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EFFECT OF SITAGLIPTIN ON LIPID PROFILES AND THEIR CORRELATION WITH PASI SCORE IN PATIENTS WITH PLAQUE PSORIASIS

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Abstract

Psoriatic patients with plaque psoriasis particularly those with high body mass index have increasing risk of developing a diabetes mellitus type 2 (DM2) and hyperlipidemia. Since both conditions are associated with dysregulation in DPP-IV, DPP-IV inhibitors have been suggested as therapeutic drugs for both diseases. Sitagliptin yields a significant decrease in serum concentration of TG, LDL and cholesterol in diabetic patients particularly those with high baseline TG levels and those using statins. To determine the effect of sitagliptin on lipid profiles and their correlation with PASI score in psoriatic patients with DM. The study was conducted on 50 diabetic patients with moderate to severe plaque psoriasis who were divided into two groups: Placebo group (n=25) Patients were administered placebo 100mg once daily plus dietary control and exercise for 3 months ; Sitagliptin group (n=25) Patients were administered sitagliptin tablet 100mg once a day plus dietary control and exercise for 3 months. PASI score for all patients was assessed before and after 12 weeks of treatment. The blood samples were obtained from the patients in both groups at baseline and after 12 week of therapy were used to measure the concentration of triglyceride (TG), cholesterol, low density lipoprotein(LDL), very low density lipoprotein(VLDL) and high density lipoprotein(HDL). Compared with baseline in sitagliptin group and control group after 12week, the level of TG, cholesterol, LDL, and VLDL were significantly reduced and correlated with PASI score after 12 week of sitagliptin treatment ($P < 0.05$) , in contrast the level of HDL was significantly increased with a negative correlation with PASI score ($P < 0.05$). The current results revealed that sitagliptin improves psoriasis possibly via a reduction in lipid profiles which were significantly correlated with PASI score.

Key words : Psoriasis, Diabetes, Sitagliptin, PASI score , Lipid profiles

Introduction

Psoriasis represents a complex chronic systemic cell immune- mediated inflammatory disease characterized by erythematous scaly plaques of skin and joints (1). It is now well known that psoriatic patients are at risk for developing metabolic syndrome (2). It is interesting that psoriasis and obesity share the same inflammatory mediators involved in chronic inflammatory process such as IL-6 and TNF-α (3). A tough correlation between increased body weight, abdominal fat, and psoriasis has been shown and proved by many researchers (4,5).The recent studies reported that psoriasis may potentiate a spectrum of systemic diseases which is ranged from insulin resistance and diabetes to a disturbances in lipid metabolism manifested as hypertriglycerdemia and hypercholesterolemia which caused by elevated serum concentration of many T-helper inflammatory cytokines such as IL-17, IL-6 and TNF-α (6,7). Methotrexate and TNF-α antagonists therapeutic effect in psoriasis is further proved by their ability to reduce insulin resistance and serum level of above mentioned cytokines and increase in HDL level (8,9). Gliptins are a novel class of oral anti-diabetic agents that enhance and prolong the physiological actions of incretin hormones by competitively antagonizing the enzyme that metabolize or degrade these hormones called dipeptidyl peptidase-4 (DPP-IV) (10). Seventeen years old female psoriatic patients with type 2 diabetes discontinued systemic treatment with cyclosporine and topical steroid ointment given for treatment of psoriasis because of lacking satisfaction with the efficacy of these drugs. Administration of sitagliptin for control of diabetes is associated with gradual improvement in psoriatic lesions during three months of therapy without any reported adverse effects (11). A study done by Ansorge S. et al proposed that DPP-IV inhibitors could be an alternative drugs for the treatment of psoriasis when it is accompanied by diabetes mellitus (12). Sitagliptin yields a significant decrease in serum concentration of TG, LDL and cholesterol in diabetic patients particularly those with high baseline TG levels and using statins (13). Aldona pietrzak et al (14) found a significant improvement in lipid profile by sitagliptin–based therapies for diabetic patients. Monami et al 2012 (15) reported that treatment with sitagliptin for patients with type 2 diabetes is associated with a significant reduction in total cholesterol and triglycerides without significantly affecting HDL.

The aim of study to assess the clinical efficacy of sitagliptin on patients with moderate to severe plaque psoriasis by estimation of PASI score and to evaluate the effect of drug on lipid profiles, and their correlation with severity of plaque psoriasis (PASI score) after 12 week of treatment .

Material and methods

Patients and study design

The study was conducted over a period of 12 months from February 2015 till February 2016. Samples were collected from the out patients clinic of dermatology in Al-Sader Teaching Hospital in Najaf city/Iraq. The laboratory work was performed at the department of pharmacology in College of Medicine **/** University of kufa. Fifty diabetic patients with plaque psoriasis were enrolled in this study and divided into two groups:

Control group: Twenty five patients were administered placebo 100mg cap. once daily plus dietary control and exercise for 3 months.

Sitagliptin group: Twenty five patients were administered sitagliptin tablet 100mg (Januvia) once a day plus dietary control and exercise for 3 months.

Inclusion criteria:

- Male patients with moderate to severe plaque psoriasis (PASI score more than 10).
- Age 20-60.
- Diabetic patients .
- BMI > 30

Exclusion criteria

1-The psoriatic patients who received topical therapy within 4 weeks, or systemic drug therapy and photo chemotherapy within 3 months.

History and PASI score:

complete history was taken from all patients with careful attention to age, sex, duration of disease, past topical or systemic treatment or concurrent chronic diseases as mentioned before. Patients were graded according to psoriasis area and severity index (PASI) score and patients with moderate to severe type were included in the study. PASI score for all patients was assessed before and after 12 weeks of treatment.

Blood sampling

Venous blood samples were drawn from psoriatic and control patients by using disposable syringes in the sitting position. Five ml of blood were obtained from each patient by vein pierce and pressed slowly into plain disposable tubes. Blood was allowable to coagulate at 37˚C for 10-15 minutes and then centrifuged at 3000 rpm for about 10-15 minutes, then the serum was obtained and stored at -20˚C until laboratory analysis for lipid profiles would be done.

Statistical analysis

The data were coded and entered the statistical analysis using the program statistical package for social sciences (SPSS) version 16 under windows version AMD. Our results were expressed as Mean ± SE. Student's t-test was used to clarify the effect of sitagliptin on PASI score and lipid profiles. The linear regression analysis was applied to verify the relationships between different lipid profiles level in psoriatic patients in relevance to PASI score after 12 weeks of sitagliptin treatment. Statistical variation was considered as significant when the P value was < 0.05.

Results

General characteristics of placebo and Sitagliptin group of psoriatic patients.

Table (3-1): Mean and standard error mean of age, BMI , PASI score and FBS in placebo and sitagliptin groups.

Numbers of psoriasis patients according to severity of disease.

Table (3-2): Numbers of psoriasis patients according to their PASI score.

Effect of Sitagliptin on PASI score

The baseline of PASI score in sitagliptin group as well as in placebo group were statistically not significant. PASI score after 12week was significantly (p< 0.05**)** lower than that of baseline in sitagliptin group. The PASI score of sitagliptin treated group was significantly (p< 0.05**)** lower than that of placebo group after 12 week of treatment as shown in fig (1). Sitagliptin treatment resulted in marked improvement in patients with plaque psoriasis regarding scale, induration and erythema but without complete clearance of lesion as shown in fig (2)

Effect of sitagliptin on lipid profiles

The initial values (baseline) of lipid profile parameters were statistically not significant in both groups. The levels of Cholesterol, TG, LDL and VLDL were significantly decreased after 12week as compared with baseline in Sitagliptin treated group. There were a statistically significant decrement (p< 0.05**)** in Cholesterol, TG, LDL and VLDL levels in Sitagliptin group as compared to placebo group after 12 week of treatment as shown in fig (3, 4 , 5 and 6) respectively. There was a significant increase (p< 0.05**)** in HDL level after 12week in comparison with baseline in sitagliptin treated group. There were a statistically significant increment (p< 0.05**)** in HDL level in Sitagliptin-treated group when compared with placebo treated group after 12 week as shown in fig (7).

Correlation between PASI score with Lipid profiles after 12 week of Sitagliptin treatment.

Table (3) which shows a significant (p < 0.05) positive correlation between PASI score with serum cholesterol**,** TG**,** LDL and VLDL and significant negative correlation (p < 0.05) between HDL with PASI score.

Discussion

Effect of sitagliptin on PASI score

Sitagliptin showed a significant decrease in PASI score after 12 week of treatment in comparison to baseline PASI score in sitagliptin- treated group and in comparison to placebo- treated group after 12 week. Our results are in agreement with those obtained by Atsuya Nishioka T. et al (11) who reported an improvement of psoriatic lesions after 12 weeks of sitagliptin treatment for diabetic female patient with psoriasis. Maeve Lynch et al (16) reported an improvement in psoriasis severity in patients with plaque psoriasis treated by sitagliptin plus NB-UVB for 24 weeks. The results of present study are supported by Drucker DJ and Rosen CF (17) who demonstrated that exenatide and liraglutide which have an incretin like effect similar to Sitagliptin given for control of diabetes result in improvement of the PASI score in diabetic patients with plaque psoriasis. Our current results disagree with Masvidal A. et al (18) who found that Sitagliptin treatment for old diabetic woman produces un expected psoriasiform eruption on her trunk and both limbs after receiving six doses of drug, this can be explained as (rare reaction to the drug and only one case study in comparison to twenty five patients in our study) . Other randomized placebo-controlled trial, showed no significant change in psoriasis severity after 8 weeks of treatment with GLP-agonist liraglutide, those patients included in this study had no diabetes, in comparison to our study that includes only diabetic patients (19).The improvement of PASI score could be immunological due to their additional anti-inflammatory effect, as treatment with sitagliptin resulted in a reduction in the number of natural killer cells in psoriatic plaques and an increase in their number in circulation (20HYPERLINK "http://www.hoajonline.com/jdrcm/2050-0866/3/3"). Atsuya Nishioka and his colleagues (1HYPERLINK "http://www.hoajonline.com/jdrcm/2050-0866/3/3"1HYPERLINK

"http://www.hoajonline.com/jdrcm/2050-0866/3/3") observed an improvement of psoriasis lesions in diabetic patient treated with a DPP-4 inhibitors, which may be attributed to an increase in GLP-1 levels and impairment in function of immune T cells by sitagliptin, probably due to the down regulation of DDP-4 on the surface of keratinocytes and multiple immune cell subtypes (21HYPERLINK "http://www.hoajonline.com/jdrcm/2050-0866/3/3") .

Effect of Sitagliptin on lipid profiles and their correlation with PASI score

The present study showed a significant reduction in serum concentration of TG, cholesterol, LDL and VLDL and significant elevation in HDL in comparison to baseline in sitagliptin- treated group and placebo- treated group after 12 week. These results are in agreement with those obtained by Erina Shigematsu. et al (13) who suggested that sitagliptin yields a significant decrease in serum concentration of TG, LDL and cholesterol in diabetic patients particularly those with high baseline TG levels and using statins. The current results is also in concordance with those reported by Aldona pietrzak. et al (14) who found a significant improvement in lipid profile by Sitagliptin–based therapies for diabetic patients. Monami. et al 2012 (15) reported that treatment with sitagliptin for patients with type 2 diabetes is associated with a significant reduction in total cholesterol and triglycerides without significantly affecting HDL. The present results are supported by study done by van Genugten RE et al (22) who reported a highly significant elevation in HDL in Sitagliptin- treated diabetic patients and highly significant reduction in cholesterol in vildagliptin- treated diabetic patients. Kenneth R. et al (23) showed that improvement of hyperlipidemia in diabetic patients on sitagliptin treatment might be attributed to a reduction of TNF-α and IL-6 which are important for synthesis of fatty acid in the liver.

The present study showed a positive correlation between PASI score and total cholesterol , triglyceride , LDL , VLDL after 12 weeks of Sitagliptin treatment and these results are agreed with that reported by Ghazizadeh R. et al (24) who found a positive correlation between improvement in psoriasis and associated hyperlipidemia by statins therapy. Reduction in lipid profiles by Sitagliptin treatment had positive effect on PASI score are explained by Cao Y. (25) who suggested that hyperlipidemia , diabetes and atherosclerosis will lead to production of inflammatory molecules and hormone which play a vital role in etiopathogenesis of psoriatic plaques and exacerbation of disease such as vascular endothelial growth factor (VEG-F). Other contributing mechanism was suggested by Chibowska M (26) who showed that alteration in lipid metabolism regarded as important pathophysiological process in formation of psoriasis. Different study considered that psoriasis is a one of clinical manifestation of hyperlipidemia look like xanthoma (27). Other explanation was suggested by Pietrzak A. et al (28) who confirmed that hyperlipidemia and lipid deposition in reticulo-endothelial organ is associated with inflammation , dilatation of capillary loops , hyperkeratosis and parakeratosis. Other study was done by Aldona Pietrzak. et al (14) who showed a relationship between hyperlipidemia and immunological changes that contribute to psoriasis etiopathogenesis and considered a psoriasis as a triad of genetic, metabolic and immunological process.

Our current study showed a negative correlation between PASI score and HDL after 12 weeks of Sitagliptin treatment and. The negative correlation between HDL level and PASI score might be explained by a reduction in blood level of IL-6 and C-reactive protein (CRP) by elevation in HDL level which are implicated in initiation and exacerbation of psoriasis (29).

Conclusion

The current results reveal that Sitagliptin improves psoriasis possibly via a reduction in lipid profiles which were significantly correlated with PASI score.

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Table 1. Mean and standard error mean of age, BMI , PASI score and FBS in placebo and sitagliptin groups.

Parameter	Placebo group	Sitagliptin group	P-value
Age (year)	38.24±2.75	35.32±2.36	> 0.05
BMI (kg/m^2)	32.34± 2.25	31.84± 2.92	>0.05
PASI score	17.56±3.73	19.48±3.94	>0.05
FBS (mg/dl)	170.32±2.61	173.54±2.62	>0.05

Table 2. Numbers of psoriasis patients according to their PASI score.

No of patients	Placebo group	Sitagliptin group
Moderate PASI score	11	14
Severe PASI	12	13

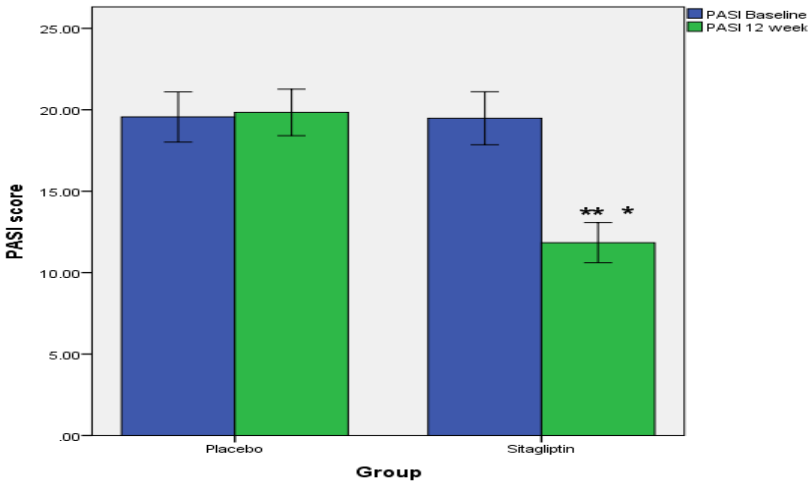

Figure 1. Changes of psoriatic patients PASI score of the placebo and sitagliptin groups. Data expressed as Mean ±SEM (N=25 in each group) using paired T- test.* P< 0.05 means significant changes in the sitagliptin group.** P< 0.05 means significant changes in comparison with placebo group.

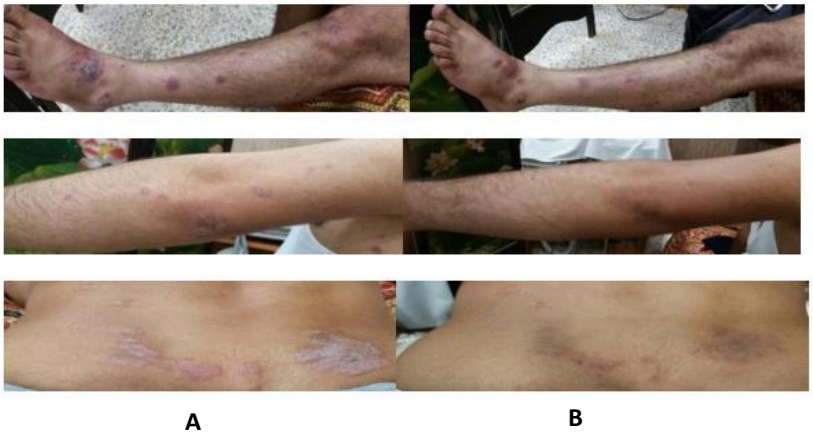

Figure 2. marked systemic antipsoriatic effect of sitagliptin in patient with plaque psoriasis without complete absence of lesions. Typical untreated skin lesions at leg/foot , elbow and trunk (back) are shown before (A) and after 12 week of therapy (B).

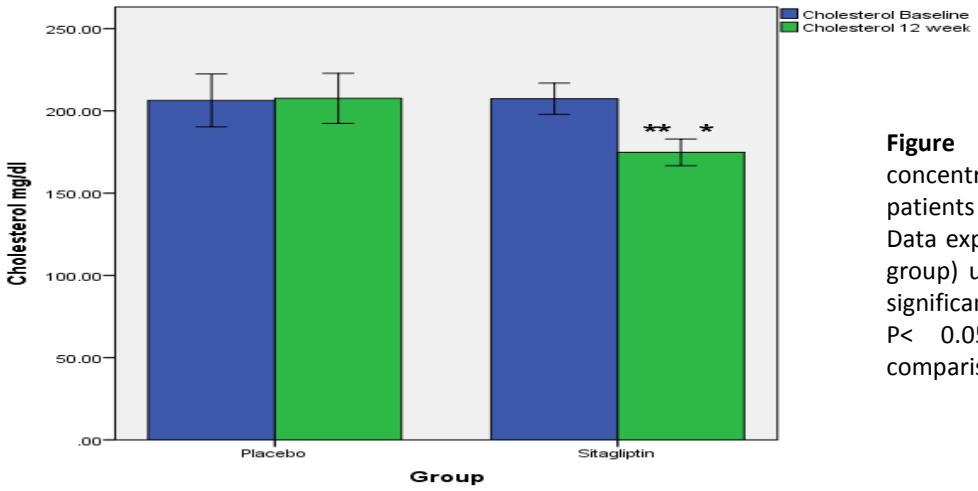

Figure 3. Changes of Cholesterol concentration (mg/dl) in sera of psoriatic patients of the placebo and sitagliptin groups. Data expressed as Mean ±SEM (N=25 in each group) using paired T- test · * P< 0.05 means significant changes in the sitagliptin group.** P< 0.05 means significant changes in comparison with placebo group.

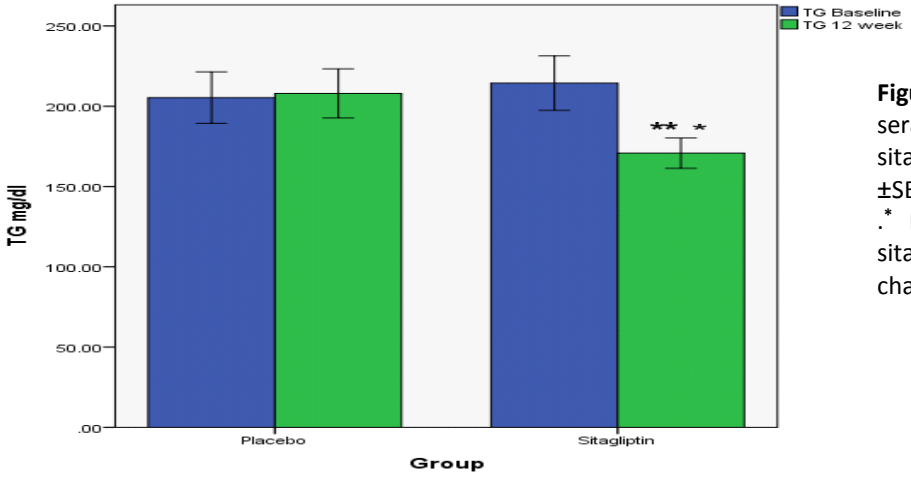

Figure 4. Changes of TG concentration (mg/dl) in sera of psoriatic patients of the placebo and sitagliptin groups. Data expressed as Mean ±SEM (N=25 in each group) using paired T- test· .* P< 0.05 means significant changes in the sitagliptin group.** P< 0.05 means significant changes in comparison with placebo group.

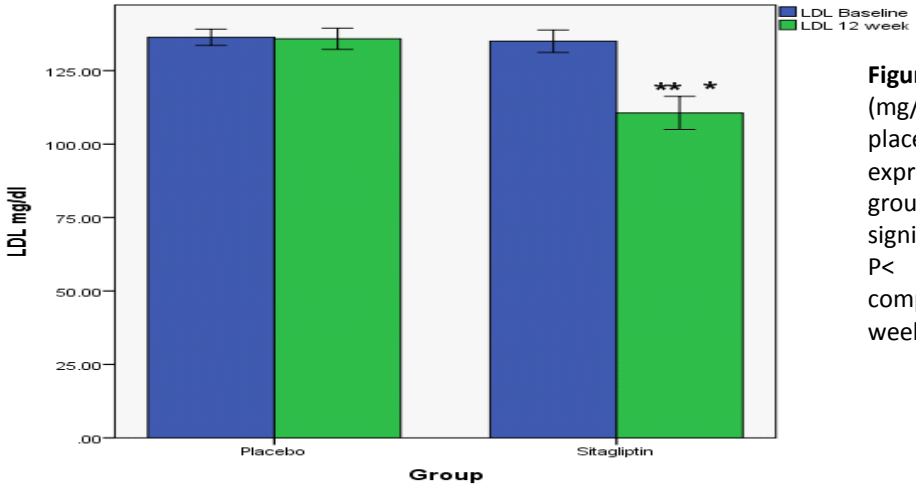

Figure 5. Changes of LDL concentration (mg/dl) in sera of psoriatic patients of the placebo and sitagliptin groups. Data expressed as Mean ±SEM (N=25 in each group) using paired T- test *P< 0.05 means significant changes in the sitagliptin group ** P< 0.05 means significant changes in comparison with placebo group after 12 week.

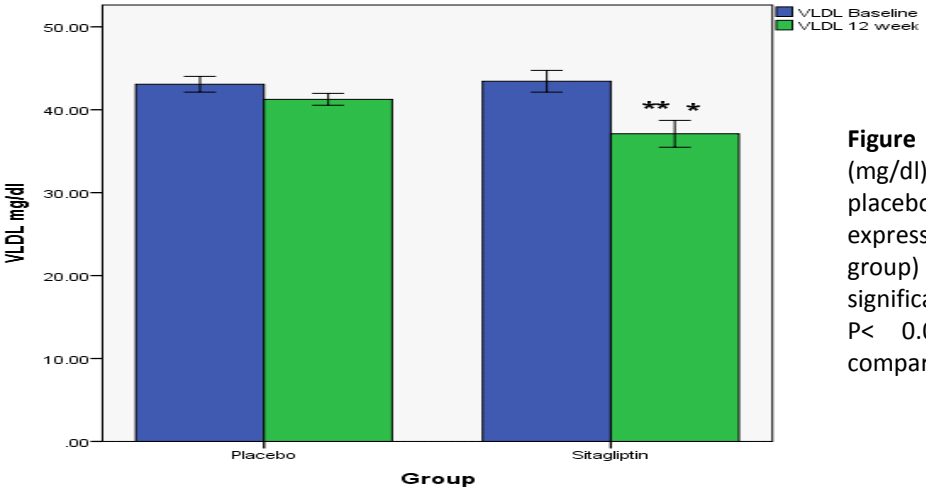

Figure 6. Changes of VLDL concentration (mg/dl) in sera of psoriatic patients of the placebo and sitagliptin groups. Data expressed as Mean ±SEM (N=25 in each group) using paired T- test .*P< 0.05 means significant changes in the sitagliptin group**.** ** P< 0.05 means significant changes in comparison with placebo group after 12 week

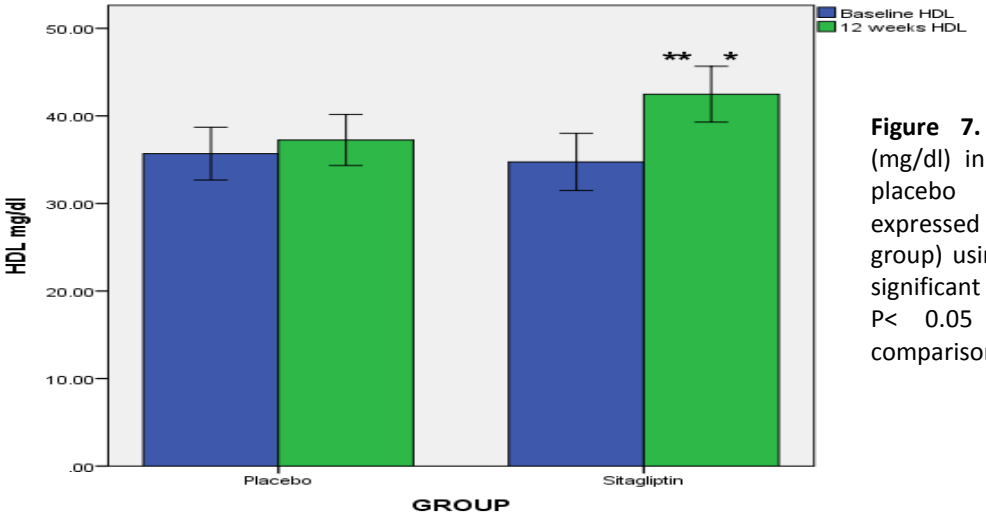

Figure 7. Changes of HDL concentration (mg/dl) in sera of psoriatic patients of the placebo and sitagliptin groups. Data expressed as Mean ±SEM (N=25 in each group) using paired T- test. .* P< 0.05 means significant changes in the sitagliptin group**.**** P< 0.05 means significant changes in comparison with placebo group**.**

Table 3. linear regression analysis of PASI score with lipid profiles, after 12 week of sitagliptin treatment.

Parameter	R	P
Cholesterol	0.382	<0.05
TG	0.43	<0.05
LDL	0.577	<0.05
VLDL	0.533	<0.05
HDL	-0.352	<0.05