Biomarkers for atopic dermatitis: a systematic review and meta-analysis

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Table S1. Data extraction

**Longitudinal studies**
Multiple measurements (mostly values before and after treatment)
- study size (number of patients)
- mean/median age of AD patients
- AD severity scoring system (SCORAD, SASSAD, EASI, LSS)
- mean length of follow-up (days)
- significant or non-significant changes in biomarker values and severity scores
- r-value (Spearman/Pearson correlation coefficient)

**Cross-sectional studies**
Single measurements in AD patients
- study size (number of patients)
- significant or non-significant correlation biomarker-scoring system?
- r-value (Spearman/Pearson correlation coefficient)

**Outcome measurements**
Correlation between: change in biomarker and change in clinical severity score
Table S2. Biomarkers

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Figure S1. Funnel plots of longitudinal studies

- **TARC**
  - Fisher's z Transformed Correlation Coefficient
  - Standard Error

- **sE-selectin**
  - Fisher's z Transformed Correlation Coefficient
  - Standard Error

- **Total IgE**
  - Fisher's z Transformed Correlation Coefficient
  - Standard Error

- **ECP**
  - Fisher's z Transformed Correlation Coefficient
  - Standard Error
Figure S2. Funnel plots of cross-sectional studies

TARC
MDC
CTACK
IL-18
LDH
IgE
ECP
CD30
Vitamin D
REFERENCES


17. Furue M, Koga T, Yamashita N. Soluble E-selectin and eosinophil cationic protein are distinct serum markers that differentially represent clinical features of atopic dermatitis. The British journal of dermatology 1999; 140.


28. Heshmat NM, El-Hadidi ES. Soluble CD30 serum levels in atopic dermatitis and bronchial asthma and its relationship with disease severity in pediatric age. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology 2006; 17.


34. Czech W, Krutmann J, Schopf E, Kapp A. Serum eosinophil cationic protein (ECP) is a sensitive measure for disease activity in atopic dermatitis. The British journal of dermatology 1992; 126.

35. Furue M, Sugiyama H, Tsukamoto K, Ohtake N, Tamaki K. Serum soluble IL-2 receptor (sIL-2R) and eosinophil cationic protein (ECP) levels in atopic dermatitis. Journal of dermatological science 1994; 7.


51. Matsumoto T, Miike T, Yamaguchi K, Murakami M, Kawabe T, Yodoi J. Serum levels of soluble IL-2 receptor, IL-4 and IgE-binding factors in childhood allergic diseases. Clinical and experimental immunology 1991; 85.


76. Park do S, Youn YH. Clinical significance of serum interleukin-18 concentration in the patients with atopic dermatitis. The Korean journal of laboratory medicine 2007; 27.


95. Lee SA, Hong S, Kim HJ, Lee SH, Yum HY. Correlation between serum vitamin D level and the severity of atopic dermatitis associated with food sensitization. Allergy, Asthma and Immunology Research 2013; 5:207-10.


125. Huang JL, Lee WY, Chen LC, Kuo ML, Hsieh KH. Changes of serum levels of interleukin-2, intercellular adhesion molecule-1, endothelial leukocyte adhesion molecule-1 and Th1 and Th2 cell in severe atopic dermatitis after intravenous immunoglobulin therapy. Annals of Allergy, Asthma & Immunology : Official Publication of the American College of Allergy, Asthma, & Immunology 2000; 84.


149. Nakazato J, Kishida M, Kuroiwa R, Fujiwara J, Shimoda M, Shinomiya N. Serum levels of Th2 chemokines, CCL17, CCL22, and CCL27, were the important markers of severity in infantile atopic dermatitis. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 2008; 19.

151. Shimada Y, Takehara K, Sato S. Both Th2 and Th1 chemokines (TARC/CCL17, MDC/CCL22, and Mig/CXCL9) are elevated in sera from patients with atopic dermatitis. Journal of dermatological science 2004; 34.


173. Kanbe T, Soma Y, Kawa Y, Kashima M, Mizoguchi M. Serum levels of soluble stem cell factor and soluble KIT are elevated in patients with atopic dermatitis and correlate with the disease severity. The British journal of dermatology 2001; 144.


221. Wang SS, Hon KL, Kong APS, Pong HNH, Wong GWK, Leung TF. Vitamin D deficiency is associated with diagnosis and severity of childhood atopic dermatitis. Pediatric Allergy and Immunology 2014; 25:30-5.
