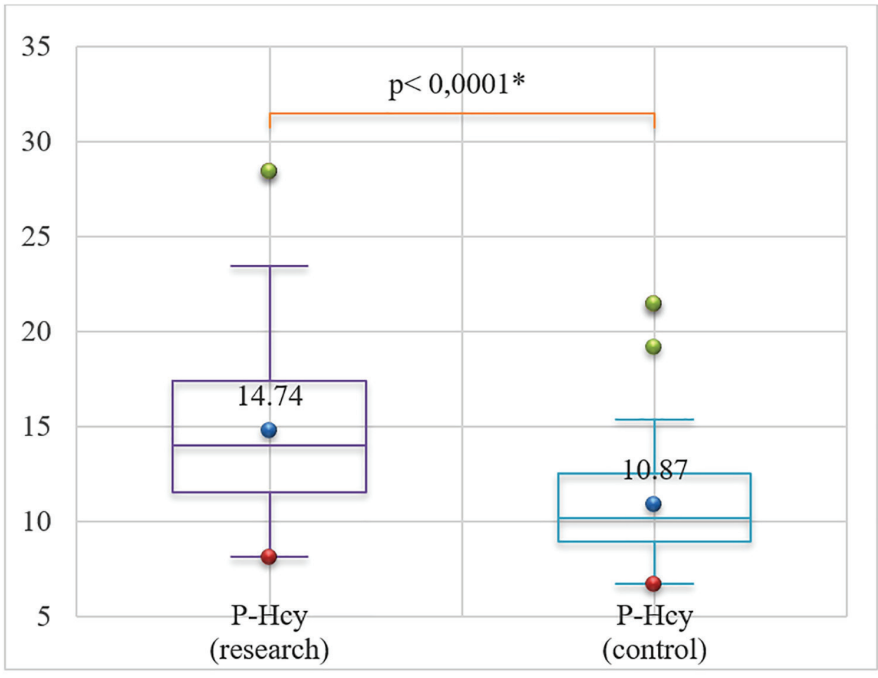

Figure 1: Comparison of plasma homocysteine level (P-Hcy) in the study and control groups.

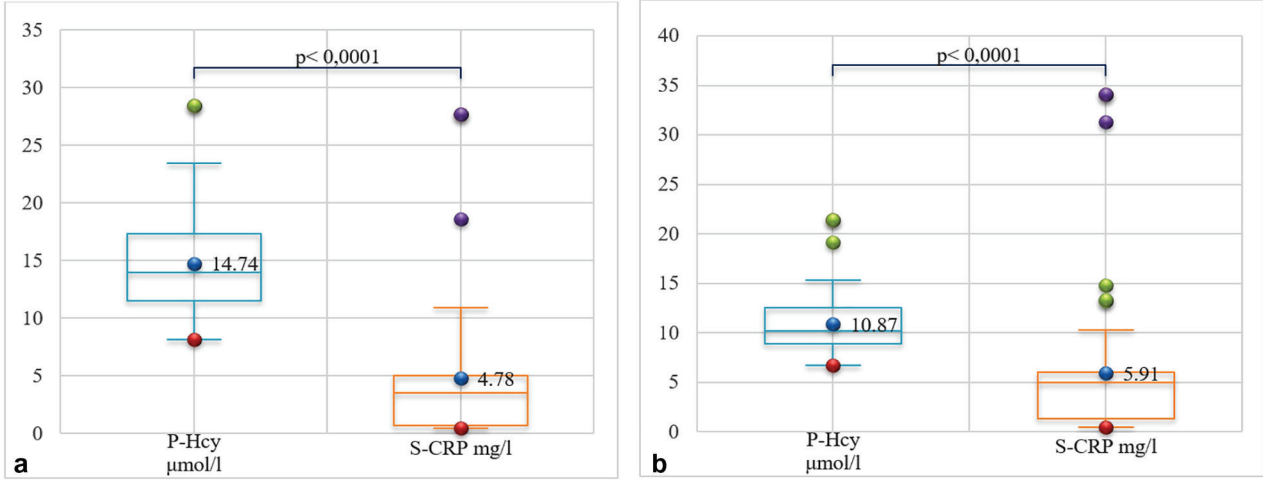

Figure 2: a) Wilcoxon test in relation to plasma homocysteine level (P-Hcy) and serum C-reactive protein (S-CRP) level in the research group. b) Wilcoxon test in relation to plasma homocysteine level (P-Hcy) and serum C-reactive protein (S-CRP) level in the control group.

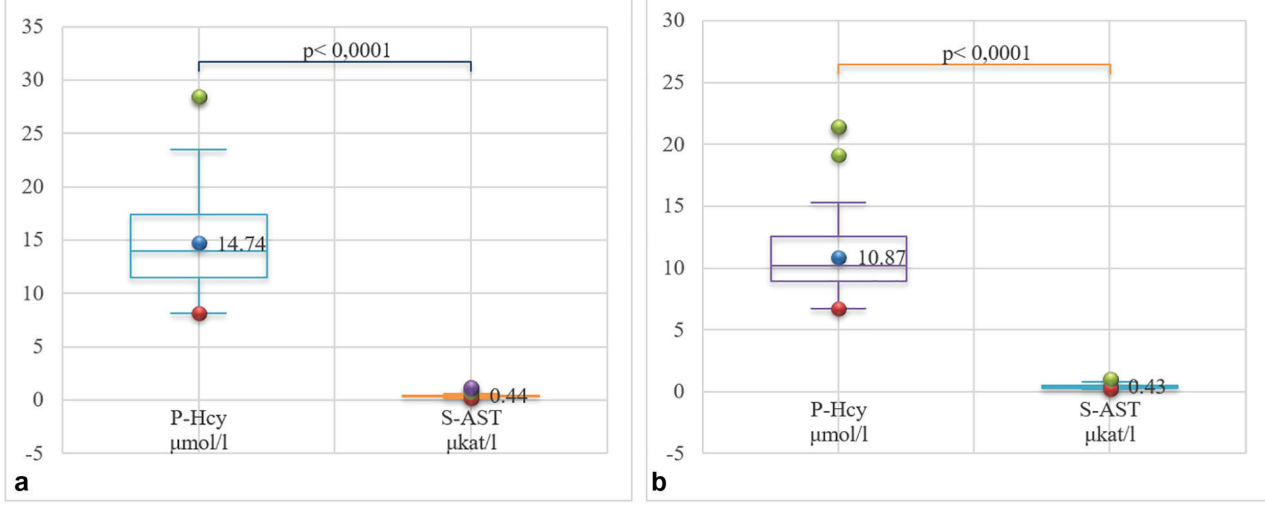

Figure 3: a) Wilcoxon test in relation to plasma homocysteine level (P-Hcy) and serum C-reactive protein (S-CRP) level in the study group. b) Wilcoxon test in relation to plasma homocysteine level (P-Hcy) and serum C-reactive protein (S-CRP) levels in the control group.

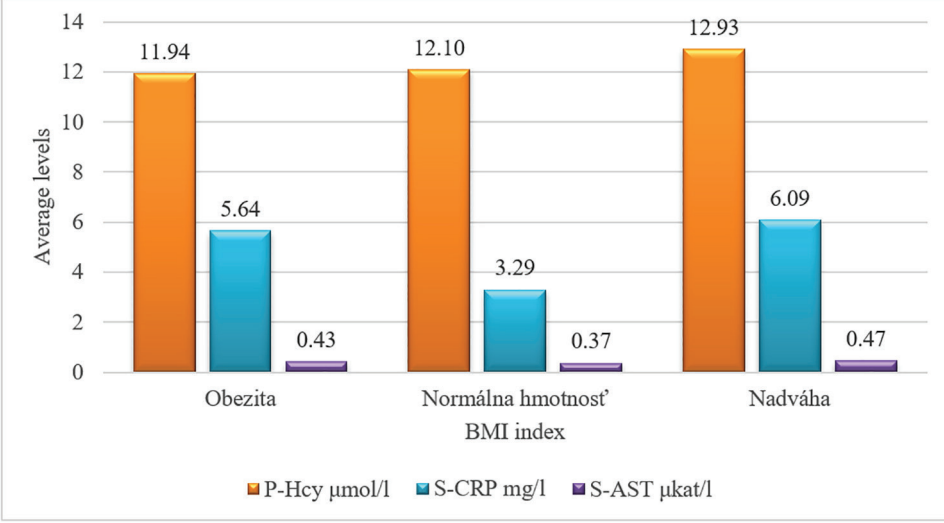

Figure 4: MANOVA test of the relationship between BMI index and individual parameters.

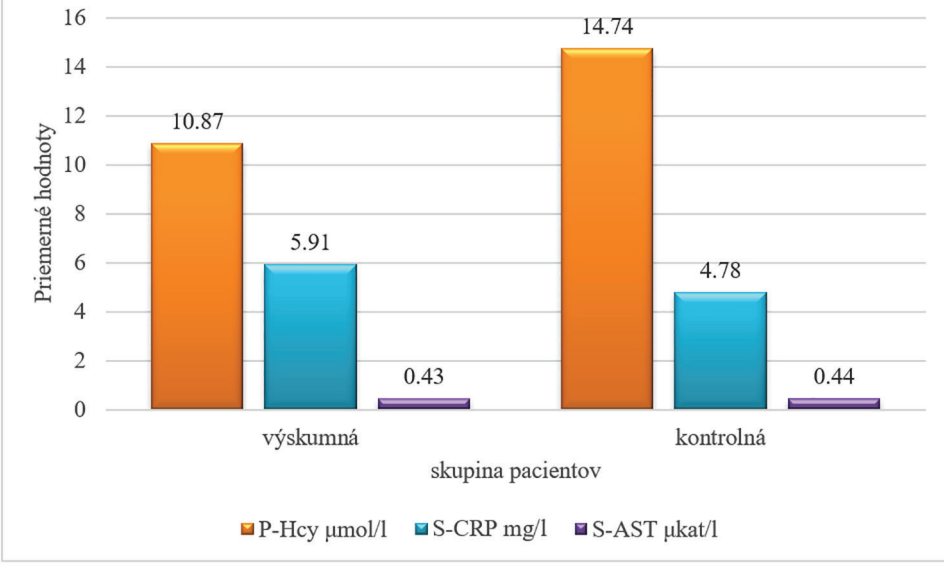

Figure 5: MANOVA test for dependence of patient group and individual parameters.

serum folic acid. The findings demonstrated if the homocysteine level increased, the resulting folic acid level would decrease based on the equation: y=-1.6095x±49.891, which illustrated that the equation could determine the assumption of the findings.

Figure 4 by employing MANOVA test compared the relationship between BMI index and individual parameters and Figure 5 by use of MANOVA test compared dependence of patient group and individual parameters. In terms of closer examination between the individual parameters of serum ferritin, folic acid, vitamin B12, vitamin D and P-Hcy levels and age group (N=63, we arrived at the below results through MANOVA test. The frequency of age categories and the mean values of the individual parameters were examined revealing that most patients were 30-39 years (N=13; 20.63%) and least in the 60-69 age group (N=7; 11.11%). The highest mean of serum ferritin parameter (84.26 mg/L) was observed in the age group 30-39 years, while the highest mean of vitamin B12 parameter (289.30 µmol/L) was noticed in the age group of 60-69 years.

Vitamin D parameter (97.48 µg/L) and folic acid values (37.45 µg/L) were dominated in the age group of 40-49 years and P-Hcy parameter (21.46 µmol/L) in the age group 50-59 years that was in the highest level. Based on the MANOVA test, the parameter λ (0.36) explained a significant effect for age on the values of the parameters (serum ferritin, folic acid, vitamin B12, vitamin D and P-Hcy levels), thus confirming the truth that the individual values differed significantly. At the same time, the calculated *p* value (*p*=0.00027) was lower than the established significance level (α) revealing the statistical significance between the patient's age category and the individual blood values of the studied parameters (serum ferritin, folic acid, vitamin B12, vitamin D and P-Hcy levels).

Discussion

In the present manuscript, we investigated the effect of B vitamins and folate on P-Hcy levels. The results showed when the levels of B vitamins and folate started to increase, the P-Hcy level decreased. Our results were supported by another study, which examined the relationship of P-Hcy and B vitamin levels with cardiovascular diseases. Their study consisted of 5522 patients aged 55 years or older who suffered from vascular diseases or diabetes. Patients were assigned to receive daily treatment with either a combination of 2.5 mg of folic acid, 50 mg of vitamin B6 and 1 mg of vitamin B12 or placebo for an average of five years. In their study subjects, mean P-Hcy level decreased by 2.4 µmol per liter (0.3 mg/L) in the active treatment group and increased by 0.8 µmol per liter (0.1 mg/L) in the placebo group. The primary outcome events occurred in 519 patients (18.80%) assigned to active therapy and 547 (19.80%) assigned to placebo (relative risk, 0.95; 95% confidence interval, 0.84 to 1.07; p=0.41) (32).

A study conducted by Yuan *et al.* demonstrated a relationship between the reduction of plasma homocysteine mediated by B vitamins, which may ultimately significantly reduce the risk of stroke, especially the subarachnoid haemorrhage and ischemic stroke. The research was conducted using data for 12 target cardiovascular disease markers, from a large genetic consortia (Biobank UK, FinGen). The results showed association of higher genetically predicted folate level with reduced risk of coronary artery diseases (OR SD=0.88; 95%CI=0.78, 1.00, p=0.049) and stroke (OR SD=0.86; 95%CI=0.76, 0.97, p=0.012), as well as between higher genetically predicted vitamin B6 level and lower risk of ischemic stroke (OR SD=0.88; 95%CI=0.81, 0.97, p=0.009) and higher risk of peripheral artery diseases (OR SD1=30; 95%CI=1.09, 1.54, p=0.004); while genetically determined vitamin B12 level was not associated with any cardiovascular diseases (33).

Bonetti *et al.* demonstrated a relationship between dementia and hyperhomocysteinemia. The hyperhomocysteinemia (>15 µmol/L) was associated with a higher incidence of cognitive and functional impairment and dementia (OR=1.98, 95%CI=1.13-3.48) to be independent of blood glucose variability (BGV) status and other factors. Participants with hyperhomocysteinemia with normal BGV status had the worst functional status and the highest incidence of dementia (high homocysteine/normal BGV versus normal homocysteine/normal BGV, OR=3.20, 95%CI=1.65-6.21). Homocysteine level was negatively correlated with folate and vitamin B12 levels and glomerular filtration rate, and positively correlated with free thyroxine and uric acid levels (model coefficient of determination=0.43) (34).

Clarke *et al.* illustrated that supplementation with B vitamins in patients with elevated plasma homocysteine level reduced the risk of cardiovascular diseases. Through a meta-analysis of randomized trials, the authors found that in populations whose diets were not fortified with folic acid, folic acid supplementation reduced homocysteine level by 23.00% or, when given in combination with vitamin B12 (cyanocobalamin), it was by 30. The effect of B vitamins supplementation was somewhat less pronounced in populations with pre-existing mandatory folic acid fortification, even the combined treatment usually reduced homocysteine level by 20.00% (35). Considering the above studies to significantly improve the health status, we would suggest that increasing regular daily doses of B vitamins and folate may affect (reduce) P-Hcy level.

Conclusion

Plasma homocysteine level was shown to have a significant impact on patient's health, not only in relation to cardiovascular diseases, but also in relation to respiratory, reproductive and other diseases. Lowering blood serum homocysteine level was demonstrated to be achieved by incorporating food types with higher levels of vitamins B, D, ferritin and folic acid. It was shown that adding a vitamin component, whether in the form of supplement or diet, can significantly impact not only in reduction of plasma Hcy, but also in the overall health status of the patient too, and ultimately serve as a precaution against worsening health conditions or outbreaks of other related diseases.

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Authors' Contribution

All authors have read and approved the manuscript. Supervision: SD and JB; Conceptualization and Data curation: GH; Project administration: GH; Methodology and Formal analysis: GH; Writing – original draft: GH; Writing – review and editing: GH

Conflict of Interest

There is no conflict of interest.

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