Platelet Activity in Psoriatic Patients

Nabila M Thabet[1], Taghreed M Kamal-ElDin[1], Esraa S Abdel-Hafeez[*1], Reham M Abdel-Gaber[2]

[1]Clinical Pathology Department, Faculty of Medicine, Assiut University, Assiut, Egypt.
[2]Dermatology and Venereal Diseases Department, Faculty of Medicine, Assiut University, Assiut, Egypt.
Corresponding author: Esraa S. Abdel-Hafee**z**
E-mail: esraasamir8097@yahoo.com

Abstract

Background: Psoriasis is a common chronic inflammatory and relapsing immune-mediated skin disorder. The incidence of complications by comorbidities is higher in psoriasis patients compared to the normal population. The circulating blood of patients with psoriasis has more platelet macro and micro-aggregates. However, few investigations were found to explain the cause of these platelet aggregates in psoriasis.

This study aimed to (1) assess platelet activity in psoriasis patients, (2) compare cases associated with comorbidity and those without, and (3) study the effect of therapy.

Patients and Methods: This study was performed on 40 psoriasis patients and 20 healthy controls. Among those patients, 19 cases have dyslipidemia, and 21 do not. They also include 20 newly diagnosed cases compared to 20 under therapy. Complete blood count (CBC), including platelet (PLT) count and mean platelet volume (MPV), lipogram, platelet aggregation study using adenosine-diphosphate (ADP), collagen, Ristocetin, and arachidonic acid (AA) were done.

Results: The groups had no significant differences in the mean platelet (PLT) count and mean platelet volume (MPV). However, there was a significant increase in the mean values of platelet aggregation by ADP ($p < 0.0001$), Collagen ($p < 0.001$), Ristocetin, and Arachidonic acid ($p < 0.01$ for each) comparing all psoriasis patients and normal control. There was a significant increase in the mean value of aggregation by ADP, Ristocetin ($p < 0.03$ for each), and Arachidonic acid ($p < 0.01$), but not in the mean value of collagen in complicated group with dyslipidemia when compared to the group without. When comparing newly diagnosed to patients under therapy, there was a significant increase in the mean values of aggregation by ADP ($p < 0.0001$), Ristocetin, Collagen, and Arachidonic acid ($p < 0.01$ for each) in the newly diagnosed patients.

Conclusion: These findings could explain the cause of platelet hyperactivity in psoriasis patients and the presence of macro and micro platelet aggregates in these cases.

Keywords: Psoriasis, Platelet aggregation, ADP, Ristocetin, Collagen, Arachidonic acid.

Abbreviations: ADP: Adenosine diphosphate; CVDs: Cardiovascular diseases; CBC: Complete blood count; PLT: Platelet; MPV: Mean platelet volume; (PASI) score: Psoriasis area and severity index score; WBCs: White blood count; EDTA: Ethylene diamine tetra acetic acid; SPSS: Statistical Package for Social Sciences.

Background

Psoriasis is a common, chronic inflammatory skin disorder that can significantly impact life quality. The chronological order of the underlying mechanisms leading to the development of psoriatic plaques ***(Benhadou et al., 2018)*** and the presence of macro and micro platelet aggregates remain to be understood entirely.

Psoriasis is frequently associated with significant comorbidities, including diabetes mellitus, obesity, dyslipidemia, inflammatory bowel syndrome, psychiatric disorder, osteoporosis, and obstructive sleep apnea as well as cardiovascular diseases (CVDs), e.g., atherosclerosis, hypertension, myocardial infarction, and stroke ***(Machado-Pinto et al., 2016, & Gruchała et al., 2019)***.

Psoriasis negatively affects the quality of life and increases mortality risk ***(Horreau et al., 2013).*** Therefore, early detection of subclinical atherosclerosis in patients with psoriasis would help to reduce cardiovascular morbidity and mortality ***(Schwingen et al., 2020).*** Increased low-density lipoprotein is an independent risk factor for atherosclerosis. Patients with dyslipidemia may be at risk factor for cardiovascular complications even if LDL is at goal ***(Beatriz and Frank, 2011).***

In psoriasis, immune response mechanisms alone cannot fully account for the development and the extent of macro- and micro-vascular complications. So, other pathogenic mechanisms may be involved, such as increased platelet activation ***(Tamagawa-Mineoka et al., 2010) Canpolat et al., (2010) & Mahrous (2018).*** Those authors also found that MPV is significantly higher in psoriasis patients than in healthy subjects.

The role of platelets in hemostasis is vital. Normally, platelets circulate in a quiescent disc-shaped state. As they activate, they transform disc to sphere shape with the development of pseudopodia. Consequently, this leads to an increase in their size and mean platelet volume (MPV). MPV is an indicator of the average size and a marker of activation of platelets. Higher MPV is an independent risk factor for CVDs ***(Chu et al., 2010).***

Large platelets contain more dense granules, producing large amounts of thromboxane A2 and exhibiting hyper-responsiveness to ADP and collagen-induced aggregation ***(Jennings, 2009 & Herster et al., 2019).*** Platelet activation and aggregation are central processes in the pathophysiology of micro- and macro-vascular disease (e.g., cerebrovascular, coronary, and peripheral arterial disorders) ***(Herster et al., 2019).*** This leads to long-term macro- and micro-vascular complications ***(Ahmad et al., 2014).***

Thrombosis and inflammation are linked processes ***(Wagner and Burger, 2003).*** Increased platelet activation is also implicated in atherosclerotic plaque formation and destabilization ***(Jennings, 2009).*** There is a paucity of data examining the risk of dyslipidemia in patients with psoriasis and the explanation for the presence of platelet aggregates in such cases.

This study was designed to:

1. Study comorbidity in psoriatic patients (presence or absence of diabetes mellitus and dyslipidemia).
2. Assess platelet activity by estimation of PLT count, MPV, and platelet aggregation (using ADP, collagen, Ristocetin, and arachidonic acid) in psoriasis patients compared to normal control.
3. Assess platelet activity in psoriasis patients with and without comorbidity.
4. Assess Platelet activity in psoriasis patients before and following therapy.

Patients and Methods

The study was approved by Assiut University Hospital's local ethics and research committee with approval number (17100231). A written informed consent was obtained from every eligible patient before study enrollment.

This case-control study was performed on 40 patients with psoriasis and 20 healthy volunteers with matched sex and age ranges. Patients were selected from those attending the outpatient clinics of the Department of Dermatology and Venereal Diseases, Assiut University Hospital, from Oct 2016 to Oct 2018. The age range of the studied patients was 18-60 years old who were receiving treatment for a period ranging from 6 months to 5 years, including local systemic corticosteroids and ultra-violet (UV) rays according to Psoriasis area and severity index (PASI) score and attending the outpatient clinics for follow up. The study was performed in the Clinical Pathology Department of Assiut University Hospital.

The studied 40 patients (Group 1) included 21/40 males and 19/40 females, whereas the 20 healthy volunteers (controls) included 14/20 males and 6/20 females. The age range of the studied patients was 18-60 years old, whereas the control group was 22-58 years old. The 20 healthy volunteers were labeled as (Group 2). Most patients who attended the outpatient clinics for follow-up reported ***chronic plaque,*** which is a type of psoriasis. Disease severity was assessed using the PASI score. The 40 studied patients included 21 psoriasis cases with no dyslipidemia (Group A) and 19 with dyslipidemia as a complication (Group B). The 40 patients also included 20 newly diagnosed cases (Group 3) compared to 20 under therapy for psoriasis (Group 4).

Inclusion Criteria:

- Newly diagnosed psoriasis patients.
- Patients complicated by comorbidity in the form of dyslipidemia.
- Psoriatic patients under therapy.

Exclusion criteria:

- Systemic diseases such as chronic liver disease, diabetes mellitus, kidney disease, and hypertensive patients.
- Drugs having anti-platelet effects as Aspirin.

Ethical Consideration:

Written consent was obtained from each patient, and the Institutional Ethics Research Committee approved the study before the start of the work. No risks to the subjects included in the study were present, and no harmful investigations were done.

All patients and control cases underwent complete history taking and full clinical examination.

Material and Methods:

Sample Collection, Storage, and Handling:

A venous blood sample (13ml) was collected from each patient and control and divided as follows:

- **Venous blood in a tube containing ethylene diamine tetra acetic acid (EDTA) for CBC, including** PLT count and MPV. The blood sample was analyzed within 4 hours after collection. CBC was done using (ADVIA 2120i analyzer Bayern, Germany, supplied by SIEMENS Company).

- Blood sample without anticoagulant for lipogram and blood glucose. The lipogram was performed on **(Cobas Integra 400 plus Roche, Germany) using kits (Roche Company) provided.**

- The blood sample was added to a citrated tube (3.2% trisodium citrate at a ratio of 9:1) for platelet aggregation. The sample was covered and inverted 4-5 times with gentle mixing, maintained vertically at room temperature (15-28°C) until processed.

Platelet aggregation function study was done using ADP, Collagen, Ristocetin, and Arachidonic acid agonists; aggregation was done by **(Platelet aggregation profiler 0.4 USA)** using kits provided by **(BIO/DATA CORPORATION, SPECTRA, USA)** for evaluation of platelet dysfunction or platelet activation.

Reagents

All reagents (ADP, Collagen, Ristocetin, and Arachidonic Acid) were kept at room temperature (15°- 28°C) before reconstitution. The concentration of these

agonists was ADP (**final concentration** 2.5 µmol/l), Collagen **(final concentration** 1µg/ml), Ristocetin (**final concentration** 14mg/ml), Arachidonic Acid **(final concentration** 10mmol/L).

Statistical Analysis:

The findings were tabulated and statistically analyzed using Statistical Package for Social Sciences (SPSS) for Windows. ***Student T-test:*** An independent T-test was used to compare two groups with normally distributed data: parametric data**.** Bars blot was used to compare the groups. The horizontal bars represent the median percentiles, whiskers represent the range of data, circles refer to outlier values, and stars refer to extreme values in each group.

Results

The age range of the studied patients was 18-60 years old. The studied patients included 21/40 males and 19/40 females. The age range of the control group was 22-58 years old; 14/20 males and 6/20 females. The 40 patients were labeled as (Group 1), and 20 healthy volunteers or controls were labeled as (Group 2).

Considering the absence and presence of disease complications among the 40 patients, the blood glucose level was normal in all patients. 21 psoriasis patients had no dyslipidemia (Group A), and 19 patients had dyslipidemia as a complication (Group B). The lipogram pattern of patients and control is represented in **Tables** (1), (2) and (3).

Comparison between the studied variables in the 40 studied patients (Group 1) and controls (Group 2):

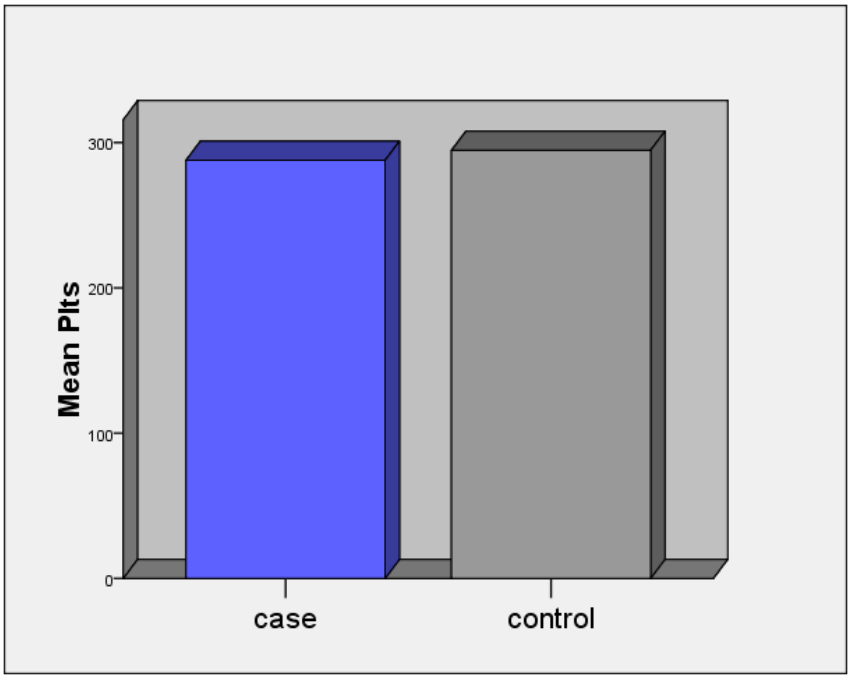
There was no significant difference in the mean PLT count or MPV values when comparing all studied psoriasis patients and the control group. There were significant increases in the mean values of platelet aggregation by ADP ($p < 0.0001$), Collagen ($p < 0.001$), Ristocetin, and Arachidonic acid ($p < 0.01$ for each) as shown in **table (1) & figure (1)**.

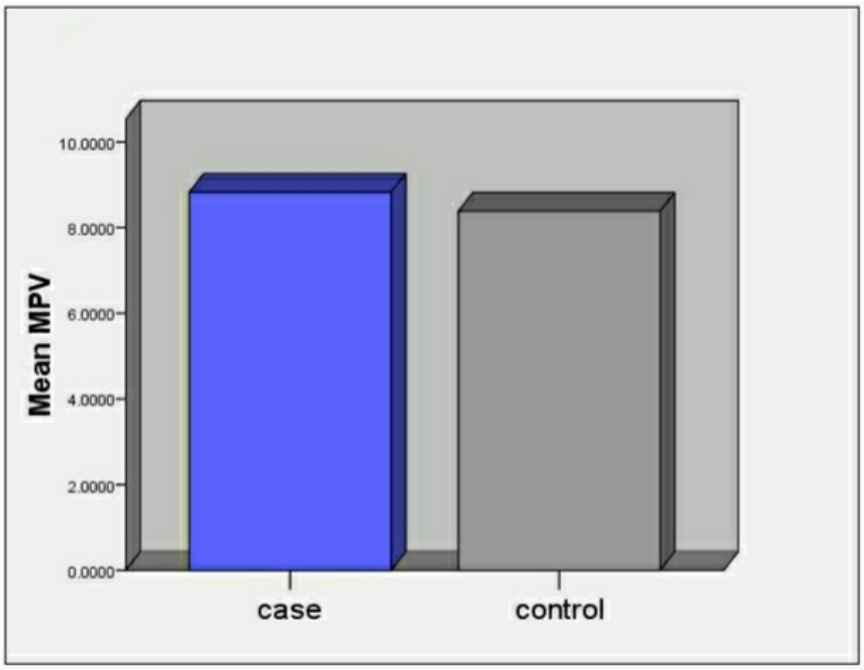
Table (1): Comparison between different parameters in all studied patients (Group 1) and Control group (Group 2)

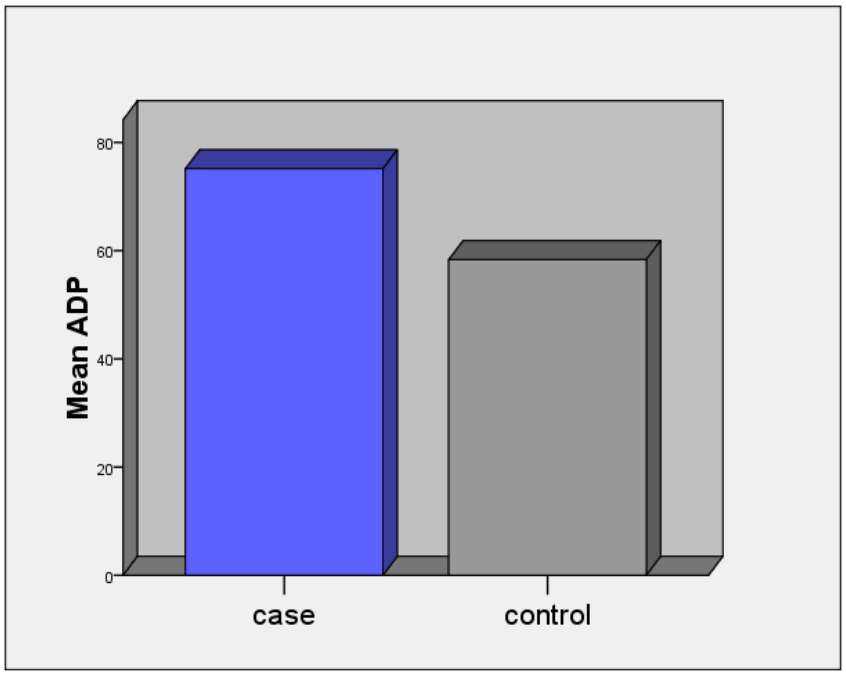
Variables	All studied patients (40) Group 1 Mean ± SD	Control (20) Group 2 Mean ± SD	P-value <
PLT count (10^9/L)	288± 87	295±94	0.782 NS
MPV (fL)	8.8±1.4	8.4±0.9	0.206 NS
Cholesterol (mg/dl)	225.8±50.6	158.7±31.5	**0.0001**
Triglycerides (mg/dl)	155.4±46.8	107.6±57	**0.001**
HDL (mg/dl)	49.982±20.69	49.5±14.5	0.932
LDL (mg/dl)	162±40	92.6±34.4	**0.0001**
Aggregation by:			
ADP (2.5 µmol/l)	75.2±13.8	58.4±7.4	**0.0001**
Ristocetin (1.4mg/ml)	76.6±14	66.2±10.2	**0.01**
Collagen (1µg/ml)	74.2±13.6	63±8.4	**0.001**
Arachidonic acid (10 mmol/L)	74.1±10.9	65.5±10.6	**0.01**

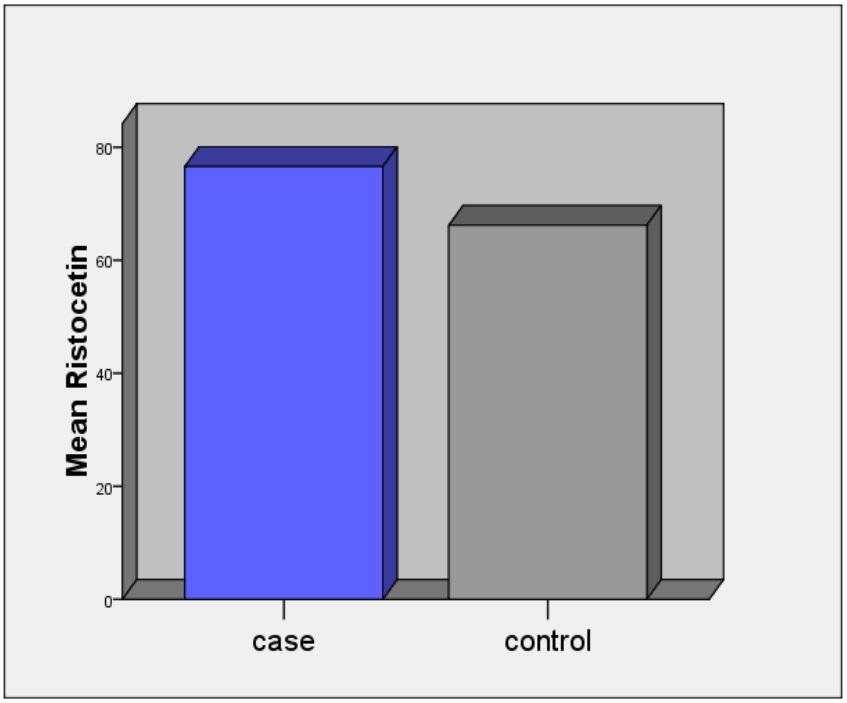
P- Independent Student T-Test calculated value.
P-value < 0.05 is statistically significant.

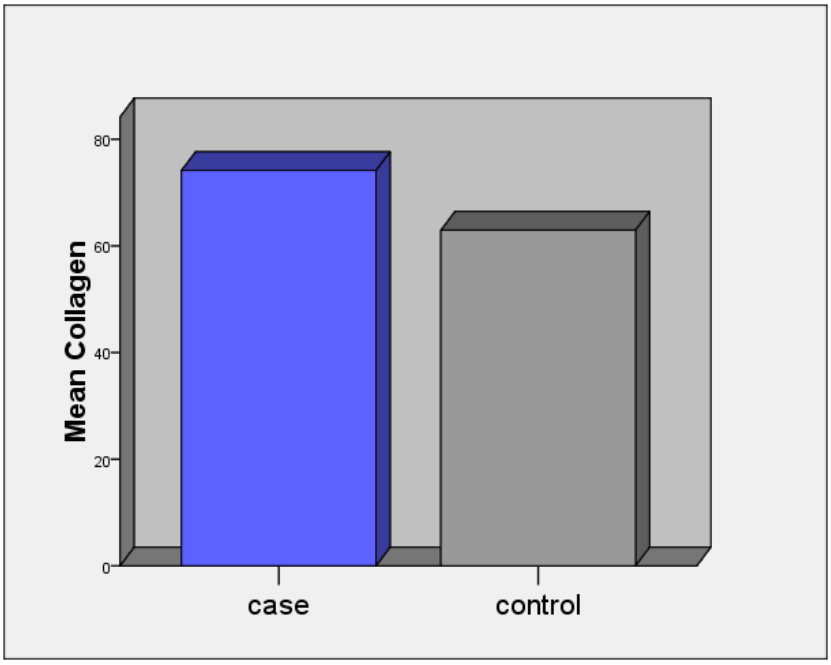
Figure (1): Comparison of the mean values of **a: PLT** count, **b: MPV** and aggregation by **c: ADP** ($p < 0.0001$), **d: Ristocetin** ($p < 0.01$), **e: Collagen** ($p < 0.001$), and **f: Arachidonic acid** ($p < 0.01$) in all psoriasis patients versus the control group.



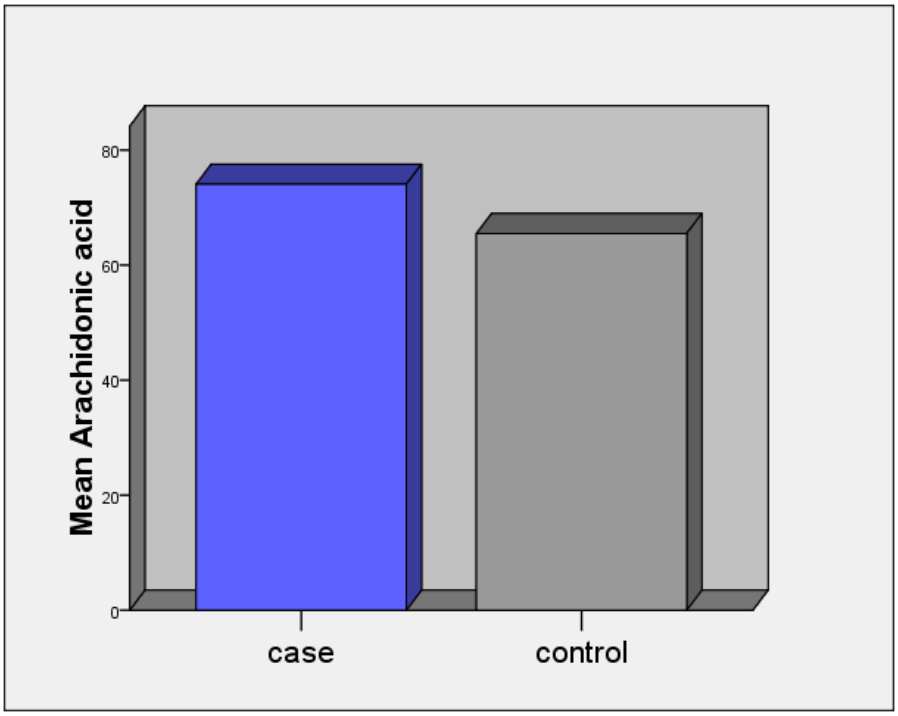



Mean ADP
80
60
40
20
0
case
control


Mean Ristocetin
80
60
40
20
0
case
control


Mean Collagen
80
60
40
20
0
case
control

\\


Mean Arachidonic acid
80
60
40
20
0
case
control

Statistical comparison between the studied parameters in Newly diagnosed patients (Group 3) and patients under treatment (Group4): Table (2) and Fig (2)

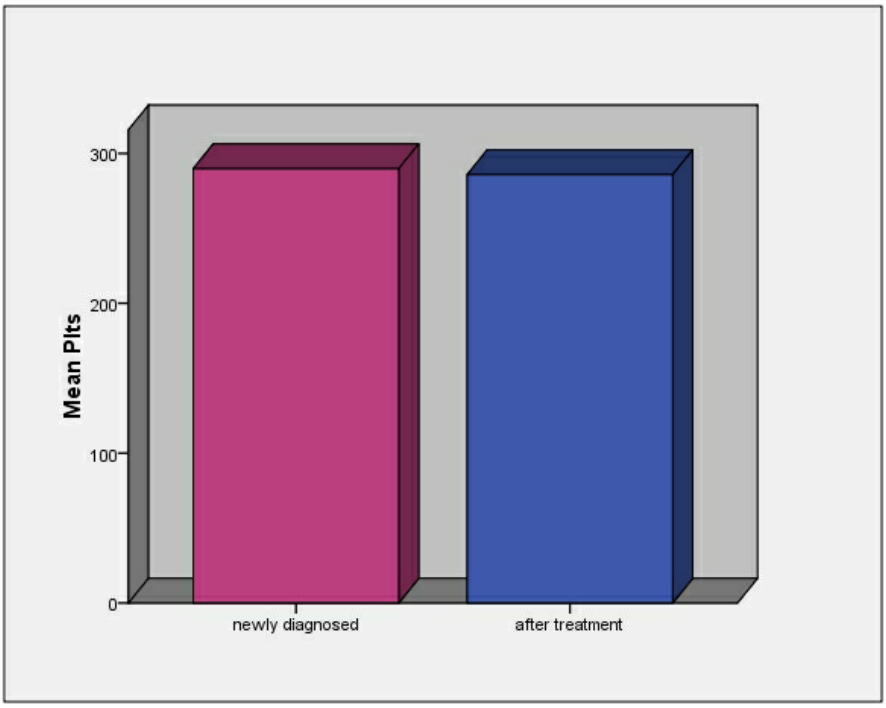
There was no significant difference in the mean PLT count and MPV value when comparing newly diagnosed and under-treatment patients. There was a significant increase in the mean aggregation values by ADP ($p < 0.0001$). Ristocetin, collagen, and Arachidonic acid ($p < 0.01$ for each) in the newly diagnosed patients compared to patients under treatment.

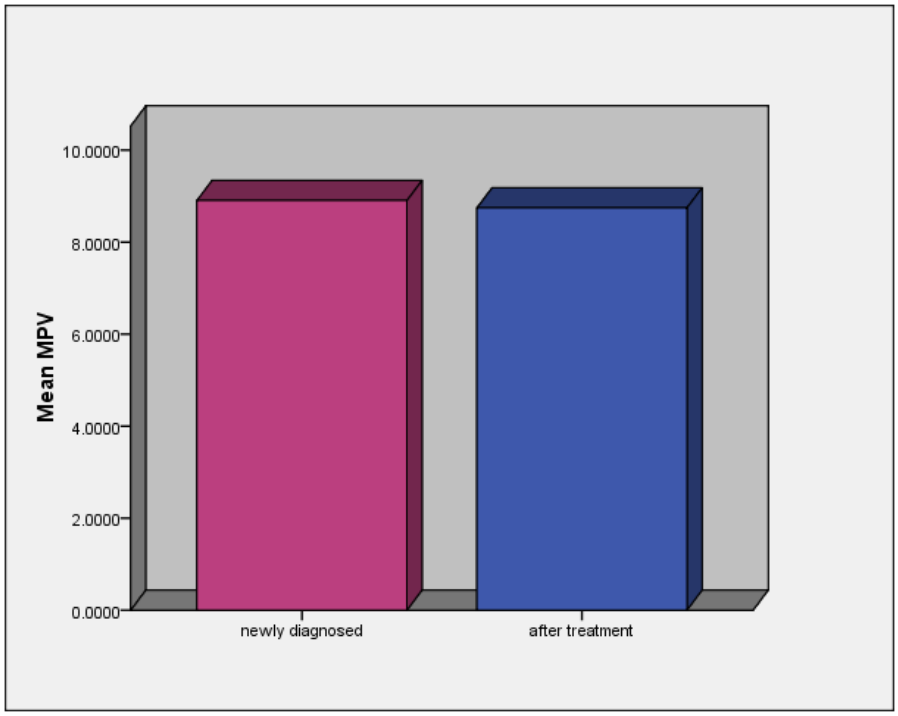
Table (2): Statistical comparison between the studied parameters in Newly diagnosed patients (Group 3) and patients under treatment (Group 4).

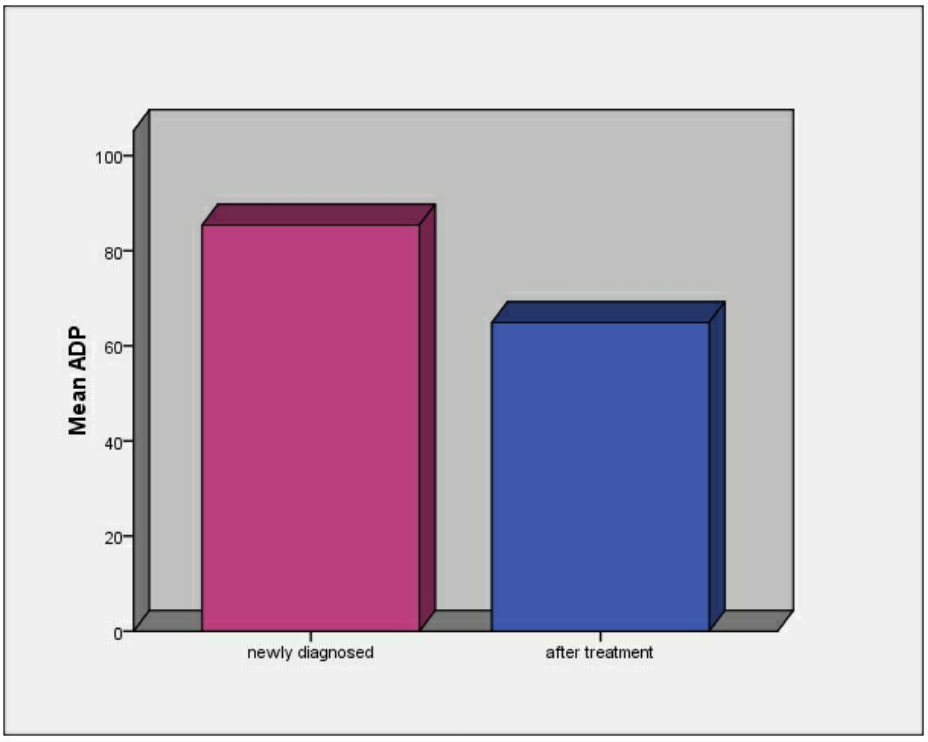
Variables	**Newly diagnosed (20) Group 3 Mean ± SD**	**Under-treatment (20) Group 4 Mean ± SD**	**P-value<**
PLT count (10^9/L)	289.9±92	286±85	0.9 (NS)
MPV (fL)	8.9±1.6	8.75±1.3	0.7 (NS)
Cholesterol (mg/dl)	242.4±48.2	209±48.5	**0.04**
Triglycerides (mg/dl)	174±43.6	136.6±43	**0.01**
HDL (mg/dl)	49.8±21.9	50±20	0.95 (NS)
LDL (mg/dl)	167±37	156.7±43.2	0.42(NS)
Aggregation by:			
ADP(2.5 µmol/l)	85.4±10	64.9±8.5	**0.0001**
Ristocetin(1.4mg/ml)	82.3±13.4	71±12.7	**0.01**
Collagen(1µg/ml)	79.4±11.4	69±13.9	**0.01**
Arachidonic acid (10mmol/L)	78.4±10.2	70±10	**0.01**

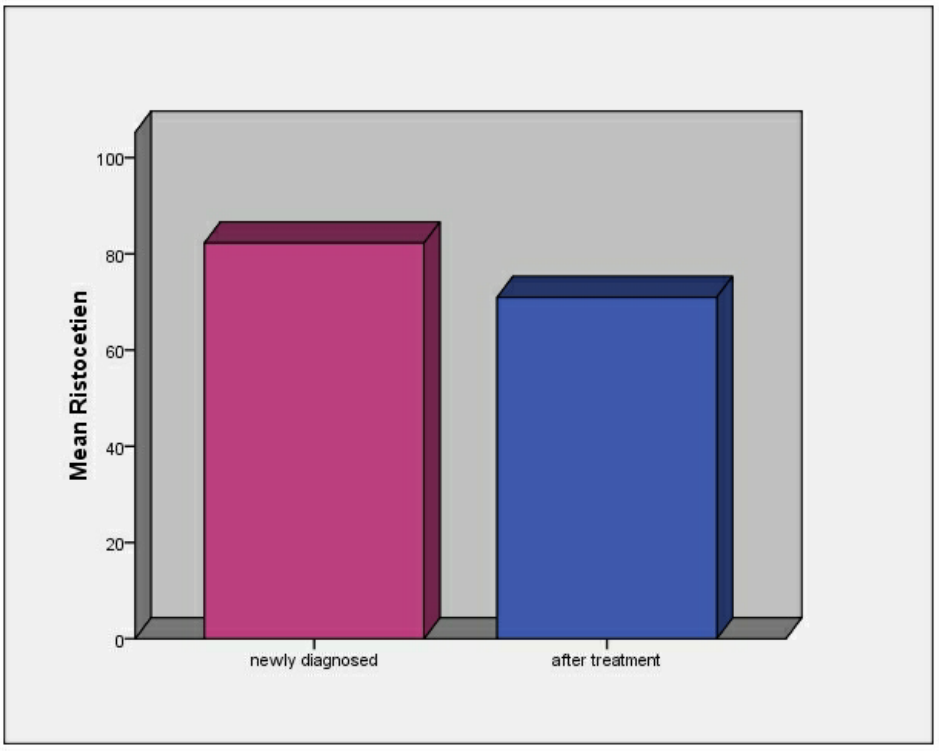
P-Value calculated by ***student t-test/ independent t-test*** (Normally Distributed Data**)**, P-value < 0.05 is statistically significant.

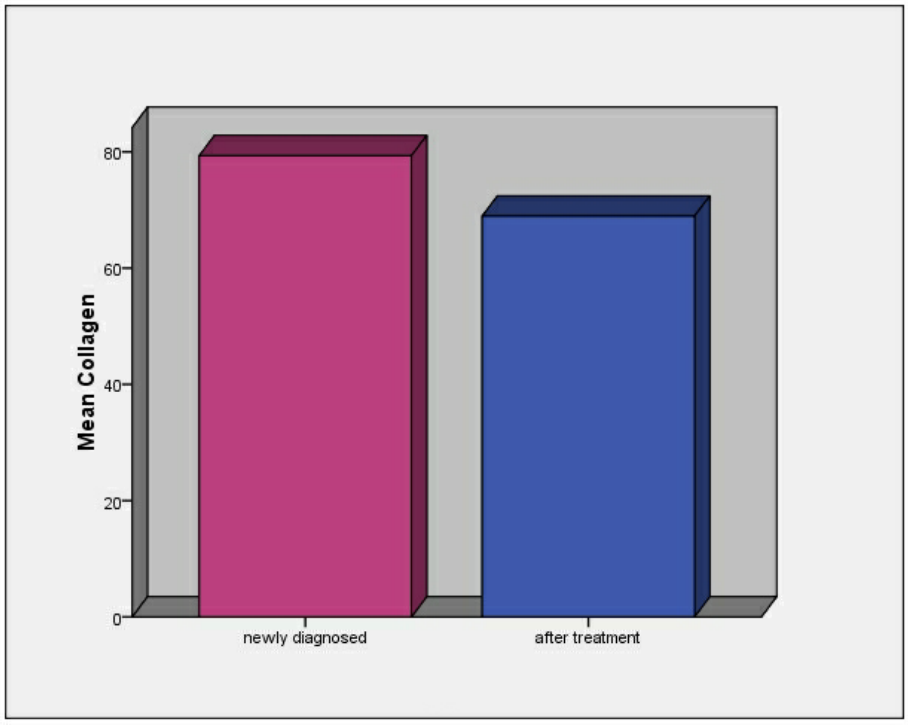
Figure (2): Comparison of the mean values of **a: PLT** count, **b: MPV,** and aggregation by **c: ADP** ($p < 0.0001$), **d: Ristocetien**, **e: Collagen**, and **f: Arachidonic acid** ($p < 0.01$ for each) in newly diagnosed patients versus patients under-treatment.

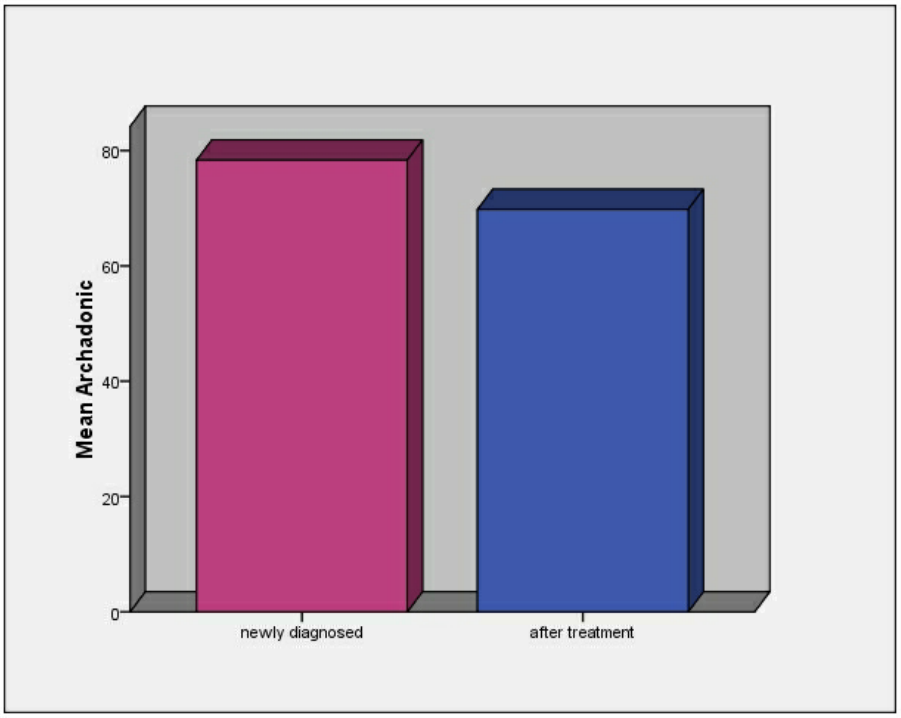





Mean ADP
100
80
60
40
20
0
newly diagnosed
after treatment


Mean Ristocetien
100
80
60
40
20
0
newly diagnosed
after treatment


Mean Collagen
80
60
40
20
0
newly diagnosed
after treatment


Mean Archadonic
80
60
40
20
0
newly diagnosed
after treatment

Comparison between the mean values of different parameters in non-complicated (Group A) and complicated Group (B) patients:
Table (3) and Fig. (3)

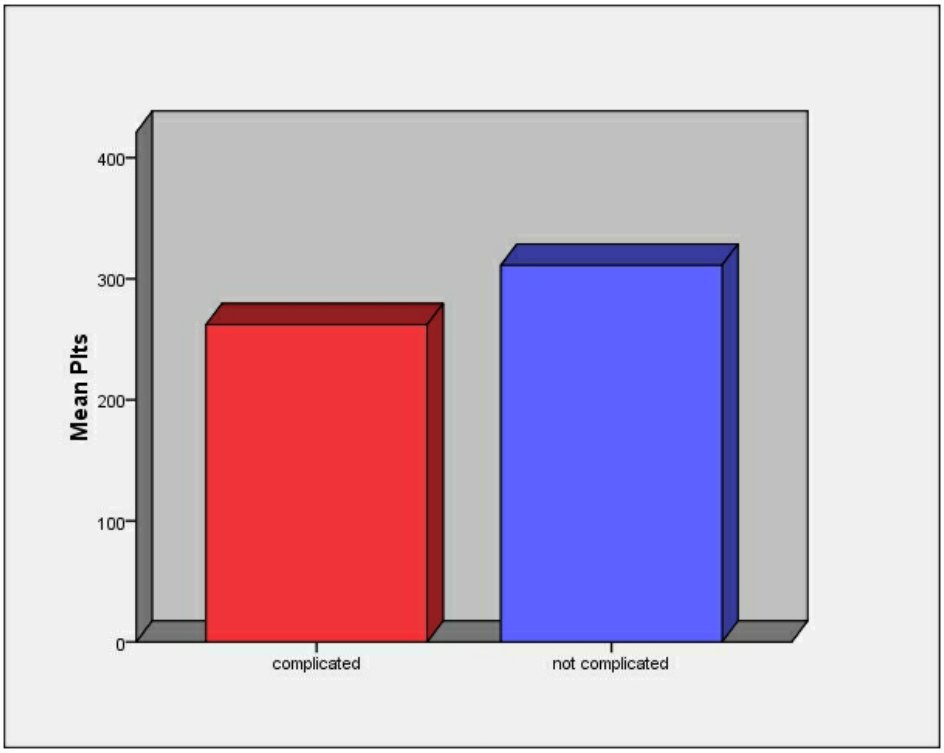
No significant difference was found in the mean PLT count or MPV value comparing non-complicated (non-dyslipidemia) and complicated (dyslipidemia) psoriasis patients. There was a significant increase in the mean value of aggregation by ADP, Ristocetin ($p < 0.03$ for each), and Arachidonic acid ($p < 0.01$), but not in the mean value of collagen in the complicated group compared to non-complicated psoriasis patients (**Table 3, Figure 3**).

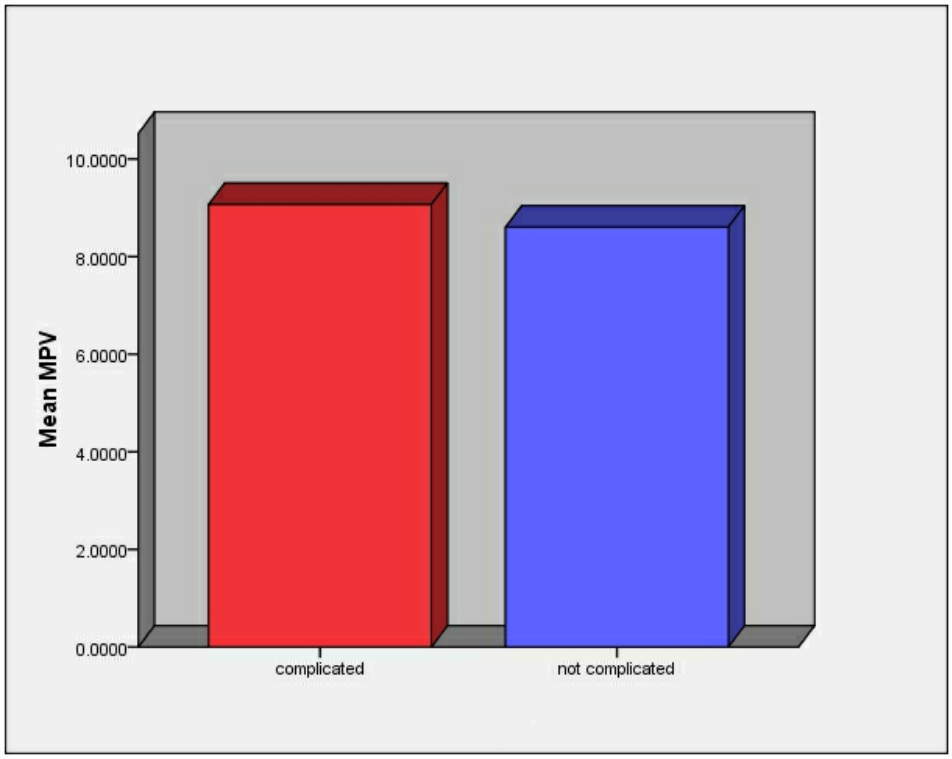
Table (3): Comparison between different parameters in Non-dyslipidemia (Group A) and dyslipidemia (Group B) patients.

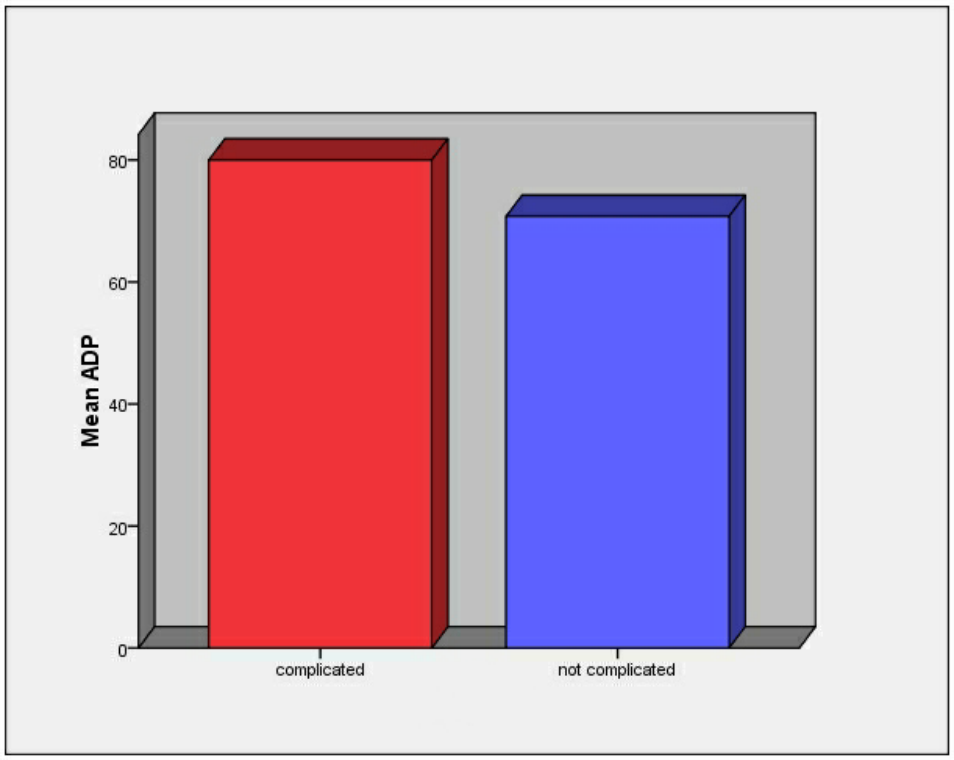
Variables	**Group A Non-complicated patients (21)**	**Group B Complicated patients (19)**	**P-value**
	Mean ± SD	**Mean ± SD**	
PLT count (10^9/L)	311.2±95.6	262.1±71	0.076 NS
MPV(fL)	8.6±1.4	9.1±1.5	0.311 NS
Cholesterol (mg/dl)	204.19±45.8	249.6±45.5	**0.003**
Triglycerides (mg/dl)	129.4±39.9	184.2±36.3	**0.0001**
HDL (mg/dl)	50.7±17.7	49.2±24	0.825
LDL (mg/dl)	145.96±38.12	179.3±35.26	**0.01**
Aggregation by:			
ADP (2.5 µmol/l)	70.76±11.9	80±14.4	**0.03**
Ristocetin (1.4mg/ml)	71.9±10.67	81.8±15.8	**0.03**
Collagen (1µg/ml)	72.7±15.1	75.7±11.9	0.49
Arachidonic acid (10mmol/L)	69.9±8	78.7±11.9	**0.01**

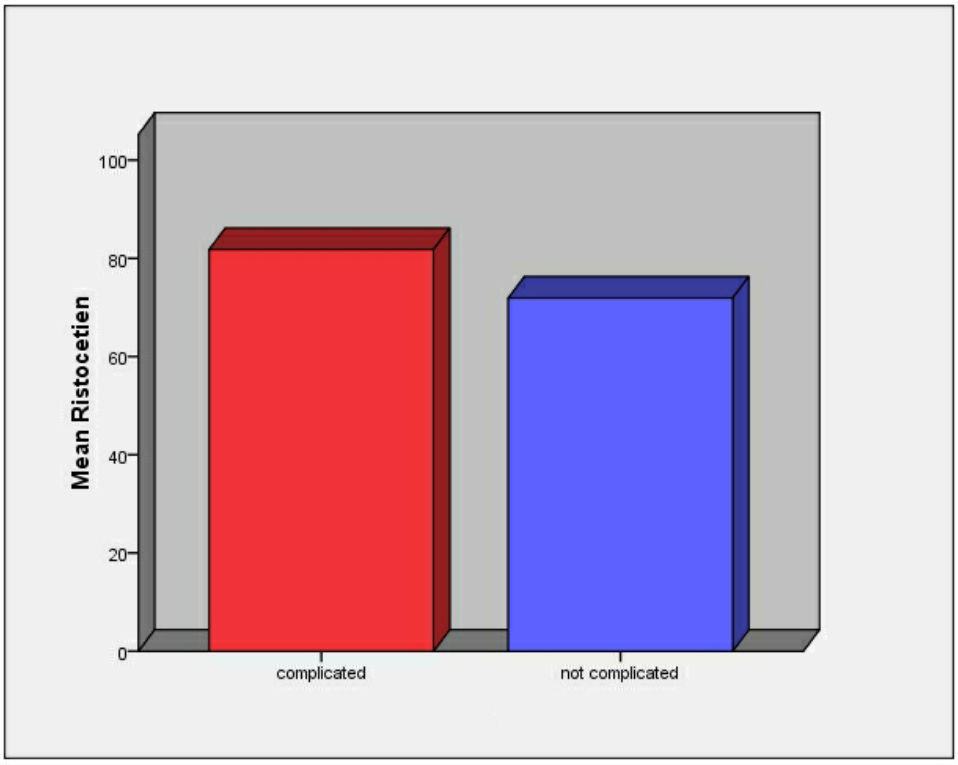
P-value calculated by ***student t-test/ independent t-test*** (Normally Distributed Data**)**, P-value < 0.05 is statistically significant.

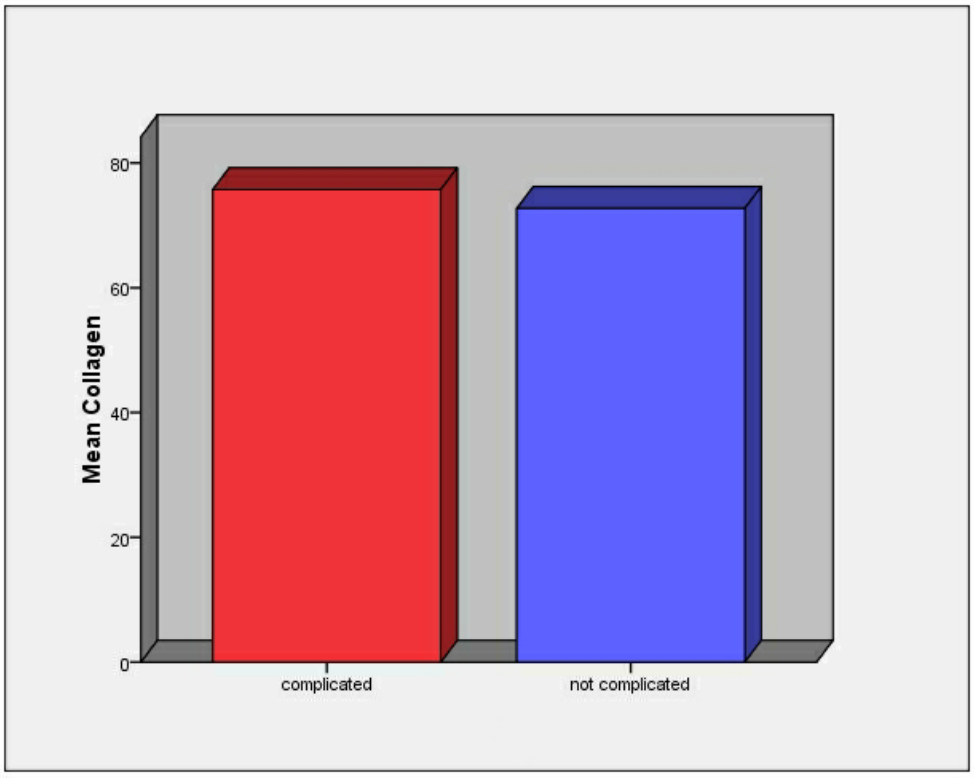
Figure (2): Comparison of the mean values of **a: PLt** count, **b: MPV** and aggregation by **c: ADP**, and **d: Ristocetien** ($p < 0.03$ for each), **e: Collagen** and **f: Arachidonic acid** ($p < 0.01$), in psoriasis patients complicated by dyslipidemia versus in non-complicated psoriasis patients.

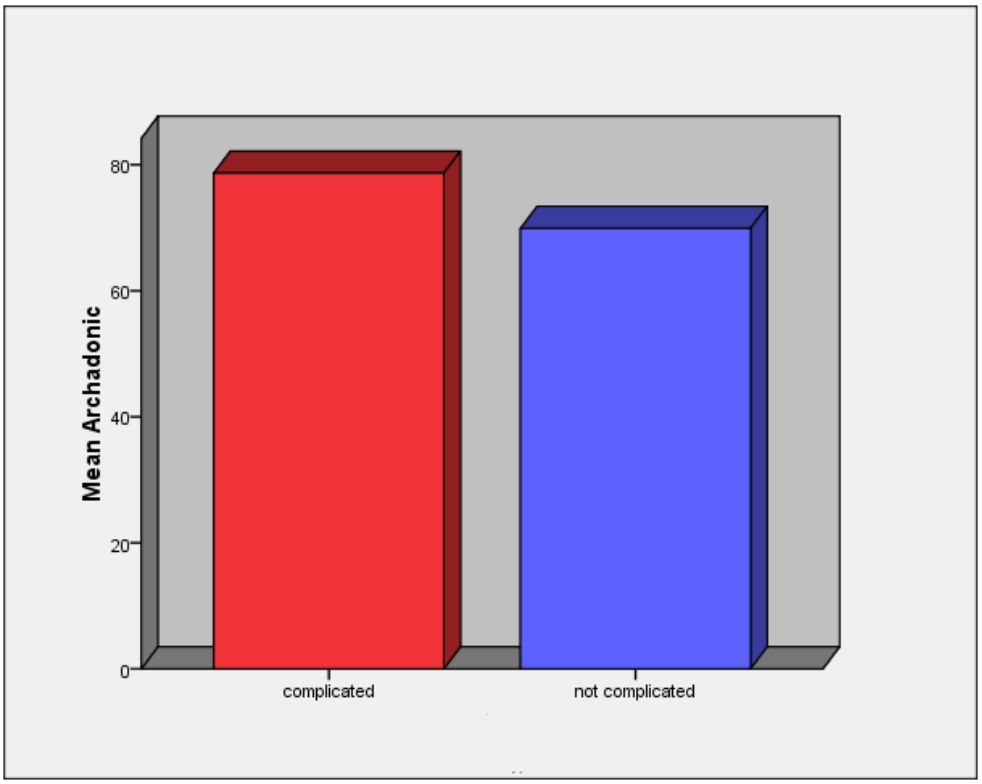





Mean ADP
80
60
40
20
0
complicated
not complicated


Mean Ristocetien
100
80
60
40
20
0
complicated
not complicated


Mean Collagen
80
60
40
20
0
complicated
not complicated


Mean Archadonic
80
60
40
20
0
complicated
not complicated

Discussion

Psoriasis is a common, chronic inflammatory skin disorder that can significantly impact life quality. The current study showed a wide age range of the patients (18-60 years old). This is similar to the present study's matched healthy participants (controls). In Dermatology inpatients and outpatient clinics of Menoufia University Hospital, ***Mahrous (2018)*** found that the age of onset of psoriasis ranged between 19 and 67 years, similar to what was found in this study. Also, in the report of ***Ahmed and his colleagues (2014),*** who studied 60 subjects, 30 psoriasis patients, and 30 healthy individuals, the age range of the patients was 21-56 years, which is a little bit shorter than ours.

However, ***Icen et al. (2009),*** in their study on 90 Italian patients, found that the age range of the disease was 18- 80 years, which is a wider age range than we have found. This may be attributed to the long life span of Italians compared to the European and Egyptian populations.

Psoriasis affects both sexes equally ***(Levine and Gottlieb, 2009).*** This study showed that 21/40 (52.5%) of the studied patients were males and 19/40 (47.5%) were females. This finding is closely similar to that reported by ***Ahmed et al. (2014),*** who found that out of their 30 studied patients, 16 (53.3%) were males and 14 (46.7%) were females.

The present study showed no significant difference in the mean value of **PLT** count and **MPV** when comparing all studied psoriasis patients and the control group, newly diagnosed patients under therapy, or patients with dyslipidemia to those without. These findings regarding **PLT** count were previously reported by ***Tamagawa-Mineoka et al. (2008)***.

In contrast, ***Raghavan et al. (2017)*** found that the **PLT** count was significantly lower in the studied ***patients*** compared to healthy control. This difference in **PLT** count could be attributed to the difference in drug therapy on the one hand; on the other hand, it could be probably because they included some patients complaining of thrombocytopenia in their study. While ***Unal (2016)*** found a statistical increase in **PLT** count in the studied psoriasis patients compared to healthy control.

As regards MPV, our findings were similar to those ***previously*** reported by ***Saleh et al. (2013), Isik et al. (2016)*** and ***Yavuz and Yavuz (2019).*****In contrast,** ***Canpolat et al. (2010)***, ***Ahmed et al. (2014), Kim et al. (2015b)***, ***Kilic et al. (2017)***, ***Raghavan et al. (2017),*** and ***Mahrous (2018)***found that **MPV** was significantly higher in psoriasis patients compared to healthy control. Our finding, contrary to the findings of previous studies, implicates that **MPV** might not be a significant parameter in patients with psoriasis.

Saleh et al. (2013) included only 25 patients, and our study included 40. Both showed no significant difference in the mean value of MPV comparing psoriasis patients with the controls, while studies done by ***Canpolat et al. (2010)*** and ***Kim et al. (2015b)*** included more patients, 106 and 176, respectively. So, the **MPV** level could increase in psoriasis patients compared to controls, and it is recommended that the study be done on many patients.

In literature, there is a paucity of data discussing platelet aggregation markers in psoriasis. Our findings come in agreement with ***Tamagawa-Mineoka et al. (2008),*** who reported that platelet aggregation induced by ADP is greatly enhanced in psoriatic patients compared with controls, and this elevated platelet aggregation is markedly decreased after improvement of psoriatic skin lesions by therapy. In addition, the present study showed significantly increased aggregation with more agonists (collagen, ristocetin, and arachidonic acid). This increased aggregation supports the possibility of increased liability of platelets to form macro and micro aggregates and platelet thrombi in psoriasis patients, and this effect might be reduced by treatment.

Psoriasis is frequently associated with significant comorbidities, including diabetes

mellitus, obesity, dyslipidemia, inflammatory bowel disease, psychiatric disorders, osteoporosis, and obstructive sleep apnea, as well as CVDs, e.g., hypertension, myocardial infarction, and stroke ***(Machado-Pinto et al., 2016, & Gruchala et al., 2019)***.

In the present study, it was observed that 19 out of 40 patients had dyslipidemia and that the platelet aggregations with ADP, Ristocetin ($p < 0.03$ for each), and Arachidonic acid ($p < 0.01$) were also increased significantly in this group when compared to those without. Dyslipidemia is a leading cause of atherosclerosis. Therefore, early detection of dyslipidemia in patients with psoriasis would help to reduce cardiovascular morbidity and mortality ***(Schwingen et al., 2020).***

Conclusions: Platelet count and MPV may not be a good marker for early detection or predicting complications in psoriasis patients. There is generally **increased liability for platelet aggregation** with disease activity as assessed by ADP, Collagen, Ristocetien, and Arachidonic acid. This could explain the macro and micro platelet aggregates in those patients. The liability for aggregation increased with the presence of dyslipidemia and decreased after treatment. There may be a link between cardiovascular morbidity and disease activation.

References:

1. **Benhadou F, Mintoff D, Del Marmol V (2018**). Psoriasis: Keratinocytes or Immune Cells - Which Is the Trigger? Dermatology, 235:91-100.
2. **Machado-Pinto J, Diniz Mdos S, Bavoso NC (2016).** Psoriasis: new comorbidities. An Bras Dermatol. 91(1):8-14.
3. **Gruchała A , Cisłak A, Golański J (2019).** Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as an alternative to C-reactive protein in diagnostics of inflammatory state in patients with psoriasis. Our Dermatol Online: 10 (1):7-11
4. **Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, et al (2013).** Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. J Eur Acad Dermatol Venereol. Suppl 3:12-29.
5. **Schwingen J , Kaplan K, Kurschus FC (2020).** Current Concepts in Inflammatory Skin Diseases Evolved by Transcriptome Analysis: In-Depth Analysis of Atopic Dermatitis and Psoriasis. Int. J. Mol. Sci. 699: 1-39
6. **Beatriz G Tslayero and Frank M Sacks (2011).** The role of triglyceride in atherosclerosis.Current Cardiol Rep.2011 Dec 13 (6):544-52 doi: 10.1007/s11886-011-0220-3
7. **Tamagawa-Mineoka R, Katoh N, Kishimoto S (2010).** Platelet activation in patients with psoriasis: increased plasma levels of platelet-derived microparticles and soluble P-selectin. J Am Acad Dermatol. 62(4):621-626.
8. **Canpolat F, Akpinar H, Eskioğlu F (2010).** Mean platelet volume in psoriasis and psoriatic arthritis.Clin Rheumatol. 29(3):325-8.
9. **Mahrous EAM (2018).** The relationship between platelet volume and risk of atherosclerosis in patients with psoriasis The Egyptian Journal of Dermatology and Venereol. 38 (1): 29-36.
10. **Chu SG, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B, et al (2010).** Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Hemost.8(1):148-56.
11. **Jennings LK (2009).** Mechanisms of platelet activation: need for new strategies to protect against platelet-mediated atherothrombosis.Thromb Hemost.102 (2):248-257.
12. **Herster F, Bittner Z, Codrea MC, Archer NK, Heister M, Löffler MW, et al (2019).** "Platelets Aggregate With Neutrophils and Promote Skin Pathology in Psoriasis." Frontiers in immunology vol. 10 1867.

13. **Ahmad Z, Akhtar SJ, Arif Maan M, Khalid U, Hussain A (2014).** Comparison of mean platelet volume in patients with psoriasis and healthy individuals. J Pakist Asso Dermatol. 24 (1):4-7.
14. **Wagner DD, Burger PC (2003).**Platelets in inflammation and thrombosis. Arterioscler Thromb Vasc Biol. 23(12):2131-2137.
15. **Jennings** LK (**2009**). Mechanisms of platelet activation: need for new strategies to protect against platelet-mediated atherothrombosis.Thromb Hemost.102 (2):248-257.
16. **Icen M, Crowson CS, McEvoy TM, Dann FJ, Gabrie Sl, Kreme HM (2009).** Trends in incidence of adult-onset psoriasis over three decades: a population-based study. J Am Acad Dermatol. 60:394-401.
17. **Levine D, Gottlieb A (2009).** Evaluation and management of psoriasis: an internist's guide. Med Clin North Am. 93(6):1291-303.
18. **Tamagawa-Mineoka R, Katoh N, Ueda E, Masuda K, Kishimoto S (2008).** Elevated platelet activation in patients with atopic dermatitis and psoriasis: increased plasma levels of beta-thromboglobulin and platelet factor 4. Allergol Int.57(4):391-396.
19. **Raghavan V, Radha RKN, Rao RK, Kuberan A (2017).** A Correlative Study between Platelet Count, Mean Platelet Volume and Red Cell Distribution Width with the Disease Severity Index in Psoriasis Patients. J Clin Diag Res.11(9): EC13-EC16.
20. **Unal M (2016).** Platelet mass index is increased in psoriasis. A possible link between psoriasis and atherosclerosis. Arch Med Sci Atheroscler Dis. 1(1):e145-e149.
21. **Saleh HM, Attia EA, Onsy AM, Saad AA, Abd Ellah MM (2013).**Platelet activation: a link between psoriasis perse and subclinical atherosclerosis--a case-control study. Br J Dermatol. 169 (1): 68-75.
22. **Işik S, Kılıç S, Öğretmen Z, Çakır DÜ, Türkön H, Cevizci S, et al (2016).**The correlation between the psoriasis area severity index and ischemia-modified albumin mean platelet volume levels in patients with psoriasis. Postepy Dermatol Alergol. 33(4):290-293.
23. Yavuz **and Yavuz (2019).**Novel inflammatory markers in patients with psoriasis. East J Med. 24(1):63-68
24. **Kim DS, Lee J, Kim SH, Kim SM, Lee MG (2015b).**Mean platelet volume is elevated in patients with psoriasis vulgaris.Yonsei Med J. 56 (3): 712-718.