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Evaluation of serum levels of folic acid, vitamin B12 and homocysteine in patients with chronic plaque psoriasis in Iraqi patients

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Background: Plaque psoriasis is the most frequent form of psoriasis and produces dry, raised and red lesions on the skin (plaques) covered with silver scales. Plaques can cause itching or pain, and may be few or many. They can appear anywhere in the body, such as the genitals and soft tissue inside the mouth. **Aim of the study:** To evaluate the serum level of folic acid, vitamin B12 and homocysteine in patients with chronic plaque psoriasis. **Patients and methods:** a case control study, performed in dermatology and venereology out- patient clinic of Imam Sadiq and Merjan teaching hospital in Hilla city in the center of Iraq during the period from the first of April 2019 to the end of August 2019. A number of 40 patients with Psoriasis and 40 healthy controls were enrolled in the present study. **Results:** psoriasis cases had significant higher levels of Serum homocysteine compared to healthy controls, the mean serum homocysteine level was17.11± 6.07 vs. 12.98 ± 4.39 (µmol/L), respectively, (P. value = 0.001), Folic acid levels of psoriasis cases were significantly lower than that of controls, the mean folicacidlevelwas5.94±2.20vs.7.19±2.33,(ng/ml),respectively,(P.value = 0.048). The mean Vitamin B12 level was relatively lower in Psoriasis group compared to that of controls; 384.52 ± 87.24 vs. 410.32 ± 50.94 (pg/ml). **Conclusion:** This study suggests that there is a highly significant increase of Homocystiene in psoriatic cases than that in normal health group.While highly significant decrease of folic acid and decrease with no significant difference for B12 in case group than that in control group.

Keyword: Psoriasis, Folic acid, Vitamin B12, Homocystiene

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Introduction:

Psoriasis is an immune mediated skin disease typically characterized by chronic inflammatory skin lesions having well demarcated, erythematous, scaly plaques.Psoriasis may also have systemic inflammatory involvement and is associated with a number of comorbid diseases, including psoriatic arthritis, gastrointestinal disease, cardiometabolic disease and infection. Hyperproliferation and abnormal differentiation of keratinocytes

are the two critical outcomes of the underlying patho-physiologic dysregulation in psoriasis. Histological features of plaque psoriasis are: marked thickening of the epidermis, elongated epidermal rete pegs, parakeratosis, loss of the granular layer, suprapapillary thinning, micro-abscess of Munro (collection of neutrophils in the stratum corneum), spongiform pustule of Kojog (epidermal spongiotic pustule with neutrophilic infiltration)[1].Clinical phenotypes of psoriasis include :plaque, Guttate, Pustular, Erythrodermic psoriasis. Differential diagnosis includes atopic dermatitis, contact dermatitis, lichen planus, secondary syphilis, mycosis fungoides, tinea corporis, and pityriasisrosea. Careful observation often yields the diagnosis. For more atypical presentations, a skin biopsy might be helpful [2].Vitamin B12, also referred to as cobalamin (Cbl), is one of eight B group vitamins and is thought to play a large role in the formation of blood as well as key roles in brain and nerve function. The vitamin has several different structural forms depending on method of synthesis and processing. Hydroxocobalamin is the most commonly formed structure synthesized by bacteria.Vitamin B12 under normal circumstances is introduced to the body bound to protein following the ingestion of food.In the stomach vitamin B12 is cleaved from protein by gastric pepsin produced in the parietal cells. The parietal cells also produce and secrete intrinsic factor (IF), another essential factor related to vitamin B12 absorption. Unbound vitamin B12 within the stomach is then preferentially bound by haptocorrin (TC I). Degradation of TC I occurs in the upper intestine by pancreatic proteases as it leaves the stomach.The rereleased vitamin B12 is now available to be bound by IF forming an IF-vitamin B12 complex[3] . This complex travels through the intestine to the ilium, where it is taken up by the IF receptor, cubilin, located on gut epithelial cells[4].The IF-vitamin B12complex is degraded in the ileal cell endosome releasing vitamin B12, which eventually reaches the abdominal surface of the ileal cell and enters the bloodstream attached to transcobalamin II (TC II)[5].Vitamin B12 has two known functions in the human body, including serving as a cofactor in the methylation of homocysteine to methionine, and as a cofactor in the rearrangement of L-methylmalonyl-coenzyme A to succinyl- coenzyme A [6].Vitamin B9 has been known as Folic acid (FA) since 1941, the word “folic” comes from the Latin (leaf), “folia” or “folate”. It was given this name because FA is found naturally in green leafy plants, as well as in fresh fruit, and liver[7] Folic acid is vital for many bodily functions, including cell division in the body, cell growth, DNA synthesis and reproductive health .FA and vitamin B12 are essential for human health [8]. These vitamins work together for the DNA metabolism in the human body [9].Folate is an important component for function in the human body since it is part of DNA and RNA syntheses which are required for the production and maintenance of new cells in human body [10], One of the most significant functions of folate acid is occurring during periods of growth, such as gestation and infancy [11].Low intakes of folates have been associated with higher risk of giving birth to infants with neural tube defects (NTD) and possibly with other birth defects. Also, folate deficiency can increase the risk of cardiovascular diseases, cancer, and some cognitive problems in adulthood [12,13].Homocysteine is a sulphur-containing amino acid generated by the catabolism of methionine. It is largely catabolized by trans-sulphuration to cysteine but it may also be re-methylated to methionine. Vitamin B12, vitamin B6 and folate are important cofactors in its metabolism [14].Plasma homocysteine is now established as a clinical risk factor for coronary artery disease, as well as other arterial and venous occlusive diseases. Homocysteine is thought to have thrombophilic properties due to an oxidative stress damaging vascular endothelium [15].For this reason, hyperhomocysteinaemia may constitute an independent risk factor for cardiovascular disease [16].Recent case control studies have demonstrated that patients with psoriasis have lower levels of folate in comparison to normal controls [17].The exact etiology of this association remains unclear. Postulated mechanisms include alterations in gut absorption of folate due to microscopic inflammatory changes seen in the bowel mucosa of patients with active psoriasis and psoriatic arthritis. A more likely

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explanation however probably relates to the accelerated keratinocyte turnover seen in patients with psoriasis.This action results in excessive consumption of folate used to methylate DNA in these actively dividing cells thus lowering folate levels [18].Conversely homocysteine levels are elevated in psoriasis patients. In one case-controlled study this was found to directly correlate with disease severity and to be inversely related to plasma folate levels [19].Plasma homocysteine is an independent risk factor for cardiovascular disease, peripheral vascular disease, cerebrovascular disease and possibly Alzheimer's diseases [20].

Hyperhomocysteinemia (>15 umol/L) is thought to favour atherosclerosis and vascular thrombosis by a number of mechanisms. These include damaging endothelial cells, promoting clot formation, decreasing flexibility of blood vessels leading to aortic stiffness, and reducing blood flow velocity [21]. The endothelial dysfunction is thought to result from the accumulation of asymmetrical dimethylarginine (ADMA) which is a natural inhibitor of nitric oxide synthase. As a result there is a reduction in the production of the vasodilator nitric oxide which protects the vessel wall against the pathogenesis of atherosclerosis and thrombosis. It has been suggested that hyperhomocysteinemia in addition to other factors may be caused by reduced levels of folate in these patients[17,19]. Coenzymes methylene tetra-hydrofolate, methylcobalamin, and pyridoxal phosphate are essential for three of the enzymes involved in the metabolism of homocysteine and are dependent on folate, vitamin B12 and B6, respectively. Hence in patients with severe psoriasis who have large areas of rapid skin turnover and increased keratinocyte activity, there is excessive consumption of folate. This in turn results in reduced breakdown and elevated serum levels of homocysteine with all of its adverse effects [22].The objective of the present study is to evaluate the serum level of folic acid, vitamin B12 and homocysteine in patients with chronic plaque psoriasis.

Patients and methods: This is a case control study, performed in dermatology and venereology out- patient clinic of Imam Sadiq and Merjan teaching hospital in Hilla city in the center of Iraq during the period from the first of April 2019 to the end of August 2019.A number of 40 patients with Psoriasis and 40 healthy controls were enrolled in the present study. The age and gender matched controls were taken from patients admitted to the dermatology clinic for other dermatological conditions, the patients were diagnosed clinically by the dermatologist as having Psoriasis at any site of the body.All patients were interviewed and a detailed history was taken. Exclusion criteria:Chronic renal or hepaticdiseases,D.M,Thyroid diseases (hypo orhyperthyroidism),Any type of malignantdiseases,Any drugs that affect the levels of homocysteine in around one month before participated in thestudy, Drugs used for treatment of psoriasis (like biologic agents, methotrexate, acitretin andcyclosporin), Patients were prohibited from drinking alcohol or coffee one week before enrolled in the study and protein of animal origin should not be intake 1 day before drawing of the venousblood.5 cc of venous blood were drawn from the patients and control (who starving for 12 h before the investigation) to measure Folic acid, B12 and Homocysteine. The normal value of serum homocysteine is between (5–17μmol) and it can be measured by high-performance liquid chromatography.While the serum folic acid normal level is (> 2.7 ng/mL) and for the vitamin B 12 is (145–980pg/mL) and it can be measured by chemiluminescence immunoassay microparticle method. All patients were giving informed consent before entering the study.Data of patients in both studied groups were entered managed and analyzed using the statistical package for social sciences version 25,IBM, US, 2017. Descriptive statistics of the variables and studied parameters presented as frequencies, percentages, mean, standard deviation and ranges according to the variable type . Gender presented as frequencies and proportions with male to female ratio. Independent two samples student's t test was used to compare mean difference of aparameter and also used to compare mean age betweenboth groups. Chi square test was used to compare age groups between psoriasis and control groups .Bivariate Pearson's correlation test was used to assess the correlation between PASI score and each of Serum

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homocysteine, Folic acid and Vitamin B12, correlation coefficient (R) value was calculated. Statistically the R value ranged between zero and one; where zero value indicates complete no correlation and value of one indicates perfect correlation, however the R value closetooneindicatesthestrongercorrelation,furthermore,Rvaluebelow0.1-0.3 indicates small or weak correlation, 0.31-0.5 medium (moderate) and 0.51–1.0 indicates large (strong) correlation[23].The sign of R is an indicator for the direction of the correlation, R value with negative(minus) sign indicates an inverse correlation while no signed R (positive) indicates a direct(positivecorrelation).Analysis of variances (ANOVA) test used to compare the mean levels ofthe three parameters across the diseaseseverity.Level of significance, P. value, was set at less than 0.05 to be significant difference or correlation.Finally results were presented in tables and figures with explanatory paragraphs for each usingMicrosoft Office Word Software for windows version2013[24].

Results:

There were 40 patients with psoriasis and 40 healthy control subjects were enrolled in this study, cases and controls were almost matched for age and gender, with a mean age in psoriasis group of 40.20 ± 11.6 years and 39.8 ± 9.7 years in controls, (P = 0.867, not significant), majority of the cases and controls aged 50 years or less. Regarding the gender, males represented 57.5% of psoriasis cases and 60% of controls, (P. value = 0.820 not significant), the male to female ratio was 1.36 to 1 in psoriasis group and 1.5 to 1 in controls. The comparison of Serum homocysteine levels of cases and controls revealed that psoriasis cases had significant higher levels of Serum homocysteine compared to health controls, the mean Serum homocysteine level was17.11±6.07vs.12.98±4.39(µmol/L),respectively,(P-value=0.001),
(**Table 1**)

Table 1. Comparisons of Serum homocysteine levels of psoriasis cases and controls

Serum homocysteine (µmol/L)	Groups		Statistical test	P. value
	Psoriasis (n = 40)	Control (n = 40)		
Mean	17.11	12.98	t test = 3.49	**0.001 sig**
SD	6.07	4.39		
Range	8.97 – 31.66	6.54 – 27.87		

SD: standard deviation, sig: significant.

As it shown in (**Table 2**) Folic acid levels of psoriasis cases were significantly lower than that of controls, compared to health controls, the mean folic acid level was 5.94 ± 2.20 vs. 7.19 ± 2.33, (ng/ml) , respectively, (P. value =0.048).

Table 2. Comparisons of folic acid levels of psoriasis cases and controls

Folic acid(ng/ml)	Groups		Statistical test	P. value
	Psoriasis (n = 40)	Control (n = 40)		
Mean	5.94	7.19		

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SD	2.20	2.33	*t* test = 2.01	**0.048** **sig**
Range	2.60– 15.92	4.10 – 16.86		

SD: standard deviation, sig: significant.

The mean Vitamin B12 level was relatively lower in Psoriasis group compared to that of controls; 384.52 ± 87.24 vs. 410.32 ± 50.94 (pg/ml), however, the difference did not reach the statistical significance (P. value > 0.05), (Table 3)

Table 3.Comparisons of Vitamin B12 levels of psoriasis cases and controls

Vitamin B12 (pg/ml)	Groups		Statistical test	P. value
	Psoriasis (n = 40)	Control (n = 40)		
Mean	384.52	410.32	*t* test = 1.615	0.110 ns
SD	87.24	50.94		
Range	235.28 – 589.74	357.27 -642.28		

SD: standard deviation, ns: not significant

According to PASI score, psoriasis cases were categorized into three categorise to have mild, moderate or severe psoriasis**.** Cases with mild psoriasis were 26(65.0%) represented 65% of the total cases, those with moderate psoriasis were 11 (27.5%) and cases with severe psoriasis were 3 (7.5%) **.** Additionally, themean PASI score was 8.7 ± 3.6 and range of 2.4 – 25.9.

Correlation between PASI score and other parameters

Using the bivariate analysis, Pearson's correlation test to assess the correlation between PASI score from one side and each of Serum homocysteine, Folic acid and vitamin B12 from the other side, the correlation matrix is shown in (Table 4) where a direct (positive) significant correlation had been found between PASI score and Serum homocysteine levels (R . value = 0.607, P. value = 0.001). The correlation analysis revealed an inverse (negative) significant correlation between PASI score and Folic acid level, (R = - 0.487, P. value = 0.001). Furthermore, an inverse correlation was found between PASI score and vitamin B12 but the correlation was statistically insignificant (R = -0.195, P. value = 0.229). From other point of view, there was an inverse significant correlation between Serum homocysteine and folic acid (R = - 0.312, P. value 0.005) and also an inverse correlation was found between Serum homocysteine and vitamin B12 but it was statistically insignificant (R = -0.216, P. value = 0.065), these findings are summarized in (**Table 4**) and graphically presented using regressioncurve estimation in (**Figures 1,2&3**)

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Table 4. Correlation between PASI score and other parameters

		PASI score	Serum homocysteine (µmol/L)
Serum homocysteine (µmol/L)	*R*	**0.607**	
	P. value	**0.001**	
Folic acid(ng/ml)	*R*	**-0.487**	**-0.312**
	P. value	**0.001**	**0.005**
Vitamin B12 (pg/ml)	*R*	-0.195	-0.216
	P. value	0.229	0.065

R : Correlation coefficients (Pearson's test)

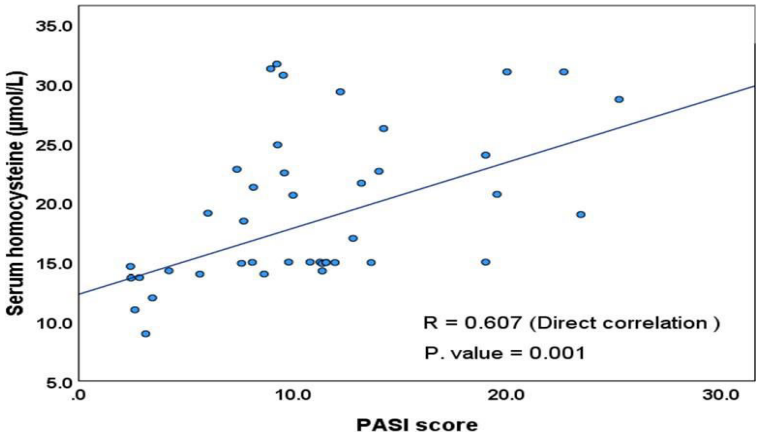

Figure 1. Regression curve estimation diagram for the significant direct correlation between PASI Score Serum homocysteine

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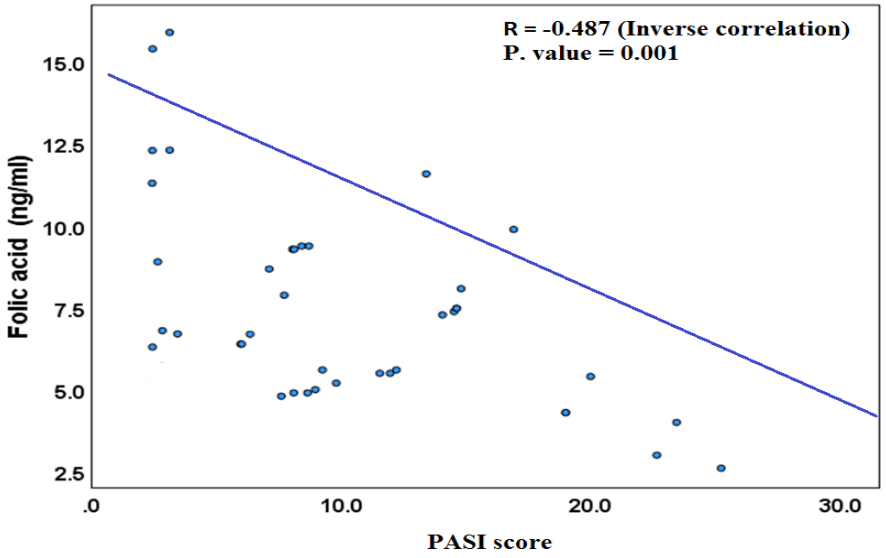

Figure2. Regression curve estimation diagram for the significant inverse correlation between PASI Score Folic acid

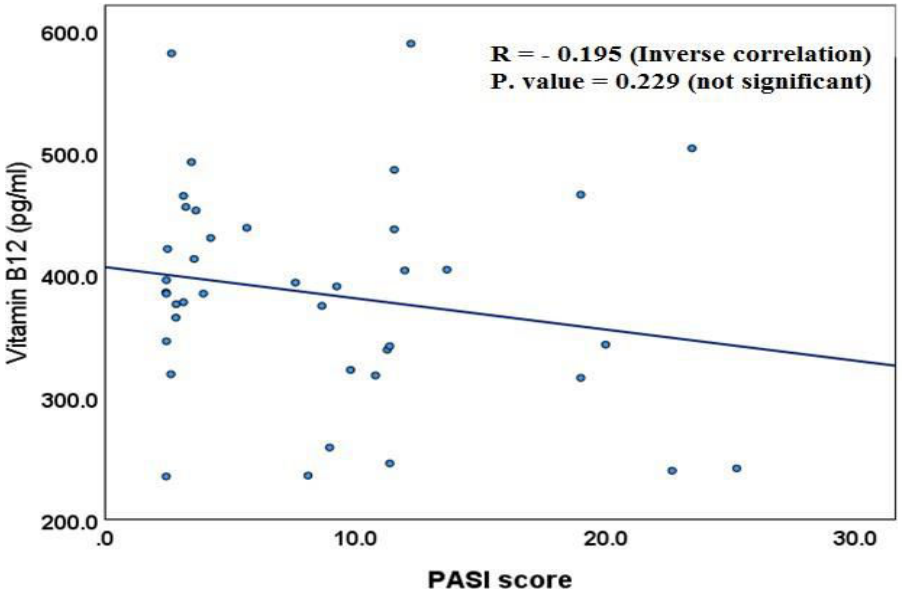

Figure 3. Regression curve estimation diagram for the inverse correlation between PASI Score vitamin B12 levels (correlation was insignificant)

Further comparisons of the mean levels of the three parameters; Serum homocysteine , Folic acid and Vitamin B12 were applied using analysis of variances (ANOVA) test which revealed that cases with severe psoriasis had significantly higher level of Serum homocysteine (P. value = 0.006) compared to those with moderate and mild psoriasis. Cases with severe psoriasis had significantly lower folic acid levels than those with moderate and mild disease, (P. value = 0.032). No significant difference had been found in mean vitamin B12 level across the severity categories, (P. value > 0.05), nonetheless, cases with severe psoriasis showed the lower levels of vitamin B12, (Table5).

Table 5. Comparison of mean Serum homocysteine, Folic acid and Vitamin B12 according to the severity of psoriasis in 40 psoriasiscases

	Psoriasis severity			
	Mild	Moderate	Severe	P. value*
Serum homocysteine (µmol/L) (mean ± SD)	15.45 ± 4.92	18.55 ± 6.35	26.23 ± 6.37	**0.006 Sig**
Folic acid(ng/ml) (mean ± SD)	6.9 ± 1.52	4.5 ± 1.12	3.2 ± 0.94	**0.032 sig**
Vitamin B12 (pg/ml) (mean ± SD)	382.63 ± 80.94	404.23 ± 85.54	328.63 ± 76.31	0.416 ns

*Analysis of variances (ANOVA) test was used in comparison across severity categories

SD: standarddeviation, ns: not significant, sig: significant

Discussion

Psoriasis is one of the most common skin diseases that affect 2-3% population. The mean age in psoriasis group of 40.20 ± 11.6 years and 39.8 ± 9.7 years in controls. Regarding the gender, males represented 57.5% of psoriasis cases and 60% of controls; the male to female ratio was 1.36 to 1 in psoriasis group and 1.5 to 1 in controls.Giannoni M et al in the study included 52 patients who have psoriasis: the male were more than female (27 and 25 respectively), and the mean age of the cases was 49 years (range 18–78), and mean age of control was 51.7 years (range 19–75)[25].Homocysteine is a sulfur-containing amino acid that is the product of processing in the body of the so-called irreplaceable amino acid methionine. It was called irreplaceable because it is not itself formed in the body and should come only with food. Methionine is contained in products of animal origin (in meat, dairy products, eggs) and when it is digested and absorbed by the body, homocysteine is formed from methionine [14].Tobin AM et al, in his study revealed that there is an increase level of homocysteine in patients with psoriasis [17]. Moreover Das M et al, 2017 concluded that the level of homocystiene were associated with higher PASI scores [16]. This is in agreement with that found in the current study when direct (positive) significant correlation had been found between PASI score and Serum homocysteine levels. The correlation analysis revealed an inverse (negative) significant correlation between PASI score and Folic acid level, Furthermore, an inverse correlation was found between PASI score and vitamin B12 but the correlation was statistically insignificant. This is similar to that found by Cakmak S et al[26].Malerba M et al, in case control study revealed that the homocystiene level was correlate directly with the severity of the disease and its relation were inversely with levels of folate in plasm[19].The degree of homocystiene risk to the human is same to the risk of smoking or dyslipidemia as it is independent risk factor for many cardiovascular, cerebrovascular diseases[20].The level of homocystiene should be decreased to decrease its effect on cardiovascular or cerebrovascular, so the physicians must give the treatment that decreases the level of plasmatic homocystiene. The folic acid, vitamin B6 and B12 all are take part in homocystiene breakdown in the blood, so daily intake by the patients is recommended. This treatment not only decreases the areas of atherosclerotic plaque but also reduce the risk of stroke, DVT and ischemic heart (IH) disease. Abedini R et al, revealed that there is no significant association were foundbetween case and control group regarding to the Serum homocysteine levels[27].Galnikina S et al, revealed that during the study, conducted in 2003 by Dutch scientists, 36,000 adults were surveyed; disaster of the disease in people between the ages of 20 and 59. Additionally patients' case histories were analyzed, died in the last 10 years by heart in vascular diseases. During the processing, they took into account the results of determining the traction in theblood

plasma of total homocysteine, as well as folic acid, pyridoxal phosphate and vitamin *B* 12. In men with high concentrations of homocysteine in blood plasma risk of developing coronary disease coil increased in 1.14 times compared to the low or normal concentration. In women the indicator increased twice. Unlike men, women with high folate levels in blood were more protected from the development of heart diseases. Plasma vitamin concentration of *B*6 and *B* 12 did not affect the risk of cardiac development -in vascular diseases neither in men nor in women. Scientists have not found significant evidence of due to the high level of homocysteine and mortality from cardiovascular disease [(28)].McDonald I, et al, in his study found that the level of folic acid was decreased and homocystien level were increased than that in control group. Folate is used for long time in combination with methotrexate in the treatment of psoriasis,psoriatic arthritis, and rheumatoid arthritis. In psoriasis it is action to decrease the side effect of gastrointestinal and liver function test abnormalities(18)The current study found that folic acid levels of psoriasis cases were significantly lower than that of controls, compared to health controls which is in accordance with that mentioned by Brazzelli et al., 2010 when revealed that the significant association between case and control regarding the level of folic acid [(29)]. Moreover it is inagreement with Gisondi et al., 2010 [(30)]. But it is not in agreement with Cakmaketal., 2009 when shown that there is no significant association between them [(26)]. This may be due to Cakmak et al., was detect the folic acid in erythrocyte not the serum folic acid.The level of serum vitamin B12 and folate always decrease in psoriatic patients,thiswillbeexplainedbytheincreaseneedofthese2vitaminsbypsoriasis keratinocytes with high turnover rate, and from microscopic inflammatory changes in colon mucosa that may be responsible for folic acid malabsorption.The current study shows that the serum level of B12 was relativelylower in Psoriasis group compared to that of controls, the difference did not reach the statistical significance. Which is compatible with Kural B et al, in the study carried on 60 respondents; 30 patients with psoriasis and other 30 controls respondents, found that decrease level of vitamin B12 in case group than that in control [(31)].Of note, McDonald I et al in his study mentioned that changes in vitaminB12 levels can be in line with folate level, this may be due to nutritional status(18). In Conclusion This study suggests that there is a highly significant increase of Homocystien in psoriatic cases than that in normal health group.While highly significant decrease of folic acid and B12 in case group than that in controlgroup.

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