Circulating FABP4 is a marker of metabolic and cardiovascular risk in SLE patients

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ABSTRACT

Background: Patients affected by Systemic Lupus Erythematosus (SLE) show an increase in cardiovascular mortality and morbidity, but this accelerated atherosclerosis cannot be entirely explained by traditional cardiovascular risk factors. The presence of some metabolic disturbances, such as atherogenic dyslipidaemia and metabolic syndrome, seem to be more prevalent due to inflammatory mechanisms. Circulating levels of adipose fatty acid-binding protein 4 (FABP4) are associated with adiposity, insulin resistance, metabolic syndrome, diabetes and cardiovascular diseases.

Aim: To determine if circulating FABP4 plasma levels are a possible marker of metabolic risk in SLE patients.

Methods: Sixty patients with SLE and 34 non-SLE age-matched controls were recruited for the study. Total plasma lipids and circulating FABP4 were determined. Subclinical atherosclerosis was evaluated by measuring carotid intimae-media thickness (c-IMT) by sonography, and the distribution of lipoprotein subclasses was analysed by nuclear magnetic resonance (NMR) spectroscopy.

Results: Plasma levels of FABP4 did not differ between the SLE and control groups. In the SLE group, FABP4 was associated with insulin resistance, atherogenic dyslipidaemia, as measured by NMR, and the presence of subclinical atherosclerosis. FABP4 was associated with increased c-IMT independent of the inflammatory state of the patient.

Conclusions: Circulating FABP4 is involved in the metabolic disturbances of SLE affecting lipid metabolism and insulin resistance and is a determinant of subclinical atherosclerosis in this population.

Abbreviations: SLE: systemic lupus erythematosus; FABP4: adipocyte fatty acid binding protein-4, MetS: Metabolic syndrome, c-IMT: carotid intimae media thickness; NMR: nuclear magnetic resonance.

INTRODUCTION

Patients affected by Systemic Lupus Erythematosus (SLE) show an increase in cardiovascular mortality and morbidity despite improvements in the control of disease activity and complications. (1,2) These data are supported by the results of several studies showing a higher prevalence of subclinical atherosclerosis in this young population.(3-5) The accelerated atherosclerosis observed in patients with SLE cannot be entirely explained by the traditional cardiovascular risk factors. The presence of some metabolic disturbances, such as atherogenic dyslipidaemia (6) and metabolic syndrome (MetS), seem to be more prevalent in SLE patients due to inflammatory mechanisms. (7-9) Other non-classical cardiovascular risk factors related to inflammation that have been associated with this accelerated atherosclerotic process include C-reactive protein (CRP), cytokines, the complement system (10,11) and some adipokines. (12)

SLE patients are at a higher risk to develop MetS, which is a cluster of cardiovascular risk factors including insulin-resistance (IR), central obesity, dyslipidaemia, and hypertension.(13,14) The diagnosis of MetS in the general population is an independent predictor of additional risk of cardiovascular morbidity and mortality beyond the sum of the individual risk factors.(15) The higher prevalence of MetS in SLE patients seems to be linked to its association with inflammatory factors and alterations in adipose tissue function that promote insulin resistance.(16,17)

Fatty acid-binding proteins (FABPs) are cytosolic proteins that function as chaperones and regulate fatty acid uptake and intracellular transport. (18) The adipocyte fatty acid-binding protein 4 (FABP4) is a marker of adipocyte dysfunction. Recent works have

shown a pivotal role for FABP4 in fatty acid transport, glucose metabolism and inflammation in macrophages. (19-22)

FABP4 deficiency *in vitro* and in animal models has been linked to reduced inflammation and lipolysis and protection from the development of atherosclerosis and insulin resistance. (23,24)

In humans, several metabolic pathologies linked to adipose tissue dysfunction and inflammation show enhanced serum levels of FABP4 such as MetS, type 2 diabetes, human immunodeficiency-virus associated lipodystrophy, polycystic ovary syndrome and non-alcoholic steatohepatitits. (25-27) Circulating FABP4 levels are also associated with the presence of carotid atherosclerosis and plaque instability in animal models and to poor clinical outcomes in patients with acute ischemic stroke. (28,29) Moreover, serum FABP4 levels predict the development of type 2 diabetes, MetS and atherogenic dyslipidaemia in the general population. (30,31)

Given the increased prevalence of MetS components in SLE patients we hypothesised that FABP4 might be implicated in these inflammation-related metabolic and vascular disturbances such as atherogenic dyslipidaemia and accelerated atherosclerosis.

MATERIAL AND METHODS

Subjects

This is a cross-sectional study. Sixty women with SLE attending the autoimmune diseases out-patient program at *Sant Joan University Hospital* (Reus-Spain) were recruited. Patients fulfilled at least four classification criteria for SLE as defined by the American College of Rheumatology, as revised in 1997. (32) None of the subjects

presented with active disease as defined by an SLE disease activity index (S LEDAI) >4. Thirty-four healthy age matched women were recruited as controls from the same region.

Neither diabetes mellitus nor impaired renal function had been evident in these patients, and none of them presented ischemic or adverse cardiovascular events.

All patients provided fully informed consent to participate, and the Ethics Committee of *"Sant Joan" University Hospital* approved the study.

Biochemical analyses

Fasting venous blood samples were collected in EDTA or sera tubes and centrifuged immediately for 15 min at 4ºC and 1500 x g. The samples were then divided into aliquots and stored at -80ºC until analysis.

Standard laboratory methods were used to quantify the glucose, HbA_{1c}, total cholesterol, triglyceride and HDL cholesterol levels. LDL cholesterol was calculated by the Friedewald formula. (33) Measurements of the apolipoproteins were performed with immunoturbidimetric assays using antisera specific for apoA-1 and apoB (Hoffman-La Roche, Basel, Switzerland) and lipoprotein (a) (Incstar Corporation, Stillwater, MN, USA). High-sensitive C-reactive protein (hs-CRP) levels were measured with a high sensitive near-infrared particle immunoassay (NIPIA) rate methodology (Beckman Coulter, Fullerton, California, USA) on a SYNCHRON LXi PRO System automated autoanalyser (Beckman Coulter, Fullerton, California, USA). Insulin and FABP4 levels were measured in fasting sera with commercial ELISA kits (Mercodia AB, Uppsala, Sweden and BioVendor Laboratory Medicine Inc., Brno, Czech Republic, respectively). The antibodies used in the human FABP4 ELISA are highly specific for human FABP4, with no detectable cross-reactivity to human FABP1, FABP2, FABP3 or FABP5.

Insulin resistance (IR) was estimated using the homeostasis model assessment index (HOMA-IR), calculated as fasting glucose (in mmol/l) multiplied by fasting insulin (in mIU/l) divided by 22.5.

Definition of metabolic syndrome

Patients with metabolic syndrome were identified based on The National Cholesterol Education Program Adult Treatment Panel III (NCEP) (34) and the modified WHO definitions. (35)

The NCEP defines metabolic syndrome as the presence of three or more of the following five criteria: (1) central obesity with a waist ≥102 cm in men and ≥88 cm in women, (2) hypertriglyceridaemia of ≥150 mg/dl, (3) HDL <40 mg/dl in men and <50 mg/dl in women, (4) blood pressure ≥130/85 mm Hg or the use of drugs for high blood pressure and (5) fasting glucose ≥110 mg/dl.

The WHO definition requires the presence of insulin resistance defined by any of the following three criteria: a homeostasis model assessment (HOMA-IR) in the top quartile of a population without diabetes, increased fasting glucose (>110 mg/dl) or diabetes. In addition, two of the following three criteria are also required: (1) central obesity with a waist >94 cm in men and >88 cm in women, (2) dyslipidaemia defined as triglycerides ≥150 mg/dl or HDL <40 mg/dl in women or <35 mg/dl in men and (3) blood pressure ≥140/90 mm Hg or the use of drugs for hypertension. On the basis of the Study of Inherited Risk of Coronary Atherosclerosis data, we defined a HOMA-IR >2.114 as representing the top quartile of a population without diabetes. (36)

Nuclear magnetic resonance (NMR) lipo-profile, separation and quantification of remnants lipoproteins cholesterol (RLPc)

Total plasma lipids and the distribution of subclasses of lipoproteins were analysed by nuclear magnetic resonance spectroscopy (NMR Lipo-Profile, Raleigh, USA). This technique allows for the determination of three discrete subclasses of very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), four low density lipoprotein (LDL) subclasses, and three high density lipoprotein (HDL) subclasses. The NMR was carried out on EDTA plasma stored at -80ºC and thawed just prior to the analysis.

Additionally, RLPc was measured in plasma using the method described by Nakajima et al. using RLP-Cholesterol Assay Kits (Jimro-II, Otsuka, Japan Immunoresearch Laboratories, Japan). (37)

Carotid Intima-Media Thickness assessment

We used a My Lab 50 X-Vision sonograph (Esaote S.p.A, Indianapolis, USA) with a linear array ultrasound probe and 8-12 MHz transducer to identify the intima-media complex of the far wall of the common carotid, the bulb and the internal branch of the left and right carotid arteries. The images were digitised and stored. Assessment of c-IMT was performed by radiofrequency in *in vivo* images.

The images were obtained and measured by a single operator to reduce observer variability. We averaged the measurements of three images of the left and the right carotid arteries to obtain the mean IMT (mIMT). Maximum IMT (maxIMT) was the maximum value of IMT from all measurements in each subject. (38,39)

Statistical analyses

Analyses were performed using SPSS (version 18.0, SPSS Inc., Chicago, IL, USA). All data are presented as the means ±SD except when otherwise stated. The normality of the

distribution was assessed using the Kolmogorov-Smirnov test. A log-transformation was performed before analyses where variables had a skewed distribution. The differences between means were assessed by ANOVA or the nonparametric Mann-Whitney-U test. Spearman correlation coefficients between FABP4 and other continuous variables were determined using a bivariate correlation test. A multiple linear regression analysis including age, SBP, BMI, HOMA-IR, IDL, small HDL, RLPc, hs-CRP and FABP4 plasma levels was performed to find the variables with an independent association with c-IMT mean. Two-tailed *P* values <0.05 were considered statistically significant.

RESULTS

1. General characteristics of participants and correlations with FABP4 levels

The anthropometry, clinical characteristics and biochemical data of SLE patients and the controls are shown in **Table 1**. SLE patients showed higher levels of SBP (118.45±19.26 mmHg vs. 107.42±12.94 mmHg; $P = 0.007$) and TG (0.98±0.48 mmol/dL vs. 0.74±0.35 mmol/dL; $P = 0.029$) than the controls, though both were within the normal range.

No significant differences in the presence of cardiovascular risks factors between groups was observed; however, SLE-patients presented an increased c-IMT mean (0.701±0.143 mm) with respect to the control group (0.613±0.093 mm; $P = 0.004$) and an increased c-IMT max value (0.773±0.166 mm vs. 0.867±0.117 mm; $P = 0.031$).

We did not find differences in the FABP4 levels between groups.

The age, BMI, SBP and DBP and the total cholesterol, LDL cholesterol, ApoB100 and glucose levels were correlated with FABP4 levels in the control group, while in the SLE

group increased FABP4 was associated with increased triglyceride levels (r = 0.391, P <0.005) and parameters of insulin resistance such as the insulin levels *(r* = 0.485, P <0.001), HOMA-IR (r = 0.489, P <0.001) and HbA_{1c} levels (r = 0.399, P <0.005).

Figure 1. **Table 1**

2. FABP4 levels in MetS and its components.

The results are shown in **Table 2**. The prevalence of MetS was low in the SLE group when using the NCEP definition (3.3%) but was higher when the WHO definition was used (11.4%). Under both definitions, MetS patients showed a significant increase in FABP4 levels **(Table 2)**. Within the components of MetS, hyperglycaemia and insulin resistance were significantly associated with higher levels of FABP4 in the SLE group.

3. Lipid profile assessed by NMR and RLPc

To investigate the association between FABP4 levels and the presence of atherogenic dyslipidaemia, we used lipid profile data determined by NMR and the direct determination of remnant lipoprotein cholesterol in the plasma. **(Table 3)**

In the SLE patients, we found a direct correlation between FABP4 levels and lipoprotein levels that are indicative of atherogenic dyslipidaemia such as large VLDL (r = 0.288, P = 0.001), IDL (r = 0.303, P = 0.020) and the smaller HDL particles (r = 0.409, P = 0.001)**(Figure 2).** FABP4 was also correlated with RLPc levels (r = 0.409, P = 0.001).

In the control group, circulating FABP4 was only associated with the total LDL particle number (r = 0.407, P = 0.039).

4. FABP4 and subclinical atherosclerosis

SLE patients had an increased c-IMT mean compared to the control group (0.707±147 mm vs. 0.613±94 mm, $P = 0.014$).

In SLE patients we also found a direct correlation between the FABP4 levels and the mean and the maximum c-IMT ($r = 0.316$, P = 0.014 and $r = 0.346$, $P = 0.006$, respectively) **(Figure 2).**

In the multivariate analyses used to investigate if FABP4 serum levels are determinants of the c-IMT values in the SLE patients, we included age, SBP, BMI, FABP4 levels, RLPc levels, IDL concentration and the concentration of small HDL particles in the model.

Between these variables, only age (β = 0.003 (0.002-0.005), $P < 0.002$), BMI (β = 0.008 (0.002-0.005), $P < 0.001$) and FABP4 levels (β = 0.002 (0.000-0.003), $P <0.058$) were predictors of the mean c-IMT in SLE patients. **Table 3.**

DISCUSSION

Metabolic disturbances in SLE patients have received increasing attention in recent years due to the higher cardiovascular morbidity and mortality in this population. A chronic proinflammatory status seems to be the underlying mechanism directly promoting an atherogenic process on the vessel wall and has been associated with metabolic disturbances such as atherogenic dyslipidaemia, similar to diabetic or metabolic syndrome patients.

FABP4 plasma levels could be a good marker for these metabolic disturbances involving adipocyte dysfunction, insulin resistance and atherogenic dyslipidaemia, as it has been previously described in the general population (24,25,30).

We have observed a strong relationship between the FABP4 levels and serum markers of insulin resistance. It is noteworthy that the prevalence of MetS among the recruited

patients was low when the NCEP criteria were used, but increased when using the WHO definition. In this young population, such variability may be explained by the inclusion of insulin resistance in the WHO classification as it is most likely the earliest-onset MetS component in this population. Because insulin resistance measurements are seldom performed in clinical settings, MetS is likely to be under detected in SLE patients. In this setting, an elevated FABP4 concentration could attract attention to the presence of early manifestations of metabolic disturbances.

Moreover, we observed that FABP4 levels in the SLE patients were also associated with lipoprotein alterations seen with the atherogenic dyslipidaemia found in metabolic syndrome and type 2 diabetic patients. FABP4 plasma levels were positively correlated with concentrations of the TG-rich lipoprotein remnants VLDL, chylomicrons, IDL and small dense HDL as measured by NMR. This technique allows a more accurate study of lipid abnormalities by detecting alterations not observed by the standard lipid profile measurements that, in the case of SLE patients, could be considered normal (37).

In this study, we cannot confirm that this SLE population possesses the association between FABP4 levels and inflammatory markers such as CRP that has been observed in population-based and *in vitro* studies (21,22,24). Therefore, we consider that FABP4 associations observed in this study are independent of inflammatory factors.

Aside from the associations between FABP4 and metabolic disturbances, we have observed a direct association between FABP4 levels and the presence of subclinical atherosclerosis in univariate and multivariate analyses. FABP4 levels have already been associated not only with the presence of carotid atherosclerosis but also with the coronary plaque burden and instability and endothelial dysfunction (29,40,41).

Recently, FABP4 levels have also been proposed as a clinical outcome predictor in acute stroke patients. (27,28) Therefore, FABP4 plasma levels could be a biomarker to

detect those SLE patients with an increased susceptibility to metabolic and vascular alterations.

Our study has some limitations, one of which is its small sample size. Another is that our patients were under treatment and in a well-controlled phase of the disease and therefore not representative of the chronic proinflammatory situation. Most likely, the measurement of other inflammatory markers beyond CRP, such as IL-6 or TNF, could reveal stronger associations between the metabolic, vascular and inflammatory status of these patients.

In SLE patients, high FABP4 levels are associated with the presence of insulin resistance and atherogenic dyslipidaemia including the atherogenic lipoprotein subclasses characterised by NMR. FABP4 levels are also associated with the presence of subclinical arteriosclerosis.

We can therefore conclude that FABP4 is a marker of metabolic disturbances in SLE patients that affect lipid metabolism and insulin resistance, which are determinants of subclinical atherosclerosis in this population. We postulate that FABP4 levels in SLE could be a useful clinical biomarker of metabolic and cardiovascular risk in these usually young and non-obese patients.

DISCLOSURERS

All authors disclose non conflicts of interest in the elaboration of this work.

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LEGENDS TO FIGURES AND TABLES

Table 1. General characteristics of SLE patients, the control group and bivariate correlations with FABP4 levels.

Table 2. Percentage of patients with the MetS components according the NCEP and WHO classifications. Differences in FABP4 levels segregated by the components of MetS.

Table 3. Correlations between FABP4 levels and lipoprotein particles by NMR.

Figure 1. Bivariate correlation between insulin, HOMA-IR and FABP4 levels.

Figure 2 Bivariate correlation between atherogenic dyslipidaemia components as determined by NMR and FABP4 levels.

Figure 3. Bivariate correlation between the mean and the maximum c-IMT measurements and FABP4 levels.

Figure 4. Variables that predict c-IMT value.

Variables included in the model: age, SBP, BMI, CRP-hs, HOMA-IR, remnants, IDL, small HDL particles and FABP4

Table 1. General characteristics of SLE patients and their correlations with FABP4

	SLE group			Control group		
Variable	**Mean±SD**	**r**	***P***	**Mean±SD**	**r**	***P***
Anthropometric						
Age	49±16.8	0.132	NS	48.7±13.2	0.582	0.002
BMI, Kg/m^2	26.3±5.8	0.166	NS	24.5±3.2	0.525	0.006
SBP, mmHg	118.5±19.3	0.164	NS	107.4±12.9*	0.465	0.017
DBP, mmHg	75.7±11	0.098	NS	72.2±7.7	0.513	0.017
Waist circ, cm	86.7±11.7	-0.116	NS	81.2±8.9	0.633	0.001
Factors of disease activity and inflammation						
Anti DNA antibodies, IFI	23.9±55.7	0.158	NS	-	-	-
C3, g/L	1.049±0.3	-0.001	NS	-	-	-
C4, g/L	0.174±0.1	0.042	NS	-	-	-
CH50, U arb CH50	49.55±16.1	0.083	NS	-	-	-
IgM-anticardiolipin, MPL-U/mL	8.87±12.84	0.010	NS	-	-	-
IgG-anticardiolipin, GPL-U/mL	17.69±32.0	0.126	NS	-	-	-
IgG-β2-glicoprotein, U/mL	7.21±12.7	0.013	NS	-	-	-
IgM-β2-glicoprotein, U/mL	6.42±14.8	0.049	NS	-	-	-
Hs-CRP, mg/L	2.47±2.6	0.186	NS	1.93±1.71	0.386	0.063
ESR, mm/h	17.98±2.5	0.22	NS	-	-	-
Metabolism						
Gluc, mmol/L	4.9±0.6	0.167	NS	5.1±0.6	0.499	0.009
Insulin, mIU/L	8.0±5.3	0.485	<0.001	6.6±3.1	0.203	NS
HOMA-IR	1.7±1.2	0.489	<0.001	1.5±0.9	0.346	NS
HbA_{1c}, %	4.7±0.6	0.399	0.002	-	-	-
Apo-A1, g/L	1.46±0.1	0.031	NS	1.48±0.37*	0.104	NS
Apo-B,g/L	0.89±0.2	0.217	NS	0.92±0.18*	0.424	0.035
TG, mmol/L	0.98±0.5	0.391	0.002	0.75±0.36*	0.187	NS
Tot Chol, mmol/L	4.9±1.1	0.236	NS	4.95±0.85	0.414	0.036
LDL-c, mmol/L	2.82±0.2	0.204	NS	3.06±0.71	0.487	0.012
HDL-c, mmol/L	1.7±0.4	0.053	NS	1.56±0.43	-0.209	NS
Creatinine, µmol/L	67.5±15.4	0.285	0.028	64.7±10.6	0.163	NS
FABP4, microg/L	24.8±16.8	-	-	27.2±10.4	-	-
Mean c-IMT, mm	0.707±147	0.316	0.014	0.613±94*	0.280	NS
Max c-IMT, mm	0.867±173	0.348	0.006	0.773±166	0.011	NS

ESR erythrocyte sedimentation rate *p < 0.05 vs. SLE group

Table 2. Percentage of patients with the MetS components according the NCEP and WHO classifications. Differences in FABP4 levels segregated by the components of MetS.

NCEP definition	SLE patients (%)		FABP4 levels	P
1) Waist circumference	40	YES	27.55(15.20)	NS
		NO	26.84(15.9)	
2) Hypertension	36.7	YES	28.02(15.99)	NS
		NO	24.62(15.00)	
3) Hypertriglyceridaemia	8.5	YES	33.94(14.27)	NS
		NO	24.66(14.84)	
4) Low HDL	15.3	YES	24.28(13.09)	NS
		NO	25.38(15.30)	
5) Hyperglycaemia	3.4	YES	48.74(2.63)	0.023
		NO	24.63(14.60)	
Total definition	3.4	YES	43.41(11.84)	0.040
		NO	25.04(15.07)	
WHO definition				
1) Insulin resistance	23.3	YES	41.73(18.54)	<0.001
		NO	19.46(11.35)	
2) Dyslipidaemia	25.4	YES	26.19(14.84)	NS
		NO	23.66(17.12)	
3) Hypertension	20	YES	28.99(18.55)	NS
		NO	24.99(14.61)	
4) Central obesity	40	YES	27.55(15.20)	NS
		NO	26.84(15.9)	
Total definition	11.7	YES	38.83(12.29)	0.005
		NO	24.00(14.76)	

Table 3. Correlations between FABP4 levels and lipoprotein particles by NMR

		SLE group		Control group	
Variable		**r**	***P***	**r**	***P***
Remnants lipoprotein cholesterol, mg/dL		0.409	0.001	0.318	NS
VLDL and chylomicron concentrations, nmol/L	VLDL and chylomicrons	0.288	0.027	0.195	NS
	Large VLDL and chylomicrons	0.293	0.024	-0.028	NS
	Medium VLDL	0.271	0.038	0.011	NS
	Small VLDL	0.282	0.030	0.285	NS
LDL concentrations, nmol/L	Total LDL	0.236	0.071	0.407	0.039
	IDL	0.303	0.020	0.222	NS
	Large LDL	0.040	NS	-0.063	NS
	Small LDL	0.168	NS	0.323	NS
	Medium LDL	0.141	NS	0.333	NS
	Very small LDL	0.175	NS	0.331	NS
HDL concentrations, nmol/L	Total HDL	0.202	NS	-0.249	NS
	Large HDL	0.073	NS	-0.378	NS
	Medium HDL	-0.082	NS	-0.021	NS
	Small HDL	0.285	0.029	-0.092	NS
Mean sizes, nm	VLDL	-0.158	NS	-0.203	NS
	LDL	-0.144	NS	-0.255	NS
	HDL	-0.121	NS	-0.253	NS