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Study of the Role of Nicotinamide Phosphoribosyl Transferase/Visfatin in Egyptian Patients with Systemic Lupus Erythematous and Lupus Nephritis

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Abstract: *Introduction*: Lupus nephritis (LN) is common and carries a high burden of morbidity in SLE patients. The adipokine ‘‘visfatin’’is highly expressed in visceral fat, exerts several pro inflammatory functions and was demonstrated as a marker of endothelial dysfunction (ED) in chronic kidney disease (CKD). *Aim of the work*: to evaluate the state of serum visfatin in SLE patients and to detect its possible correlation to disease activity and kidney affection. Also, to define a possible correlation between the level of visfatin before and after a treatment regimen of combined mycophenolate mofetil and corticosteroids. *Patients and methods*: visfatin was assayed using enzyme-linked immunosorbent assay (ELISA), chemical and immunological markers of SLE and LN were measured in 50 SLE patients (included 25 patients with LN and 25 patients without LN), and compared with 25 age and sex matched healthy controls. Disease activity was assessed using SLE Disease Activity Index (SLEDAI). Renal biopsies were taken from LN subgroup and were classified according to the modified WHO classification. [1] *Results*: There was statistically highly significant difference ($P < 0.001$) as regards serum visfatin between patients (mean 8.31 ± 3.60, median 8, 64), and controls (mean 4.60 ± 2.01), serum visfatin showed significantly higher levels in LN compared to the non-lupus nephritis group (mean 8.78 ± 3.81 ng/ml,) versus (mean 7.85 ± 3.38 ng/ml,). Also, visfatin level was significantly higher among the active (mean 9.30 ± 3.14,) compared to the inactive group (mean 4.37 ± 2.46). Visfatin had a highly significant positive correlation with SLEDAI, disease duration, corticosteroids treatment duration, ESR and CRP. Also, a significant inverse correlation existed between visfatin, WBCs and Platelets count, correlation studies between visfatin level and low level of C3, C4 were significant. The correlation between serum visfatin level and Carotid artery intima media thickness by carotid Doppler imaging was also significant. There was a significant decrease ($P= 0.041$) between pre-treatment visfatin level and post treatment level after 3 months of MMF and high dose CS treatment, Visfatin mean decreased from (8.78 ± 3.81 ng/ml) to (8.29 ± 3.44 ng/ml). *Conclusion*: visfatin is closely associated with SLE activity especially with lupus nephritis revealing the promising role of this adipokine in SLE activity measurement and prediction of renal involvement in SLE patients.

Keywords: Systemic Lupus Erythematosus, Lupus Nephritis, Nicotinamide Phosphoribosyl Transferase/Visfatin

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by an abnormal response to self-antigens is thought to drive the development of SLE, Disease severity is wide ranging, with most suffering milder forms; however, it is potentially fatal depending on organ

involvement. [1]

Lupus nephritis (LN) is common and carries a high burden of morbidity in SLE patients, both directly and as a result of treatment complications. [2]

Adipose tissue is an endocrine organ producing a variety of secreted factors including TNF-α, IL-6 and IL-8, plasminogen-activator inhibitor type 1, leptin, adiponectin, resistin, and others. Several of these mediators are predominantly synthesized by adipose tissue and called adipocytokines. [3]

Recently, the adipocytokine family has been extended by a novel member (visfatin). Visfatin is a 52-kDa secreted molecule termed pre-B cell-enhancing factor (PBEF) and was strongly induced by pokeweed mitogen and cycloheximide and enhanced the effect of IL-7 and stem cell factor on pre-B cell colony formation [4], visfatin level was found to be disturbed in some rheumatic disorders like rheumatoid arthritis, ankylosing spondylitis and systemic sclerosis. [5, 6]

Some reports demonstrated that it has a good association with lupus nephritis and was considered a promising biomarker for prediction of renal involvement in those patients. [7]

Mycophenolate mofetil (MMF) has emerged as an alternative therapy for both induction and maintenance treatment of LN [8] because of its favorable toxicity profile [9].

The aim of this study was to evaluate the state of serum visfatin in SLE patients and to detect its possible correlation to disease activity and kidney affection. Also, to define a possible correlation between the level of visfatin before and after a treatment regimen of combined mycophenolate mofetil and corticosteroids.

2. Patients and Methods

This is a cross sectional study included 75 subjects after taking written consents, subjects were subdivided into 3 groups:

- Group 1: 25 patients with SLE fulfilling the updated American College of Rheumatology (ACR) criteria without lupus nephritis. [10]
- Group 2: 25 patients with SLE and lupus nephritis.
- Group 3: 25 age and sex matched healthy subjects served as control group.

All patients are allowed to continue their medications (Steroids and DMARDs).

2.1. Exclusion Criteria

Patients with malignancies, overlap syndrome, metabolic syndrome, liver disease, inflammatory bowel disease and/or on hemodialysis were excluded from the study.

2.2. Clinical Assessment

- Full history taking and drug history.
- Clinical assessment of the patients which included the following:

Measurement of BMI (kg/m2) determined by weight (kg) and height (m). [11]

Assessment of the disease activity using SLE Disease activity index (SLEDAI). [12]

2.3. Laboratory Assessment

- Complete blood picture.
- Fasting plasma glucose level, postprandial plasma glucose level and glycosylated Hemoglobin.
- Lipid profile.
- Erythrocyte sedimentation rate (ESR) using Westergren method.
- CRP using latex agglutination method.
- Autoantibodies measurement: Anti-nuclear antibody and Anti-dsDNA by indirect immunofluorescent assay method.
- Kidney function tests: creatinine, urea, glomerular filtration rate measurement using Cockcroft-Gault formula. [13], creatinine clearnce and urine Albumin/creatinine ratio
- Serum complement C3 and C4 (assessed by nephelometry). [12]
- Measurement of serum visfatin by enzyme linked immunosorbent assay (ELISA).
- Assessment of serum visfatin level in the cases with lupus nephritis diagnosed by renal biopsy before and after 3 months treatment by mycophenolate mofetil (1gm/d in the form of 500 mg tab twice daily) and high dose coricosteroids (prednisone 1 mg/kg/d).

2.4. Radiology

- Ultrasonography of Abdomen and Pelvis for assessment of kidney size and other abnormalities.
- Carotid doppler ultrasonography to assess Intima-media thickness of carotid arteries in SLE cases with high visfatin level. [14]

2.5. Renal Biopsy

For the patients with Lupus Nephritis, All biopsies will be classified according to the modified WHO classification. [15]

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Comparison between different groups regarding categorical variables was tested using Chi-square test. Normally quantitative data was compared using student t-test, or F test (ANOVA), abnormally distributed data was compared using Mann Whitney test or Kruskal Wallis test, Correlations between two quantitative variables were assessed using Pearson or Spearman coefficient according to test of normality. Significance of the obtained results was judged at the 5% level.

3. Results

There was no significant difference as regards sex, age or

BMI between patients and control group. SLE activity measured by using SLEDAI, there were 40 active patients (80%) with SLEDAI > 8. While 10 patients (20%) were inactive (SLEDAI < 8).

There was statistically highly significant difference (P < 0.001) as regards serum visfatin between patients (mean 8.31 ± 3.60, median 8, 64), and controls (mean 4.60 ± 2.01, median 4.8), while in comparison between SLE patients with nephritis and patients with no nephritis, serum visfatin showed significantly higher levels in LN compared to the non-lupus nephritis group (mean 8.78 ± 3.81 ng/ml, median 9.22) versus (mean 7.85 ± 3.38 ng/ml, median 7.41). Also, visfatin level was significantly higher among the active (mean 9.30 ± 3.14, median 9.29) compared to the inactive group (mean 4.37 ± 2.46, median 3.78), (Table 1).

As seen in (Table 2), Correlation studies between visfatin level and clinical data of SLE patients showed a statistically highly significant correlation (P < 0.05) between the visfatin and SLEDAI (r = 0.782, P<0.001), disease duration (r = 0.523, P<0.001), corticosteroids treatment duration (r = 0.357, P = 0.011), ESR and CRP (r = 0.35, P <0.001 and r = 0.27, P < 0.001) respectively. Also a significant inverse correlation existed between visfatin and WBCs (r = -0.641, P <0.001) and between visfatin and Platelets count (r = -0.650, P<0.001), on the other hand non-significant correlations between visfatin and other demographic and laboratory parameters were recorded.

Correlation studies between visfatin level and low level of C3, C4 were significant (t = 3.048, P = 0.004 and t = 3.048, P = 0.004) respectively, the correlation between visfatin level and Carotid artery intima media thickness by carotid Doppler imaging was significant too (t = 3.194, P = 0.005).

As shown in (Table 3), There was a significant decrease (P 0.041) between pre-treatment visfatin level and post treatment level after 3 months of MMF and high dose CS treatment, Visfatin mean decreased from 8.78 ± 3.81 ng/ml to 8.29 ± 3.44 ng/ml after 3 months of MMF and high dose corticosteroids treatment.

Table 1. *Comparison between Patients and controls according to visfatin and relation between visfatin and activity in patients group.*

	Patients (n = 50)		**Control (n = 25)**	**T**	**P**
Visfatin (ng/ml)					
Min. – Max	1.35 – 15.51		1.70 – 8.60	5.726*	<0.001*
Mean ± SD	8.31 ± 3.60		4.60 ± 2.01		
Median	8.46		4.80		
	Without lupus nephritis (n = 25)	With lupus nephritis (n = 25)	Control (n = 25)	F	
Visfatin (ng/ml)					
Min. – Max	2.75 – 14.90	1.35 – 15.51	1.70 – 8.60		
Mean ± SD	7.85 ± 3.38	8.78 ± 3.81	4.60 ± 2.01	12.014*	<0.001*
Median	7.41	9.22	4.80		
	Activity			t	p
	Inactive (n = 10)	Active (n = 40)			
Visfatin (ng/ml)					
Min. – Max	1.35 – 9.64	3.98 – 15.51			
Mean ± SD	4.37 ± 2.46	9.30 ± 3.14	4.607*	<0.001*	
Median	3.78	9.29			

Table 2. *Correlation between Visfatin with different parameters in patients group.*

Variable	**Visfatin**	
	Test of sig.	***P***
SELDAI	r = 0.782*	<0.001*
WBCs	r = -0.641*	<0.001*
Platelets	r = -0.650*	<0.001*
Disease duration	r = 0.523*	<0.001*
Cs Duration	r = 0.357*	0.011*
CRP	r = 0.27	<0.001*
ESR	r = 0.35	<0.001*
Renal Biopsy Grade	r = 0.37	<0.001*
C3	t = 3.048*	0.004*
C4	t = 3.048*	0.004*
Carotid IMT	t = 3.194*	0.005*

Carotid IMT: Carotid intima media thickness
Cs: Corticosteroids

Table 3. *Comparison between pre-treatment and post treatment Visfatin level in LN group.*

	Pre-treatment	**Post-treatment**	**T**	**P**
Visfatin (ng/ml)				
Min. – Max	1.35 – 15.51	2.48 – 14.50		
Mean ± SD	8.78 ± 3.81	8.29 ± 3.44	2.161*	0.041*
Median	9.22	9.22		

4. Discussion

Although SLE is a chronic, potentially lifelong condition, patients unpredictably experience disease flares followed by periods of disease inactivity [16], Lupus nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). [17]

Visfatin is a fat-specific adipokine that is predominantly produced in visceral adipose tissue, particularly by the macrophages, In comparison with RA or even OA, little is known about the potential role of visfatin in SLE. The data available is somewhat scarce and contradictory. [18]

In this study, SLE patient had higher visfatin level compared with the controls (P < 0.001), many studies agreed with this result (Chung et al. [19] and De Sanctis et al. [20]) reported the same findings, in contrast, others have reported opposite findings, a study stated that visfatin was higher in the RA and active Behçet's disease (BD) groups, but not in the SLE and SSc groups. [15]

In the current study, serum visfatin level was higher among lupus nephritis group than SLE patients without nephritis (mean 8.78 ± 3.81 ng/ml, median 9.22) versus (mean 7.85 ± 3.38 ng/ml, median 7.41), P <0.001, Also, visfatin level was positively correlated with renal biopsy grade (P <0.001), This was agreed by a study by Kang et al. [21] who stated that visfatin is produced by renal cells and has an important paracrine role in the pathogenesis of nephropathy and was significantly higher in presence of nephritis.

Some studies were directed to find correlation between visfatin level and chronic kidney disease (CKD) and they reported that patients with CKD had a higher concentration of visfatin than controls [22]. Recently, visfatin, was shown to be associated with sVCAM-1 and acts as a marker of endothelial dysfunction in CKD and could be a factor linking inflammation and kidney disease. [23, 24]

In this study, there was positive relationship between elevated visfatin level and inflammatory markers like CRP and ESR (P = <0.001) which supports the role of visfatin as an inflammatory mediator. These findings are in agreement with other studies by Brentano F et al. [25], Oki et al. [26] and Bessa et al. [27]

Moreover, Busso et al. [28] have showed that visfatin is a key mediator in inflammatory arthritis, administration of a visfatin inhibitor to mice with collagen-induced arthritis reduced arthritis severity with similar effect to that produced by TNF-α inhibitor. Also, pharmacological inhibition of visfatin led to reduced levels of intracellular NAD in inflammatory cells and decreased the production of TNF-α and IL-6 in affected joints. [29] However, the mechanisms by which visfatin exerts its catabolic effect in arthritic joints are still incompletely understood.

In this study, there is a highly significant positive correlation between the mean values of visfatin and SLEDAI, (P <0.001) as well as a significantly higher visfatin level (P <0.001) among the active SLE group compared to the inactive group. Some studies agreed with this results like a study by Stofkova who described that visfatin can contribute to the inflammatory processes by triggering cytokine production and NF-kappa B activation, also it demonstrated that visfatin is up-regulated during inflammation and in response to pro-inflammatory cytokines. [30]

Some reports linked visfatin with the activity of the autoimmune diseases like Gomez et al. [31] and Duan et al. [32] who published data highlighting the importance of Visfatin in RA and OA, respectively relating it to disease activity and severity.

Also, in this study, elevated visfatin levels were significantly associated with anti ds-DNA positivity and inversely correlated with C3 and C4 levels (P = 0.004), for this reason, it can be considered a good marker of lupus activity, particularly lupus nephritis, this suggestion is supported previously in some studies like the one by Sommer G. et al. [33]

Lupus nephritis is generally considered to be the best established human model of chronic soluble complex renal disease. Terminal complement complex was suggested to be one of the most sensitive markers for disease activity. [34] In our study active disease was associated with low C3 and C4.

Furthermore, Serum visfatin was positively correlated with increased carotid intima media thickness; this was reported by some studies which described the relationship between visfatin and carotid intima media thickness. [15]

Clinical studies have shown that CKD patients are more prone to suffering from atherosclerosis than normal subjects. [24]

We have demonstrated a significant decrease between pre-treatment visfatin level and post treatment level after 3 months of MMF and CS treatment which describes the efficacy of this treatment regimen in decreasing activity of SLE and lupus nephritis, this was also reported by Chan and colleagues [35] and Ginzler et al. [36]

5. Conclusion

This study showed that serum visfatin is closely associated with SLE activity especially with lupus nephritis revealing the promising role of this adipokine in SLE activity measurement and prediction of renal involvement.

The treatment regimen of combined mycophenolate mofetil (MMF) and corticosteroids is effective in decreasing visfatin level in Lupus nephritis patients and in decreasing SLE activity and helps in achieving disease remission.

Treatment of SLE by targeting Visfatin may be promising modality especially in patients with kidney disease.

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