Serum Levels of Homocysteine in Young Psoriasis Patients Naïve for Conventional Systemic and Biologic Therapy

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Abstract:

Introduction: Psoriasis is an immune-mediated chronic inflammatory disease, affecting approximately 1-3% of the population worldwide. Psoriasis patients are more likely to be diagnosed with cardiovascular diseases and hyperhomocysteinemia; however, it remains elusive weather serum homocysteine levels correlate to disease activity and duration of disease. The aim of this study was to investigate serum levels of homocysteine in young patients with plaque psoriasis naïve for conventional systemic and biologic therapy. An additional aim was to determine correlation of homocysteine levels with disease severity, inflammation, folic acid and vitamin B12 supplies.

Materials and methods: 26 subjects were enrolled to participate in this case-control study, including 13 adult psoriatic patients naïve for systemic therapy, without comorbidities, malignancies and infectious diseases, and 13 healthy unrelated, age and sex-matched volunteers. The disease severity and life quality were assessed using standardized tools – Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI), respectively. Venous blood was collected and processed for analysis of differential blood count (DBC), erythrocyte sedimentation rate (ESR), C reactive protein (hsCRP), serum levels of homocysteine, vitamin B12 and folic acid in the routine clinical laboratory.

Results Studied cohort consisted of young participants with average age around 35 years. According to the PASI index, disease severity ranged from mild (2.10) to moderate (15.2). There was no significant difference in hsCRP and DBC levels between the groups. Psoriasis patients had significantly higher levels of homocysteine compared to healthy subjects, but there was no evidence of hyperhomocysteinemia related to psoriasis. All subjects had normal serum levels of vitamin B12 and folic acid. A moderate negative correlation was found between plasma homocysteine level and vitamin B12 and folic acid. Furthermore, homocysteine levels did not correlate to hsCRP, total leukocytes, and thrombocytes count, but did significantly positively correlate to ESR.

Conclusions: The risk of cardiovascular diseases should be considered among all psoriasis patients, regardless of age and disease severity, but larger prospective controlled studies are needed to estimate the role of homocysteine in cardiovascular morbidity and mortality in psoriatic patients.

Keywords: psoriasis, homocysteine, folic acid, cardiovascular disease

Sažetak:

Serumska vrijednost homocisteina u mladih bolesnika koji nisu primali sustavnu i biološku terapiju

Uvod: Psorijaza je imunološki posredovana kronična upalna bolest, koja pogađa otprilike 1-3% populacije u svijetu. Pacijenti oboljeli od psorijaze imaju veću vjerojatnost razvoja kardiovaskularnih bolesti i hiperhomocisteinemije, međutim, ostaje nejasna povezanost serumske razine homocisteina s aktivnošću i trajanjem bolesti.

Cilj ove studije bio je ispitati serumske vrijednosti homocisteina u mladih bolesnika s plak psorijazom, koji nisu do sada primali sustavnu, ili biološku terapiju. Dodatni cilj bio je utvrditi povezanost serumske razine homocisteina s težinom bolesti, razinom upale te razinom folne kiseline i vitamina B12.

Materijali i metode U ovo istraživanje bilo je uključeno 26 ispitanika, uključujući 13 odraslih bolesnika s psorijazom naivnih za sustanu terapiju, bez komorbiditeta, malignih oboljenja i zaraznih bolesti te 13 zdravih, nepovezanih, dobno i spolno usklađenih dobrovoljaca. Težina bolesti i kvaliteta života procijenjena je korištenjem standardiziranih testova - Psoriasis Area and Severity Index (PASI) i Dermatološkog indeksa kvalitete života (DLQI). Iz venske krvi ispitanika, u rutinskom kliničkom laboratoriju, određena je diferencijalna krvna slika (DKS), brzina sedimentacije eritrocita (SE), C reaktivni protein (hsCRP) te serumske razine homocisteina, vitamina B12 i folne kiseline.

Rezultati Istraživana skupina sastojala se od mladih sudionika, prosječne dobi oko 35 godina. Prema PASI indeksu, težina bolesti bila je u rasponu od blage (2,10) do umjerene (15,2) psorijaze. Nije bilo značajne razlike u vrijednostima hsCRP-a i DKS-a između ispitivanih skupina. Ispitanici s psorijazom imali su statistički značajno više vrijednosti homocisteina u usporedbi sa zdravim ispitanicima, ali nije bilo dokaza hiperhomocisteinemije povezane s psorijazom. Svi ispitanici imali su normalne vrijednosti vitamina B12 i folne kiseline u serumu. Utvrđena je umjerena negativna povezanost između razine homocisteina u serumu i vitamina B12 te razine homocisteina i folne kiseline. Nadalje, serumska razina homocisteina nije bila povezana s hsCRP-om, ukupnim brojem leukocita i trombocita, ali je uočena značajna pozitivna povezanost serumske razine homocisteina i sedimentacije.

Zaključak: Rizik od kardiovaskularnih bolesti treba razmotriti među svim pacijentima oboljelima od psorijaze, bez obzira na njihovu dob i težinu bolesti. Potrebna su veća prospektivna, kontrolirana ispitivanja kao bi se procijenila uloga homocisteina u razvoju kardiovaskularnih bolesti kod psorijatičnih bolesnika.

Ključne riječi: psorijaza, homocistein, folna kiselina, kardiovaskularna bolest

Introduction

Psoriasis is an immune-mediated chronic inflammatory disease, affecting approximately 1-3% of the population worldwide[1,2]. As opposed to the formerly widespread opinion that psoriasis is a skin limited disease, it is now accepted, due to an increasing number of epidemiological publications and evidence-based research, that significant systemic conditions often accompany this chronic disease[3]. In fact, psoriasis is considered as an independent risk factor for cardiovascular morbidity and mortality[4,5]. Particularly, the risk for the development of myocardial infarction, as well as other cardiovascular events, is noticeably increased in patients with severe psoriasis, especially those between 20 and 50 years old[6].

Even though the association between psoriasis and cardiovascular diseases is lately extensively studied, the exact underlying mechanisms have not yet been uncovered[7].

As suggested in some previously published studies, elevated serum homocysteine levels might contribute to the cardiovascular risk in psoriatic patients[8-10].

Homocysteine is sulfur containing amino acid, displaying atherogenic and prothrombotic features. It is produced in the metabolism of the essential amino acid methionine and can be catabolized by re-methylation to methionine in the presence of co-factors folic acid and vitamin B12 or by trans-sulfuration to cysteine in the presence of cofactor vitamin B6[8,11-15]. Moreover, homocysteine promotes endothelial dysfunction and, consequently, atherosclerosis by reducing the bioavailability of nitric oxide due to inhibition of nitric oxide synthase (eNOS) and oxidative stress, provokes endothelial cell damage, and leads to a state of chronic inflammation of the endothelium [12,16].

A meta-analysis of 24 studies showed that psoriatic patients have higher homocysteine serum levels, a greater prevalence of hyperhomocysteinemia and, conversely, have lower serum folate levels compared to controls. Yet, the two groups did not significantly differ in vitamin B12 serum levels[10].

Rapid keratinocyte proliferation with high mitotic activity of basal cells, along with intestinal malabsorption caused by microscopic inflammatory changes of the intestinal mucosa, might contribute to folate deficiency in patients with psoriasis. Since folic acid is a cofactor in the catabolism of homocysteine, the

decrease in folate serum levels is therefore one of the causes for hyperhomocysteinemia[8,17-20].

However, due to inconsistent results from several studies, it still remains unclear whether a correlation between homocysteine levels, disease activity and disease duration exists or not[8,9,19,21,22].

Another potential link between homocysteine and psoriasis lies in epigenetic changes of human leukocyte antigen (HLA) DRB1, a major histocompatibility complex (MHC) II protein[23,24]. Provided that the expression of HLA-DRB1 on antigen presenting cells (APCs) can be altered by aberrant methylation status of the gene, these methylation changes can affect the APCs capability of antigen presentation to T lymphocytes, the main role of HLA-DRB1[23]. Indeed, hypomethylation of the promoter region of HLA-DRB1 was found in the epidermis of psoriatic lesions when compared to psoriatic non-lesioned skin, whereas the mean methylation rate of HLA-DRB1 in lesioned skin negatively correlated to Psoriasis Area and Severity Index (PASI) score, suggesting that aberrant methylation of this region might play a role in the pathogenesis of psoriasis [23]. Given the fact that homocysteine, as an intermediate, plays an important role in the methylation cycle, the majority of published data supports the claim that high homocysteine serum levels are associated with global DNA hypomethylation in humans. Since the role of homocysteine in the abnormal methylation pattern seen in psoriatic lesions remains unclear, there is a need for further research to elucidate this[15,25].

The aim of this study was to investigate serum levels of homocysteine in patients with vulgar psoriasis naïve for conventional systemic and biologic therapy. An additional aim was to determine correlation of homocysteine levels with disease severity, inflammation, and folic acid and vitamin B12 supplies.

Matherials and methods

Subjects

This was a case-control study, including 13 psoriatic patients with clinically diagnosed plaque psoriasis and 13 healthy unrelated, age- and sex-matched control subjects. Subjects were recruited among the patients admitted at the Department of Dermatology and Venereology of the University Hospital Osijek (Croatia). At the time of enrollment, psoriasis patients had a clinically active and histopathological confirmed disease. The disease severity and life quality were assessed using standardized tools – the Psoriasis Area Severity Index (PASI) and Dermatology Life Quality Index (DLQI), respectively [26,27].

Exclusion criteria for this study were: (1) ongoing systemic therapy for psoriasis (including immunomodulatory therapy, cytostatic, photochemotherapy and phototherapy), (2) concomitant rheumatic and autoimmune diseases (i.e. spondyloarthropathy, rheumatoid arthritis), (3) malignant and infectious diseases, and (4) age (under 18 years). Anthropometric and demographic data, such as body height, body weight, age, gender and parity were assessed using a questionnaire.

The study was reviewed and approved by the Ethical Committee of the University Hospital Osijek (number: R2-9042 / 2018) and the Ethics Committee of the Faculty of Medicine University of Osijek (number: 2158-61-07-18-135). The study was conducted in accordance with Declaration of Helsinki, and all participants signed written informed consent prior inclusion into the study.

Methods

For the purpose of determining differential blood count, C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), serum levels of homocysteine, vitamin B12 and folic acid, venous blood was collected in the morning, after a minimum of 8-hours fasting period. Samples intended for homocysteine level analysis were immediately put on ice. All samples were delivered to the laboratory at the Clinical Department for Laboratory Diagnostics (University Hospital Osijek, Osijek, Croatia) and analyzed within 1 hour. The normal laboratory range for plasma homocysteine was 0–14 μmol/l, and hyperhomocysteinemia was defined as a homocysteine concentration >14 μmol/l[28].

Statistical analysis

All results are reported as the mean ± standard deviation (SD). The Shapiro–Wilk test was used to test the normality of data distribution. Next, data were compared by Student's t-test or the Mann-Whitney rank-sum test for normally distributed data and data that did not follow a normal distribution pattern, respectively. The correlations between serum levels of homocysteine and other assessed parameters were determined by Pearson's correlation tests. $p < 0.05$ was considered statistically significant. SigmaPlot, version 11.2 (Systat Software, Inc., Chicago, IL, USA) was used for statistical analysis.

Results

The present study included 26 subjects, of which 13 participants were psoriasis patients with an active disease, and the remaining 13 participants were age- and sex- matched healthy controls. Their demographic and clinical data are shown in Table 1. The average age of enrolled subjects in both groups was around 35. Disease severity in psoriasis patients was assessed using the PASI index and ranged from 2.10 to 15.2. The rate of smokers among psoriasis patients and healthy controls was 46.2% and 23.1%, respectively. C-reactive protein levels and differential blood count did not vary significantly between the groups (Table 1).

Psoriasis patients had significantly higher serum levels of homocysteine compared to healthy subjects (p=0.021; Table 1 and Figure 1), however, there was no evidence of hyperhomocysteinemia related to psoriasis. All included subjects had serum homocysteine levels within the normal reference range except one psoriasis patient who presented with slightly elevated level of homocysteine (15.5 μmol/L), (Table 1).

All subjects had normal serum levels of vitamin B12 and

		Psoriasis patients	Healthy controls	t test (p value)
Number of participants (N)		13	13	-
Sex	Male (N)	7	10	-
	Female (N)	6	3	-
Age (years)		34.3±7.71 (25.0, 50.0)	35.9±8.38 (24.0, 55.0)	0.630
PASI		9.16±3.91 (2.10, 15.2)	N/A	-
DLQI		5.00±5.85 (0.00, 20.0)	N/A	-
BMI		24.9±4.72 (19.1, 34.9)	25.0±4.28 (19.5, 35.8)	0.936
Smoking	Yes (N)	6	3	-
	No (N)	7	10	-
Parameter (unit; laboratory referent values)				
CRP (mg/l; <5.0)		1.86±2.03 (0.30, 7.80)	1.41±1.09 (0.12, 3.20)	0.488
Leukocytes (x10e9 /L ; 3.40-9.70)		6.77±1.67 (3.7, 9.0)	6.18±1.83 (4.50, 10.4)	0.402
Erythrocytes (x10e12/L; 3.86-5.08)		4.84±0.43 (4.08, 5.34)	5.00±0.36 (4.47, 5.73)	0.342
Thrombocytes (x10e9/L; 158.0-424.0)		271.4±58.8 (214.0, 416.0)	254.1±58.1(145.0, 391.0)	0.458
Sedimentation rate (mm/3.6 KS; 4.00-24.0)		5.45±1.69 (3.00, 8.00)	5.58±4.83 (1.00, 15.0)	0.511
Homocysteine (umol/l)		9.99±2.30 (7.10, 15.5)	8.03±1.36 (6.10, 10.5)	0.021*
Folic acid (nmol/L; 7.0-64.0)		13.7±4.72 (7.0, 19.7)	15.6±5.96 (8.00, 21.8)	0.370
Vitamin B12 (pmol/L; 138.0-652.0)		318.2±103.2 (216.0, 602.0)	291.0±141.6 (136.0, 479.0)	0.550

Data are presented as mean±SD (min, max). The differences were tested by Student's t-test or Mann-Whitney rank-sum test, where appropriate. **p<0.05 was considered significant

folic acid (Table 1). The mean plasma levels of either vitamin B12 (318.2±103.2 pmol/L in psoriasis patients versus 291.0±141.6 pmol/Lin healthy subjects, p=0.370), or folic acid (13.7±4.72 nmol/L in psoriasis patients versus 15.6±5.96 nmol/L in healthy subjects, p=0.550) were not statistically significantly different between two groups. A moderate negative correlation was found between plasma homocysteine level and vitamin B12 (r=-0.603, p=0.004) and folic acid (r=-0.638, p=0.002). Furthermore, homocysteine levels did not correlate to hsCRP (p=0.638), total leukocytes (p=0.203) and thrombocytes count (p=0.291), but did significantly positively correlate to sedimentation rate (r=0.410, p=0.0159)

Psoriasis patients included in this study had mild to moderate disease severity. Mean PASI score was 9.16±3.91, ranging from 2.10 to 15.2. There is no evidence of direct correlation between current disease severity and serum homocysteine levels

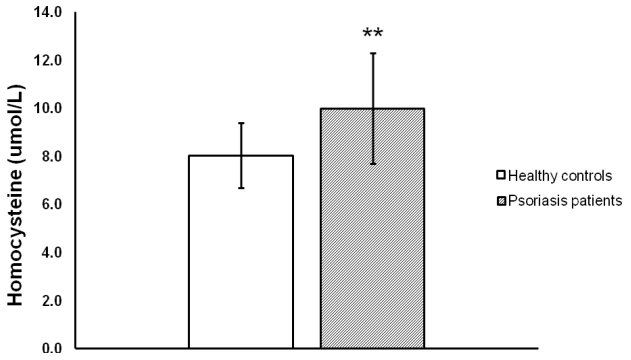

Figure 1. Psoriasis Patients Present with Higher Serum Levels of Homocysteine Compared to Healthy Controls

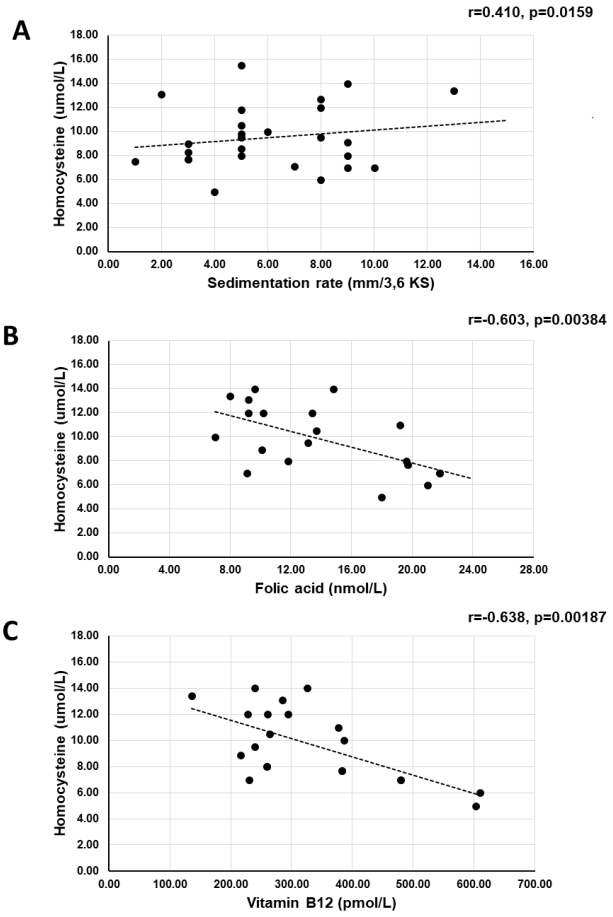

Figure 2. Homocysteine Levels Correlate to Inflammation and Body Supply of Folic Acid and Vitamin B12

(p=0.228), nor the life quality of psoriasis patients and serum homocysteine levels (p=0.392).

Discussion

Psoriasis is considered to be an independent risk factor for cardiovascular morbidity and mortality, but the exact underlying mechanisms have not yet been uncovered [3-5]. Some recent studies suggested that elevated serum homocysteine levels in psoriatic patients might contribute to the cardiovascular risk in psoriatic patients, due to their atherogenic and prothrombotic effect [11-15]. In the present study young psoriasis patients naïve for systemic and biologic therapy presented with significantly higher serum levels of homocysteine compared to the healthy subjects, but still their serum homocysteine levels were within normal reference range. In addition, all participants had normal serum levels of B12 vitamin and folic acid. These results partly correspond to previous studies that are included in the meta-analysis performed by Tsai TY et al[10]. The authors reported significantly higher serum homocysteine level in 18 out of 24 studies, a higher prevalence of hyperhomocysteinaemia in seven studies, a lower serum folate level in 14 studies, and no difference in serum vitamin B12 levels between psoriasis patients and the healthy controls[10]. Although serum levels of folic acid between two groups in our research showed no significant difference, we found a moderate negative correlation between the serum homocysteine level and vitamin B12, as well as between plasma homocysteine level and folic acid level. Similar results were found in previous research concerning negative correlation between serum homocysteine levels and folic acid levels, but none of the previous studies showed significant correlation between the serum levels of homocysteine and B12 vitamin[10]. Negative correlation between homocysteine and folic acid as well as homocysteine and B12 vitamin could be related to the fast epidermal overgrowth and higher mitotic basal cell activity of the psoriasis patients[20]. An additional reason for the higher homocysteine levels among psoriasis patients could be the reduced absorption of folic acid and B12 vitamin in the intestine due to micro damage of the intestinal villi that is caused by long term chronic inflammation in psoriatic patients[29,30]. Furthermore, normal folate levels observed in our study, which is contrast to previous reports, might be explained by younger age (35 years old) of subjects and shorter exposure to systemic inflammation[10]. Additionally, homocysteine levels did not correlate to hsCRP and total leukocytes count, but did significantly positively correlate to sedimentation rate. Consistent to previous reports, we failed to find direct correlation between current disease severity and serum homocysteine levels[10]. These results suggest that hyperhomocysteinemia and cardiovascular comorbidity rise as a result of prolonged exposure to systemic inflammation.

Conclusion

Based on the results of the present study, homocysteine has

the potential as a biomarker of cardiovascular risk in psoriasis patients, primarily during long term follow-up. Single measurements of serum homocysteine levels in population of young psoriasis patients are likely to fall within the normal reference range, and thus could not be used for prediction of cardiovascular risk. In addition, etiology of cardiovascular diseases is complex, including genetic, environmental and other factors thus large prospective controlled studies are needed to overcome immense heterogeneity among them. Here we would like to emphasize

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