Evaluation of Lipid Profile in Psoriatic Patients Treated by Methotrexate And Retinoid

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Abstract

Background: Psoriasis is a common disease with the population prevalence ranging from 2% to 3%. Its prevalence in the population is affected by genetic, environmental. Psoriasis is associated with an atherogenic lipid profile but longitudinal changes in lipids around disease onset are unknown. Because of the wide range of comorbid conditions associated with psoriasis, comprehensive screening and treatment must be implemented to most effectively manage psoriasis patients. The aim of this study is to examine the effect of type of treatment (methotrexate & retinoid) on serum lipid profiles for psoriatic patients. **Methods:** Compared the changes in lipid profiles in a psoriatic 50 patient , 20 of them as a control group never take a treatment, 15 psoriatic patient treated by methotrexate, and 15 psoriatic patient treated by retinoid. All lipid measures index data were abstracted. Random-effects models adjusting for age, sex and calendar year were used to examine trends in lipid profiles. **Result:** Decrease serum total cholesterol, low density lipoprotein, and high density lipoprotein in psoriatic patient on methotrexate, while increase triglyceride level with systemic retinoid. **Conclusions:** Psoriatic patients could be considered as a group with an increased atherosclerotic risk because of susceptibility in lipid profile.

Key words: Psoriasis, MTX, Retinoid

تقييم مستوى الدهون لمرضى الصدفية الذين عولجوا بأدوية الميثوتريكسات و الريتينويد

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الملخص

الخلفية: الصدفية مرض شائع مع ازدياد نسبة السكان تتراوح نسبة الاصابة من 2% إلى 3%. ويتأثر انتشاره بين السكان بعوامل وراثية وبيئية. ان مرض الصدفية يرتبط مع تغيير مستوى الدهون ولكن التغييرات في الدهون مع المرض غير معروفة بسبب وجود عوامل واسعة من المضاعفات المرتبطة بالمرض والفحص الشامل والعلاج الأكثر فعالية لمرضى الصدفية. ان **الهدف** من هذه الدراسة هو معرفة تأثير نوع من العلاج (الميثوتريكسات و الريتينويد) على مستوى الدهون في مصل مرضى الصدفية. **الطريقة:** مقارنة التغييرات في مستويات الدهون في خمسين مريضا مصابا بالصدفية، 20 منهم كمجموعة سيطرة لم تأخذ علاج بعد وان خمسة عشر منهم يعالجون بدواء الميثوتريكسيت والخمسة عشر الباقين يعالجون بدواء الريتينويد. تم تلخيص جميع البيانات في تأثر مستوى الدهون. واستخدمت مقاييس التأثيرات العشوائية كضبط العمر والجنس والسنة التقويمية لدراسة الاتجاهات في مستويات الدهون. **النتائج:** انخفاض الكوليستيرول الكلي ومستوى الكوليسترول عالي الكثافة ومستوى الكوليسترول قليل الكثافة في المرضى المعالجين بدواء الميثوتريكسات، بينما وجد زيادة في مستوى الدهون الثلاثية للمرضى المعالجين بدواء الريتينويد. **الاستنتاجات:** ان المرضى المصابين بالصدفية يجب ان يعاملوا كمجموعة معرضة لزيادة مخاطر تصلب الشرايين بسبب احتماليات تغيير مستوى الدهون لديهم.

Introduction

Psoriasis is a common disease affecting, as presumed, approximately 120–180 million people worldwide [(1)]. The most characteristic lesions consist of red, scaly, sharply demarcated, indurate plaques, present particularly over extensor surfaces and scalp. The disease is enormously variable in duration, periodicity of flares and extent that may affect any part of the skin surface [(2)]. Different clinical types of psoriasis have been reported, and the commonest one is psoriasis vulgarism; which can affects 80%-90% of psoriatic patients. The size of psoriatic lesions (plaques) was varied from small spots to large scaly patchy lesions, with multiple shapes and appearance [(3)]. Psoriasis has been shown to be associated with a higher incidence of myocardial infarction, stroke, and cardiovascular mortality [(4)]. In moderate to severe psoriasis, a significantly deteriorated lipid profile was observed compared to healthy controls, with higher values of low-density lipoprotein (LDL), triglycerides (TG) and significantly decreased high density lipoprotein (HDL) level. Recent studies clearly demonstrated that inflammation impairs reverse cholesterol transfer in vivo [(5)], lipid metabolism disorders may play a role in psoriasis pathogenesis [(6)]. Treatment of psoriasis depends on the type and severity of the disease. Typically, topical therapies are used to treat mild and localized psoriasis. Topical treatments are the foundation for mild to moderate psoriasis. However, this approach can decrease the number and thickness of the plaque lesions, and reduce the percentage of body surface involved. In general, pharmacological treatment should start with the use of topical corticosteroids [(7)]. Systemic retinoid (derivatives of vitamin A) are utilized for patients with severe psoriasis [(8)]. Methotrexate (MTX) is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by a biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses [(9)]. Systemic retinoid (derivatives of vitamin A) are utilized for patients with severe psoriasis, including pustular and erythrodermic forms, and in patients with HIV-associated psoriasis. The retinoid of choice in psoriasis is acitretin. Monitoring for hypertriglyceridemia and hepatotoxicity are required with retinoid therapy. Common side effects include cheilitis and alopecia [(8)]. The aim of this study is to examine the effect of type of treatment (methotrexate & retinoid) on serum lipid profiles for psoriatic patients.

Materials and Methods

This is a hospital-based, case control study included fifty psoriatic patients admitted in the Department of Dermatology of Rezgary Hospital in Kirkuk city. Through the period from March 2015, till the September 2015 who was Twenty of these new case psoriatic patient never used any treatment before selected as a control group. Fifteen patients treated with methotrexate, and fifteen patients treated with systemic retinoid. Exclusion criteria were: diabetes, obesity (body mass index higher than 30Kg/m2), family history of dyslipidemia, renal and liver failure, hypothyroidism, taking systemic drugs especially lipids lowering agents, smoking and drinking spirits (alcoholic beverages) in order to eliminate damaging factors on serum lipids level of the patients. Most participants usually had breakfast and lunch at work with a similar diet. Subjects who had high-fat foods at dinner were excluded. After explaining the purpose of the study and obtaining consent letter, data were recorded on questionnaires for each patient. After a 14 h fasting period, 5 mL venous blood was taken in sterile syringe in the morning from all cases and submitted to the laboratory analysis.

Table (1):- Mean levels of lipid profile of methotrexate treated group in compared to controls group

Variable	MTX		Control		P value
	Mean	Std. deviation	Mean	Std. deviation	
Total cholesterol (mg/dl)	130	42	169.25	36.32	0.003
Triglyceride (mg/dl)	64.5	43	73.15	32.52	0.472
HDL (mg/dl)	42	6	50.75	7.72	0.001
LDL (mg/dl)	74.88	35.85	103.87	36.38	0.01

Table (2):- Mean levels of lipid profile of retinoid group in comparison to controls group

Variable	Retinoid		Control		P value
	Mean	Std. deviation	Mean	Std. deviation	
Total cholesterol (mg/dl)	189	28	169.25	36.32	0.08
Triglyceride (mg/dl)	237.2	58.9	73.15	32.52	0.001
HDL (mg/dl)	47	6	50.75	7.72	0.132
LDL (mg/dl)	94.29	25.88	103.87	36.38	0.37

Serum levels of total cholesterol (TC) , (TG), LDL, and HDL were measured by the using of enzymatic colorimetric method, using cholesterol enzymatic biolabo kit (maizy, France). The severity of psoriasis was evaluated based on the standard criteria of psoriasis.[8] **Statistical analysis:** Analysis of date was done by SPSS for windows version"17" whereas the P value < 0.05 insignificant.

Results

Comparison of Lipids Profile between Methotrexate treated group and Control group

The current study showed that serum level of TC, HDL, and LDL were significantly lower in MTX group than the control group (P <0.05), with no significant difference in the serum TG levels between the two groups as shown in table 1. In addition a significant positive correlation were found between the duration of treatment with both TC and TG among MTX group as shown in figures 1, and 2 respectively.

Comparison of Lipids Profile between retinoid treated group and Control group

The current study showed that serum level of TG were significantly lower in control group than the retinoid group (P <0.05), with no significant difference in the serum TC , HDL, and LDL levels between the two groups as shown in table 2. In addition a significant negative correlation were found between the duration of treatment with both TC and TG among retinoid group as shown in figures 3, and 4 respectively. P value of LDL is that is 0.370 no significant LDL. As shown in table (2). And we found negative significant duration of treatment with total cholesterol in retinoid treated group (R: 0.732) as we seen in Figure (3), but negative significant correlations of duration of treatment with triglyceride in retinoid treated group. As seen in Figure (4)

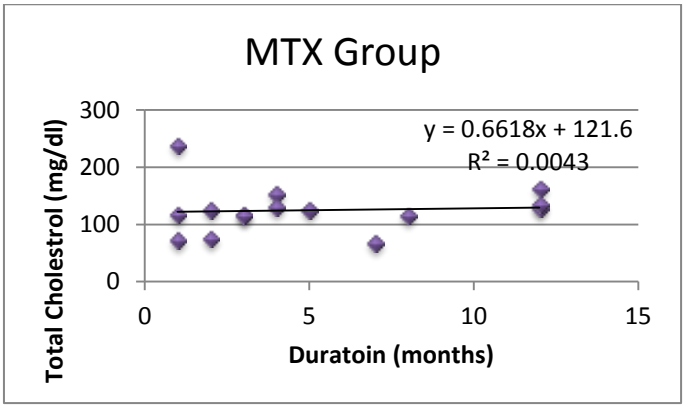

Fig.(1):- Correlations between the duration of treatment with total cholesterol level MTX group

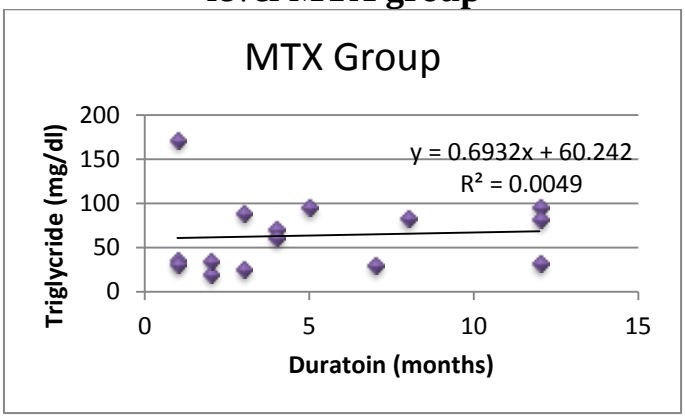

Fig.(2):- Correlation between the duration of treatment with triglyceride level in MTX treated group

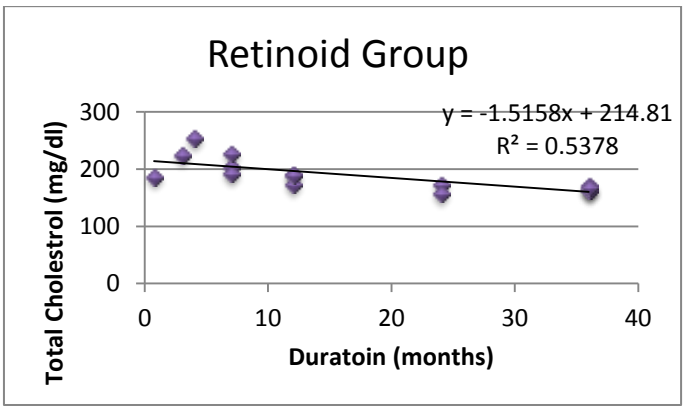

Fig.(3):- Correlation between the duration of treatment with total cholesterol in retinoid treated group .

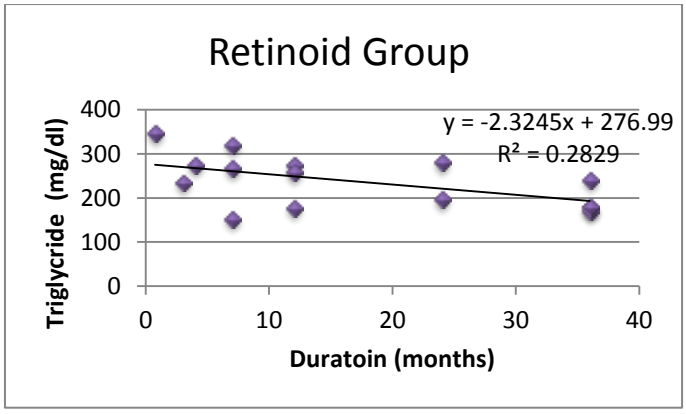

Fig.(4):- Correlations between the duration of treatment with triglyceride in retinoid treated group.

Discussion

The abnormality of lipids can often be recognized at the early stage of the psoriasis and some time at onset of the disease. This fact gives us an idea about genetic predisposition or determination of lipid dysregulation or abnormalities. Other pro-atherogenic lipid abnormalities in psoriatic patients indicated a high serum concentrations of total cholesterol had been reported. Study by AysunToker, A [(10)] concerning with total serum cholesterol concentrations in patients with psoriasis, showed that the results varies from normal, low or some time elevated values had been reported by AysunToker *et al.*[(10)]. Many studies through the past time demonstrates disturbed lipid metabolism in psoriatic patients and shows clear changes in the compositions of lipid components (lipid profile) in their serum. These abnormalities in plasma lipid in psoriatic patients may have a major role in the initiation and proceeding of atherosclerotic process in many inflammatory conditions including psoriasis. Study by Bernard FX, [(11)] revealed that psoriasis is associated with atherogenic dyslipidemia with elevated plasma concentrations of TC, TG, LDL, very low density lipoprotein (VLDL) and decreased serum levels of HDL [(11)]. A number of drugs that were frequently used to treat psoriasis, such as cyclosporine and retinoid, are well known to adversely affect serum lipid levels and could contribute to the differences between studies .[(12)]

The Effect of Methotrexate on lipid profile

The present study indicated that the level of serum (TC) was significantly lower in MTX group compared to control group, and these findings were disagreed with the results obtained by Der-Yuan Chen [(13)] who found that no differences were observed in the blood lipid profiles. The potential impacts of MTX on cholesterol metabolism should not be overlooked, and their lipid indicators fell within the normal range. HDL was significantly lower in MTX group compared to control group and this may be due to that MTX suppresses immune system lead to decrease inflammation so lead to decrease lipid profile. The studies of haider [(14)] and Wakkee M. [(15)] reported that reduction in serum level of (HDL) in psoriatic patients could be due to decrease synthesis and structural changes in (HDL) as a result of several biochemical disturbances like abnormalities in the receptors function, alteration in hepatic structure and function with changes in the activity of hepatocytes membranes [(15)]. The present study not demonstrated difference in the level of (TG) in the MTX treated patients compared to control group as shown in table (1), however, the present study findings not agreed to that reported by haider [(14)] who detected elevation in (TG) level. Long term treatment with MTX lead to decrease (TC) correlated with the time of duration of psoriasis as seen in the figure (1) . And decrease (TG) correlated with the time of duration of psoriasis as seen in the figure (2) . This finding agree with study of R

Sotoudehmanesh [16] who found MTX transaminases is common complication of long term treatment with MTX as based on liver enzyme evaluation that affected the level of lipid value.

The Effect of retinoid treatment on lipid profile

The present study demonstrated significant increase in the level of (TG) in psoriatic patients on retinoid treatment in compared to control groups shown in Table (2) (p. value is 0.001). The result of this study agreed with studies reported by Ormerod, E. Campalani [17]. Hypercholesterolemia, seen in 10–30% of patients treated with acitretin, relates to increases in both the (VLDL and ⁄or LDL) fractions. The LDL ⁄HDL ratio (atherogenic index) has been directly correlated to the risk of developing cardiovascular disease, and therefore fasting lipids should be regularly checked in all patients receiving treatment with acitretin [17]. On the other hand there was no significant change in serum (TC) level (p. value is 0.080) as shown in Table (2) and (HDL) (p. value is 0.594) and (LDL) (p. value is 0.545). These results agreed with study reported by Terry A. [18] who uses acitretin, for the treatment of severe and therapy-resistant psoriasis, and found that acitretin has a less pronounced effect on the lipid profile. (TC) and (HDL) levels remain unchanged, and (TG) levels increase by up to 60%. Measurement of lipid levels before onset of acitretin therapy and after a few weeks of treatment is also recommended [18]. However this study disagrees with study reported by Catherine Ni. [19] who found decrease (HDL) . Significant alterations in serum (TG) levels were not detected in this study, likely due to the low doses of acitretin used By contrast, a significant decrease in serum HDL. Both the increase in insulin levels and the decrease in (HDL) were transient, suggesting that in the long term other metabolic regulatory pathways may override the subtle alterations in glucose and lipid metabolism induced by retinoid [19]. However there was significant effect on (TC) and (TG) of psoriatic patients use retinoid for long term as seen in the figure (3). This disagreed with study reported by S Corbetta, R Angioni, [20] who suggested acitretin treatment did not effect on serum (TC), (LDL) and (TG) at 1 or 3 months of therapy. Conversely, serum High density lipoprotein (HDL) levels were significantly reduced by 1 month of therapy, and returned to baseline after 3 months [20].

Conclusions

Regarding to the results of this study, we can conclude the following:

- The serum TC, LDL and HDL levels were significantly lower in MTX group than the newly diagnosed psoriatic patients.
- The Serum TG level was significantly higher in retinoid group than the newly diagnosed psoriatic patients.
- Significant positive correlation between the duration of MTX with both TC and TG.
- Significant negative correlation between the duration of retinoid with both TC and TG.

References

1. Taheri, S., Hedayati, M.T., Shokohi, T. and HajHeydari, Z. Study on serum lipids and lipoproteins in patients with psoriasis. Arch Iran Med. 2014; 17(5): 343 – 346.
2. Burns, T., Breathnach, S., Cox, N., Griffiths, Ch. Rook's Textbook of Dermatology, 8th ed, Wiley-Blackwell publishing Ltd. 2010; vol (I): 20.1-20.60
3. Di Lernia, V., Ficarelli, E. and Lallas, A. *et al*. Familial aggregation of moderate to severe plaque psoriasis. Clin. Exp. Dermatol.2014; 39(7): 801-815.
4. Ahlehoff, O., Gislason, G. H., and Charlot, M. *et al*. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. Journal of Internal Medicine.2011; 270 (2): 147–157

5. Hasit lad. A study of lipid profile in patients suffering from psoriasis marker of cardiovascular disease risk. Int. J. Pharm. Bio. Sci.2015; 6(2): 1226 – 1232.

6. Malcolm, P., Manjunath, M., Spandana, P. and Vishal, B. Psoriasis: Not just skin deep. 2015; 3(2):266-271.

7. Nast, A., Boehncke, W.H., and Mrowietz, U. *et al*. S3 - Guidelines on the treatment of psoriasis vulgaris Update. J Dtsch Dermatol Ges. 2012; Mar;10 (2):S1-95.

8. Patricia Shu Kurizky, Clarissa de Castro Ferreira, *et al*. Treatment of psoriasis and psoriatic arthritis during pregnancy and breastfeeding. An Bras Dermatol. 2015; 90(3): 367–375.

9. Bedford Laboratories. Methotrexate for injection prescribing information. Bedford, OH. 2012; April.

10. AysunToker, A., Kadı, M., Yıldırım, K. *et al*. Serum lipid profile paraoxonase and arylesterase activities in psoriasis. Cell Biochem Funct.2009; 27: 176–180.

11. Bernard, F.X., Morel, F. and Camus, M. *et al*. 2012. Keratinocytes under Fire of Proinflammatory Cytokines: Bona Fide Innate Immune Cells Involved in the Physiopathology of Chronic Atopic Dermatitis and Psoriasis. J Allergy (Cairo).2012; 718:725

12. Tobin, A. M., D. J. Veale, O. Fitzgerald, S. Rogers, P. Collins, D. O'Shea, and B. Kirby. 2010. Cardiovascular disease and risk factors in patients with psoriasis and psoriatic arthritis. The Journal of rheumatology. 2010; 37: 1386-1394.

13. Der-Yuan Chen, Hui-Min Chih, and Joung-Liang Lan. Blood lipid profiles and peripheral blood mononuclear cell cholesterol metabolism gene expression in patients with and without methotrexate treatment. BMC Medicine.2011; 9(1):4.

14. Alammar haider. Evaluation of some serum adipokines, oxidized low density lipoprotein and lipid profile before and after methotrexate treatment of chronic plaque psoriasis. Baghdad University.2015.

15. Wakkee, M. Psoriasis: comorbidity and treatment. Journal of the American College of Cardiology. 2010; 55(15), 1611-18.

16. Sotoudehmanesh, R., Anvari, B., Akhlaghi, M., Shahraeeni, S. and Kolahdoozan, S. Methotrexate hepatotoxicity in patient with rheumatoid arthritis. middle east journal of digestive disease. 2010; 2(2): 104–109.

17. Ormerod, A.D., Goodfeild MJ, and Campalani, E. *et al.* The efficacy and use of acitretin in dermatology British Association of Dermatologists. British Journal of Dermatology. 2010; 162, 952–63.

18. Terry, A. Jacobson, Matthew K. Ito, Kevin C. Maki, *et al*. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia. Journal of lipidology.2015; 9(2) : 129–169.

19. Catherine Ni, Melvin W Chiu. Psoriasis and comorbidities: links and risks PMC. J Clin Cosmet Investig Dermatol.2014; 7: 119–132.

20. Corbetta, S. and Angioni, R. *et al*. Effects of retinoid therapy on insulin sensitivity, lipid profile and circulating adipocytokines. Italy European Journal of Endocrinology.2012; 154: 83–86.