Association between dietary and metabolic factors and IgM antibodies to phosphorylcholine and malondialdehyde in patients with systemic lupus erythematosus and population-based matched controls

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Abstract

Objective

Immunoglobulin M (IgM) antibodies against phosphorylcholine (anti-PC) and malondialdehyde (anti-MDA) are implicated in systemic lupus erythematosus (SLE) as markers with potential protective properties. Low IgM anti-PC levels are more common in SLE than in control population. Little is known what influences the levels of these antibodies. We here studied associations between dietary and metabolic factors and levels of IgM anti-PC and anti-MDA.

Methods

This study included 109 SLE patients and 106 controls from SLE Vascular Investigation Cohort (SLEVIC). Data on dietary intake (food frequency questionnaires) and metabolic factors were linked with IgM anti-PC and anti-MDA (determined by enzyme-linked immunosorbent assay). Associations between the dietary, metabolic factors and antibodies were analysed with logistic regression. Antibody levels ≤1st tertile were defined as low level.

Results

Low IgM anti-PC and anti-MDA were associated with SLE (odds ratio (OR)=2.5 [95% confidence interval (CI) 1.4–4.4] and OR=1.7 [95% CI 1.0–3.1, respectively). Among SLE patients, overweight/obesity (body mass index >25), elevated high-density lipoprotein (>1.6 mmol/L) and dietary fibre intake (>25.9 g/day) were associated with low IgM anti-PC (OR=2.29 [95% CI 1.06–4.97], OR=2.36 [95% CI 1.01–5.53] and OR=1.24 [95% CI 1.24–6.15], respectively). Further, dietary intake of total fat (>64.0 g/day), specifically saturated fat (>27.1 g/day), was associated with low IgM anti-MDA level (OR=2.55 [95% CI 1.14–5.64] and OR=2.47 [95% CI 1.11–5.51], respectively). Micronutrients were not associated with measured antibodies.

Conclusion

Some dietary and metabolic factors were associated with IgM anti-PC and anti-MDA, though it is not clear whether the associations also represent causation.

Key words

systemic lupus erythematosus, diet, BMI, antibodies, phosphorylcholine malondialdehyde.

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Introduction

Systemic lupus erythematosus (SLE) could be described as a prototypic autoimmune disease, with unknown cause, which for long time has been known to affect different organ systems. During recent years, it has become clear that the risk of atherosclerosis and especially atherosclerotic plaques and ensuing cardiovascular disease (CVD) such as stroke and myocardial infarction is increased in this condition. A combination of traditional and non-traditional risk factors has been implicated in the development of atherosclerosis in SLE (1-4).

In a development of the hygiene/old friend's hypothesis, that the lack of exposure to evolutionarily old microorganisms (exposing phosphorylcholine (PC)) could contribute to autoimmune conditions such as SLE and also CVD and atherosclerosis (5, 6). levels of immunoglobulin M (IgM) anti-PC were reported to be negatively associated with increased risk of CVD and atherosclerosis, independent of established risk factors (7). Further, low levels of IgM anti-PC are associated with SLE (2, 8-10). Low IgM anti-PC could contribute to both atherosclerosis and SLE, since IgM anti-PC increases uptake of apoptotic cells (11), is anti-inflammatory (8), and decreases foam cell formation (12).

Diet in SLE has become a more highlighted topic in the last decade, but has not yet been well explored. However, we have previously reported a higher dietary intake of carbohydrates and a lower dietary intake of fibre, omega-3 and omega-6 fatty acids in SLE patients compared to controls (13). Also, we have recently shown that several dietary micronutrients, such as riboflavin (vitamin B_2), phosphorus, selenium and thiamin (vitamin B_1), have been inversely associated with atherosclerotic plaque in SLE patients (14). Moreover, we have reported that dietary intake of beta-carotene, linoleic acid (omega-6 fatty acid) and vitamin B6 in SLE patients have been inversely associated with increased glucocorticoid dose/higher disease activity (15).

Oxidised (or enzymatically modified) low density lipoprotein (oxLDL) could play an important role in atherogenesis by promoting: inflammation; activation of dendritic cells and T cells; cell death and uptake by macrophages that develop into inert, fat-filled foam cells (7, 16, 17). In SLE, oxLDL is raised and associated with CVD (18). oxLDL activates T cells (19), through dendritic cells (16) and inflammatory lipids exposing PC in oxLDL could play an important role (20).

Another major antigen in oxLDL is generated during lipid peroxidation, like PC, namely malondialdehyde (MDA). This compound forms adducts with proteins, modifying lysine into a stable antigenic product which is antigenic (21). We reported that low IgM against MDA is associated with atherosclerosis in SLE, and also with risk of CVD among 60 year olds (11, 22). IgM anti-MDA (like IgM anti-PC) increases clearance of dead cells and inhibits foam cell formation (11).

Based on the findings presented above, we hypothesised that dietary and metabolic factors may be associated with low levels of IgM anti-PC and anti-MDA in SLE patients. In order to delineate the influence of these factors on IgM anti-PC and anti-MDA in SLE the association was also studied in population-based controls matched to SLE patients. The implications of our findings are discussed.

Materials and methods

Study participants

This study included SLE patients and controls from the SLE Vascular Investigation Cohort (SLEVIC), Karolinska University Hospital, Stockholm, Sweden (2). The SLE patients fulfilled the 1997 update of 1982 revised criteria of the American College of Rheumatology (ACR) for SLE (23). The controls were matched by age and gender from the general population. Participants who were lacking measurements of IgM anti-PC and anti-MDA were excluded. This study was approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden and was performed in accordance with the Declaration of Helsinki. All subjects gave written informed consent before entering the study.

Clinical assessments

SLE disease activity was measured

with Systemic Lupus Activity Measure (SLAM) and SLE Disease Activity Index (SLEDAI) (24, 25). Organ damage was assessed with Systemic Lupus International Collaboration Clinics damage index (SLICC) (26). Body mass index (BMI) was calculated based on weight and height (kg/m^2). C-reactive protein (CRP), high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose as well as IgM anti-PC and anti-MDA were measured from overnight fasting venous blood samples, taken at inclusion. IgM anti-PC and anti-MDA levels were measured by enzyme-linked immunosorbent assay, this procedure has previously been described (2, 11).

Dietary assessment

SLE patients and controls were asked to complete a food frequency questionnaire (FFQ) at inclusion. This self-reported FFQ included questions regarding the participants' estimated food intake during the previous year, and involved intake of 88 frequently consumed food items, including beverages, in Sweden (27). Completed FFQs were evaluated and an estimation of daily mean intake of several nutrients was calculated. The nutrient calculations were carried out by multiplying the average frequency of consumption of each food item by the nutrient content of the specified portions using nutrient composition values from the Swedish National Food Administration data (28).

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 23. Baseline characteristics and dietary intake between SLE patients and controls were compared with Mann-Whitney U-test for continuous variables (mean and standard deviation) as well as Pearson's chi-square test for proportions (%). Associations between dietary nutrients and levels of IgM anti-PC and anti-MDA were analysed with logistic regression (odds ratio (OR), 95% confidence interval (CI)). All nutrient variables were divided into lower (≤median) and higher (>median) intake, where lower intake was the referent group. Levels of IgM anti-PC and anti-MDA were divided into tertiles, the low levels were defined as ≤1st tertile and high levels as >3rd tertile. The level of significance was 0.05.

Table I. Characteristics of the study participants.

	SLE patients (n=109)	Controls (n=106)	*p*-value
Age (years), mean ± SD	48.0 ± 13.2	48.7 ± 12.8	0.700
Female, n (%)	95 (87.2)	96 (90.6)	0.427
BMI (kg/m^2), mean ± SD	24.9 ± 4.5	25.4 ± 5.5	0.687
Smokers, n (%)	16 (14.7)	15 (14.3)	0.924
CRP (mg/L), mean ± SD	**4.5 ± 6.6**	**2.1 ± 3.4**	**0.002**
HDL (mmol/L), mean ± SD	1.8 ± 1.5	1.7 ± 0.6	0.829
LDL (mmol/L), mean ± SD	**2.5 ± 0.9**	**2.8 ± 0.8**	**0.036**
Glucose (mmol/L), mean ± SD	**4.6 ± 0.9**	**4.9 ± 1.0**	**<0.001**
Hypertension, (>140/90), n (%)	**63 (57.8)**	**27 (25.5)**	**<0.001**
SLAM, median (IQR)	6 (4-9)	-	-
SLEDAI, median (IQR)	2 (0-6)	-	-
SLICC, median (IQR)	1 (0-3)	-	-
IgM anti-PC* (mean ± SD)	111.8 ± 109.4	99.9 ± 62.5	0.147
Low levels (≤1st tertile), n (%)	**47 (43.1)**	**25 (23.6)**	**0.002**
High levels (>3rd tertile), n (%)	36 (33.0)	34 (32.1)	0.882
IgM anti-MDA* mean ± SD	109.5 ± 75.8	122.2 ± 69.9	0.066
Low levels (≤1st tertile), n (%)	43 (39.4)	29 (27.4)	0.060
High levels (>3rd tertile), n (%)	32 (29.4)	40 (37.7)	0.193
GC use, n (%)	6 (30.7)	-	-
Dose (g/day), median (IQR)	2.5 (xx – xx)	-	-

BMI: body mass index; CRP: C-reactive protein; GC: glucocorticoid; IgM: immunoglobulin M; IQR: interquartile range; LDL: low density lipoprotein; MDA: malondialdehyde; PC: phorphorylcholine; SLAM: systemic lupus activity measure; SLE: systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index; SLICC: systemic lupus international collaboration clinics damage index. *arbitrary unit *p*-values shows difference of mean values and proportions. Baseline characteristics and dietary intake between SLE patients and controls were compared with Mann-Whitney U-test for continuous variables (mean and standard deviation) as well as Pearson's chi-square test for proportions (%).
IgM anti-PC ≤1st tertile ≤31.9 arbitrary unit. IgM anti-MDA ≤1st tertile ≤52.7 arbitrary unit.

Results

Baseline characteristics

This study included 109 SLE patients and 106 controls. Baseline characteristics of the study sample are presented in Table I. SLE patients had significantly higher levels of CRP than controls as well as higher proportion of hypertension. However, controls had significantly higher levels of LDL and glucose than SLE patients. The SLE patients had an overall low disease activity and severity according to SLEDAI, SLAM and SLICC, and approximately one third of the patients used low dose GC treatment.

Levels of IgM anti-PC and anti-MDA

Low IgM anti-PC and low IgM anti-MDA were more common in SLE patients than controls (OR=2.5 [95% CI 1.4–4.4] and OR=1.7 [95% CI 1.0–3.1], respectively).

Among SLE patients, overweight/obesity (BMI >25 kg/m^2), HDL (>1.6 mmol/L) and dietary fibre intake (>25.9 g/day) were associated with low IgM anti-PC (OR=2.29 [95% CI 1.06-4.97], OR=2.36 [95% CI 1.01–5.53] and OR=1.24 [95% CI 1.24–6.15], respectively). Further, dietary intake of total fat (>64.0 g/day) and specifically saturated fat (>27.1 g/day) were associated with low IgM anti-MDA level (OR=2.55 [95% CI 1.14–5.64] and OR=2.47 [95% CI 1.11–5.51], respectively).

Among controls, male gender was associated with low levels of both IgM anti-PC and anti-MDA (OR=0.17 [95% 0.04–0.64] and OR=0.23 [0.07–0.78], respectively). In addition, energy intake (>1927.9 kcal/day) was associated with low IgM anti-MDA (OR=2.70 [95% CI 1.09–6.69]). Similar to the SLE patients, total fat (>64.0 g/day) and specifically saturated fat (>27.1 g/day) were associated with low IgM anti-MDA (OR=2.55 [95% CI 1.01–6.39] and OR=3.00 [95% CI 1.19–7.56], respectively). Moreover, dietary

Table II. Associations between clinical measures, dietary intake and levels of low IgM anti-PC and anti-MDA among SLE patients and controls.

		SLE (n=109)			Control (n=106)		
		OR	95% CI	*p*-value	OR	95% CI	*p*-value
Low anti-PC ≤31.9*	Female gender	1.01	0.33-3.15	0.983	**0.17**	**0.04-0.64**	**0.009**
	Smoking	0.94	0.55-1.61	0.834	0.63	0.32-1.27	0.196
	BMI >25 kg/m^2	**2.29**	**1.06-4.97**	**0.036**	1.67	0.68-4.13	0.265
	Current GC use	1.38	0.63-3.06	0.421	-	-	-
	GC dose >2.5 mg/day	1.04	0.95-1.14	0.411	-	-	-
	Total cholesterol >4.7 mmol/L	1.05	0.49-2.25	0.906	1.05	0.49-2.25	0.906
	HDL >1.6 mmol/L	**2.29**	**1.06-4.97**	**0.036**	0.82	0.32-2.07	0.672
	LDL (>2.6 mmol/L)	1.03	0.48-2.21	0.948	2.41	0.93-6.20	0.069
	Energy (>1927.9 kcal/day)	1.61	0.74-3.51	0.228	2.01	0.80-5.09	0.140
	Alcohol (>3.52 g/day)	0.77	0.35-1.68	0.503	1.63	0.62-4.25	0.319
	Protein (>87.5 g/day	1.89	0.86-4.1	0.111	1.45	0.58-3.64	0.426
	Carbohydrate (225.8 g/day)	1.04	0.48-2.24	0.929	0.88	0.35-2.22	0.782
	Fibre (>25.9 g/day)	**2.76**	**1.24-6.15**	**0.013**	1.90	0.73-4.95	0.189
	Total fat (>64.0 g/day)	1.06	0.49-2.28	0.891	1.55	0.62-3.91	0.352
	SFA (>27.1 g/day)	1.01	0.47-2.19	0.976	**3.68**	**1.37-9.91**	**0.010**
	MUFA (>22.1 g/day)	0.85	0.39-1.83	0.673	2.05	0.80-5.24	0.135
	PUFA (>9.4 g/day)	1.41	0.65-3.05	0.387	1.4	0.56-3.53	0.476
	Omega-3 FA (>0.6 g/day)	0.90	0.42-1.96	0.798	0.76	0.31-1.91	0.565
	Omega-6 FA (>7.2 g/day)	1.26	0.58-2.74	0.560	1.26	0.50-3.19	0.620
Low anti-MDA ≤52.7*	Female gender	0.60	0.19-1.84	0.368	**0.23**	**0.07-0.78**	**0.018**
	Smoking	0.92	0.54-1.59	0.789	1.41	0.79-2.51	0.242
	BMI >25 kg/m^2	1.42	0.67-3.04	0.362	**3.20**	**1.32-7.76**	**0.010**
	Current GC use	0.81	0.37-1.76	0.592	-	-	-
	GC dose >2.5 mg/day	0.94	0.85-1.03	0.178	-	-	-
	Total cholesterol >4.7 mmol/L	1.38	0.64-2.99	0.416	1.38	0.64-2.99	0.416
	HDL >1.6 mmol/L	1.04	0.48-2.26	0.914	0.48	0.19-1.22	0.124
	LDL >2.6 mmol/L	0.95	0.45-2.13	0.954	1.45	0.61-3.45	0.396
	Energy (>1927.9 kcal/day)	1.51	0.69-3.31	0.302	**2.70**	**1.09-6.69**	**0.032**
	Alcohol (>3.52 g/day)	0.93	0.42-2.06	0.861	1.08	0.44-2.65	0.862
	Protein (>87.5 g/day	1.51	0.69-3.31	0.302	1.59	0.66-3.86	0.304
	Carbohydrate (225.8 g/day)	1.33	0.61-2.92	0.472	1.53	0.63-3.70	0.347
	Fibre (>25.9 g/day)	2.10	0.95-4.65	0.068	1.27	0.52-3.10	0.596
	Total fat (>64.0 g/day)	**2.55**	**1.14-5.64**	**0.023**	**2.55**	**1.01-6.39**	**0.047**
	SFA (>27.1 g/day)	**2.47**	**1.11-5.51**	**0.028**	**3.00**	**1.19-7.56**	**0.020**
	MUFA (>22.1 g/day)	1.71	0.78-3.76	0.179	**2.69**	**1.07-6.76**	**0.036**
	PUFA (>9.4 g/day)	1.10	0.50-2.39	0.816	1.22	0.50-2.95	0.663
	Omega-3 FA (>0.6 g/day)	0.60	0.27-1.32	0.204	0.46	0.19-1.14	0.094
	Omega-6 FA (>7.2 g/day)	1.13	0.52-2.48	0.757	1.34	0.55-3.27	0.517

BMI: body mass index; CI: confidence interval; FA: fatty acids; GC: glucocorticoids; HDL: high density lipoprotein; LDL: low density lipoprotein; MDA: malondialdehyde; MUFA: monounsaturated fatty acids; OR: odds ratio; PC: phorphorylcholine; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids; SLE: systemic lupus erythematosus.
Levels of IgM anti-PC and anti-MDA are divided into tertiles, low levels are defined as ≤1st tertile. *arbitrary units.
The level of significance is 0.05. Significant results are presented in bold text.
All nutrient variables were divided into lower (≤median) and higher (>median) intake, where lower intake was the referent group.

saturated fat was associated with low IgM anti-PC (OR=3.68 [95% CI 1.37–9.91]) and monounsaturated fat were associated with low IgM anti-MDA (OR=2.69 [95% CI 1.07–6.76]), these findings were not seen in SLE patients. Intake of alcohol, protein and carbohydrates were neither associated with IgM anti-PC nor anti-MDA in both SLE patients and controls. (Table II) There was no significant association between micronutrients and measured antibodies (data not shown).

Discussion

We here showed the associations between dietary and metabolic factors and levels of IgM anti-PC and anti-MDA in SLE patients and population-based matched controls.

Of note, IgM anti-PC and anti-MDA show no strong correlation even though both being natural IgM antibodies, they have lower affinity and avidity to their respective antigens than adaptive immune responses involving immunoglobulins G (7, 11, 22, 29). Even though both are protection markers (and potentially protection factors, having a causative role), they could thus differ in profile.

Newborns have almost non-detectable levels of IgM anti-PC (30), so these antibodies, which in adults represent 5–10% of all circulating IgM, are thus most likely developed through contact with the microbiome and other external antigens and microorganisms, though the detailed nature of this is unknown in humans. It is interesting that the microbiome differs in obese as compared to people with normal weight, and the possibility that the microbiome's composition determines the IgM anti-PC levels deserves further studies, there are differences in the microbiome among SLE patients compared to controls, which could contribute to the low levels of IgM anti-PC in SLE (2, 8-10).

Little is known about the role of diet for antibodies IgM anti-PC and anti-MDA. We have previously reported that in RA patients, who were randomised and followed gluten-free vegan diet, disease activity decreased in parallel with increased IgM anti-PC levels. However, we could not determine if it was the vegan- or gluten-free diet that was associated with increased IgM anti-PC or if the decrease of the disease activity that contributed (31). Treatment with TNF-inhibitors in RA was associated with an increase in IgM anti-PC levels, and non-responders had significantly lower baseline levels (32). We have also reported that high IgM anti-PC and anti-MDA in SLE, especially in combination, are strikingly associated with atherosclerosis and echolucent, potentially vulnerable plaques (11). In addition, we have suggested that of micronutrients could play a role in SLE disease activity and atherosclerosis (14, 15). However, we found no significant associations between the micronutrients and antibodies in this present study.

We found that higher BMI was associated with low IgM anti-PC among SLE patients. This is a novel finding to the best of our knowledge both in rheumatic diseases and in other populations studied so far. High BMI, above 25, is a risk factor for CVD (33) and also for other conditions, including osteoarthritis where low IgM anti-PC have been reported to be a risk marker (34). Among SLE patients, this association was only present for IgM anti-PC but not anti-MDA, implying that these antibodies have somewhat different profiles in risk evaluation (11). Given the cross-sectional and not prospective or experimental nature of this study, we cannot know if low levels of IgM anti-PC is a cause or effect of high BMI (or represents some other underlying mechanism). In the developed world, a proinflammatory state is common in conditions as CVD, atherosclerosis (advanced), diabetes mellitus, dementia, and obesity. Hypothetical, low IgM anti-PC could cause high BMI by promoting chronic inflammation. Irrespective of cause of low IgM anti-PC in overweight SLE-patients, this could contribute to complications as CVD.

The surprising finding in this study is the association between low IgM anti-PC (but not low IgM anti-MDA) and dietary intake of fibre (which we have previously reported to be lower among SLE patients than controls (13)). Since intake of fibre is usually believed to be beneficial, not least in the context of CVD and also mortality (35, 36), this finding is somewhat counterintuitive if IgM anti-PC is beneficial, and it should be noted that chance findings cannot be excluded in this kind of study. It should be taken into consideration that even though fiber is beneficial in studies in the general population (regarding weight regulation, effect on blood pressure and glycaemic control), the effects are not large, and underlying mechanisms are not well described. A beneficial role of fibre in SLE is not established to the best of our knowledge. In our previous studies fibre intake was not associated with plaque occurrence or disease activity in SLE, and (13, 15). Among controls, the association between fibre intake and low IgM anti-PC was not significant though increased (OR 1.90), though one should interpret findings in a much selected control group as here with caution. Further studies are needed to determine a potential role of fibre, for example through influencing the gut microbiome, in regards to IgM anti-PC levels.

Higher HDL was associated with low IgM anti-PC in SLE, also this a somewhat unexpected finding since HDL is in general believed to be an anti-atherosclerotic compound through several mechanisms, including reverse cholesterol transport with anti-inflammatory and anti-oxidative effects (7). This association was not present in controls. Of note, in inflammatory conditions, such as rheumatoid arthritis and SLE, HDL does not have the same protective properties and its function is altered, which may even increase the risk of atherosclerosis in these conditions (37). The definition of higher HDL as levels above 1.6, which was presented only in few patients, could likely lead to paradoxical results.

We reported an association between dietary fat intake and low levels of IgM anti-MDA in SLE patients and controls. In contrast, there were no associations between fat intake and IgM anti-PC, again suggesting a difference between these antibodies in SLE. Although among controls, saturated fat and monounsaturated fat were strongly associated with low IgM anti-PC and anti-MDA, respectively, these findings were not seen in SLE patients. In our previous study, we did not detect any differences in the total diet energy intake between SLE patients and controls (13). The role of fat intake, saturated in particular, in the general population has been previously discussed and is not the topic of this study. Although saturated fat has been promoted as a risk factor, supported for example by a recent Cochrane review, this issue is still discussed (38). Trans fats have also been discussed as a confounder (39, 40). Further, incomplete publication could also have contributed to overestimation of dangers with saturated fat as opposed to vegetable oils rich in linoleic acid (omega-6 fatty acids) (41). Further studies are needed to clarify if IgM anti-PC or anti-MDA are related to fat intake or to carbohydrate or protein intake (which were not associated herein). Nevertheless, little is known about the role of saturated fat in SLE and risk of complications associated with diet in prospective studies, which is now under way in our laboratory.

One limitation with this study is the cross-sectional design, which prevents conclusions about causative associations. Our observations could be hypothesis-generating. Another limitation is that self-reported data are prone to biases and potentially results in non-differential misclassification of different dietary components. Further, the intake of dietary components was not adjusted for the total calorie intake. Our analyses were however unlikely threatened because the total diet energy intake in SLE patients and controls did not differ. Taken together, both low IgM anti-PC and anti-MDA showed association with different factors in relation to metabolism, blood lipids and dietary intake. Further prospective and experimental studies are needed to clarify the role of diet in disease development, maintenance and therapy response as well as potential prevention of complications.

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