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Original Research

Serum homocysteine level, vitamin B12 levels, and erythrocyte folate in psoriasis: A case-control study☆,☆☆

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ABSTRACT

Background: One of the most important organ involvements in psoriasis is atherosclerotic cardiovascular disease. Homocysteine is known to have atherogenic properties, but some inconsistency exists in the literature about its probable role as a risk factor of cardiovascular disorder in patients with psoriasis.
Objective: Because of some controversies, we compared homocysteine levels and related parameters of metabolic cycles in patients with psoriasis and healthy individuals.
Methods: This case-control study was conducted on 50 patients with psoriasis and 50 healthy individuals as the controls. Serum homocysteine, vitamin B12 levels, and erythrocyte folate concentrations were checked in all participants.
Results: Mean serum homocysteine, erythrocyte folate, and vitamin B12 levels did not show any significant difference between the two groups ($p > .05$), but interestingly, in patients with psoriasis, men had a significantly higher incidence of hyperhomocysteinemia and lower levels of erythrocyte folate ($p = .14$). Overall, there is no significant difference in serum levels of homocysteine and metabolic-related parameters between the case and control group. There was no significant relationship between the severity of psoriasis and the body mass index of patients ($p > .05$).
Conclusion: Patients with psoriasis had a higher body mass index and higher levels of homocysteine in men. Hyperhomocysteinemia could be a predisposing factor of cardiovascular events, but more evaluations as a part of metabolic syndrome in patients with psoriasis are needed.

Introduction

Psoriasis is well known in the field of dermatology as a common disorder with a world-wide distributed that presents with long-lasting immune system inflammation and many extracutaneous manifestations. Because of the chronic inflammatory basis of psoriasis, many other disorders can be involved, including metabolic syndrome, risk of cardiovascular diseases, inflammatory bowel disease, and even malignancies (Lajevardi et al., 2014; Patel et al., 2011).

Many articles address the association between psoriasis and markers of metabolic syndrome or the effectiveness of special medication, such as pioglitazone, in treatment of psoriasis (Neimann et al., 2006; Ehsani et al., 2016; Hallaji et al., 2016; Lajevardi et al., 2015). Moreover, psoriasis is recognized as an independent risk factor with myocardial and cerebral infarction and peripheral vascular disease, especially moderate-to-severe psoriasis. The risk is more prominent in young patients, directly related to increased severity of psoriasis (Patel et al., 2011; Gelfand et al., 2006, 2009; Kimball et al., 2010).

Given the atherogenic and prothrombotic effects of homocysteine, hyperhomocysteinemia is associated with numerous thrombotic vascular events (Rosenson et al., 2011). Homocysteine converts to methionine with vitamin B12 and folate as co-factors of this process. In the metabolic cycle of homocysteine synthesis, a decrease in vitamin B12 and folate leads to higher levels of homocysteine and lower levels of methionine. As proposed in recent studies, the proliferation of epidermal keratinocytes in psoriasis and use of folic acid as a result may decrease serum folate levels by dividing cells (trough

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DNA methylation) or impairing intestinal folate absorption after microscopic inflammatory changes of intestinal mucosa, which leads to increased levels of serum homocysteine (Malerba et al., 2006a; McDonald et al., 2012; Tobin et al., 2010).

Findings from several studies have shown that there are some inconsistencies in hyperhomocysteinemia folate and vitamin B12 levels in patients with psoriasis and their association with disease severity (Brazzelli et al., 2010; Cakmak et al., 2009; Gisondi et al., 2010; Karabudak et al., 2008; Malerba et al., 2006a; McDonald et al., 2012; Patel et al., 2011; Tobin et al., 2010, 2011; Vanizor Kural et al., 2003). New investigations confirm higher serum homocysteine levels and related metabolites in the L-arginine-NO pathway (especially ADMA) and its direct correlation with disease severity (Bilgiç et al., 2015; Giannoni et al., 2015). However, some studies have not found any significant difference between serum homocysteine levels in cases and controls; these studies have introduced other inflammatory mediators, such as sC40L, lipocalin 2, and STNFR-1, as more important in the pathogenesis of psoriasis (Ataseven et al., 2014; Erturan et al., 2014).

Therefore, for better management, we designed a comparative study to analyze serum homocysteine, erythrocyte folate, and vitamin B12 levels in psoriasis as a case-control study.

Patients and methods

This case-control study was performed at the Razi Hospital in Tehran, Iran, in 2012. Fifty patients with psoriasis as the case group and 50 healthy individuals as the control group were enrolled in the study. Ethics approval was obtained from the ethics committee of the Tehran University of Medical Science, and all patients completed the informed consent form.

None of the participants were taking supplement therapy. Patients with plaque type psoriasis who were not taking systemic therapeutic regimens for psoriasis during the past month were selected as cases. The controls were selected from consenting age- and sex-matched healthy individuals who were admitted to the hospital for cosmetic surgeries with no history of inflammatory skin disorders. For all participants, chronic liver or kidney disease, hypo- or hyperthyroidism, diabetes mellitus, history of vascular events, malignancy, taking drugs with an effect on serum homocysteine levels (i.e., phenytoin, carbamazepine, penicillamine, theophylline, vitamins, oral contraceptive pills, azathioprine, metformin, and thiazide diuretics), and cigarette smoking were considered as the exclusion criteria.

Demographic data of the participants and their body mass index (BMI; weight [kg]/height $[m]^2$) were recorded, as was the Psoriasis Area and Severity Index (PASI; Carlin et al., 2004) score for the case group.

A sample of 4 ml of blood was taken from both groups. The samples were centrifuged, and total serum homocysteine (free and protein-bound) levels were measured with the Diazyme Homocystein Assey kit from Roche Company and read with the Elecsys 2010 and enzyme colorimetry method. Serum vitamin B12 and erythrocyte folate levels were measured with Roche kits and the Elecsys 2010 device.

Data was entered in SPSS, version 22, and analyzed. To describe the quantitative data, mean, median, and standard deviation were used. T and χ^2 tests and Pearson correlation coefficients were used to compare between two normally distributed qualitative variables; otherwise, a Spearman correlation test was performed.

Results

Age and sex

The case and control groups were matched for age and sex. The mean age of patients was 39.2 ± 14.2 years. Fifty-six men and 44 women were enrolled in the study. In each group, 28 men (56%) and 22 women (44%) participated. The overall mean BMI in this study was 28.5 ± 5.1, and the mean BMI was 29.7 ± 5.3 and 26.9 ± 4.4 in the case and control groups, respectively, which was statistically significant ($p = .008$).

The serum homocysteine levels were within the normal range of 5 to 20 μmol/L; overall, the mean serum homocysteine level was 14.2 ± 9.8 μmol/L, with 15.15 ± 9.19 μmol/L in the case group and 13.66 ± 7.09 μmol/L in the control group and showed no significant difference ($p > .05$).

Erythrocyte folate levels were within the normal range of 120 to 860 ng/ml, and total mean serum erythrocyte folate level was 343.6 ± 180.9 ng/ml. The mean serum erythrocyte folate levels were 351.79 ± 235.82 ng/ml and 384.30 ± 160.27 ng/ml in the case and control groups, respectively, and the difference was not statistically significant ($p > .05$).

Serum vitamin B12 levels were within the normal range of 160 to 970 pg/ml. Overall, the mean serum vitamin B12 level was 325.4 ± 278.8 pg/ml. In the case group, the level was 300.16 ± 280.9 pg/ml, and in the control group it was 370.88 ± 340.97 pg/ml, which was not statistically significant ($p > .05$).

The mean range of PASI scores in the case group was 10.4 ± 5.3. Despite the association between BMI and psoriasis ($p = .008$), there was no significant relationship between disease severity (PASI) and BMI ($p > .05$). In addition, we found that the BMI of patients with psoriasis (case group) was higher than that of the controls ($p = .008$). 2) Also, in both groups, men had lower serum folate levels than women ($p = .026$).

Vitamin B12 levels had a weak direct relationship with folate levels, but it was not statistically significant ($p = .062$; $r = .14$). Erythrocyte folate levels in 22% of patients in the case group was lower than the normal range; however, in all controls, the levels were normal. Serum homocysteine levels in 22% of the case group and 24% of the control group exceeded the normal range. Sixteen percent of the case group and 8% of the control group had a vitamin B12 deficiency, but the difference was not statistically significant. Table 1 shows a comparison between the case and control groups with regard to measured variables.

Discussion

Previous studies have provided strong evidence about the role of homocysteine as an independent risk factor for atherosclerotic vascular disorders (Bilgiç et al., 2015; Boushey et al., 1995; Clarke et al., 1991; Cleophas et al., 2000; Fallon et al., 2001; Giannoni et al., 2015; Vanizor Kural et al., 2003).

According to an increased prevalence of cardiovascular disease and its association with a higher mortality in patients with psoriasis, determining relevant risk factors in these patients would be very important and valuable. Research supports that patients with psoriasis are more obese than the normal population (Bryld et al., 2010; Duarte et al., 2010; Herron et al., 2005; Sterry et al., 2007). In addition, a direct correlation between disease severity and obesity has been found (Bryld et al., 2010; Herron et al., 2005; Langan et al., 2012). In this study, BMI was significantly higher in the case group than in the controls, and although there was a direct relationship between a higher BMI and the presence of psoriasis, no significant relationship was found with its severity (PASI score). These findings ae similar to those by Tobin et al. (2011).

Serum homocysteine levels were not significantly different between the case and control groups, which was not compatible with the results of most similar studies that showed higher homocysteine levels in patients with psoriasis (Bilgiç et al., 2015; Brazzelli et al., 2010; Giannoni et al., 2015; Gisondi et al., 2010; Karabudak et al., 2008; Malerba et al., 2006a; Tobin et al., 2011; Vanizor Kural et al., 2003). Other studies have indicated a direct relationship between homocysteine levels and the severity of psoriasis; however, in the study

Table 1
Comparison between mean levels of measured variables in case and control groups

	Patients with psoriasis (cases)	Age- and sex-matched healthy controls	p-value
Body mass index kg/m2	29.7 ± 5.3	26.9 ± 4.4	< .05
Serum homocysteine, μmol/L	15.15 ± 9.19	13.66 ± 7.09	> .05
Erythrocyte folate, ng/ml	351.79 ± 235.82	384.30 ± 160.27	> .05
Serum vitamin B12, pg/ml	300.16 ± 280.9	370.88 ± 340.97	> .05

by Cakmak et al. (2009), this direct relationship was not observed, which is consistent with the results of our study (Ataseven et al., 2014; Cakmak et al., 2009; Erturan et al., 2014).

In this study, a significant inverse relationship was detected between homocysteine and vitamin B12 levels that are reasonable with regard to homocysteine metabolism (Rosenson and Kang, 2011). About relationship between sex and homocysteine and erythrocyte folate levels; in both case and control groups; men had higher homocysteine and lower folate levels. (erythroctye is better than serum in assessing folate level because it is less affected by the dietary regimen) (Brazzelli et al., 2010; Cakmak et al., 2009; Malerba et al., 2006b; McDonald et al., 2012). In both the case and control groups, men had higher homocysteine and lower folate levels. Previous studies have not shown any similar relationships, and these findings could generate the hypothesis that folate deficiency might be a risk factor for increasing homocysteine levels and cardiovascular events.

Erythrocyte folate levels were not significantly different between the case and control groups, and only one study (Cakmak et al., 2009) has reported results similar as ours. Other studies have mentioned a significant decrease in folate levels in patients with psoriasis (Brazzelli et al., 2010; Gisondi et al., 2010; Karabudak et al., 2008; Malerba et al., 2006a; Tobin et al., 2011; Vanizor Kural et al., 2003).

No significant differences in vitamin B12 levels were revealed in the case and control groups, which is compatible with the results by Cakmak et al. (2009) and Malerba et al. (2006a). Other studies, such as the study by Tobin et al. (2011), demonstrated a significant difference in vitamin B12 levels in both the case and control groups. Vitamin B12 levels had a weak direct relationship with folate levels; however, this was not statistically significant like the significant relationship between vitamin B12 and folate levels in many other studies (Brazzelli et al., 2010; Cakmak et al., 2009; Malerba et al., 2007; McDonald et al., 2012).

Of note, changes in folate levels can be in line with vitamin B12 levels, possibly because of nutritional status (Brazzelli et al., 2010; Cakmak et al., 2009; Malerba et al., 2007; McDonald et al., 2012). A study by Tobin et al. (2011) highlighted a relation between BMI and psoriasis, but not with PASI score. A variety of findings have been reported by other researchers, such as a significant correlation between homocysteine and folate levels with severity of disease (Malerba et al., 2007) and between homocysteine levels and severity of disease (Bilgiç et al., 2015; Cakmak et al., 2009; Giannoni et al., 2015).

Our results showed that although the difference between mean folate and vitamin B12 levels in both groups were not statistically significant, the prevalence of folate and vitamin B12 deficiency among patients in the case group was higher than that in the control group (22% of patients and 0% of healthy individuals for folate levels, and 16% of patients and 8% of healthy individuals for vitamin B12 levels).

Malerba et al. (2007) reported the percentage of the variables as follows: 62.5% of patients and 20% of healthy individuals had hyperhomocysteinemia (unlike in our study), and 32.5% of patients but none of the controls had folate deficiency (similar to our study). Additionally, none of the participants had a vitamin B12 deficiency (unlike this study).

Limitations and recommendations

Nutritional issues can influence results (e.g., prevalence of vitamin deficiencies in different societies), and by increasing the sample size, we can eliminate the influence of such confounding factors and discuss significant relationships more confidently. More accurate studies with larger sample sizes in different groups of patients with psoriasis that consider other cardiovascular risk factors should be conducted to confirm the definite role of hyperhomocysteinemia and folate deficiency in atherosclerotic events.

Conclusions

Although we could not show any significant difference between the case and control groups with regard to serum homocysteine levels and related parameters, there was a higher presence of hyperhomocysteinemia in the male patients with psoriasis. According to our findings, patients with psoriasis had a higher BMI, which was not related to their PASI score. Logically, this is a predisposing factor of cardiovascular events that needs more evaluation as part of metabolic syndrome in patients with psoriasis. Finally, the administration of folic acid and vitamin B12 as a supplement should be studied in patients with high-risk psoriasis as a preventive strategy.

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Conflict of Interest

None.

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Study Approval

NA.

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