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Original Article

Negative Correlation between Fetuin-A and Indices of Vascular Disease in Systemic Lupus Erythematosus Patients with and without Lupus Nephritis

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Abstract

Introduction: Fetuin-A, a systemic calcification inhibitor, has been negatively related to vascular calcification (VC) and cardiovascular mortality. In this study we investigated the association between fetuin-A levels and atherosclerotic vascular complications in systemic lupus erythematosus (SLE) patients with and without lupus nephritis (LN).

Methods: We recruited 20 SLE patients without LN, 20 SLE patients with LN and 20 healthy controls. We determined serum creatinine, lipid profile, high sensitivity C-reactive protein (hsCRP), calcium, phosphate and fetuin-A levels, and calculated the calcification risk index (CRI) and SLE disease activity index (SLEDAI) for all subjects. Vascular disease burden was assessed by quantification of carotid artery intima-media-thickness (IMT) and the ankle-brachial index (ABI).

Results: Fetuin-A levels were significantly lower in LN patients (0.47 ± 0.1 g/L) compared to SLE patients without LN (0.54 ± 0.1 g/L) and both were significantly lower than controls (0.78 ± 0.2 g/L). CRI was significantly higher in LN patients (89.1 ± 12.1 mg/L) compared to SLE patients without LN (67.2 ± 9.3 mg/L) and both were significantly higher than controls (34.2 ± 6.2 mg/L). Peripheral arterial disease (ABI < 0.9) was significantly more common in LN patients (55%) compared to SLE patients without LN (30%) as well as controls (0%). Fetuin-A levels showed significant negative correlations with serum creatinine, hsCRP, CRI, IMT and ABI in SLE patients with and without LN.

Conclusion: Fetuin-A levels were decreased in SLE patients with and without LN and negatively correlated with vascular complications. This suggests a potentially important role for fetuin-A deficiency as marker of vascular disease in SLE patients with and without LN.

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by the production of autoantibodies, which can affect all organ systems, especially the kidneys. Premature and accelerated atherosclerosis is increasingly recognized as being prevalent in young female patients with SLE. Cardiovascular disease (CVD) develops in 6-9% of SLE patients and accounts for up to 36.4% of deaths in SLE [1]. Moreover, lupus nephritis (LN) patients develop chronic kidney disease (CKD) and experience cardiovascular disease risk that is much higher than that in age- and sex-matched populations with normal kidney function [2]. Several epidemiological studies have demonstrated accelerated vascular calcification in CKD [3, 4]. Pathological studies have shown that persons with end stage renal disease (ESRD) experience accelerated atherosclerosis, and also high rates of vascular medial calcification [5].

Although traditional cardiovascular risk factors apply, lupus-associated activation of the immune system contributes to the accumulation of vascular damage [6]. Defining the autoimmune mechanisms underlying these vascular complications is essential to optimize risk reduction and develop targeted therapy for prevention of CVD in SLE patients. Vascular calcification (VC) in SLE may be the main pathogenic factor underling CVD with its associated morbidity. In fact, vascular disease can practically be used as a diagnostic parameter to evaluate the severity of SLE [7]. Measurement of coronary calcification may even help detect asymptomatic lupus

in patients. Such patients might benefit from aggressive interceptive measures, should their condition be detected early. Additionally, vascular calcification has far more reaching and diverse effects in SLE; which reflects the wider diversity of effects produced by vascular disease when it is associated with SLE than it does in other circumstances [8].

Vascular calcification (VC) was previously thought to be a passive process aggravated by hyperphosphatemia and hypercalcemia that could be controlled adequately with careful attention to mineral balance [9]. However, accumulating evidence suggests that VC is a regulated process affected by intra- and extra-cellular mechanisms as well as serum-based proteins [10]. Because human serum is supersaturated with respect to calcium and phosphorus, the existence of serum-based precipitation inhibitors has long been postulated. Human fetuin-A (alpha-2-Heremans Schmid glycoprotein), a protein produced by the liver and secreted into serum in high concentrations, is a major serum-based inhibitor of VC and accounts for roughly 50% of the inhibition of calcium and phosphorous precipitation [11]. Several studies have linked low fetuin-A levels to VCs and flow-limiting aortic stenosis [12]. Also, fetuin-A has been negatively related to VCs and cardiovascular mortality in dialysis patients [13]. However, there are only scarce and contradictory data on fetuin-A levels in moderate CKD and their effect on vessel health. Also, it is still unsolved whether in patients with kidney disease the basic biology underlying CVD is similar to that acknowledged for patients without kidney disease. Many other risk factors are present as a consequence of the renal dysfunction and thus involved in the accelerated atherosclerotic process [14]. The situation is even more complex in patients with SLE, who generally suffer from advanced systemic atherosclerosis.

To clarify the relation between fetuin-A and vascular complications in SLE patients with and without lupus nephritis, we studied the correlation between fetuin-A levels and parameters of kidney function, SLE disease activity, and vascular disease in SLE patients with and without LN.

Methods

Forty SLE patients and twenty controls were randomly recruited from persons attending the internal medicine department of Kasr El-Aini teaching hospital, Cairo, Egypt. The study protocol was approved by the institutional ethics committee in Kasr El-Aini teaching hospital, Cairo University, and all participants signed a written informed consent. Patients and controls were subjected to full medical history taking and thorough clinical examination. SLE patients fulfilled the diagnostic criteria of the American College of Rheumatology (revised in 1982 and updated in 1997) [15]. They were all females, their ages ranged from 18-41 years, with a mean age of 27.3±6.1 years. Exclusion criteria included dialysis dependency, serum creatinine > 6 mg/dl, coagulation disturbances, cancer, diabetes, current intake of oral contraceptives or hormone replacement therapy, the presence of any critical illness within the last 6 months and specific treatment with calcium supplements, phosphate binders, or vitamin D. The SLE disease activity was assessed at the time of enrollment in the study using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score. The use of corticosteroid therapy was quantified in terms of the average daily dose over the preceding five years of the study. SLE patients were divided into two groups according to the presence or absence of LN. Patients with LN included also those who had documented proteinuria associated with hematuria or renal casts in at least two separate urine samples in addition to patients with overt CKD. The control group included twenty healthy females whose age ranged from 19-43 years, with a mean age of 29.2±5.4 years. All controls had no clinical evidence of cardiovascular disease, no evidence of SLE, nephropathy, or any immunological disturbances.

Urine and blood samples were collected from all subjects for analysis. Blood was collected after an overnight fast (12 h) from the cubital vein. Serum samples were used to determine the levels of blood urea nitrogen (BUN), serum creatinine, ANA, anti-dsDNA, triglycerides, total cholesterol and HDL cholesterol. LDL cholesterol levels were calculated by using the Friedewald formula [16]. High sensitivity C-reactive protein (hsCRP) was measured using the Roche Integra assay [17]. Complement C3 was assayed by Assay Max Human C3 complement ELISA kit (EC2101-1) [18]. Serum calcium was adjusted for serum albumin according to the equation [19]:

Adjusted calcium (mg/dl) = measured calcium (mg/ dl) + [(4.0–serum albumin in g/dl) ×0.8]

Inorganic phosphate level was measured by CHRONOLAB phosphomolybdate UV kit (101- 0458) [20]. Fetuin-A was measured in duplicates by an ELISA (Epitope Diagnostics, Inc., San Diego, USA) according

to the manufacturer's protocol. The intra- and inter- assay variations were 5.3 and 7.1%, respectively [21].

The collected data were further used to calculate the 'Systemic Lupus Erythematosus Disease Activity Index' (SLEDAI) [23] and the 'Calcification Risk Index' (CRI) [22]. CRI was calculated by the formula:

CRI = Calcium level × inorganic phosphate level / Fetuin-A

For manifestations of atherosclerosis, we defined the intima-media thickness (IMT) of carotid arteries and calculated the ankle-brachial index (ABI). The IMT, were detected by carotid ultrasonography using high-resolution B-mode ultrasound (Voluson 730 Kretz, Tiefenbach, Austria) of the extracranial carotid arteries, bilaterally [24]. The whole imaging and quantification procedure was performed digitally at the time of study entry by a single investigator blinded for clinical data. The measurements of IMTs were performed at four points of both common carotid arteries ~10 mm proximal to the carotid bulb, avoiding areas of atherosclerotic plaque formation. The mean of the resulting eight single measurements was taken as mean IMT for statistical analyses in this study. The ABI was detected by simultaneous measurement of the brachial and posterior tibial artery systolic pressure [25], using the 5 MHz Mini Dopplex® doppler device (Huntleigh Diagnostic Products, Cardiff, UK). Pressure was taken at the posterior tibial artery only and the ratio of ABI from both sides was taken for analyses. Patients were further classified to have prevalent peripheral arterial disease (PAD) (ABI < 0.9), no PAD (ABI 0.9-1.3), or mediasclerosis (ABI > 1.3).

All data were expressed as mean ± SD. Statistical analyses were performed using the SPSS® 15.0 software package (SAS Institute Inc., NC, USA). Analysis of variance was used to estimate the difference between means. Student-t test was used to compare two independent means, and Chi-square test was used to compare categorical variables. The correlation between clinical and biochemical parameters was calculated using Pearson's correlation coefficient. P value < 0.05 was considered statistically significant.

Results

The clinical and laboratory characteristics of patient groups and control subjects are summarized in Table-1. There were no significant differences between groups regarding their age, sex, body mass index (BMI), or disease duration. LN patients showed significantly higher SLEDAI score, BUN, serum creatinine and blood pressure readings compared with SLE patients without nephritis. All patients used steroids treatment during the course of their disease. Other immunosuppressive treatments were used in 11 patients with LN (azathioprine in 5, and cyclophosphamide in 2 patients) and hydroxychloroquine in 4 patients.

The blood levels of calcium and inorganic phosphate were significantly higher in SLE patients compared with healthy control subjects. LN patients showed significantly more elevations of phosphate level compared with SLE patients without nephritis. Fetuin-A levels were significantly lower in SLE patients with and without nephritis compared with healthy controls and this reduction in fetuin-A level was significantly more marked in LN patients compared with SLE patients without nephritis. The Calcification Risk Index (CRI) was significantly higher in SLE patients compared to healthy controls and more marked elevations were found in LN patients. We found significantly increased IMT in SLE patients compared with healthy controls but no significant difference between SLE patients with and without LN. Peripheral arterial disease (PAD) was detected in significantly more patients with LN than SLE patients without nephritis (30% vs. 55%; P < 0.001), while no PAD were found in any of the control subjects. Only one case of mediasclerosis (ABI > 1.3) was detected in the group of LN patients.

Correlation studies and their significance levels are presented in Table-2. Significant negative correlations were observed between fetuin-A levels and serum creatinine, SLEDAI, hsCRP, CRI, IMT and ABI in SLE patients with and without LN. The IMT showed significant positive correlations with CRI and hsCRP in SLE patients with and without lupus nephritis. The ABI showed significant positive correlations with CRI in SLE patients with and without LN.

Discussion

Among persons with ESRD, vascular calcification has emerged as a powerful and potentially modifiable risk factor of all-cause mortality [26]. Mortality from atherosclerosis may be up to 10 times greater in patients with SLE than in age- and sex-matched controls [6]. Fetuin-A, a potent systemic inhibitor of soft tissue calcification, has been negatively related to VCs and cardiovascular mortality in dialysis patients [13]. Serum concentrations of fetuin-A

Table-1: Clinical data, diagnostic indices, and blood biochemical analysis for SLE patients without LN, with LN and healthy controls.

Clinical data	SLE without LN (n = 20)	LN (n = 20)	Controls (n = 20)
Age (years)	25.6 ± 4.1	28.3 ± 4.6	29.2 ± 5.4
BMI (kg/m2)	26.9 ± 5.4	31.2 ± 7.5	28.1 ± 4.5
Systolic blood pressure (mmHg)	127 ± 24	154 ± 37*$	122 ± 21
Diastolic blood pressure (mmHg)	76 ± 18	98 ± 21*$	73 ± 15
Duration of SLE disease (years)	5.2 ± 1.5	5.9 ± 1.8	-
Drugs used: Current steroids	16/20	13/20	-
Former steroids	4/20	7/20	-
Immunosuppressives	-	11/20	-
SLE Disease Activity Index (SLEDAI)	23.6±5.7	28.9±7.1$	-
Blood Urea Nitrogen (mg/dL)	37.2±11.4	183.5±34.1*$	25.1±6.1
Serum Creatinine (mg/dL)	1.2±0.3	3.9±1.1*$	0.8±0.2
hsCRP (mg/L)	2.4±0.6*	4.1±0.8*$	1.3±0.4
C3 Complement Level (g/L)	81.4±21.5*	75.8±16.9*	129.4±28.0
Triglycerides (mg/dL)	162.6±24.1*	171.5±29.3*	134.6±18.7
Total Cholesterol (mg/dL)	184.4±36.9*	198.5±31.2*	155.3±27.6
HDL–Cholesterol (mg/dL)	33.2±8.1*	31.2±7.4*	42.7±8.9
LDL–Cholesterol (mg/dL)	108.5±21.5*	117.4±26.8*	93.6±19.3
Calcium (mg/dL)	9.8±1.4*	9.3±1.3*	8.6±1.1
Inorganic Phosphate (mg/dL)	3.7±0.7*	4.5±0.9*$	3.1±0.6
Calcification Risk Index (CRI)	67.2±9.3*	89.1±12.1*$	34.2±6.2
Fetuin–A (g/L)	0.54±0.1*	0.47±0.1*$	0.78±0.2
Intima–Media Thickness (IMT, mm)	0.6±0.3*	0.8±0.3*	0.3±0.1
Peripheral Arterial Disease (ABI < 0.9)	6/20 (30%)*	11/20 (55%)*$	0/20 (0%)

Values are presented as mean ± SD or proportions.
* significant change as compared to healthy controls.
$ significant change as compared to SLE patients without nephritis.

are depressed in patients with ESRD, and lower serum concentrations were independently associated with risk of cardiovascular and all-cause mortality in this population [27]. Also, serum fetuin-A levels were found to be lower in SLE patients and its level correlates with disease activity [22]. Whether serum fetuin-A concentrations are associated with kidney function, and whether the protein acts as a key calcification inhibitor in mild-to-moderate CKD such as LN, is unknown. Yet, associations of novel biomarkers such as fetuin-A with metabolic markers or complications do help in understanding their role in the pathophysiology of vascular disease.

Current results showed that LN patients have significantly higher blood pressure, serum creatinine, BUN and SLEDAI score, which are expected to be associated with active kidney affection. SLE patients with or without LN showed significantly high levels of TG, total cholesterol, LDL, but low levels of HDL, as compared to healthy controls. These results are in accordance with those reported by Thomas *et al* [1], stating that SLE patients exhibit an atherogenic lipid profile characterized by elevated TG and VLDL, with reduced HDL. This form of dyslipidemia is attributed to the interplay between multiple disease parameters. For instance, elevated levels

Table-2: Correlation coefficients and significance levels among clinical indexes and blood biochemical parameters in SLE patients with and without LN.

	SLE without LN		SLE with LN	
	R	**P**	**R**	**P**
Fetuin–A (g/l)				
Serum creatinine (mg/dL)	– 0.68	< 0.001	– 0.74	< 0.001
SLE Disease Activity Index (SLEDAI)	– 0.49	< 0.01	– 0.61	< 0.01
hsCRP (mg/dL)	– 0.47	< 0.01	– 0.35	< 0.05
Calcification Risk Index (CRI)	– 0.83	< 0.001	– 0.88	< 0.001
Intima–Media Thickness (IMT, mm)	– 0.57	< 0.01	– 0.70	< 0.001
Ankle–Brachial index (ABI)	– 0.62	< 0.001	– 0.59	< 0.01
Intima-Media Thickness (IMT, mm)				
Serum creatinine (mg/dL)	0.17	> 0.05	0.38	< 0.05
SLE Disease Activity Index (SLEDAI)	0.36	< 0.05	0.26	> 0.05
hsCRP (mg/dL)	0.47	< 0.05	0.63	< 0.01
Calcification Risk Index (CRI)	0.52	< 0.01	0.58	< 0.01
Ankle–Brachial index (ABI)	0.25	> 0.05	0.09	> 0.05
Ankle-Brachial index (ABI)				
Serum creatinine (mg/dL)	0.30	> 0.05	0.54	< 0.01
SLE Disease Activity Index (SLEDAI)	0.21	> 0.05	0.16	> 0.05
hsCRP (mg/dL)	0.06	> 0.05	0.15	> 0.05
Calcification Risk Index (CRI)	0.78	< 0.001	0.69	< 0.001

of interleukin–1 and interferons have been reported to suppress lipoprotein lipase activity [28], and in turn reduce the catabolism of TG-rich VLDL and subsequent formation of LDL. Steroid therapy further elevates TG levels; possibly through a similar effect on lipoprotein lipase activity or by promoting insulin resistance [29]. These disturbances, alongside the pro-inflammatory, pro-oxidative state shown to exist in SLE, add up to enhance the atherogenic propensity in SLE.

In addition to the atherogenic lipid profile, autoantibodies are also thought to play a major role in SLE-related atherogenesis, especially those directed against apolipoprotein H and against the endothelium [30]. The latter are of particular interest clinically because of their direct, relation to endothelial apoptosis observed in SLE [31]. The immune complexes deposited in vascular walls at sites of vascular injury activate the complement pathway which, in turn, evokes further inflammatory and autoimmune responses that accelerate atherogenesis and vascular calcification [32]. The levels of hsCRP were significantly higher in SLE patients, and the increase was significantly more marked in patients with LN, reflecting the active inflammatory condition. Complement C3 levels were significantly lower in all SLE patients with and without LN, compared with the control group. These results are in line with the observations by Grevink *et al* [33], stating that complement factors facilitate the clearance of apoptotic cells and, when decreased, might result in an increased amount of apoptotic cells, such as those found in SLE patients. In fact, low levels of one or more complement factors, due to increased catabolism, are found in the majority of patients with SLE.

In our study, calcium and inorganic phosphate levels were significantly higher in SLE patients compared with healthy controls. LN patients showed less elevation of calcium, but more elevation of phosphate levels compared to SLE patients without nephritis. Fetuin-A levels were significantly lower and calcification risk index (CRI) was higher in SLE patients, and these changes were more marked in patients with LN. Mehrotra *et al* [27]

observed higher serum concentrations of fetuin-A among patients with advanced diabetic nephropathy (CKD stages 1 to 4) as compared with persons with diabetes but without kidney disease. Osawa and colleagues [34] reported no association between serum fetuin-A concentrations and total and albumin-corrected calcium, and an inverse correlation with serum phosphorous concentrations among healthy Japanese volunteers without kidney disease. In an unadjusted analysis, Ix *et al* [12] found that higher serum fetuin-A concentrations were associated with higher serum calcium and phosphorous concentrations, independent of kidney function. Fetuin-A, a binder/carrier of serum calcium–phosphate, stabilizes the concentration of serum calcium and prevents its precipitation. It promotes phagocytosis of redundant calcium and thus, it is regarded as a potent circulating inhibitor of cardiovascular calcification [35]. The present study showed the existence of significant correlations between low fetuin-A levels and serum creatinine, SLEDAI, CRI, IMT and ABI in SLE patients, with and without nephritis. Low serum fetuin-A levels were previously observed in SLE patients and were found to correlate with SLEDAI and IMT [22]. Mori *et al* [36] reported that feutin-A levels are related to carotid arterial stiffness, regardless of the nature of contributing atherogenic factors.

In young population with mild-to-moderate alterations in renal function and with less traditional cardiovascular risk factors, Kanbay *et al* [14] observed small modifications in serum levels of fetuin-A early in the course of disease evolution that can predict the extent of coronary artery disease. Ketteler *et al* [21] demonstrated that lower fetuin-A concentrations were independently associated with cardiovascular and all-cause mortality in dialysis patients. These results were recently confirmed in incident hemodialysis and peritoneal dialysis patients [37]. As fetuin-A is a potent inhibitor of vascular calcification and as low levels had been associated with coronary artery and valvular calcification [38], the hypothesis was generated that the excess mortality risk observed in these studies may have been due to accelerated cardiovascular calcification among ESRD patients with lower serum concentrations of fetuin-A. Our results indicated significantly increased IMT of carotid arteies in SLE patients and this was more marked in LN patients. The IMT had significant positive correlations with CRI and hsCRP, but significant negative correlations with fetuin-A levels. These observations seem to fall in accordance with the findings of other investigators who pointed to non–traditional risk factors as the most probable reason behind the high prevalence of atherosclerosis in SLE patients [39]. However, recent studies showed a strong association between fetuin-A levels and events of CVD. Weikert *et al* [40] obtained a significantly increased risk for myocardial infarction and ischemic stroke for individuals in the highest compared with the lowest quintile of fetuin-A in a model adjusted for cardiovascular risk factors including age, sex, diabetes, BMI, HDL, and hsCRP. Also, Fisher *et al* [41] have suggested that fetuin-A and fetuin-A gene polymorphisms may play a causal role in the pathophysiology of atherosclerosis leading to CV events.

Contradictory results have also been published regarding the role of fetuin-A in macrovascular disease in patients with type-2 diabetes. While some studies associated lower fetuin-A levels with peripheral arterial disease (PAD) [25], others observed an association of increased fetuin-A levels with coronary artery calcification [27, 42]. Estimation of the ankle-brachial index (ABI) in this study detected peripheral arterial disease (PAD) in significantly more LN patients than SLE patients without nephritis. This correlated significantly with CRI, but correlated negatively with serum fetuin-A levels. ABI also correlated significantly with serum creatinine in LN patients. These findings support the hypothesis that low fetuin-A might result in vascular calcification. Also, Eraso *et al* [25] found that patients with type-2 diabetes and PAD have lower levels of fetuin-A than patients with type-2 diabetes alone. However, Lorant *et al* [42] demonstrated that patients with type-2 diabetes who additionally suffer from PAD have significantly higher fetuin-A levels than patients with diabetes but without any atherosclerotic burden. Low fetuin-A was also associated with mediasclerosis in patients with diabetes and PAD.

The role of fetuin-A and its involvement in atherosclerosis seems to be very complex and is not yet understood. Atherosclerotic plaques, in general, provoke fibrosis and vascular calcification, which is a marker of increased vulnerability to cardiovascular events and mortality. Reduced fetuin-A levels are associated with inflammation and increased cardiovascular calcification (CVC) [43]. In experimental mice with kidney disease that were provided high phosphate feeding, wild-type mice developed high serum calcium and phosphorous levels, but did not develop extra-osseous calcification. In contrast, fetuin-A knockout mice developed significant soft tissue calcification while maintaining normal serum calcium and phosphorous levels [44]. These findings

suggest that under certain conditions, elevated serum concentrations of calcium and phosphorus may reflect improved ion solubility. The presence of pre-existing CVD and alterations in mineral metabolism conferred by CKD may have led to the up-regulation of fetuin-A in association with elevated calcium and phosphorous levels, perhaps to offset the propensity towards dystrophic mineralization [12]. Structure–function studies have suggested that fetuin-A solubilizes calcium phosphate crystals by direct and reversible binding, reminiscent of the process in which apolipoproteins solubilize lipids in solution [45]. In humans so far the available data has been inconsistent. Lower fetuin-A levels are associated with mortality and coronary vascular disease events in cohorts with ESRD [26], while a population based study linked high plasma fetuin-A levels to an increased risk of myocardial infarction and ischemic stroke [40]. Yet, no association could be detected between fetuin-A, and traditional cardiovascular risk factors, cardiovascular outcome or the metabolic syndrome in patients with manifest CHD in a 6-year follow up study [46]. Our results detected an inverse correlation between serum fetuin-A levels and hsCRP levels in SLE patients with and without LN. However, Hennige *et al* [47] found a positive correlation between circulating fetuin-A and hsCRP, a systemic marker of subclinical inflammation. Contrariwise to renal dialysis patients, several studies showed that high levels of fetuin-A were associated with atherosclerosis and its manifestations in non-renal patients [40]. This possible involvement of fetuin-A in the pathogenesis of cardiovascular disease has been confirmed by a recent trans-European cohort study with 2,520 patients [41]. Thus, it seems that high levels of fetuin-A are associated with atherosclerosis and its manifestations in non-renal patients.

Because those studies were cross-sectional, it is not impossible that fetuin-A had detrimental effects on the vasculature. It is possible that fetuin-A is upregulated to protect against calcification but deteriorates atherosclerosis [12]. Nevertheless, patients with media artery sclerosis showed significantly lower levels of fetuin-A. This is in line with the calcification inhibition competence of fetuin-A [42]. It is to be noted that, in the past few years, many biological parameters in humans were shown to follow not a simple linear association, but a U-shaped relationship (such as BMI, hemoglobin). Ix *et al* [12] suggested a U-shaped relationship also for fetuin-A values with CVD. They considered either high or low levels of fetuin-A to predict cardiovascular events. High levels by associations with metabolic syndrome and atherogenic lipids result in CVD and low levels by associations with vascular calcification also result in CVD.

A point worthy emphasis in this study is the effect of medication on lupus-associated atherosclerosis. All patients used steroids treatment during the course of the disease; most of them were current users of steroids in a dose range of 20 to 60 mg/day. More than half the patients with LN used immunosuppressive treatment, in addition to steroids. Corticosteroid therapies have been shown to have adverse effects on the traditional risk factors of atherosclerosis such as blood pressure, lipid profile, obesity, and blood glucose level [29]. Although there is very little dispute about the beneficial anti–inflammatory effect of corticosteroid therapy, there seems to be, a disagreement about the criteria defining an 'adequate' corticosteroid dose. Several investigators suggested that, as far as SLE patients are concerned, corticosteroid doses are considered sufficient only if they are enough to prevent premature atheromatosis [48]. Certain findings in this study may add some justification to that approach as it was observed, by comparing the patient's histories, that patients with increased IMT always had less prednisone medication, in both frequency and dose.

A relative strength of our study is the availability of several parameters of kidney function and measurement of multiple potential risk factors for vascular disease. However, there are several limitations that should be considered when interpreting our results. Our study could not evaluate the association of advanced CKD and serum fetuin-A. For now, the mechanisms explaining the association between CKD and vascular calcification remain elusive. Whether a threshold of kidney function exists, at which fetuin-A concentrations decline cannot be addressed in our study sample. A better understanding of the regulation of fetuin-A in the presence and absence of uremia and vascular disease and at varying concentrations of calcium and phosphorus is required. The cross-sectional design of our study does not allow for causal inference or evaluation of direction of associations. Finally, our study participants were all females and had SLE; and therefore results may not be generalizable to men or to persons without SLE disease.

Conclusion

In conclusion, fetuin-A levels were decreased in SLE patients with and without LN and these levels were inversely correlated with vascular complications. This suggests a potentially important role for fetuin-A deficiency as a biomarker of vascular disease in patients with SLE and LN.

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