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Serum Homocysteine, Folic Acid and Vitamin B12 Levels in Patients with Psoriasis Vulgaris

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ABSTRACT

Background: Psoriasis is a chronic inflammatory skin condition with increased risk of cardiovascular disease. Hyperhomocysteinaemia might account for the increased susceptibility to CV diseases in psoriasis patients. Homocysteine metabolism is dependent in part on folate and vitamin B12 so deficiency of these vitamins may lead to hyperhomocysteinaemia.

Objective: This study aimed to investigate the association between homocysteine, folic acid and vitamin B12 levels and psoriasis vulgaris and to evaluate the correlation between homocysteine, folic acid and vitamin B12 levels and the severity of psoriasis vulgaris.

Patients and methods: This case control study included 80 subjects who were distributed into two groups; Cases group (Group A): included 50 patients with chronic plaque psoriasis vulgaris, and Control group (Group B): included 30 non psoriatic healthy, age and sex matched, subjects.

Results: The mean folic acid level in the psoriasis group was 3.69 (SD 0.96) nmol/l which was statistically significantly lower as compared with the control group (5.67 ± 1.31 nmol/l) ($p< 0.001$). The mean vitamin B12 level in the psoriasis group was 186.94 (SD 64.90) pmol/l which was statistically significantly lower as compared with the control group (353.73 ± 76.76 pmol/l) ($p<0.001$). The mean homocysteine level in the psoriasis group was 18.54 (SD 4.18) nmol/mL which was statistically significantly higher as compared with the control group (11.09 ± 1.78 nmol/mL) ($p<0.001$).

Conclusion: hyperhomocysteinaemia, decreased serum folate levels, and decreased serum B12 levels are common in patients with psoriasis. Serum homocysteine level was negatively correlated with serum folate level. No significant correlation was found between psoriasis severity (as measured by psoriasis area and severity index) and serum levels of homocysteine, folic acid, or vitamin B12.

Keywords: Psoriasis vulgaris, Serum homocysteine, Folic acid, Vitamin B12.

INTRODUCTION

Psoriasis is a T helper cell (Th1- and Th17-) mediated chronic inflammatory disease with a worldwide prevalence of around 2% [(1)]. Psoriasis derives from a complex interaction between genetic background, environmental factors and immune response, which leads to a chronic, low-grade inflammatory status [(2)].

Psoriasis has a significant impact on health related quality of life because of lifelong chronicity, extent of severity, periodicity of flares and from associated comorbidities [(3)].

A growing body of evidence from clinical and epidemiological research has revealed an association between psoriasis and cardiovascular diseases (CVD), such as stroke, coronary heart diseases and peripheral vascular diseases [(4)].

The precise mechanisms underlying this association are unclear. Some have speculated that Th1- and Th17-mediated chronic inflammation is an integral part of psoriasis pathogenesis, also plays a part in the development of atherosclerosis [(1)]. Other studies have suggested that hyperhomocysteinaemia might account for the increased susceptibility to CVD in patients with psoriasis [(5)]. Furthermore, cardiovascular risk factors, such as dyslipidaemia, hypertension, oxidative stress, diabetes mellitus and metabolic syndrome are more prevalent among patients with psoriasis [(6)].

Hyperhomocysteinaemia is defined as a medical condition characterized by an abnormally high level (above 15 μmol/L) of homocysteine in the blood [(7)]. Hyperhomocysteinaemia is a well-known risk factor for atherosclerosis [(8)] and venous thrombosis [(5)]. Homocysteine can mediate pathogenesis of CVD by several mechanisms such as adverse effects on vascular endothelium and smooth muscle cells with alterations of arterial structure and function. Some of the presumed mechanisms include increase in proliferation of vascular smooth muscle cells, endothelial dysfunction, oxidative damage, collagen synthesis and deterioration of arterial wall elastic tissue [(9)].

Homocysteine metabolism is dependent in part on folate and vitamin B12 so deficiency of these vitamins may lead to elevated homocysteine levels, which in turn impair endothelial function [(8)].

Reduced plasma folate and vitamin B12 levels in psoriasis patients have been attributed to their increased utilization in the skin, reduced absorption from the gut, or as an adverse effect of systemic medications like methotrexate. Deficiencies in vitamin B12 and folate have been associated with increased levels of plasma homocystiene [(3)].

This study aimed to investigate the association between homocysteine, folic acid and vitamin B12 levels and

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psoriasis vulgaris through; (1) Estimation of serum levels homocysteine, folic acid and vitamin B12 in psoriasis vulgaris patients in comparison to controls. (2) Searching for any correlation between the serum levels of homocysteine, folic acid and vitamin B12 and severity of psoriasis as defined by psoriasis area and severity index (PASI) score.

PATIENTS AND METHODS

This was a case control study that aimed to investigate the association between homocysteine, folic acid and vitamin B12 levels and psoriasis vulgaris. All subjects were recruited from the outpatient clinic of Dermatology Department, Mansoura University Hospital (Mansoura, Egypt) during the period between October 2019 and October 2020.

The study included 80 subjects who were distributed into two groups; **case group (Group A):** included 50 patients with chronic plaque psoriasis vulgaris, and **control group (Group B):** included 30 non psoriatic healthy, age and sex matched, subjects. This group was recruited from medical students, healthcare personnel and patients presenting at the dermatological outpatient clinic. They were selected not to have any autoimmune, inflammatory illness, systemic infection, or interfering medications.

Inclusion criteria:

1. Clinical diagnosis of chronic plaque psoriasis (i.e., lasting at least 2 months).
2. Cases and controls will be recruited if aged ≥18 years.

Exclusion criteria:

1. Patients with other types of psoriasis (guttate, pustular and erythrodermic).
2. Subjects with any chronic illness, cancer, or hyperuricemia.
3. Patients with a history of systemic anti psoriatic therapy within 4 weeks.
4. Subjects taking any antifolate medications (e.g. anticonvulsants, methotrexate, penicillin, levodopa, cyclosporine, and isoniazid).
5. Drugs that cause hyperhomocysteinemia (phenytoin, carbamazepine, theophylline, oral contraceptives, azathioprine, thiazide diuretics, and metformin).
6. Subjects with a history, clinical evidence, or laboratory evidence of: Eating disorders (e.g. anorexia nervosa and bulimia nervosa), acute or chronic infection, heavy smokers, alcoholism, chronic renal or liver disease, autoimmune diseases, and other inflammatory skin diseases

Data collection: The medical records of patients were reviewed using computerized sheet including all studied data for each patient.

Ethical consent:

A written informed consent was obtained from all participants before inclusion in the study, explaining the value of the study, plus the procedures that will be conducted. The whole study design was approved by the Institutional Review Board (IRB) (Code Number MS.19.06.697), Faculty of Medicine, Mansoura University. Confidentiality and personal privacy were respected in all levels of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All cases in the study were subjected to the following:

I. **Complete history taking,** including: Personal history, history of the present illness, history of medications, family history of psoriasis or other dermatoses, and past history of any associated systemic, dermatological diseases or major surgical operations.

II. **Complete physical examination,** including:
   - **A-** Through general examination: to exclude any systemic diseases.
   - **B-** Calculation of BMI: It is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). BMI values between 18.5 and 24.99; kg/m^2 are considered normal; individuals with BMI values from 25 to 29.9 kg/m^2 are considered overweight and those with values greater than 30 kg/m^2 are considered obese [(10)].
   - **C-** Full dermatological examination:
     - **i.** Full dermatological examination was done including skin, hair, nails and mucous membranes to assess the clinical type of psoriasis, distribution and severity and to exclude autoimmune skin diseases.
     - **ii.** Lesions were scored according to PASI score [(11)].
       - The PASI measures erythema, scaling and thickness of lesions and is weighted by the area of involvement.
       - PASI score classifies patients with psoriasis into mild psoriasis (PASI ≤10), moderate psoriasis (PASI >10 - <20), severe psoriasis (PASI ≥20) [(12)].

III. **Assessment of serum homocysteine, vitamin B12 and folic acid:**

Samples collection:

Blood sample were collected (5 ml of venous blood) from all included subjects after fasting for 10-12 hours and centrifuged at 3000 rpm for 20 minutes. Sera were separated and divided into 3 aliquots and kept at 20ºC until analysis, and blood samples were kept on ice until serum separated.

Samples analysis:

Vitamin B 12: Serum vitamin B12 was determined via ELISA technique utilizing commercially-available kits named human vitamin B12 ELISA kit supplied by 1008 Junjiang Inter.Bldg.228Ningguo Rd. Yangpu Dist. Shanghai, China.

Folic acid: Serum folic acid was determined via ELISA technique utilizing commercially-available kits named human folic acid ELISA kit supplied by 1008 Junjiang Inter.Bldg.228Ningguo Rd. Yangpu Dist. Shanghai, China.

Homocysteine level: Homocysteine level was determined via ELISA technique utilizing commercially-available kits named human homocysteine ELISA kit supplied by 1008 Junjiang Inter.Bldg.228Ningguo Rd. Yangpu Dist. Shanghai, China.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data), while Mann Whitney U test was used for non-normally distributed Data (non-parametric data). One way analysis of the variance (One way ANOVA) was used to compare between more than two groups of parametric quantitative data. Spearman's correlation was used to test the correlation between two variables with non-parametric quantitative data. P value ≤ 0.05 was considered significant.

RESULTS

Table (1) illustrates the basic demographic data of the subjects included in the study. The mean age of the cases in the psoriasis group is 35.47 (SD 7.34) years while in the control group was 31.92 (SD 5.13) years with no statistically significant difference between the two groups (p=0.135). The percentage of males and females in the psoriasis group was 54% and 46% respectively while in the control group there was 46.7% males and 53.3% females with no statistically significant difference between the two groups (p=0.179).

The mean BMI of the cases in the psoriasis group was 30.69 (SD 6.44) kg/m^2, while in the control group was 29.13 (SD 2.86) kg/m^2 with no statistically significant difference between the two groups. There was no statistically significant difference in the marital status between the two groups. The mean age of onset of psoriasis in the psoriasis group was 37 (SD 14.43) years with range between 10 and 63 years. The mean duration of the disease in the psoriasis group was 8.37 (SD 8.07) years with range between 1 and 40 years. Among the cases with psoriasis, there were 4 cases (8%) with positive family history of the disease.

Table (1): Analysis of demographic data in the two study groups.

Variable		Psoriasis group	Control group	Test of significance
Age (years) (Mean ± SD)		35.47 ± 7.34	31.92 ± 5.13	t= 1.869 p = 0.135
Gender	Male: n (%)	27(54%)	14(46.7%)	$\chi 2$= 1.805 P= 0.179
	Female: n (%)	23(46%)	16(53.3%)	
BMI (Kg/m2) (Mean ± SD)		30.69 ± 6.44	29.13 ± 2.86	t= 1.090 p = 0.287
Marital status	Married: n (%)	42 (84%)	26(86.7%)	$\chi 2$= 1.439 P= 0.215
	Single: n (%)	6 (12%)	3(10%)	
	Widow: n (%)	2 (4%)	1(3.3%)	
Disease onset (Years)	Mean ± SD	37 ± 14.43		NA
	Median (min-max)	35 (10 - 63)		
Disease duration (Years)	Mean ± SD	8.37 ± 8.07		NA
	Median (min-max)	6 (1 - 40)		
Family history	Positive: n (%)	4(8**%)**		NA
	Negative: n (%)	46(92%)		

SD, standard deviation; NA: not applicable P: probability. Continuous data expressed as mean±SD.
Categorical data expressed as Number (%), T= independent samples.
t-test. $\chi 2$= Chi-square test. *: statistically significant ($p \leq 0.05$)

The mean PASI was 14.28 (SD 8.98) with range between 1.8 and 37. According to PASI classification, there were 17 cases (34%) with mild psoriasis, 21 cases (42%) with moderate psoriasis and 12 cases (24%) with severe psoriasis (Table 2).

Table (2): Analysis of the disease criteria in the psoriasis group

Items		Study cases (n=50)
PASI	Mean ± SD	14.28 ± 8.98
	Median (min-max)	13.65 (1.8 - 37)
Psoriasis severity		
Mild		17 (34%)
Moderate		21 (42%)
Severe		12 (24%)

Continuous data expressed as mean±SD and median (range). Categorical data expressed as Number (%).

The mean folic acid level in the psoriasis group was 3.69 (SD 0.96) nmol/l which was statistically significantly lower as compared with the control group (5.67 ± 1.31 nmol/l) (p<0.001). The mean vitamin B12 level in the psoriasis group was 186.94 (SD 64.90) pmol/l which was statistically significantly lower as compared with the control group (353.73 ± 76.76 pmol/l) (p<0.001). The mean homocysteine level in the psoriasis group was 18.54 (SD 4.18) nmol/mL which was statistically significantly higher as compared with the control group (11.09 ± 1.78 nmol/mL) (p<0.001) (Table 3).

Table (3): Analysis of laboratory parameters in the two study groups.

Variable	Groups		Test of significance
	Psoriasis group (N=50)	Control group (N=30)	
Folic acid (nmol/l)	3.69 ± 0.96	5.67 ± 1.31	t= -7.814 p < 0.001*
Vitamin B12 (pmol/l)	186.94 ± 6.90	353.73 ± 7.76	t= -10.385 p < 0.001*
Homocysteine (nmol/mL)	18.54 ± 4.18	11.09 ± 1.78	t= 9.274 p < 0.001*

P: probability.Continuous data expressed as mean±SD. T= independent samples t-test. *: statistically significant (p< 0.05).

There was no statistically significant difference between the cases with mild, moderate and severe psoriasis as regards of the serum folic acid level, vitamin B12 level and homocysteine level (Table 4).

Table (4): Analysis of laboratory parameters, according to the disease severity (as measured by PASI) in the psoriasis group.

Variable	Groups			Test of significance
	Mild psoriasis (N=17)	Moderate psoriasis (N=21)	Severe psoriasis (N=12)	
Folic acid (nmol/l)	3.72 ± 0.97	3.61 ± 1.07	3.78 ± 0.77	F = 0.116 p = 0.891
Vitamin B12 (pmol/L)	176.71 ± 8.96	195.81 ± 7.41	185.92 ± 6.12	F = 0.399 p = 0.673
Homocysteine (nmol/mL)	18.65 ± 1.61	17.58 ± 4.06	20.08 ± 3.30	F = 1.404 p = 0.256

P: probability. Continuous data expressed as mean ± SD. F= One-Way ANOVA test.

There was a statistically significant negative correlation between homocysteine level and folic acid level. There was a statistically non-significant positive correlation between folic acid level and vitamin B12 level. There was no statistically significant correlation between folic acid with other clinical variables in the psoriasis group (Table 5).

Table (5): Correlation between folic acid with other variables in the psoriasis group.

Variable	Folic acid	
	r	p
Age	- 0.132	0.360
BMI	0.023	0.873
PASI	- 0.039	0.791
Disease onset	- 0.138	0.338
Disease duration	- 0.087	0.546
Vitamin B12	0.214	0.136
Homocysteine	-0.850	0.001*

r: Pearson's correlation. *: statistically significant (p≤0.05)

There was a statistically non-significant negative correlation between homocysteine level and vitamin B12 level. There was a statistically non-significant positive correlation between folic acid level and vitamin B12 level. There was no statistically significant correlation between vitamin B12 with other clinical variables in the psoriasis group (Table 6).

Table (6): Correlation between vitamin B12 with other variables in the psoriasis group.

Variable	Vitamin B12	
	R	p
Age	0.145	0.316
BMI	0.106	0.463
PASI	0.035	0.808
Disease onset	0.134	0.353
Disease duration	0.082	0.571
Folic acid	0.214	0.136
Homocysteine	-0.266	0.062

r: Pearson's correlation.*: statistically significant (p≤0.05)

There was a statistically significant negative correlation between homocysteine level and folic acid level. There was a statistically non-significant negative correlation between homocysteine level and vitamin B12 level. There was no statistically significant correlation between homocysteine with other clinical variables in the psoriasis group (Table 7).

Table (7): correlation between homocysteine with other variables in the psoriasis group.

Variable	Homocysteine	
	R	p
Age	0.126	0.384
BMI	0.124	0.392
PASI	0.146	0.312
Disease onset	0.134	0.355
Disease duration	- 0.020	0.890
Folic acid	-0.850	0.001*
Vitamin B12	-0.266	0.062

r: Pearson's correlation. *: statistically significant (p≤0.05)

DISCUSSION

Serum homocysteine, folate and vitamin B12 were estimated in psoriasis patients with controversial results. Up to our knowledge, measuring of the three elements was not reported in Egyptian studies.

The current study was conducted to investigate the relationship between homocysteine, folic acid and vitamin B12 levels and psoriasis vulgaris. This study included 50 psoriatic patients and 30 age and sex matched healthy subjects as a control group.

In the current study, the mean homocysteine level in the psoriasis group was 18.54 (SD 4.18) nmol/mL, which was statistically significantly higher as compared with the control group (11.09 ± 1.78 nmol/mL) ($p<0.001$). The mean folic acid level in the psoriasis group was 3.69 (SD 0.96) nmol/l which was statistically significantly lower as compared with the control group (5.67 ± 1.31 nmol/l) ($p<0.001$). Also, the mean vitamin B12 level in the psoriasis group (186.94 ± 64.90 pmol/l) was statistically significantly lower as compared with the control group (353.73 ± 76.76 pmol/l) ($p<0.001$). A statistically significant negative correlation was found between serum homocysteine and serum folic acid. No statistically significant correlation was found between psoriasis severity (as measured by PASI) and serum levels of homocysteine, folic acid, or vitamin B12.

Our results agreed with the results of **Tsai *et al.*** [13] who revealed that psoriasis was associated with hyperhomocysteinaemia and folate deficiency with statistically negative correlation between serum levels of homocysteine and folic acid. In contrast to our results, the last study revealed no difference in serum vitamin B12 levels between those with and without psoriasis. In agreement with our study, hyperhomocysteinaemia in psoriasis was reported also by many other studies [5, 14, 15, 16].

On the other hand, studies done by **Abedini *et al.*** [17] **and Uslu *et al.*** [18] did not find any statistically significant difference in homocysteine level between psoriatic patients compared to control group [17, 18]. The discrepancy in the result may be attributed to genetic polymorphisms of the enzymes regulating the homocysteine metabolism in the different studied populations. As already mentioned, the mean folic acid level in our psoriasis patients was statistically significantly lower as compared with the control group. These results were in agreement with the results of other studies that mentioned a significant decrease in folate levels in patients with psoriasis [14, 19, 20]. On the contrary, other authors reported that folate levels were not significantly different between the case and control groups [17, 21]. The discrepancy in the result may be attributed to different dietary habits with adequate intake of folic acid by patients in the later studies.

Hyperhomocysteinaemia in psoriasis patients may be attributable to serum folate deficiency, as folate levels in psoriasis may be depleted by rapid epidermal turnover and increased mitotic activity of basal cells [14]. This proposed explanation can be corroborated by the inverse correlation between serum homocysteine and folate levels revealed by our study and other authors [13].

Additionally, folate deficiency with subsequent hyperhomocysteinemia can be explained by impaired absorption of folate in the bowel in psoriasis patients. Patients with psoriasis and psoriatic arthritis have been found to have microscopic inflammation in the intestinal mucosa even without clinical bowel symptoms [22]. It is speculated that subclinical mucosal inflammation in psoriasis leads to malabsorption of folate, engendering increased serum homocysteine levels. Lastly, low serum folate levels have also been found to be correlated with obesity which is more prevalent in patients with psoriasis than in the general population [23]. However, the mechanisms explaining the association between obesity and low folate levels are poorly understood [13]. The genetic polymorphism of methylenetetrahydrofolate reductase, an enzyme that affects serum homocysteine levels, might also play a role [13]. On the other hand, many psoriasis patients have normal homocysteine and folate levels [18,24], and this can be explained by adequate intake of vegetables and herbal foods which contain large amounts of folic acid and can compensate for folate deficiency in such patients [18]. In this work, the mean vitamin B12 level in the psoriasis group was statistically significantly lower as compared with the control group. Our results came in accordance with other authors who demonstrated significant lower levels of vitamin B12 levels in patients compared to control [20, 25]. On the contrary, other studies reported no difference in serum vitamin B12 levels between patients with psoriasis and the control groups [13, 17]. Normal vitamin B12 level in the result may be attributed to different study designs or different nutritional habits with adequate intake of vitamin B12.

In the current study, the mean PASI was 14.28 (SD 8.98) with range between 1.8 and 37. According to PASI classification, there were 17 cases (34%) with mild psoriasis, 21 cases (42%) with moderate psoriasis and 12 cases (24%) with severe psoriasis. There were no statistically significant differences between the cases with mild, moderate and severe psoriasis as regards the serum levels homocysteine level, vitamin B12 and folate levels. Also, no significant correlation was found between psoriasis severity (as measured by PASI) and serum levels of homocysteine level, vitamin B12 and folate levels. This was in accordance with other studies which revealed no statistically significant correlation between homocysteine level and either disease severity by PASI score or the duration of the psoriasis [18, 20].

In contrast to our study, other authors reported a statistically significant positive correlation between homocysteine level and disease severity as measured by PASI [5, 16, 21, 26]. The difference between our results and those of other studies may be related to the number of patients enrolled in the other studies and the severity of psoriasis assessed by PASI.

The efficacy of homocysteine-lowering interventions has been studied extensively in patients with cardiovascular diseases. Lowering homocysteine levels with vitamin B6, B9 (folic acid) or B12 supplements, either alone or in combination, was not associated with a reduced incidence of myocardial

infarction, but did have an effect on preventing stroke [27]. **Khandanpour *et al.*** [28] concluded in a randomized controlled trial that lowering serum homocysteine levels with folate supplements slightly but significantly enhanced arterial function in patients with peripheral arterial diseases. Vitamin supplementation appears to be promising for preventing cardiovascular events, but the results of such studies are inconsistent. This is perhaps not unexpected, because hyperhomocysteinaemia is only one of many factors implicated in the etiology of CVD. However, no similar studies were done in psoriasis patients [13].

The present study has some limitations, as it was a single-center study with limited external validity, and the sample size may be considered relatively small especially that the control group had fewer patients than the case group, which restricts the power of conclusions.

CONCLUSION

Our study indicates that hyperhomocysteinaemia, decreased serum folate levels, and decreased serum B12 levels are common in patients with psoriasis. Serum homocysteine level was negatively correlated with serum folate level. No significant correlation was found between psoriasis severity (as measured by PASI) and serum levels of homocysteine, folic acid, or vitamin B12. Hyperhomocysteinaemia can be considered as an independent risk factor for CVD in psoriasis patients and does not correlate with the severity of the disease.

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Author contribution: Authors contributed equally in the study.

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