Moderate-to-severe atopic dermatitis patients show increases in serum C-reactive protein levels, correlating with skin disease activity [version 2; peer review: 3 approved]

Previously titled: Atopic dermatitis patients show increases in serum C-reactive protein levels, correlating with skin disease activity

Anjali S. Vekaria1*, Patrick M. Brunner2*, Ahmad I. Aleisa1, Lauren Bonomo1, Mark G. Lebwohl1, Ariel Israel3, Emma Guttman-Yassky1,2

1Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, 10029, USA
2The Laboratory for Investigative Dermatology, The Rockefeller University, New York, NY, 10065, USA
3Department of Family Medicine, Clalit Health Services, Jerusalem, 954323, Israel

* Equal contributors

Abstract

Background: Atopic dermatitis (AD), the most common chronic inflammatory skin disease, is evolving as a systemic disease, and associated systemic inflammation is possibly linked to increases in cardiovascular disease.

Methods: We assessed levels of the inflammatory marker CRP in 59 patients with moderate-to-severe AD compared to matched healthy controls, and to determine correlation with skin disease severity. Clinical severity was measured using SCORing of Atopic Dermatitis (SCORAD) and body surface area (BSA). Control subjects (n=118), matched by age, gender, smoking status and ethnicity, were obtained from the National Health and Nutrition Survey (NHANES).

Results: AD patients had significantly increased serum CRP levels compared to controls (0.7±1.0 vs. 0.4±0.7mg/dl; p=0.001), and 52.5% of them showed CRP levels >0.3mg/dl, predicting high cardiovascular risk. CRP levels were significantly correlated with both SCORAD (r=0.427, p=0.0008) and BSA (r=0.407, p=0.0015). IgE levels in AD were highly elevated (median 2903U/ml, IQR [234,10655]), but only weakly correlated with SCORAD (r=0.282, p=0.0427) and BSA (r=0.382, p=0.0052), but not with CRP levels. AD patients also showed increased LDH levels, but without significant correlations with disease severity (SCORAD, BSA) or CRP.

Conclusions: Our study strongly supports CRP as a marker for disease severity in moderate-to-severe AD patients, further demonstrating its chronic systemic nature.
Keywords
Atopic dermatitis, C-reactive protein, systemic inflammation, disease biomarker

Corresponding author: Emma Guttman-Yassky (Emma.Guttman@mountsinai.org)

Author roles: Vekaria AS: Data Curation, Investigation, Project Administration, Resources, Validation, Writing – Original Draft Preparation; Brunner PM: Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation; Aleisa AI: Data Curation; Bonomo L: Data Curation, Writing – Review & Editing; Lebwohl MG: Writing – Review & Editing; Israel A: Data Curation, Formal Analysis; Guttmann-Yassky E: Conceptualization, Funding Acquisition, Investigation, Methodology, Resources, Supervision, Writing – Review & Editing

Competing interests: PMB has received personal fees from LEO Pharma and Sanofi. EGY is a board member for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Celsus, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae, Leo Pharma, Abbvie and Asana Biosciences; has received consultancy fees from Regeneron, Sanofi, MedImmune, Celgene, Stiefel/GlaxoSmithKline, Celsus, BMS, Amgen, Drais, AbbVie, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, LEO Pharma, Novartis, Pfizer, Vitae, Mitsubushi Tanabe, Eli Lilly, Abbvie, and Asana Biosciences; and has received research support from Janssen, Regeneron, Celgene, BMS, Novartis, Merck, LEO Pharma, Dermira, Glenmark, Innovaderm, and UCB. The rest of the authors declare that they have no relevant conflicts to disclose.

Grant information: PMB was supported in part by grant # UL1 TR0001866 from the National Center for Advancing Translational Sciences and National Institutes of Health, Clinical and Translational Science Award program. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2017 Vekaria AS et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Data associated with the article are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

How to cite this article: Vekaria AS, Brunner PM, Aleisa AI et al. Moderate-to-severe atopic dermatitis patients show increases in serum C-reactive protein levels, correlating with skin disease activity [version 2; peer review: 3 approved] F1000Research 2017, 6:1712 https://doi.org/10.12688/f1000research.12422.2

First published: 20 Sep 2017, 6:1712 https://doi.org/10.12688/f1000research.12422.1
Introduction

Atopic dermatitis (AD), the most common chronic inflammatory skin disease, frequently starts during infancy, and in adults it has usually been present for several decades. Similar to moderate-to-severe psoriasis, there is now evolving evidence that AD also has a systemic component beyond the classic atopic/allergic comorbidities, with increases in cardiovascular risk factors such as obesity, and associations with cardiovascular diseases in population-based studies. A comparison of AD and psoriasis patients with healthy individuals, using cardiac computed tomography angiography, showed higher rates of coronary artery disease in both psoriasis and AD, compared to controls. Systemic immune activation in adult moderate-to-severe AD patients is reflected by highly activated circulatory T-cells as measured using T-cell activation markers (ICOS and HLA-DR), at even higher frequencies than in psoriasis. Also, several inflammatory blood biomarkers (e.g. Thymus and Activation Regulated Chemokine/TARC or CCL17) were consistently shown to correlate with AD clinical severity. The important contribution of chronic inflammation to the development of atherosclerosis and cardiovascular disease events is now well established. Therefore, C-reactive protein/CRP, an acute phase reactant reflecting systemic inflammation, has been suggested as potential biomarker for cardiovascular disease. In patients with a history of myocardial infarction, the anti-inflammatory monoclonal antibody canakinumab (IL-1β blocker) led to a significant decrease in cardiovascular events. Patients also showed reductions in serum CRP levels, without changes in their lipid profile, demonstrating that anti-inflammatory treatment can indeed have an impact on cardiovascular disease. In psoriasis, it has been demonstrated that CRP is significantly elevated and associated with disease severity. One recent study suggests that CRP levels are also increased in adult chronic AD patients vs. matched controls, but it remains to be determined whether CRP could serve as a marker for disease severity. In contrast to adults, studies in children and adolescents with active AD did not show increases in overall CRP levels compared to controls, and elevated CRP levels early in life were claimed to have a protective role against the development of AD and allergic sensitization, suggesting that chronic low-grade inflammation in infants might provide some protection from allergen sensitization. In order to better clarify the potential role of CRP as disease biomarker, we sought to investigate CRP serum levels in moderate-to-severe adult AD patients in relation to skin disease severity.

Methods

Study population

We retrospectively assessed CRP levels in serum from 59 adult AD patients (>18yo), with active AD and a Body Surface Area/BSA>10% (mean 59.6±27.9%, range 11–99%), that had presented to the outpatient clinic of the Department of Dermatology at Mount Sinai Hospital, New York, NY. All patients reported chronic AD since early infancy, and were off systemic anti-inflammatory AD treatment. Clinical severity was measured using SCORing of Atopic Dermatitis (SCORAD), and the vast majority of patients were in the moderate-to-severe category (mean SCORAD 62.2±20.86, range 15–97.5). Other demographic data was also collected, including age (mean 39.5±15.2, range 18–67 years), gender (49.25±18.5% F:M), BMI (mean 27.5±5.6kg/m², range 18.99–41.62), blood pressure (mean 123.5/77.1mmHg, range systolic 80–154, diastolic 58–109), smoking status (11.9% smokers), total serum IgE (median 293U/ml, IQR [234,10655]), ethnicity, comorbid conditions, concomitant medications and lipid profiles (Dataset 1). We also evaluated serum lactate dehydrogenase/LDH (mean 293.8U/L±115.3, range 117–597U/L), previously reported as a possible serum biomarker of AD severity. None of the patients showed clinical signs of active skin infection.

Matching

Matched control subjects were obtained with a ratio of 2-to-1 (n=118) from the National Health and Nutrition Survey/NHANES (https://www.cdc.gov/nchs/nhanes/nhanes). They were matched to AD patients for age, gender, smoking status and ethnicity, using the R procedure MatchIt, method ‘nearest’, with a ratio of 2 control subjects for each case subject. We used individuals from the SPRINT survey nationwide between the years 2005 and 2010, for which CRP laboratory data were available. There were no changes (from the previous 2 years of NHANES) to equipment, laboratory methods or lab site.

CRP serum level measurement

Serum CRP levels in AD patients were assessed using an immunoturbidimetric test (Abbott Laboratories, Lake Bluff, Illinois). For NHANES, CRP levels were assessed using a Siemens/Behring Nephelometer (Siemens Healthcare Diagnostics, Deerfield, IL), as described at https://www.cdc.gov/nchs/Nhanes/2009-2010/CRP_F.htm. Both assays had a lower limit of detection of 0.02mg/dl. While different assays were used to measure CRP levels in patients and controls, both methods have the same lower level of detection (0.02mg/dl) and were shown to be comparable.

Statistical analysis

For comparisons between AD and the control group, we used the two sample t-test for age; Fisher exact test for gender, ethnicity and smoking status; and the two sample Wilcoxon test for biomarkers. When variables were missing for some of the individuals, comparison was performed only for the individuals for which the variable was available.

Pearson correlation coefficients were used to calculate the association between the logarithm of the biomarkers (CRP, LDH, total serum IgE) and disease activity measures SCORAD and BSA. We used a univariate linear regression formula to draw the regression line for these correlations. Each correlation was performed only for the individuals for which relevant biomarker data was available. All analyses were performed using R statistical software (Version 3.3).
Results

There were no significant differences between demographic data of AD patients and controls (age, gender, ethnicity), blood lipids (triglycerides, LDL, HDL), body mass index (BMI), or smoking status (Table 1).

AD patients had significantly increased serum CRP levels (0.7±1.0mg/dl) when compared to controls (0.4±0.7mg/dl; p=0.001; Table 1 and Figure 1a). CRP levels in AD ranged from undetectable in one patient (<0.02mg/dl) to a maximum value of 6.2mg/dl in a patient with very severe AD and a SCORAD of 95 (Dataset 11). 23 out of 59 patients (39%) showed CRP levels outside the reference range of 0-0.5mg/dl. Furthermore, CRP levels were significantly correlated with both SCORAD (Figure 1b) and BSA (Figure 1c). As 14 patients reported a history of asthma, a disease that has been shown to be associated with increased CRP blood levels20, we performed a sensitivity analysis to assess the non-asthma AD patients (Supplementary Table 1). However, differences between CRP levels in AD patients and controls remained highly significant after exclusion of all the patients with a history of asthma (Figure 2, Supplementary Table 1).

Consistent with previous publications18, the AD patients also showed increased LDH levels, but without significant correlations with disease severity measures (SCORAD, BSA) or CRP (Figure 3a–c). While IgE levels in AD were highly elevated

| Table 1. Baseline characteristics and blood biomarker levels. |
|---------------------------------|-----------------|-----------------|
|                                | Control         | Atopic Dermatitis | p-value |
| Age in years, mean (SD)        | 40.3 (14.2)     | 39.5 (15.2)     | 0.707   |
| Female gender                  | 58 (49.2%)      | 29 (49.2%)      | 1.000   |
| Race and Ethnicity (%)         | 0.883           |                 |         |
| Hispanic                       | 8 (6.8%)        | 6 (10.2%)       | 0.555   |
| Non-Hispanic White             | 71 (60.2%)      | 35 (59.3%)      | 1.000   |
| Non-Hispanic Black             | 21 (17.8%)      | 9 (15.3%)       | 0.832   |
| Other                          | 18 (15.3%)      | 9 (15.3%)       | 1.000   |
| Smoking (%)                    | 1.000           |                 |         |
| Missing                        | 4 (3.4%)        | 2 (3.4%)        | 1.000   |
| NO                             | 100 (84.7%)     | 50 (84.7%)      | 1.000   |
| YES                            | 14 (11.9%)      | 7 (11.9%)       | 1.000   |
| CRP mg/dL (SD)                 | 0.4 (0.7)       | 0.7 (1.0)       | **0.001 |
| LDH U/L (SD)                   | 132.7 (30.3)    | 293.8 (115.3)   | ***<0.00001 |
| Triglycerides mg/dL (SD)       | 136.1 (158.3)   | 130.0 (69.8)    | 0.482   |
| LDL mg/dL (SD)                 | 116.1 (31.3)    | 111.5 (38.2)    | 0.357   |
| HDL mg/dL (SD)                 | 54.1 (14.4)     | 60.6 (27.8)     | 0.376   |
| Body Mass Index kg/m² (SD)     | 28.1 (6.8)      | 27.5 (5.6)      | 0.781   |

Comparisons of AD patients with matched healthy controls. Two samples t-test (age), Fisher exact test (gender, ethnicity, smoking), Wilcoxon test (CRP, LDH, triglycerides, LDL, HDL, BMI).

Figure 1. C-reactive protein levels are increased in AD patients. Comparison of CRP levels (mg/dL) in AD patients and healthy control subjects; Wilcoxon-test: p=0.001 (a); Pearson correlation and linear regression of CRP levels with SCORAD (b) and body surface area/BSA (c).
Figure 2. C-reactive protein levels are increased in AD patients without asthma. CRP levels (mg/dL) in AD patients excluding those with a history of asthma, compared to matched healthy control subjects; Wilcoxon-test: p<0.001.

Figure 3. Blood biomarker and skin correlations. LDH and total serum IgE levels correlated with SCORAD, body surface area/BSA and CRP levels (a–f); Pearson correlation and linear regression.
However, increases in CRP levels can be a result of various conditions such as infections and malignancies, which needs to be taken into account.

Our study harbors a few limitations. Besides being a retrospective study, healthy controls were not available at our site and were based on published historic controls matched for age, gender, and ethnicity. Also, it focused on a moderate-to-severe AD patient population (all but two patients had moderate-to-severe AD, i.e. a SCORAD $>25^{16}$) in a large tertiary academic center in New York, while controls were obtained across the United States, which might introduce some bias. To ensure that our results are applicable to the general AD population across ethnicities, larger international studies across different ethnic backgrounds that will also evaluate for existence of “silent” cardiovascular disease in chronic AD patients are needed. However, our data supports the role that persistent skin disease has in the systemic burden of inflammation in AD patients, mandating further investigation.

**Ethical statement**

This study has been approved by the IRB of the Icahn School of Medicine at Mount Sinai, New York, NY (approval number, 16-00717), according to the Declaration of Helsinki.

**Data availability**

Dataset 1: Individual demographics, biomarkers and comorbid conditions of the AD study patients. doi, 10.5256/f1000research.12422.d177784

**Competing interests**

PMB has received personal fees from LEO Pharma and Sanofi. EGY is a board member for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Celsus, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae, Leo Pharma, Abbvie and Asana Biosciences; has received consultancy fees from Regeneron, Sanofi, MedImmune, Celgene, Stiefel/GlaxoSmithKline, Celsus, BMS, Amgen, Drais, AbbVie, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, LEO Pharma, Novartis, Pfizer, Vitae, Mitsubishi Tanabe, Eli Lilly, Abbvie, and Asana Biosciences; and has received research support from Janssen, Regeneron, Celgene, BMS, Novartis, Merck, LEO Pharma, Dermira, Glenmark, Innovaderm, and UCB. The rest of the authors declare that they have no relevant conflicts to disclose.

**Grant information**

PMB was supported in part by grant # UL1 TR001866 from the National Center for Advancing Translational Sciences and National Institutes of Health, Clinical and Translational Science Award program.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Supplementary material

Supplementary Table 1. Baseline characteristics and blood biomarker levels of AD subset without asthma. AD patients excluding those with a history of asthma, compared with matched healthy controls. Two samples t-test (age), Fisher exact test (gender, ethnicity, smoking), Wilcoxon test (CRP, LDH, triglycerides, LDL, HDL, BMI).

Click here to access the data.

References

1. Weidinger S, Novak N: Atopic dermatitis. Lancet. 2016; 387(10023): 1109–22. PubMed Abstract | Publisher Full Text
2. Brunner PM, Silverberg JI, Gutman-Yassky E, et al.: Increasing Comorbidities Suggest that Atopic Dermatitis Is a Systemic Disorder. J Invest Dermatol. 2017; 137(1): 18–25. PubMed Abstract | Publisher Full Text
3. Silverberg JI, Greenland P: Eczema and cardiovascular risk factors in 2 US adult population studies. J Allergy Clin Immunol. 2015; 135(3): 721–8.e6. PubMed Abstract | Publisher Full Text
4. Zhang A, Silverberg JI: Association of atopic dermatitis with being overweight and obese: a systematic review and metaanalysis. J Am Acad Dermatol. 2015; 72(4): 606–16.e4. PubMed Abstract | Publisher Full Text
5. Silverberg JI: Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. Allergy 2015; 70(10): 1300–8. PubMed Abstract | Publisher Full Text
6. Hjuler KF, Böttcher M, Vestergaard C, et al.: Increased Prevalence of Coronary Artery Disease in Severe Psoriasis and Severe Atopic Dermatitis. Am J Med. 2015; 128(12): 1325–34.e2. PubMed Abstract | Publisher Full Text
7. Czarnowicki T, Malajian D, Shemer A, et al.: Skin-homing and systemic T-cell subsets show higher activation in atopic dermatitis versus psoriasis. J Allergy Clin Immunol. 2015; 136(1): 208–11. PubMed Abstract | Publisher Full Text
8. Thjis J, Krastev T, Weidinger S, et al.: Biomarkers for atopic dermatitis: a systematic review and meta-analysis. Curr Opin Allergy Clin Immunol. 2015; 15(5): 453–60. PubMed Abstract | Publisher Full Text
9. Youssif O, Mohanty BD, Martin SS, et al.: High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? J Am Coll Cardiol. 2013; 62(5): 387–408. PubMed Abstract | Publisher Full Text
10. Ridker PM, Everett BM, Thuren T, et al.: Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017; (in press). PubMed Abstract | Publisher Full Text
11. Strober B, Teller C, Yamauchi P, et al.: Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol. 2000; 159(2): 322–30. PubMed Abstract | Publisher Full Text
12. Wang J, Suárez-Farinas M, Estrada Y, et al.: Identification of unique proteomic signatures in allergic and non-allergic skin disease. Clin Exp Allergy. 2017. PubMed Abstract | Publisher Full Text
13. Silverberg JI: Association between childhood atopic dermatitis, malnutrition, and low bone mineral density: a US population-based study. Pediatr Allergy Immunol. 2015; 26(1): 54–61. PubMed Abstract | Publisher Full Text
14. Marsch E, Kuitunen M, Kukkonen K, et al.: Probiotics in infancy induce protective immune profiles that are characteristic for chronic low-grade inflammation. Clin Exp Allergy. 2008; 38(4): 611–8. PubMed Abstract | Publisher Full Text
15. Mustonen K, Orivuori L, Keski-Nisula L, et al.: Inflammatory response and IgE sensitization at early age. Pediatr Allergy Immunol. 2013; 24(4): 396–401. PubMed Abstract | Publisher Full Text
16. Pucci N, Lombardi E, Novembre E, et al.: Increased Prevalence of Coronary Artery Disease in Severe Psoriasis and Severe Atopic Dermatitis. J Allergy Clin Immunol. 2015; 136(10): 1300–8. PubMed Abstract | Publisher Full Text
17. Vekaria AS, Brunner PM, Alesa AI, et al.: Dataset 1 in: Atopic dermatitis patients show increases in serum C-reactive protein levels, correlating with skin disease activity. F1000Research. 2017. Data Source
18. Morishima Y, Kawashima H, Takekuma K, et al.: Changes in serum lactate dehydrogenase activity in children with atopic dermatitis. Pediatr Int. 2010; 52(2): 171–4. PubMed Abstract | Publisher Full Text
19. Mali B, Armbruster D, Seredaik E, et al.: Comparison of immunoturbidimetric and immunonephelometric assays for specific proteins. Clin Biochem. 2009; 42(15): 1568–71. PubMed Abstract | Publisher Full Text
20. Agassandian M, Shurin GV, Ma Y, et al.: C-reactive protein and lung diseases. Int J Biochem Cell Biol. 2014; 53: 77–88. PubMed Abstract | Publisher Full Text
21. Navarii AA, French LE, Holfbauer GF: Interrupting IL-6-receptor signaling improves atopic dermatitis but associates with bacterial superinfection. J Allergy Clin Immunol. 2011; 128(5): 1128–30. PubMed Abstract | Publisher Full Text
22. Koppes SA, Brans R, Ljubojovic Hadzavdic S, et al.: Stratum Corneum Tape Stripping: Monitoring of Inflammatory Mediators in Atopic Dermatitis Patients Using Topical Therapy. Int Arch Allergy Immunol. 2016; 170(3): 187–93. PubMed Abstract | Publisher Full Text | Free Full Text
23. Kaul S, Morrissey RP, Diamond GA: By Jove! What is a clinician to make of JUPITER? Arch Intern Med. 2010; 170(12): 1073–7. PubMed Abstract | Publisher Full Text
Open Peer Review

Current Peer Review Status: ✔️ ✔️ ✔️

Reviewer Report 21 November 2017

https://doi.org/10.5256/f1000research.14051.r27679

© 2017 Menter A et al. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Alan Menter
Division of Dermatology, Baylor University Medical Center, Dallas, TX, USA

Isabel Haugh
Baylor Dermatology Residency Program, Baylor University Medical Center, Dallas, Texas, USA

This is a quality and important review by Vekaria et al from the Dermatology program of Mount Sinai in New York with Emma Guttman-Yassky- a leading clinician and researcher in the field of Atopic Dermatitis worldwide as corresponding author.

The nature of Atopic Dermatitis as a systemic inflammatory disease with comorbidities has been significantly accelerated over the past five years, especially with the initiation of the International Eczema Council (IEC) by Dr.s Guttman-Yassky and Paller. Of interest are the 3 meetings the IEC has had with the International Psoriasis Council (IPC) comparing the immunopathogenesis and comorbidities of Atopic Dermatitis and Psoriasis.

Of interest, in this C-reactive protein review of 59 patients in Atopic Dermatitis Reference #11 (B. Strober et al) mentions the increased levels of CRP in psoriasis. It is important to recognize now that psoriasis has been demonstrated to be a systemic immune-mediated disease that CRP levels in psoriasis patients with moderate to severe disease are significantly lower than in psoriasis patients who develop Psoriatic Arthritis and also are lower than other immune-mediated systemic disease, e.g. Crohn's or Rheumatoid Arthritis.

We do believe it should be emphasized in the title and abstract that this CRP review was carved out in adults only. In addition, it should be clarified in the method section that data was obtained retrospectively.

We all recognize that CRP is an acute phase reactant that can increase with infections/autoimmune/cancer as well as cardiovascular disease. Thus, reference should be made in this article to comorbidities in this group of 59 Atopic Dermatitis patients which could have possibly played a role in the increases of CRP.
References
1. Strober B, Teller C, Yamauchi P, Miller JL, et al.: Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol. 2008; 159 (2): 322-30 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Psoriasis

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 20 November 2017
https://doi.org/10.5256/f1000research.14051.r27404

© 2017 Navarini A. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Alexander A. Navarini
Department of Dermatology, University Hospital of Zurich, Zurich, CH-8091, Switzerland

Thank you, my concerns have now been fully addressed.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Inflammatory skin disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 06 November 2017

https://doi.org/10.5256/f1000research.14051.r27475

© 2017 Su J. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

John C. Su
Department of Dermatology, Eastern Health Clinical School, Monash University, Melbourne, Vic, Australia

1. This is an interesting and considered study, a single-centre series of 59 adult patients matched 1:2 with controls from the nationwide NHANES survey. CRP, LDH and sIgE were correlated with AD severity, assessed by SCORAD and BSA.

Was there a reason for choosing SCORAD over objective SCORAD or EASI, which rely only on objective measures? Of interest, was CRP in adult AD vs non-AD using the NHANES data itself done (cf Silverberg Pediatr Allergy Immunol 2015)?

2. CRP, a marker of cardiovascular risk, was found to be elevated in AD, and correlated with AD severity. sIgE correlated with AD severity, but not with CRP. LDH did not show significant correlation with AD severity or CRP.

In addition to the Silverberg pediatric paper, Park et al\(^1\) presented a pediatric inpatient study of 67 children examining the relationship between eczema severity (mild-moderate vs severe) and a
number of laboratory markers. They did not find correlation with CRP, LDH or skin cultures. That paper was pediatric, written in Korean and also has limitations, but may be worth referencing for comparison.

3. Some potential confounders were considered. Sensitivity analysis was performed for non-asthma AD patients; this subgroup still showed correlation between CRP and AD severity. The patients did not have clinical infection. Were any swabs done? Some patients in the dataset had other co-morbidities that could have contributed to the CRP. The nature of the control group may not allow ready comparison of these, but a comment about possible or unlikely confounding from co-morbidities as the case may be worth considering.

References
1. Park G, Park J, Hwang Y, Sung M, et al.: The correlation between the severity of atopic dermatitis classified by SCORing atopic dermatitis index and the laboratory tests. Allergy Asthma & Respiratory Disease. 2013; 1 (1). Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?  Yes

Is the study design appropriate and is the work technically sound?  Yes

Are sufficient details of methods and analysis provided to allow replication by others?  Yes

If applicable, is the statistical analysis and its interpretation appropriate?  Yes

Are all the source data underlying the results available to ensure full reproducibility?  Yes

Are the conclusions drawn adequately supported by the results?  Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatric dermatology and inflammatory skin disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Alexander A. Navarini
Department of Dermatology, University Hospital of Zurich, Zurich, CH-8091, Switzerland

Vekaria, Brunner et al. present a nice and clear clinical Investigation into AD severity and CRP levels.
The title should be adapted to "Moderate-to-severe AD patients ..." as you have really investigated just this population.

In the correlations, the patients with high CRP Levels are omitted for some (graphical?) reason. Please state why and whether the Pearson r is calculated with or without them. I don't think this changes the conclusion of the paper but IMHO should be shown. If you have access to the raw SCORAD data, you might be able to check whether subcomponents of the SCORAD have a closer connection to the Serum CRP than others:
- eczema involvement of some body regions
- crusting, oozing
- excoriations (scratch marks)

I think it may be worth adding to the abstract that >50% of the moderate-to-severe AD patients were in the range of cardiovascular high-risk CRP levels. Also, you should probably discuss all ways to lower the high CRP. The best of them may be anti-IL6R, which also works in atopic dermatitis according to a case series.

**Is the work clearly and accurately presented and does it cite the current literature?**
Yes

**Is the study design appropriate and is the work technically sound?**
Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**
Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**
Partly

**Are all the source data underlying the results available to ensure full reproducibility?**
No

**Are the conclusions drawn adequately supported by the results?**
Yes

**Competing Interests:** No competing interests were disclosed.
Reviewer Expertise: Inflammatory skin disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 17 Oct 2017
Emma Guttman-Yassky, Icahn School of Medicine at Mount Sinai, New York, USA

We thank the reviewer for his positive and encouraging comments. We have changed the title accordingly.

All patients have been included in the graphs. We have now corrected the axis labeling for a more clear display of CRP levels in the correlation graphs Figures 1b and 1c, and Figures 3c and 3d.

Due to the retrospective nature of the study, we do not have access to the sub-components of SCORAD. Therefore, we cannot calculate these correlations.

We have now modified the abstract and the discussion section accordingly.

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com