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High mobility group box 1 levels in large vessel vasculitis are not associated with disease activity but are influenced by age and statins

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Abstract

Introduction: Takayasu arteritis (TA) and giant cell arteritis (GCA) are large vessel vasculitides (LVV) that usually present as granulomatous inflammation in arterial walls. High mobility group box 1 (HMGB1) is a nuclear protein that acts as an alarmin when released by dying or activated cells. This study aims to evaluate whether serum HMGB1 can be used as a biomarker in LVV.

Methods: Twenty-nine consecutive TA patients with 29 healthy controls (HC) were evaluated in a cross-sectional study. Eighteen consecutive GCA patients with 16 HC were evaluated at the onset of disease and some of them during follow-up. Serum HMGB1 levels were measured by enzyme-linked immunosorbent assay.

Results: In GCA patients at disease onset mean serum HMGB1 levels did not differ from HC (5.74 ± 4.19 ng/ml vs. 4.17 ± 3.14 ng/ml; p = 0.230). No differences in HMGB1 levels were found between GCA patients with and without polymyalgia rheumatica (p = 0.167), ischemic manifestations (p = 0.873), systemic manifestations (p = 0.474) or relapsing disease (p = 0.608). During follow-up, no significant fluctuations on serum HMGB1 levels were observed from baseline to 3 months (n = 13) (p = 0.075), 12 months (n = 6) (p = 0.093) and at the first relapse (n = 4) (p = 0.202). Serum HMGB1 levels did not differ between TA patients and HC [1.19 (0.45–2.10) ng/ml vs. 1.46 (0.89–3.34) ng/ml; p = 0.181] and no difference was found between TA patients with active disease and in remission [1.31 (0.63–2.16) ng/ml vs. 0.75 (0.39–2.05) ng/ml; p = 0.281]. HMGB1 levels were significantly lower in 16 TA patients on statins compared with 13 patients without statins [0.59 (0.29–1.46) ng/ml vs. 1.93 (0.88–3.34) ng/ml; p = 0.019]. Age was independently associated with higher HMGB1 levels regardless of LVV or control status.

Conclusions: Patients with TA and GCA present similar serum HMGB1 levels compared with HC. Serum HMGB1 is not useful to discriminate between active disease and remission. In TA, use of statins was associated with lower HMGB1 levels. HMGB1 is not a biomarker for LVV.

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t1.1 Table 1 Demographic, disease features and therapy of patients with giant cell arteritis at disease onset and Takayasu arteritis

| Variables                      | GCA (n = 18) | HC (n = 16) | p    | Variables                      | TA (n = 29) | HC (n = 29) | p    |
|--------------------------------|-------------|-------------|------|--------------------------------|-------------|-------------|------|
| t1.1 Demographic features      |             |             |      | t1.1 Disease features and therapy |             |             |      |
| t1.2 Age, years                | 72.0 (63.7–75.0) | 68.5 (63.0–72.0) | 0.643 | t1.2 Females, n (%)           | 14 (77.8)   | 11 (68.8)   | 0.551 |
| t1.3 Females, n (%)            |             |             |      | t1.3 GCA Result               |             |             |      |
| t1.4 Constitutional symptoms, n (%) | 8 (44.4) |             |      | t1.4 Headache, n (%)          | 12 (66.7)   |             |      |
| t1.5 Active disease, n (%)     | 6 (33.3)    |             |      | t1.5 Jaw claudication, n (%)  | 4 (22.2)    |             |      |
| t1.6 Visual symptoms, n (%)    | 4 (22.2)    |             |      | t1.6 ESR, mm/1h               | 69.6 ± 28.7 |             |      |
| t1.7 Polymyalgia rheumatica, n (%) | 4 (22.2) |             |      | t1.7 CRP, mg/l                | 40.0 (20.2–84.2) |             |      |
| t1.8 Headache, n (%)           | 12 (66.7)   |             |      | t1.8 Positive TAB, n/total    | 8/11        |             |      |
| t1.9 ESR, mm/1h               | 69.6 ± 28.7 |             |      | t1.9 Positive PET-CT scan, n/total | 13/15   |             |      |
| t1.10 Constitutional symptoms, n (%) | 8 (44.4) |             |      | t1.10 Disease features and therapy |             |             |      |
| t1.11 Active disease, n (%)    | 6 (33.3)    |             |      | t1.11 Headache, n (%)         | 12 (66.7)   |             |      |
| t1.12 Visual symptoms, n (%)   | 4 (22.2)    |             |      | t1.12 Active disease, n (%)   | 6 (33.3)    |             |      |
| t1.13 Polymyalgia rheumatica, n (%) | 4 (22.2) |             |      | t1.13 Visual symptoms, n (%)  | 4 (22.2)    |             |      |
| t1.14 Active disease, n (%)    | 6 (33.3)    |             |      | t1.14 Visual symptoms, n (%)  | 4 (22.2)    |             |      |
| t1.15 Polymyalgia rheumatica, n (%) | 4 (22.2) |             |      | t1.15 Polymyalgia rheumatica, n (%) | 4 (22.2) |             |      |
| t1.16 Headache, n (%)          | 12 (66.7)   |             |      | t1.16 Headache, n (%)         | 12 (66.7)   |             |      |
| t1.17 ESR, mm/1h               | 69.6 ± 28.7 |             |      | t1.17 ESR, mm/1h              | 69.6 ± 28.7 |             |      |
| t1.18 CRP, mg/l                | 40.0 (20.2–84.2) |             |      | t1.18 CRP, mg/l               | 40.0 (20.2–84.2) |             |      |
| t1.19 Positive TAB, n/total    | 8/11        |             |      | t1.19 Positive TAB, n/total   | 8/11        |             |      |
| t1.20 Positive PET-CT scan, n/total | 13/15   |             |      | t1.20 Positive PET-CT scan, n/total | 13/15 |             |      |

Continuous variables are presented as mean ± standard deviation or as median and interquartile range.

C-reactive protein, ESR erythrocyte sedimentation rate, GCA giant cell arteritis, HC healthy controls, n number of patients, PET-CT positron emission computed tomography, TA Takayasu arteritis, TAB temporal artery biopsy.
Methods

Study population

The study comprised 18 GCA patients with 16 healthy controls (HC), both from the University Medical Center Groningen (UMCG), The Netherlands (Table 1), and 29 consecutive TA patients from Universidade Federal de São Paulo (UNIFESP), Brazil with 29 HC from the same region (Table 1). Inclusion criterion for TA patients was the fulfillment of the 1990 American College of Rheumatology (ACR) classification criteria [28] while the exclusion criteria were current chronic infectious disease, malignancy, and pregnancy. GCA patients were included if they fulfilled the 1990 ACR criteria [29] or when presenting compatible manifestations associated with an enhanced 18F-fluorodeoxyglucose uptake in large vessels by positron emission computed tomography (18FDG-PET/CT). Exclusion criteria for GCA included current chronic infectious disease and malignancy. The study was approved by the Ethics Committee on Research from UNIFESP and by the Medical Ethical Committee of UMCG and complied with the Declaration of Helsinki. All necessary consent was provided from all participants involved in this study.

Active disease in GCA was considered if patients presented manifestations of active disease (e.g. temporal headache, optic neuritis, jaw claudication) not attributable to other causes and/or polymyalgia rheumatica (PMR) symptoms with an increase in ESR > 30 mm/hour whereas remission was considered in the absence of GCA manifestations with normal ESR [30]. Kerr’s criteria and the Indian Takayasu activity score 2010 (ITAS2010) with acute phase response (ITAS.A) using ESR or CRP were employed to ascertain disease activity in TA [31, 32].

In the 18 GCA patients, blood samples were collected at disease onset prior to glucocorticoid therapy and follow-up samples were obtained from 13 patients at 3 months and from six patients at 12 months. Blood samples were collected from 29 TA patients as a cross-sectional evaluation.

Serum HMGB1

Serum HMGB1 levels were determined by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Shino Test Corp., Sagamihara, Kanagawa, Japan) according to the manufacturer's instructions. Results were expressed in nanograms per milliliter.

Statistical analysis

Statistical analysis was performed using IBM SPSS software for Windows version 20.0 (IBM Corp, Armonk, NY, USA) and graphs were created with GraphPad Prism version 3.02 (GraphPad Software, La Jolla, CA, USA). Mean ± standard deviation or median and interquartile range were used to present normally distributed and nonnormally distributed continuous variables, respectively. Categorical variables were presented as total number and percentage.

Comparisons between groups were performed using Student's t test or Mann–Whitney U test for continuous data or using chi-square test or Fisher’s exact test for categorical variables. Correlations between numerical data were performed with Spearman’s correlation coefficient. A linear regression model was built to analyze whether age and the diagnosis of LVV were independently associated with serum HMGB1 levels. Receiver operating characteristic (ROC) analysis was performed to find out the HMGB1 cutoff with the best sensitivity and specificity to differentiate GCA from TA. The cutoff value was chosen from the maximized sum of sensitivity and specificity. Paired t test or Wilcoxon’s test were used to analyze longitudinal data. The significance level accepted was 5 % (p < 0.05).

Results

Disease features and therapy of GCA and TA patients

Disease features and therapy of GCA and TA patients are described in Table 1. After the first evaluation, all GCA patients were treated with high-dose prednisolone (60 mg/day) with slow tapering after improvement of disease symptoms and laboratory abnormalities. Disease relapse was observed in four (22.2 %) GCA patients and the median time to the first relapse after diagnosis was 6.0 months (6.0–15.0). Methotrexate 10–15 mg per week was added to two patients (11.1 %) after the first relapse during steroid tapering. Five GCA patients (27.8 %) were on statins at disease onset.

Previous ischemic events in TA included unstable angina (four patients), stroke (three patients), acute myocardial infarction (two patients), transient ischemic attacks and mesenteric ischemia in one patient each. Two TA patients were treated only with prednisone whereas the remainder used either an immunosuppressive drug or a biologic agent. ESR, ITAS.A ESR and ITAS.A C-reactive protein (CRP) values were significantly higher in TA patients with active disease than in those in remission, whereas there was a trend for higher serum CRP levels in patients with active disease. No significant differences could be found between patients with active disease and remission regarding therapy (Table 2).

HMGB1 levels in giant cell arteritis

In GCA patients with active disease at onset and prior to therapy mean serum HMGB1 levels did not differ between patients and HC (5.74 ± 4.19 ng/ml vs. 4.17 ± 3.14 ng/ml; p = 0.230) (Fig. 1). Furthermore, among GCA patients mean serum HMGB1 levels at onset were not higher in patients with or without PMR [1.25 (0.21–10.50) ng/ml vs. 5.42 (2.94–8.92) ng/ml; p = 0.167], cranial ischemic manifestations (5.56 ± 3.31 ng/ml vs. 5.89 ± 4.95 ng/ml; p = 0.873), constitutional symptoms (4.92 ± 3.90 ng/ml vs. 4.03 ± 2.50 ng/ml; p = 0.390).
Mean serum HMGB1 levels in GCA patients were 5.74 ± 4.19 ng/ml at baseline, 5.18 ± 3.98 ng/ml at 3 months, 8.19 ± 6.80 ng/ml at 12 months, and 6.23 ± 2.48 ng/ml at the first relapse. During follow-up, no significant fluctuations on serum HMGB1 levels were observed from baseline levels to 3 and 12 months (Fig. 2).

Moreover, serum HMGB1 levels in relapsing patients were not different from their levels at disease onset (p = 0.825), at 3 months (p = 0.629), at 12 months (p = 0.601) and from HC (p = 0.170) (Table 3). In GCA patients no correlation was present between HMGB1 and ESR (rho = 0.220; p = 0.380) or between HMGB1 and CRP levels (rho = -0.258; p = 0.301).

**Serum HMGB1 in Takayasu arteritis**

As depicted in Fig. 3, serum HMGB1 levels did not differ between TA patients with active disease [1.31 (0.63–2.16) ng/ml], patients in remission [0.75 (0.39–2.05) ng/ml] and HC [1.46 (0.89–3.34) ng/ml] (p = 0.220). Similar median serum HMGB1 levels were found in TA patients with and without previous ischemic events [1.53 (0.42–3.34) ng/ml vs. 0.97 (0.50–1.93) ng/ml; p = 0.486]. There was no difference in serum HMGB1 levels in TA patients under prednisone therapy compared with those not receiving prednisone [1.13 (0.45–2.34) ng/ml vs. 1.31 (0.36–1.94) ng/ml; p = 0.676] or between TA patients receiving immunosuppressive agents compared with those on biological agents [1.59 (0.43–2.45) ng/ml vs. 0.59 (0.42–0.96); p = 0.140]. However, serum HMGB1 levels were significantly lower in TA patients on statins compared with
patients not receiving these agents [0.59 (0.29–1.46) ng/ml vs. 1.93 (0.88–3.34) ng/ml; \( p = 0.019 \)] (Fig. 4).

No correlation could be observed between serum HMGB1 levels and ESR (\( \rho = 0.104; \ p = 0.590 \)), CRP (\( \rho = 0.090; \ p = 0.642 \)), ITAS2010 (\( \rho = 0.230; \ p = 0.231 \)), ITAS.A ESR (\( \rho = 0.216; \ p = 0.261 \)) or ITAS.A CRP (\( \rho = 0.070; \ p = 0.720 \)).

**Comparison between Takayasu arteritis and giant cell arteritis regarding serum HMGB1 levels**

GCA patients at disease onset presented significantly higher median serum HMGB1 levels compared with TA patients with active disease [4.70 (2.55–8.92) ng/ml vs. 1.31 (0.63–2.16) ng/ml; \( p = 0.0075 \)] (Fig. 5). Even when GCA and TA patients without statins were analyzed separately, serum HMGB1 levels were significantly higher in GCA patients compared to TA patients [5.06 (2.86–10.0) ng/ml vs. 1.80 (0.63–3.34); \( p = 0.015 \)].

Higher serum HMGB1 levels observed in GCA compared with TA seems to be an effect of aging, since serum HMGB1 levels were also higher in GCA controls than in TA controls [2.98 (1.70–6.23) ng/ml vs. 1.46 (0.89–3.34) ng/ml; \( p = 0.019 \)]. A weak correlation was found between serum HMGB1 levels and age in all study participants (\( \rho = 0.244; \ p = 0.019 \)) while in a linear regression model, age was independently associated with serum HMGB1 levels (\( \beta = 0.056; \ p = 0.003; \ R^2 = 0.099 \)), regardless of the diagnosis of LVV or control status.

ROC analysis of GCA and TA patients showed that the best HMGB1 cutoff value for differentiating GCA from TA is 2.17 ng/ml with 83.3 % sensitivity and 79.3 % specificity.

**Discussion**

In this study, we observed that patients with active LVV present similar serum HMGB1 levels compared with patients in remission and HC. TA patients in remission and those with relapsing disease were already under therapy and the use of statins was associated with lower serum HMGB1 levels. Furthermore, in GCA patients with active disease prior to therapy, serum HMGB1 levels were not different from HC but were higher than HMGB1 levels found in TA patients with active disease.

The need for reliable biomarkers for disease activity is an issue of utmost importance in TA. The evaluation of disease activity is a challenge; since the disease course is protracted and silent relapses are common, occurring in up to 96 % of patients who attained remission. It is not easy to define when the disease is actually in remission and most patients develop new angiographic lesions over time usually without clear manifestations of disease.

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**Table 3 Longitudinal data on disease activity and serum HMGB1 levels in patients with giant cell arteritis**

| Variables | Baseline (n = 18) | 3 months (n = 13) | 12 months (n = 6) | Relapse (n = 4) |
|-----------|------------------|------------------|------------------|----------------|
| HMGB1, ng/ml | 5.74 ± 4.19 | 5.18 ± 3.98 | 8.19 ± 6.80 | 6.23 ± 2.48 |
| ESR, mm/hr | 69.6 ± 28.7 | 15.1 ± 6.6 | 21.0 ± 4.9 | 57.5 ± 24.2 |
| CRP, mg/l | 40.0 (20.2–84.2) | 2.5 (2.5–7.0) | 8.0 (5.1–14.7) | 38.5 (12.0–82.2) |
| Prednisolone, mg/day | – | 20.0 (18.7–27.5) | 18.7 (3.7–30.0) | 6.2 (1.2–9.3) |

Continuous variables are presented as median and interquartile range or as mean ± standard deviation.

CRP C-reactive protein, ESR erythrocyte sedimentation rate, HMGB1 high mobility group box 1.
activity [33]. In this context, a novel biomarker would help medical decisions for TA.

Granulomatous inflammation and vessel wall necrosis are well-known features of LVV [34]. Either necrosis or infiltrating macrophages are important sources of HMGB1 release into the extracellular milieu that in turn activate innate and adaptive immunity [35]. Patients with GPA and predominant granulomatous inflammation present higher serum HMGB1 levels compared with GPA patients with predominantly vasculitic manifestations [25]. Thus, we evaluated associations between disease activity in LVV and serum HMGB1 levels. Unfortunately, no difference could be found between patients with active disease and remission or between patients with LVV and HC.

On the other hand, GCA patients at disease onset and prior to therapy presented serum HMGB1 levels that were similar to those of HC, and no association could be found between HMGB1 and acute phase reactants, disease manifestations or disease relapse. Moreover, during follow-up no significant fluctuations in serum HMGB1 levels were observed in GCA patients. Novel biomarkers in GCA would help to recognize active disease in patients with signs and symptoms of GCA but normal acute phase reactants. However, serum HMGB1 levels were not increased in patients with active disease.

Serum HMGB1 levels were significantly higher in GCA patients than in TA patients, and even though the ROC analysis showed that a cutoff value of 2.17 ng/ml in HMGB1 levels would help to differentiate GCA from TA, we believe that it is unlikely that in clinical practice it would replace the 50-year-old cutoff point used to differentiate both entities [1]. Furthermore, GCA controls had higher serum HMGB1 than TA controls. These findings indicate that serum HMGB1 levels increase during aging and may be influenced by the burden of atherosclerosis in older individuals. In mice, the age-dependent DNA double-strand break is associated with a reduction of nuclear HMGB1 in neurons leading to an increased release of extracellular HMGB1 [36]. However, in a population study performed in Japan with 626 subjects, aging did not seem to affect serum HMGB1 levels in healthy subjects [37]. In the present study, although only a weak correlation was found between age and serum HMGB1 levels, age was independently associated with serum HMGB1 levels regardless of the diagnosis of LVV or control status.

We found a strong association between statins and lower serum HMGB1 levels in 16 patients with TA (55.2%). Recently, lower HMGB1 levels were observed in hyperlipidemic patients and in GPA patients in remission both on statin therapy [38, 39]. Moreover, atorvastatin was able to reduce in vitro the release of HMGB1 in stimulated human umbilical vein endothelial cell (HUVEC) cultures. This indicates that the inhibition of HMGB1 release by activated cells is one of the pleiotropic effects of statins [39]. Other drugs may also influence HMGB1 release from cells such as dexamethasone and metformin [40, 41]. These findings may explain in part why TA patients already under treatment presented serum HMGB1 levels similar to HC.

The role of statins in GCA has still to be determined. No impact on relapse rate or on the prevention of severe ischemic events was observed in retrospective studies. However, conflicting results were found regarding the influence of statins on acute phase reactants and daily glucocorticoid dose in GCA patients using statins [42–44]. In TA patients, a retrospective study could not find any difference in ischemic events between patients with and without statins but associations with disease activity were not analyzed [45]. In the present study, more TA patients used statins than GCA patients at diagnosis although this difference was not statistically significant (data not shown). This could be due to the long disease course of our TA patients in comparison with the GCA patients who were evaluated at disease onset.

Limitations of this study are its mainly cross-sectional nature and the inclusion of patients already on therapy for TA, whereas the low number of patients and the short-term follow-up period are limitations for the GCA patients. Nevertheless, the data seem robust enough to conclude that HMGB1 is not a suitable biomarker in LVV in contrast to SLE [23].

Conclusions

Serum HMGB1 levels were neither different between patients with LVV and HC, nor between patients with active disease and those in remission. Therefore, serum HMGB1 is not a useful biomarker for LVV. Moreover, serum HMGB1 levels were not associated with any...
356 disease phenotypes in LVV. In long-standing TA, therapy with statins seems to lead to lower serum HMGB1 levels.

357 Abbreviations

358 359 18FDG-PET/CT: 18F-fluorodeoxyglucose positron emission computed tomography;

360 ACR: American College of Rheumatology; ANCA: antineutrophil cytoplasmic antibody; BAFF: B cell-activating factor; CRP: C-reactive protein; CXCL9: chemokine (C-X-C motif) ligand 9; ELISA: enzyme-linked immunosorbent assay; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; GPA: granulomatosis with polyangiitis; HC: healthy controls; HMGB1: high mobility group box 1; HUVEC: human umbilical vein endothelial cell; IFN: interferon; Ig: immunoglobulin; IL: interleukin; ITAS: Indian Takayasu activity score; ITAS: ITAS with acute phase response; LPS: lipopolysaccharide; LV: large vessel vasculitides; MCP-1: monocyte chemoattractant protein-1; MMP-9: matrix metalloproteinase 9; PMR: polymyalgia rheumatica; RANTES: regulated on activation, normal T cell expressed and secreted; ROC: receiver operating characteristic; SLE: systemic lupus erythematosus; TA: Takayasu arteritis; Th: T helper cell; TNF-α: tumor necrosis factor alpha; UMC: University Medical Center Groningen; UNIFESP: Universidade Federal de São Paulo.

361 Competing interests

362 All authors declare that they have no competing interests.

363 Authors’ contributions

364 AWSS contributed to the study design, performed laboratory tests, conducted the statistical analysis, and drafted the manuscript. KSMG contributed to the study design, evaluated the study participants, collected data from medical records, and revised the manuscript. MB contributed to the study design, helped with the interpretation of results, and revised the manuscript. LECA contributed to the study design, helped with the interpretation of data and revised the manuscript. CGMK conceived the study, contributed to the study design, evaluated the study participants, collected data from patients, conducted the statistical analysis, and drafted the manuscript. KSMG is the guarantor for this manuscript. All authors read and approved the manuscript.

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