


## RESEARCH ARTICLE



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# Serum fetuin-A level is independent of *Helicobacter pylori* postinfection status in systemic lupus erythematosus

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## ABSTRACT

*Helicobacter pylori* is a common pathogen causing gastric inflammation and malignancy. Fetuin-A is a multifunctional protein that is involved in the regulation of calcification, insulin resistance and inflammation. Reports on serum levels of fetuin-A in acute *H. pylori* infection are contradictory. We intended to see whether *H. pylori* post-infection status has a long-term effect on serum fetuin-A levels in a well-characterized series of systemic lupus erythematosus cases.

In this cross-sectional study 117 patients with systemic lupus erythematosus were enrolled. *Helicobacter* infection status and serum fetuin-A concentration were determined by ELISA and radial immunodiffusion, respectively. *H. pylori* positive patients had higher serum fetuin-A concentration than negative ones: 517 (456–603) vs. 476 (408–544) mg L<sup>-1</sup>, median (25–75% percentiles),  $P = 0.020$ . No other parameters differed between these groups. During univariate regression analysis fetuin-A levels were associated with Erythrocyte sedimentation rate (ESR), White blood cell count (WBC), C-reactive protein (CRP), serum total protein, albumin, and the SLEDAI index at the time of diagnosis but only serum albumin remained a significant determinant in multivariate regression study.

## KEYWORDS

fetuin-A, *Helicobacter pylori*, infection, systemic lupus erythematosus

## INTRODUCTION

*Helicobacter pylori* infection can lead to chronic gastritis, peptic ulcer and gastric cancer [1, 2]. In addition its association with obesity [3, 4], insulin resistance [5] and metabolic syndrome [6] is also known. There are studies suggesting that a *H. pylori* increases the risk of development of non-alcoholic fatty liver [7], whereas others debate it [8].

Human fetuin-A is a secretory multifunctional glycoprotein that is synthesized mainly in the liver in adulthood [9]. Fetuin-A inhibits ectopic calcification [10] and behaves as a negative acute phase reactant [11]. Low serum fetuin-A concentration is a good predictor of mortality in alcoholic liver cirrhosis [12] and end-stage renal disease [13]. Fetuin-A inhibits insulin receptor autophosphorylation and signaling, thereby increasing insulin resistance [14–17].

Reports on serum fetuin-A concentration in *H. pylori* infection are contradictory. Kebapcilar et al. observed decreased fetuin-A and elevated C-reactive protein (CRP) and macrophage migration inhibitory factor (MIF) levels in *H. pylori* infected patients with

dyspepsia compared to healthy controls [18]. Concentrations of CRP and MIF decreased whereas those of fetuin-A increased following eradication [18]. In contrast with these observations Manolakis et al. found elevated serum fetuin-A concentrations in *H. pylori* positive patients [19]. The difference between *H. pylori* positive and negative patients remained following adjustment for age, gender, smoking habits, body mass index (BMI), blood lipids and CRP levels [19]. They described elevated serum insulin and HOMA-IR levels. Based on these findings and on the positive correlation between HOMA-IR and fetuin-A levels they suspected that fetuin-A could be responsible for the increased insulin resistance observed in *H. pylori* infection [19].

Based on these findings we found it interesting to see whether *H. pylori* postinfection status can affect fetuin-A levels in serum. We tested this hypothesis in a well-characterized cohort of patients with systemic lupus erythematosus.

## PATIENTS AND METHODS

One-hundred and seventeen patients (14 men, 103 women, mean age: 43.6 years, median: 43 years, Q1–Q3: 31–55), who were treated at the Outpatient Service of Immunology, 3rd Department of Internal Medicine, Semmelweis University were included in the study. The study period was between 2000 and 2005. The diagnosis of SLE was established on international criteria [20]. None of the patients received eradication therapy in the past 6 months. Depending on their organ manifestations and severity of disease patients were on corticosteroid (oral prednisolone or methylprednisolone), azathioprine, chloroquine or cyclophosphamide treatment.

The study was approved by the Ethical Committee of the Hungarian Medical Research Council and all patients gave informed consent to participate in the study.

We determined serum fetuin-A concentration by radial immunodiffusion, as described earlier [21]. Anti-*Helicobacter* IgG was determined by ELISA using the NovaLisa kit (NovaTec, Dietzenbach, Germany). Values  $\leq 1.0$  were considered negative and  $>1.0$  were positive.

Other laboratory examinations were determined by conventional methods.

Statistical analysis was performed with the IBM SPSS v23 statistical program (IBM-SPSS Inc., Armonk, NY, USA). We used non-parametric tests as not all parameters followed normal distribution.

## RESULTS

### Comparison of *Helicobacter pylori* negative and positive patients with SLE

Comparison of *H. pylori* negative and positive patients is shown in Table 1. These two groups differed only in fetuin-A concentration.

### Correlation between serum fetuin-A levels and *H. pylori* status in patients with SLE

There was a weak but statistically significant correlation between *H. pylori* status and fetuin-A levels ( $r = 0.203$ ,  $P = 0.028$ ). Thus, compared to *H. pylori* negative patients a significantly higher portion of *H. pylori* positive patients was associated with higher fetuin-A concentration ranges (Table 2). Serum fetuin-A levels and *H. pylori* IgG levels, however, did not correlate significantly either in all ( $r = 0.141$ ,  $P = 0.154$ ,  $n = 117$ ) or in *H. pylori* positive patients ( $r = 0.104$ ,  $P = 0.448$ ,  $n = 62$ ).

### The association between fetuin-A concentration and other parameters of patients

Univariate regression analysis between serum fetuin-A levels and the other parameters is shown in Table 3. We observed a significant association with Erythrocyte sedimentation rate (ESR), White blood cell (WBC) count, CRP, total protein and albumin levels, the SLEDAI index at the time of diagnosis but not with the other parameters listed in Table 1.

Next, in a multiple regression model we analyzed the association of fetuin-A levels and the five parameters that were significant in the univariate regression analysis. We used serum albumin instead of total protein due to strong collinearity between these two parameters ( $r = 0.739$ ,  $P = 4.55 \times 10^{-16}$ , Table 4). Only albumin (and marginally WBC) but not the *H. pylori* status or SLEDAI showed statistically significant association with fetuin-A.

## DISCUSSION

Although serum fetuin-A concentration significantly differed between patients with past *H. pylori* infection and without it further analysis indicated that this difference was not due to the *H. pylori* status.

In two cross-sectional studies both decreased [18] and increased [19] fetuin-A levels have been observed in active *H. pylori* infection. The decrease was attributed to the negative acute phase character of the protein. The elevation of fetuin-A was not explained by molecular mechanisms but was referred to the clinical observations on the metabolic effects of the molecule (increased insulin resistance and incidence of NAFLD) [5, 19, 22, 23]. In addition the acutely protective anti-inflammatory effect of fetuin-A has also been well known [24]. As compared by Polyzos et al. [7] these above-mentioned studies on the decrease [18] and elevation [19] of fetuin-A, however, markedly differed from each other in terms of patient recruitment (age, BMI) and the methods used to diagnose *H. pylori* infection [7]. Furthermore, fetuin-A levels differed from each other by four orders of magnitude in the two studies.

We did not intend to solve this issue but rather focused on the potential long-term effect on of *H. pylori* infection on fetuin-A levels. The diagnostic value of serological testing is



Table 1. Comparison of *H. pylori* negative and positive patients. Continuous variables are represented as median (Q1–Q3 values), categorical variables as frequency (percentage), respectively

Parameter	<i>H. pylori</i> negative ( <i>n</i> = 55)	<i>H. pylori</i> positive ( <i>n</i> = 62)	<i>P</i> <sup>#</sup>
Age, years	40 (31–49)	49 (31–58)	0.087
Gender (M/F)	9/46	5/57	0.167 <sup>§</sup>
BMI, kg m <sup>-2</sup>	23 (22–26)	23 (20–27)	0.346
<b>Fetuin-A, mg L<sup>-1</sup></b>	<b>476 (408–544)</b>	<b>517 (456–603)</b>	<b>0.020</b>
ESR, mm h <sup>-1</sup>	22 (14–40)	23 (10–38)	0.569
C3, g L <sup>-1</sup>	81 (47–113)	87 (65–125)	0.131
Anti-DNA, IU/mL	12 (5–42)	18 (5–48)	0.799
Anti-C1q, U/mL	18 (9–35)	17 (10–28)	0.792
CRP, mg L <sup>-1</sup>	3.98 (1.37–9.44)	3.45 (1.37–8.58)	0.669
Total protein, g L <sup>-1</sup>	73 (64–76)	72 (68–75)	0.439
Albumin, g L <sup>-1</sup>	42 (35–47)	43 (38–45)	0.661
IgG, g L <sup>-1</sup>	12.5 (10.0–15.3)	11.8 (10.3–13.3)	0.525
IgA, g L <sup>-1</sup>	2.44 (1.76–3.56)	2.26 (1.46–3.24)	0.303
IgM, g L <sup>-1</sup>	1.06 (0.71–1.71)	1.32 (0.76–1.77)	0.611
RBC, *10 <sup>6</sup> /μL	4.3 (4.0–4.7)	4.2 (4.0–4.4)	0.288
Hematocrit	0.38 (0.35–0.42)	0.37 (0.36–0.40)	0.304
Hemoglobin, g L <sup>-1</sup>	128 (115–141)	125 (115–134)	0.172
WBC, /μL	6,100 (5,100–8,570)	6,755 (5,075–9,273)	0.574
Glucose, mmol L <sup>-1</sup>	4.58 (4.15–5.02)	4.73 (4.31–5.47)	0.331
Creatinine, μmol L <sup>-1</sup>	70 (64–81)	68 (59–81)	0.535
Bilirubin, μmol L <sup>-1</sup>	8.9 (6.8–12.4)	7.6 (6.0–10.7)	0.110
ASAT, UL <sup>-1</sup>	23 (19–29)	18 (15–25)	0.055
ALAT, UL <sup>-1</sup>	19 (15–34)	17 (12–23)	0.081
Alkaline phosphatase, UL <sup>-1</sup>	91 (60–166)	70 (53–144)	0.242
INR	1.05 (0.94–1.10)	1.03 (0.94–1.10)	0.934
Cholesterol, mmol L <sup>-1</sup>	5.05 (4.13–5.61)	4.91 (4.02–5.61)	0.799
Triglyceride, mmol L <sup>-1</sup>	1.18 (0.93–1.71)	0.97 (0.70–1.65)	0.081
SLEDAI	6.0 (2–17)	4 (3–10)	0.245
Corticosteroid treatment, yes/no	34/21	39/23	0.904 <sup>§</sup>

BMI: Body Mass Index; ESR: Erythrocyte Sedimentation Rate; C3: C3 complement component; CRP: C-reactive protein, RBC: Red blood cell count; WBC: White blood cell count; ASAT: Serum aspartate aminotransferase; ALAT, Serum alanine aminotransferase, INR: International Normalization Rate; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index at the time of diagnosis. #: Mann-Whitney test; §: Chi<sup>2</sup> test. Parameters typed in bold have statistically significant values ( $P < 0.05$ ).

to detect the postinfection status of the patient and is not suitable to detect active infection.

Although fetuin-A levels correlated with several parameters during univariate regression analysis only the association with albumin was found to be significant in the multivariate model, like in previous studies on alcoholic liver

Table 2. The number of *H. pylori* positive and negative patients in serum fetuin-A level quartiles

	Q1 0–435	Q2 436–510	Q3 511–568	Q4 569–	Total
<i>H. pylori</i> IgG negative	19	13	14	9	55
<i>H. pylori</i> IgG positive	10	19	13	20	62
Total	29	32	27	29	117

$\chi^2 = 7.736$ ,  $P = 0.052$ ; linear association coefficient = 4.867, ordinal by ordinal Spearman correlation:  $r = 0.205$ ,  $P = 0.027$

Q1–Q4: the four quartiles of a serum fetuin-A concentration (mg L<sup>-1</sup>).

Table 3. Univariate regression analysis between serum fetuin-A concentration and other laboratory parameters

Parameter	Adjusted $r^2$	Standardized $\beta$	<i>P</i>
Age	–0.008	–0.026	0.780
BMI	–0.005	0.085	0.440
<b>ESR</b>	<b>–0.123</b>	<b>–0.364</b>	<b>&lt;0.001</b>
<b>WBC</b>	<b>0.111</b>	<b>–0.347</b>	<b>0.001</b>
<b>CRP</b>	<b>0.090</b>	<b>–0.300</b>	<b>0.002</b>
<b>Serum total protein</b>	<b>0.122</b>	<b>0.349</b>	<b>0.001</b>
<b>Serum albumin</b>	<b>0.168</b>	<b>0.409</b>	<b>&lt;0.001</b>
C3	0.024	0.181	0.051
Anti-DNA	–0.002	0.086	0.369
Anti-C1q	–0.009	0.001	0.997
<b><i>H. pylori</i> status (positive/negative)</b>	<b>0.049</b>	<b>0.239</b>	<b>0.010</b>
<b>SLEDAI</b>	<b>0.053</b>	<b>–0.278</b>	<b>0.010</b>

BMI: Body mass index; ESR: Erythrocyte sedimentation rate; WBC: White blood cell count; CRP: C-reactive protein; C3: C3 complement component; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index at the time of diagnosis. Parameters typed in bold have statistically significant values ( $P < 0.05$ ).



Table 4. Multiple regression analysis of fetuin-A levels and parameters positive during univariate variable analysis

Predictor	Standardized $\beta$ (95% C.I.)	P
ESR	−0.067 (−1.351–0.829)	0.634
WBC	−0.215 (−0.011–0.000)	0.058
CRP	−0.134 (−0.896–0.265)	0.281
<b>Serum albumin</b>	<b>0.293 (0.421–7.526)</b>	<b>0.029</b>
<i>H. pylori</i> status (positive/negative)	0.163 (−11.937–74.057)	0.154
SLEDAI	0.026 (−3.075–3.881)	0.818
Modell fit: $r^2 = 0.275$ , adjusted $r^2 = 0.207$ , $P = 0.002$		

ESR: Erythrocyte sedimentation rate; WBC: White blood cell count; CRP: C-reactive protein; C3: C3 complement component; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index at the time of diagnosis. Parameters typed in bold have statistically significant values ( $P < 0.05$ ).

cirrhosis [12, 21]. Although – in contrast to alcoholic liver cirrhosis – none of our SLE patients had liver failure – we suppose that both parameters are indicators of the protein synthesizing capacity of the liver. The lack of significant regression with the positive acute phase protein CRP also supports this notion.

Parameters of SLE activity parameters did not seem to influence fetuin-A levels. We paid special attention to analyze the impact of SLE. Among SLE activity parameters only SLEDAI at the time of the diagnosis (but not anti-DNA, C3, anti-C1q) seemed to weakly predict fetuin-A levels on regression analysis, whereas SLEDAI did not differ between *H. pylori* positive and negative patients. Corticosteroid treatment had no effect on fetuin-A levels, either. This latter one was especially important since dexamethasone treatment has been shown to increase fetuin-A expression in rats [25].

In summary, in our cross-sectional study we could not confirm that *H. pylori* postinfection status by itself could determine serum fetuin-A concentration.

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