The Egyptian Journal of Hospital Medicine (July 2017) Vol.68 (2), Page 1117-1125

Glucocorticoids Induced End Organs Damage in Patients with Systemic Lupus Erythematosus

Mohammed Afify Abd-El-Atty, Eman Ahmed Hafez, Noha Hussien Shedid and Dalia Abdel Hamid El Sherbiny

Rheumatology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Corresponding author: Eman Ahmed Hafeez – Mobile: 01005296023 , Email: Eman.ahmed208@hotmail.com

ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that affects multiple organs and requires long term treatment with GCs. GC-related end organ damage in SLE appears in the form of: osteoporosis, Avascular Necrosis (AVN), cataracts, diabetes (DM) and cardiovascular disease.

Aim of the work: the present work was to assess the prevalence of the complications in SLE patients who were treated with GCs for long periods and with moderate to severe cumulative steroid doses.

Patients and Methods: This study was done on 50 SLE patients who fulfilled the SLICC criteria for diagnosis of SLE. All patients subjected to full history taking, clinical examination, slit-lamp examination to assess cataract, laboratory investigations (ESR, CRP, FBS, 2-H PP, CBC, C3, C4 and anti-dsDNA), DEXA scan, MRI scan (when needed), SLEDAI score and SLICC score assessments. All data were collected, tabulated and statistically analyzed. **Results:** Regarding the frequency of steroid induced complications, 38% were osteopenic, while 18% were osteoporotic patients. 10% had AVN. 18% had cataract. 14% had DM. There was very strong relationship between steroid duration and the frequency of DM and cataract. But in osteopenia, osteoporosis and AVN, there were weak relationship regarding steroid duration. There was very strong relationship between cumulative steroid dose and the frequency of DM, cataract, osteoporosis and AVN. There was no relationship between age and osteoporosis and AVN but in cataract and DM, there was strong relationship. There was no relationship between sex and complications (DM, cataract, osteopenia, osteoporosis and AVN). There was no relationship between disease activity (measured by SLEDAI score) and frequency of steroid complications (DM, cataract, osteopenia, osteoporosis and AVN). There was strong relationship between end organ damage (measured by SLICC damage index) and frequency of steroid complications (DM, cataract, osteoporosis and AVN). **Conclusion:** Steroid intake (duration and dose) were major risk factors for developing end organ damage in SLE patients.

Key words: SLE, steroid induced osteoporosis, AVN, cataract, DM, end organ damage.

INTRODUCTION

Systemic lupus erythematosus (SLE) results from chronic and recurrent activation of the immune system, with production of antibodies and other protein products contributing to inflammation and tissue damage [1]. It is characterized by the production of a broad array of autoantibodies, with antinuclear antibodies having the greatest sensitivity for the diagnosis and anti–double-stranded DNA antibodies having the greatest specificity [2]. It is a multi-system autoimmune disorder that disproportionally affects women, especially in their reproductive years [3]. It may manifest as a mild disease with skin or joint involvement only or may be severe, affecting vital organs such as the kidney, central nervous system (CNS), and heart. This is why SLE has been addressed as a constellation of different clinical variants, or better, as a *galaxy* [4]. Glucocorticoids (GCs) are among the most potent immunosuppressive and anti-inflammatory drugs.

Their efficacy in treating SLE is beyond doubt. However, GC-related side effects are many and serious. Indeed, prednisone use has been consistently shown to increase irreversible damage in lupus patients, a major predictor of morbidity and mortality [5]. Glucocorticoid-related damage "calculated using the SLICC damage index" is defined as avascular osteonecrosis, osteoporosis, diabetes mellitus (DM) or cataracts [6]. Glucocorticoid use is associated with significant morbidity and mortality. Osteoporosis, with resultant fractures, constitutes one of these morbid complications and is associated with significant pain and disability [7]. Glucocorticoid administration is often overlooked as the most common cause of non-traumatic osteonecrosis [8]. Chronic glucocorticoid therapy is associated with an increased risk of developing cataracts and glaucoma, and recommendations have been developed for

Received: 01 / 04 /2017
Accepted: 10 / 04 /2017

DOI : 10.12816/0039038

monitoring these side effects in patients with rheumatic diseases [9]. Glucocorticoids increase hepatic glucose production and induce insulin resistance by inhibiting insulin-stimulated glucose uptake and metabolism by peripheral tissues [10].

PATIENTS AND METHOUDS

PATIENTS:

This cross sectional observational study was conducted on a group of SLE patients who met the SLICC criteria for SLE diagnosis [11] including 50 patients with SLE who are treated with glucocorticoids "prednisolone" on a dose > 7.5 mg/day. All patients collected from inpatient departments & outpatient clinics of Rheumatology and Clinical Immunology department in Maadi Armed Forces Complex. A written consent was taken from all patients who agree to be enrolled in the study.

Exclusion criteria

1. Patients with any other connective tissue diseases.
2. Patients with history of osteoporosis or avascular necrosis before steroid treatment.
3. Patients with DM or cataract before SLE steroid treatment.

METHODS

All subjects subjected to:

1. Full medical history and thorough general, local and musculoskeletal examinations, with assessment of disease activity according to SLE Disease Activity Index (SLEDAI) [12].
2. Slit-lamp examination to assess cataract.
3. Laboratory investigations including: ESR, CRP, FBS, 2-H PP, CBC, C3, C4 and anti-dsDNA.
4. Imaging studies including: DEXA scan and MRI scan (when needed).
5. All data tabulated and statistically analyzed (data entry, processing and statistical analysis was carried out using MedCalc ver. 15.8. Tests of significance (Chi squared, student's t-test, One-way analysis of variance (ANOVA), regression, ROC Curve and Spearman's correlation coefficient) were used. P-values less than 0.05 (5%) was considered to be statistically significant.
6. The study was done after approval of ethical board of Ain Shams University and an informed written consent was taken from each participant in the study.

RESULTS

In our study, we demonstrated that SLE patients were at a great risk of developing GC-related end organ damage in the form of (osteoporosis, osteonecrosis, cataracts and diabetes mellitus). In our group of SLE patients, the majority of cases were females (86%). The mean age of patients was 37 years. The majority of cases (68%) were middle aged (25 to 45) years old. Regarding disease durations, the majority of cases (78%) were mainly below 15 years. Only (22%) had long-standing disease (above 15 years). Mean disease duration is 11 years. Regarding the cumulative dose of GCs, the majority of cases were between (15 – 30) grams, (46%), while (22%) between (30 – 60) grams, (32%) between (more than 60) grams. The mean cumulative dose is 44 grams. The most frequent SLE criteria among patients were arthritis, photosensitivity, nephritis, malar rash, oral ulcers and pleuritis (82%, 74%, 72%, 42%, 36% & 30% respectively). Regarding laboratory data, the most frequent SLE antibodies were ANA (100%) followed by Anti ds-DNA (94%). Anemia, depleted complement levels, thrombocytopenia and leucopenia were found in (30%, 20%, 4% & 2% respectively).Regarding the frequency of steroid induced complications. 38% were osteopenic, while 18% were osteoporotic patients. 10% had avascular necrosis (AVN). 18% had cataract. 14% had DM.

We further analyzed and compared SLE patients with NBMD (normal bone mineral density), osteopenia and osteoporosis according to the demographic, clinical, BMD and steroid variables among the 50 SLE patients who were included in the study.

Comparative studies using ANOVA test showed that:

1. There is significantly positive difference between the 3 groups as regards age, disease duration and SLICC score (P=0.029, P=0.001, P≤0.001 respectively) (Table 1).
2. There is significantly positive difference between the 3 groups as regards SLICC score only (P≤0.001) (Table 2).
3. There is significantly positive difference between the 3 groups as regards all variables (P≤0.05) except for steroid duration at FN (P>0.05) (Table 3).

Correlation studies using Pearson correlation test showed that:

1. There are significant negative correlations with SLICC at (LS "spine" + FN "femoral neck"), age (FN) and disease duration (FN) (P≤0.05) (Table 4).
2. There are significant negative correlations with all variables except disease duration (LS) (P≤0.05) (Table 5).

Comparative studies between patients with AVN and patients without AVN using student t test showed that:

1. There is significantly positive difference between the 2 groups as regards SLICC score (P≤0.001) (Table 6).
2. There is significantly positive difference between the 2 groups as regards cumulative, current and dose of solumedrol (P= 0.001, P≤0.001, P=0.001 respectively) (Table7).

Comparative studies between patients with cataract and patients without cataract using student t test showed that:

1. There is significantly positive difference between the 2 groups as regards age, age of onset, disease duration and SLICC score (P≤0.001, P=0.044, P≤0.001, P≤0.001 respectively) (Table 8).
2. There is significantly positive difference between the 2 groups as regards cumulative, dose of solumedrol and steroid duration (P≤0.001, P≤0.001, P≤0.001 respectively) (Table 9).

Comparative studies between patients with DM and patients without DM using student t test showed that:

1. There is significantly positive difference between the 2 groups as regards age, disease duration and SLICC score (P≤0.001, P≤0.001, P=0.001 respectively) (Table 10).
2. There is significantly positive difference between the 2 groups as regards Cumulative, dose of Solumedrol and Steroid duration (P≤0.001, P≤0.001, P≤0.001 respectively) (Table 11).

Roc-curves of cumulative steroid levels to discriminate complicated from non-complicated cases showed that:

1. By using ROC-curve, cumulative steroid dose at a cutoff point >59.75 gm. discriminated osteopenia from osteoporosis, with excellent accuracy, sensitivity= 100% and specificity= 85% (Figure 1).
2. By using ROC-curve, cumulative steroid dose at a cutoff point >44.06 gm. discriminated non-DM from DM, with excellent accuracy, sensitivity= 100% and specificity= 76.74% (Figure 2).
3. By using ROC-curve, cumulative steroid dose at a cutoff point >63.31 gm. discriminated non-cataract from cataract, with excellent accuracy, sensitivity= 88.89% and specificity= 87.8% (Figure 3).
4. By using ROC-curve, cumulative steroid dose at a cutoff point >59.75 gm. discriminated non-AVN from AVN, with good accuracy, sensitivity= 100% and specificity= 75.56% (Figure 4).

Table (1): Comparison between patients with NBMD, osteopenia and osteoporosis at LS as regard some demographic and clinical data using ANOVA test:

Variable	NBMD (LS) (26)	Osteopenia (LS) (19)	Osteoporosis (LS) (5)	ANOVA test
	Mean ± SD	Mean ± SD	Mean ± SD	p value
Age (years)	33.84 ± 9.24	42.42 ± 12.74	32.40 ± 6.06	0.029*
Age of disease onset (years)	25.42 ± 8.77	27.89 ± 7.36	23.00 ± 6.74	0.404
Disease duration (Years)	8.42 ± 2.67	14.52 ± 7.41	11.40 ± 3.57	0.001*
SLICC\ACR	1.46 ± 0.70	2.73 ± 1.44	3.40 ± 1.34	0.001 **
SLEDAI	4.34 ± 3.82	3.21 ± 3.27	7.00 ± 4.89	0.135

NBMD: normal bone mineral density, ANOVA: one way analysis of variance

Table (2): Comparison between patients with NBMD, osteopenia and osteoporosis at FN as regard some demographic and clinical data using ANOVA test:

Variable	NBMD (FN) (29)	Osteopenia (FN) (15)	Osteoporosis(FN) (6)	ANOVA test
	Mean ± SD	Mean ± SD	Mean ± SD	p value
Age (years)	35.37 ± 10.42	40.26 ± 11.03	38.00 ± 14.60	0.385
Age of disease onset (years)	26.00 ± 8.17	27.20 ±8.52	24.00 ± 7.37	0.718
Disease duration (Years)	9.37 ± 4.57	13.06 ± 5.03	14.00 ± 9.93	0.051
SLICC\ACR	1.62 ± 1.04	2.33 ± 1.11	4.16 ± 0.75	<0.001**
SLEDAI	4.17 ± 3.78	4.73 ± 3.63	2.83 ± 4.75	0.597

NBMD: normal bone mineral density, ANOVA: one way analysis of variance

Table (3): Comparison between patients with NBMD, osteopenia and osteoporosis at LS and FN as regard the cumulative, current dose and duration of steroid treatment using ANOVA test:

Variable	NBMD (LS) (26)	Osteopenia (LS) (19)	Osteoporosis (LS) (5)	ANOVA test	NBMD (FN) (29)	Osteopenia (FN) (15)	Osteoporosis (FN) (6)	ANOVA test
	Mean ± SD	Mean ± SD	Mean ± SD	p value	Mean ± SD	Mean ± SD	Mean ± SD	p value
Cumulative steroid dose (gm)	28.63 ± 13.77	58.39 ± 27.33	72.99 ± 10.04	<0.001**	32.67 ± 19.85	51.88 ± 22.43	82.20 ± 16.62	<0.001**
Current steroid dose (mg)	8.94 ± 2.93	12.63 ± 8.31	17.50 ± 5.00	=0.007**	9.05 ± 2.35	11.50 ± 5.73	20.83 ± 11.14	<0.001**
Dose of solumedrol (gm)	2.17 ± 1.39	3.55 ± 1.89	5.10 ± 0.89	<0.001**	2.50 ± 1.69	3.40 ± 1.77	4.33 ± 1.86	=0.043*
Steroid duration (years)	8.03 ± 2.48	14.00 ± 7.54	11.40 ± 3.57	=0.001*	9.03 ± 4.55	12.40 ± 5.06	14.00 ± 9.93	=0.055

Table (4): Correlation between BMD at LS and FN and some demographic and clinical data among 50 SLE patients using Pearson correlation test:

Parameters	BMD LS		BMD FN	
	r	P-value	r	P-value
Age (years)	-0.097	0.499	-0.288	0.046*
Age of disease onset (years)	0.012	0.930	-0.143	0.329
Disease duration (years)	-0.206	0.150	-0.357	=0.012*
SLICC\ACR	-0.555	<0.0001**	-0.710	<0.0001**
SLEDAI	-0.153	0.286	0.109	0.461

Table (5): Correlation between BMD at LS and FN and steroid dose and duration used among 50 SLE patients using Pearson correlation test:

Medications	BMD LS		BMD FN	
	r	P-value	r	P-value
Cumulative dose of steroids (gm)	-0.528	0.0001**	-0.663	<0.0001**
Current Oral dose of steroids (mg/day)	-0.472	0.0005**	-0.494	0.0004**
Dose of solumedrol (gm)	-0.494	0.0003**	-0.414	0.0034**
Steroid duration (years)	-0.226	0.114	-0.369	0.0098**

Table (6): Comparison between patients with AVN and patients without AVN as regard some demographic and clinical data using Student's t-test:

Variable	Normal group (45)	AVN group (5)	t test
	Mean ± SD	Mean ± SD	p value
Age (years)	37.46 ± 11.09	34.40 ± 12.17	0.564
Age of disease onset (years)	26.68 ± 8.19	21.00 ± 5.14	0.137
Disease duration (Years)	10.77 ± 5.29	13.40 ± 9.50	0.340
SLICC\ACR	1.93 ± 1.17	4.00 ± 1.00	<0.001 **
SLEDAI	4.37 ± 3.82	2.40 ± 3.57	0.276

Table (7): Comparison between patients with AVN and patients without AVN as regard the cumulative, current dose and duration of steroid treatment using Student's t-test:

Variable	Normal group (45)	AVN group (5)	t test
	Mean ± SD	Mean ± SD	p value
Cumulative steroid dose (gm)	40.59 ± 24.20	78.46 ± 12.67	=0.001**
Current steroid dose (mg)	10.00 ± 3.69	22.00 ± 13.03	<0.001**
Dose of solumedrol (gm)	2.87 ± 1.80	5.80 ± 0.83	=0.001**
Steroid duration (years)	10.33 ± 5.26	13.40 ± 9.50	=0.263

Table (8): Comparison between patients with cataract and patients without cataract as regard some demographic and clinical data using Student's t-test:

Variable	Normal group (41)	Cataract group (9)	t test
	Mean ± SD	Mean ± SD	p value
Age (years)	34.02 ± 8.49	51.44 ± 10.78	< 0.001**
Age of disease onset (years)	25.04 ± 7.82	31.00 ± 7.85	0.044*
Disease duration (Years)	8.97 ± 3.29	20.44 ± 5.29	< 0.001**
SLICC\ACR	1.75 ± 1.01	3.88 ± 1.05	< 0.001**
SLEDAI	4.365 ± 3.69	3.33 ± 4.47	0.468

Table (9): Comparison between patients with cataract and patients without cataract as regard the cumulative, current dose and duration of steroid treatment using Student's t-test:

Variable	Normal group (41)	Cataract group (9)	t test
	Mean ± SD	Mean ± SD	p value
Cumulative steroid dose (gm)	36.05 ± 18.64	82.29 ± 19.95	< 0.001**
Current steroid dose (mg)	11.34 ± 6.87	10.55 ± 2.08	0.737
Dose of solumedrol (gm)	2.58 ± 1.58	4.83 ± 1.76	< 0.001**
Steroid duration (years)	8.51 ± 2.99	20.33 ± 5.40	< 0.001**

Table (10): Comparison between patients with DM and patients without DM as regard some demographic and clinical data using Student's t-test:

Variable	Normal group (43)	DM group (7)	t test
	Mean ± SD	Mean ± SD	p value
Age (years)	34.90 ± 9.02	51.00 ± 13.40	< 0.001**
Age of disease onset (years)	25.23 ± 7.75	31.57 ± 8.56	0.054
Disease duration (Years)	9.67 ± 4.50	19.42 ± 5.82	< 0.001**
SLICC\ACR	1.90 ± 1.21	3.57 ± 0.97	= 0.001**
SLEDAI	3.97 ± 3.67	5.42 ± 4.72	0.356

Table (11): Comparison between patients with DM and patients without DM as regard the cumulative, current dose and duration of steroid treatment using Student's t-test:

Variable	Normal group (43)	DM group (7)	t test
	Mean ± SD	Mean ± SD	p value
Cumulative steroid dose (gm)	36.05 ± 18.64	82.29 ± 19.95	< 0.001**
Current steroid dose (mg)	11.34 ± 6.87	10.55 ± 2.08	0.737
Dose of solumedrol (gm)	2.62 ± 1.67	5.21 ± 0.80	< 0.001**
Steroid duration (years)	8.51 ± 2.99	20.33 ± 5.40	< 0.001**

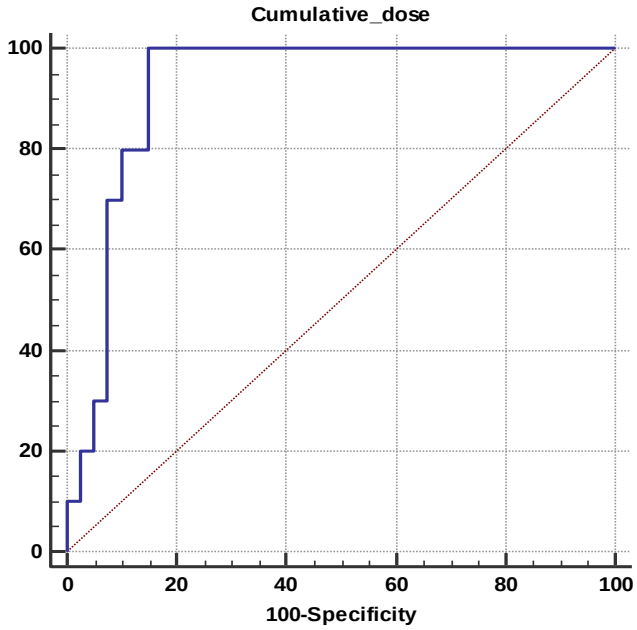

Figure (1): By using ROC-curve, cumulative steroid dose at a cutoff point >59.75 gm. discriminated osteopenia from osteoporosis, with excellent accuracy, sensitivity= 100% and specificity= 85%.

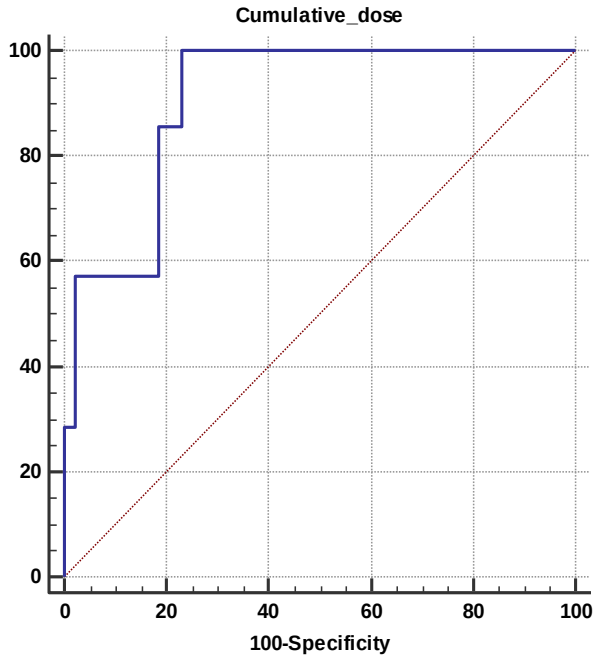

Figure (2): By using ROC-curve, cumulative steroid dose at a cutoff point >44.06 gm. discriminated non-DM from DM, with excellent accuracy, sensitivity= 100% and specificity= 76.74%.

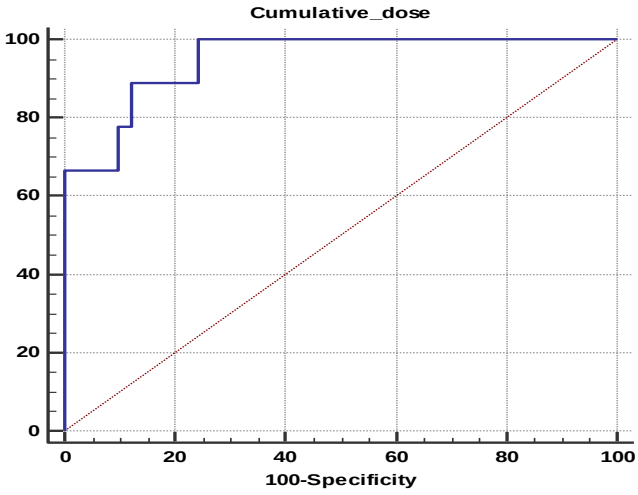

Figure (3): By using ROC-curve, cumulative steroid dose at a cutoff point >63.31 gm. discriminated non-cataract from cataract, with excellent accuracy, sensitivity= 88.89% and specificity= 87.8%.

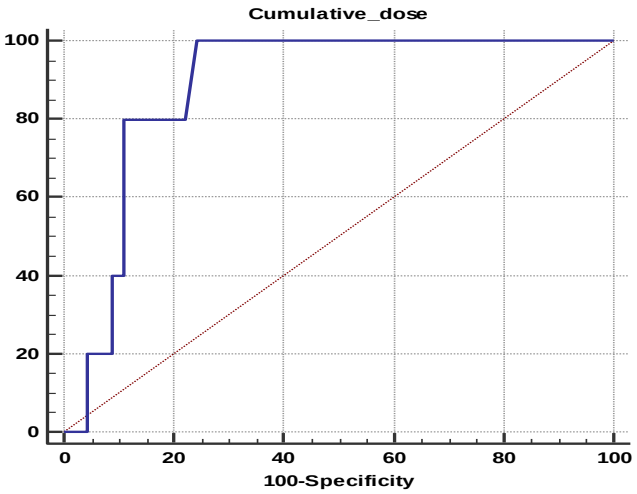

Figure (4): By using ROC-curve, cumulative steroid dose at a cutoff point >59.75 gm. discriminated non-AVN from AVN, with good accuracy, sensitivity= 100% and specificity= 75.56%.

DISCUSSION

In lupus, GCs have been related to end organ damage. Whereas lupus itself can be a cause of end organ damage e.g. CNS and kidney damage, GCs may be associated with several domains within the SLICC/ACR Damage Index (SDI): cataracts, diabetes, osteoporosis, osteonecrosis and cardiovascular disease. A number of observational studies supported this association of GCs with global damage in SLE [5]. Regarding the frequency of steroid induced complications among our SLE patients, we found that 10% had avascular necrosis (AVN). This was mainly due to intraosseous hypertension from excessive marrow fat accumulation. These results were similar to that found by Chan and Mok in 2012 [13].

We found that, 18% of our patients had cataract. This was mainly due to direct effects of GCs on lens epithelial cells and of indirect effects mediated through alterations to the lens' environment. These results were similar to that found by Carli and his co-workers in 2013 [9]. We also found that, 14% of our patients had DM "after starting SLE GC treatment". This was mainly due to impairment of multiple pathways including beta cell dysfunction and insulin resistance in other tissues.

Our results were similar to that found by Shaharir and his co-workers in 2015 as they stated that the prevalence of DM in SLE patients was around 13% [14]. Then we found that, 38% of our SLE patients were osteopenic, while 18% were osteoporotic patients. This is mainly because GCs inhibit differentiation, replication and function of osteoblasts and enhance the apoptosis of mature osteoblasts and osteocytes. These effects lead to a marked decrease in bone formation. GCs also enhance osteoclastogenesis leading to increased bone resorption. These results were similar to that found by Mendoza-Pinto and his co-workers in 2009 who stated that osteoporosis in SLE patients was around 20% [15].

On comparing SLE patients with NBMD compared to osteopenic and osteoporotic patients at LS or at FN, we found that there was highly significant difference regarding the current, pulse, and cumulative steroid dose ($p<0.001$).

Regarding steroid duration, patients with osteopenia received steroids for longer durations as compared with patients with NBMD and osteoporosis at LS, which was highly statistically significant (P=0.001). But patients with NBMD, osteopenia and osteoporosis at FN, showed comparable results regarding steroid duration ($p >0.05$).We observed that patients with osteopenia and osteoporosis at LS had received steroids for longer durations (P=0.001), than patients with osteopenia and osteoporosis at FN ($p >0.05$).These results were close to that found by Sun and his co-workers in 2015 [16].

Our results were also in accordance with Ruiz-Irastorza and his colleagues in 2012 whose results expressed that treatment with intravenous pulses of methyl-prednisolone lead to a high rate of bone loss [5]. Regarding disease damage as measured by SLICC score, we found that increased SLICC score was consistently associated with deterioration of BMD. Also Tang and co-workers in 2013 concluded that increased SLICC score was consistently associated with deterioration of BMD [17]. AVN occurrence among SLE patients was 10% in our study. It is a common type of steroid related organ damage in SLE with prevalence varying widely from 2 to 30% [18]. Our study revealed that, the patients with AVN showed an increase in SLICC score with a high significant difference ($P<0.001$) compared to SLE patients without AVN.

This came in agreement with results of Sayarlioglu and co-workers in 2012 [18]. Our study also showed that; the patients with AVN received higher cumulative, current and pulse steroid doses than patients without AVN which is highly statistically significant ($p<0.001$). It came in accordance with results of Kunyakham and his colleagues in 2012 [19]. Regarding steroid duration, there were similar results between patients with AVN and patients without AVN. This came in agreement with results of Chan and Mok in 2012 who stated that AVN doesn't need long durations of GC therapy to occur in SLE patients; otherwise it can occur after initiation of GC therapy as early as the first year. In summary, current evidence suggests that AVN may develop in patients receiving high dose GCs within a short period of time, or even after pulse therapy with high doses of GCs [13].

Cataract occurrence among SLE patients was 18% in our study. It is the 2nd most frequent item in (SLICC/ACR) Damage Index, exceeded only by osteoporotic fractures. The frequency of cataract in SLE patients ranges from 5 to 32 % [20]. Our study revealed that, the patients with cataract showed an increase in age and SLICC score with a high significant difference ($P<0.001$) compared to SLE patients without cataract, which came in agreement

with results of Alderaan and his co-workers in 2015 [20].

Our study also revealed that, the patients with cataract showed an increase in disease duration, age of disease onset which was consistent with results of Carli and his co-workers in 2013 [9]. We also found that; patients with cataract had higher FBS and 2H-PP blood sugar levels compared to patients without cataract with a high statistically significant difference (P<0.001) which was consistent with results of Alderaan and co-workers in 2015 who reported that, DM is an important risk factor for developing cataract [20].

Our study showed that; the patients with cataract received higher cumulative and pulse steroid doses and had longer durations of steroid treatment than patients without cataract which was highly statistically significant (P<0.001). But regarding current steroid dose, there were similar results.DM occurrence among SLE patients was 14% in our patients. It is a common type of steroid related organ damage in SLE. Other studies reported that AVN was found in 12.6% of patients with SLE who received high dose GCs [21].

We found that; the patients with DM showed an increase in age, disease durations and SLICC score with a high significant difference (P<0.001) which was consistent with results of Ha and his co-workers in 2011 [21]. Our study also showed that; the patients with DM received higher cumulative and pulse steroid doses and had longer durations of steroid treatment than patients without DM which was highly statistically significant (P<0.001). But regarding current steroid dose, there were similar results between patients with DM and patients without DM. Our results were consistent with results of Hwang and Weiss in 2014 who reported that, cumulative dose and steroid duration were considered risk factors for development of DM [22].

When we compared steroid duration and the frequency of complications, we found that; DM and cataract were higher in patients with steroid duration (more than 15 years) with very high statistical significant difference (P<0.001). Otherwise in osteopenia, osteoporosis and AVN, there were no statistical significant difference regarding the steroid duration (P>0.05).

Our results came in agreement with results of Ruiz-Arruza and his co-workers in 2014 [6]. When we compared steroid dose and the frequency of complications, we found that; DM, cataract, osteoporosis and AVN were higher in patients received cumulative steroid dose (more than 60 grams) with high statistical significant difference (P<0.01). But osteopenic patients show comparable results regarding steroid dose. Our results came in agreement with results of Al Sawah and co-workers in 2015 [23].

CONCLUSION

In conclusion, we found that there were statistically significant negative correlation between steroid intake (dose and duration) and BMD in LS and FN. Also, there was strong negative correlation between steroid intake (dose and duration) and damage accrual (measured by SLICC damage index) leading to increased incidence of osteoporosis, AVN, cataract and DM. Our study revealed that; DM and cataract are time and dose-dependent while osteoporosis and AVN are much more dose-dependent.

REFERENCES

1. **Mary K C (2013):** Etiology and pathogenesis of systemic lupus erythematosus. Kelley's textbook of Rheumatology. 9th ed. Philadelphia. Elsevier Saunders.
2. **Wichainun R, Kasitanon N, Wangkaew S, Hongsongkiat S, Sukitawut W and Louthrenoo W (2013):** Sensitivity and specificity of ANA and anti-dsDNA in the diagnosis of systemic lupus erythematosus. Asian Pac J Allergy Immunol., 31(4):292-8.
3. **Tower C, Crocker I, Chirico D, Baker P and Bruce I (2011):** SLE and pregnancy: the potential role for regulatory T cells. Nat Rev Rheumatol., 7 (2): 124-8.
4. **Meroni PL and Shoenfeld Y (2010):** Systemic lupus erythematosus and SLE galaxy. AutoimmunRev., 10: 1-2.
5. **Ruiz-Irastorza G, Danza A and Khamashta M (2012):** Glucocorticoid use and abuse in SLE. Rheumatology (Oxford), 51(7):1145-1153.
6. **Ruiz-Arruza I, Ugarte A, Cabezas-Rodriguez I, Medina JA, Moran MA and Ruiz-Irastorza G (2014):** Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. Rheumatology (Oxford), 53 (8): 1470-6.
7. **Grossman JM, Gordon R and Ranganath VK (2010):** American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res., 62: 1515–26.
8. **Weinstein RS (2012):** Glucocorticoid-induced osteonecrosis. Endocrine, 41(2):183–90.
9. **Carli, L, Tani C, Querci F, Della-Rossa A, Vagnani S, Baldini C and Bombardieri S (2013):** Analysis of the prevalence of cataracts and glaucoma in systemic

lupus erythematosus and evaluation of the rheumatologists' practice for the monitoring of glucocorticoid eye toxicity. Clinical rheumatology, 32(7): 1071-1073.

10. **Sabio JM, Vargas-Hitos JA and Navarrete N (2010):** Effects of low or medium-dose of prednisone on insulin resistance in patients with systemic lupus erythematosus. ClinExpRheumatol., 28:483–9.
11. **Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR and Sturfelt G (2012):** Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis & Rheumatism, 64(8): 2677-2686.
12. **Bombardier C, Gladman DD, Urowitz MB, Caron D and Chang CH (1992):** Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum., 35(6): 630-40.
13. **Chan KL and Mok CC (2012):** Glucocorticoid-induced avascular bone necrosis: diagnosis and management. The open orthopaedics journal, 6(1):22-26.
14. **Shaharir SS, Gafor AH, Said MS and Kong NC (2015):** Steroid-induced diabetes mellitus in systemic lupus erythematosus patients: analysis from a Malaysian multi-ethnic lupus cohort. International journal of rheumatic diseases, 18(5): 541-547.
15. **Mendoza-Pinto C, García-Carrasco M, Sandoval-Cruz H, Muñoz-Guarneros M, Escárcega RO, Jiménez-Hernández M and Cervera R (2009):** Risk factors of vertebral fractures in women with systemic lupus erythematosus. Clinical rheumatology, 28(5): 579-585.
16. **Sun YN, Feng XY, He L, Zeng LX, Hao ZM, Lv XH and Pu D (2015):** Prevalence and possible risk factors of low bone mineral density in untreated female patients with systemic lupus erythematosus. BioMed research international, 2015.
17. **Tang XL, Griffith JF, Qin L, Hung VW, Kwok AW, Zhu TY and Tam LS (2013):** SLE disease per se contributes to deterioration in bone mineral density, microstructure and bone strength. Lupus, 22(11): 1162-1168.
18. **Sayarlioglu M, Yuzbasioglu N, Inanc M, Kamali S, Cefle A, Karaman O, Onat AM, Avan R, Cetin GY, Gul A, Ocal L and Aral O (2012):** Risk factors for avascular bone necrosis in patients with systemic lupus erythematosus. Rheumatol Int., 32:177–182.
19. **Kunyakham W, Foocharoen C, Mahakkanukrauh A, Suwannaroj S and Nanagara R (2012):** Prevalence and risk factor for symptomatic avascular necrosis development in Thai systemic lupus erythematosus patients. Asian Pacific journal of allergy and immunology, 30(2): 152.
20. **Alderaan K, Sekicki V, Magder LS and Petri M (2015):** Risk factors for cataracts in systemic lupus erythematosus (SLE). Rheumatology international, 35(4): 701-708.
21. **Ha YJ, Lee KH, Jung SJ, Lee SW, Lee SK and Park YB (2011):** Glucocorticoid-induced diabetes mellitus in patients with systemic lupus erythematosus treated with high-dose glucocorticoid therapy. Lupus, 20(10): 1027-1034.
22. **Hwang JL and Weiss RE (2014):** Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. Diabetes/metabolism research and reviews, 30(2): 96-102.
23. **Al Sawah S, Zhang X, Zhu B, Magder LS, Foster SA, Iikuni N and Petri M (2015):** Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus—the Hopkins Lupus Cohort. Lupus science & medicine, 2(1): e000066.