Dyslipidemia among allergic rhinitis patients: Frequency and risk factors

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ABSTRACT

Background: Although cumulative data strongly suggest an association between dyslipidemia and allergic disorders, especially asthma, evidence regarding allergic rhinitis (AR) is lacking. We aimed to assess frequency and associated risk factors of dyslipidemia among patients with AR.

Methods: The current study is a cross-sectional study that recruited 150 AR patients by systematic randomization. Blood samples for serum lipid profile, total immunoglobulin E (IgE) and serum interleukin-17A (IL-17A) were withdrawn from all patients.

Results: Dyslipidemia was prevalent in 84 AR patients (56%). Higher levels of total IgE, IL17-A, and sensitization to hay dust and mixed mites significantly increased the risk of dyslipidemia among AR patients by 1.004, 1.062, 4.057 and 3.652 respectively ($P < 0.05$).

Conclusion: High serum total IgE level, high serum IL-17A level, and sensitization to hay dust and mixed mites are independent risk factors for dyslipidemia among AR patients.

Keywords: Allergic rhinitis, Interleukin-17, Dyslipidemia

INTRODUCTION

Allergic rhinitis (AR) is an inflammatory disease of the nose caused by immunoglobulin E (IgE) mediated hypersensitivity reaction that is induced by exposure to allergens. AR is characterized by 4 cardinal symptoms: watery rhinorrhea, nasal obstruction, nasal itching, and sneezing. AR is now thought to be a systemic disorder, and the resulting inflammation affects not only the respiratory passages but the entire body. One theory is that chronic airway inflammation may contribute to systemic inflammation as well as vulnerability to vascular disease. An alternative theory indicates that upregulation of cytokines in AR may promote migration and activation of inflammatory cells implicated in atherogenesis and dyslipidemia.

Lipid metabolism has been shown to skew T cell programming, promote T helper (Th)2 and Th17 polarization, and enhance Th2 and Th17 cytokine profile release (Interleukin (IL)-6, IL-1, IL-4, and IL-17) as well as downregulating synthesis of IL-10. IL-17 was found to contribute to the induction of allergen-specific Th2 cell activation,
eosinophil accumulation, and serum IgE production, thus suggesting a regulatory role of IL-17A on the established Th2-driven allergic immune response. However, the findings on IL-17 are ambiguous and the role of Th17-cells in AR remains unclear.\(^7\)

The mediators of inflammation and allergy correlate with lipid levels, advancing the hypothesis that the inflammation, allergy, and lipid profiles could be functional parts of the same network.\(^5\) Numerous case control studies have explored the relation between dyslipidemia and AR, reporting that dyslipidemia was statistically significantly higher in AR patients. However, to our knowledge, there are limited cross-sectional studies investigating the risk factors of dyslipidemia among AR patients. Therefore, this study aimed to assess prevalence and associated risk factors of dyslipidemia among patients with AR in 2 university hospitals.

**METHODS**

**Study design and study subjects**

We conducted a comparative cross-sectional study over a period of 2 months.

We enrolled 150 adult AR patients selected by systematic randomization from patients attending the Allergy & Immunology Clinic of Internal Medicine Department and Allergy & Immunology Unit of Medical Microbiology and Immunology Department from 2 university hospitals. Written and verbal consent was taken from the participating patients.

AR was diagnosed using the standard criteria by Bousquet et al, 2008.\(^8\) Inclusion criteria were atopic adult (>18 years old) AR patients with positive skin prick test (SPT) for at least 1 inhalant allergen. We excluded bronchial asthma patients, patients with acute illness (eg, high-grade fever), first 2 weeks following surgery, chronic sinusitis, non-allergic inflammatory nasal pathology, diabetes mellitus, hypothyroidism, hypertension, renal diseases, liver diseases, obesity, autoimmune disorder, other allergic diseases, and patients receiving lipid lowering drugs. No patients received systemic steroids or immunotherapy within 1 month of enrolment. Also, smokers and patients with excessive alcohol intake were excluded from the study.

Detailed medical history of allergy, thorough clinical examination (ear, nose, throat, and chest examination), and SPT to common environmental aeroallergens were performed in the clinic. Venous blood samples were withdrawn from all participants for serum lipid profile, total serum IgE, and serum level of IL-17A.

**Assessment of allergic rhinitis severity**

According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, AR was categorized, according to frequency of symptoms into: a) Intermittent (<4 days per week or <4 weeks per year), and b) Persistent (>4 days per week or >4 weeks per year). The severity of AR was measured using Visual analogue scale (VAS) score for global assessment of severity of nasal and non-nasal symptoms. AR patients were asked to globally rate the combination of the nasal and non-nasal symptoms on a provided scale (0-10 cm) as follows: Mild: 0-3; Moderate: 3.1-7; Severe: 7.1-10.\(^8\) Quality of Life (QoL) was assessed by the rhinoconjunctivitis quality of life questionnaire (RQLQ) total score.\(^9\)

**Skin Prick Testing**

Skin prick testing (SPT) was performed according to Bernstein et al, 2008.\(^10\) A panel for the most common locally encountered inhaled allergens was used including: House dust mites, cockroach, cotton, molds mix, ragweed, mugwort, Chenopodium album, hay dust, pigeon feathers, dog hair, cat hair, and rabbit hair. Histamine dihydrochloride (10 mg/mL) was used as a positive control, while saline was used as a negative control. The largest diameter of the wheal of each particular test is measured, a positive being a wheal of ≥3 mm\(^10\).

**Sample collection**

Under complete aseptic conditions, 10 mL of fasting venous blood were obtained by a clean venipuncture in the early morning from all the participants, after 9-12 h of fasting. Patients were on regular average diet 3 days before sampling. The serum was separated by centrifugation (1000×g for 15 min) and divided into 3 tubes.
Serum of 1 tube was immediately assayed for lipid profile (total cholesterol (TC), total triglycerides (TG), high density lipoproteins-cholesterol (HDL-C), and low density lipoproteins-cholesterol (LDL-C)), while the serum collected in the other tube was stored at −20 °C for subsequent assay of the serum total IgE, IL-17A concentrations. Hemolyzed samples were discarded. Repeated freezing and thawing was avoided.

Serum lipid profile

Analysis of serum lipid profile was performed on a microlab 300 semi-automated spectrophotometer (Elitech group, France). Dyslipidemia was defined according to the American College of Cardiology/American Heart Association (ACC/AHA) Blood Cholesterol 2013 Guideline, as follows: hypercholesterolemia was defined as TC level greater than 200 mg/dL and/or LDL-C level greater than 100 mg/dL, hypertriglyceridemia as TG level greater than 150 mg/dL; and low HDL-C lower than 40 mg/dL in men and 50 mg/dL in women.11

Serum total IgE concentration

Quantitative measurement of serum total IgE in the serum was done using a commercially available quantitative enzyme-linked immunosorbent assay (ELISA) Kit supplied by Calbiotech Inc. (1935 Cordell Ct., El Cajon, CA 92020, USA) according to the manufacturer’s instructions and results were expressed in IU/mL.

Serum IL-17A concentration

IL17-A was measured by commercially available quantitative ELISA Kit supplied by Thermo Fisher Scientific (Bender MedSystems gmbH/Campus Vienna Biocenter 2/1030 Vienna, Austria) according to the manufacturer’s instructions and expressed in pg/mL.

Statistical analysis

Descriptive statistics were calculated for all the variables, including continuous variables (reported as mean values and standard deviations) and categorical variables (reported as numbers and percentages). For between-group comparisons, the independent t-test, Mann Whitney test was used for continuous variables and Pearson’s χ2-test test for nominal variables, where appropriate. Binary logistic regression analysis was used to identify independent factors of dyslipidemia among AR patients with adjusted odds ratios (AORs), Crude Odds Ratio (COR) and corresponding 95% confidence intervals (CIs) calculated. All the statistical analyses were performed using SPSS version 20.0 software, and P values less than 0.05 were considered to be statistically significant.

RESULTS

Basic characteristics of study population

Out of 150 patients with AR recruited, males represented 58.7%. Mean age was 32.19 years (±8.05), and mean body mass index (BMI) was 21.815 (±2.275) Kg/m2. Nasal obstruction was the predominant symptom in 110 (73.3%) patients followed by watery nasal discharge in 95 (63.3%) patients, while itchy nose was the least presenting symptom in 19 (12.7%) patients. Approximately 62% AR patients had moderate/severe persistent AR by ARIA (Allergic Rhinitis and its Impact on Asthma guidelines). SPT revealed 52%, 46.7%, and 40.7% of patients were sensitized to house dust, mixed mites, and animal danders respectively (Table 1).

Frequency of dyslipidemia among AR patients

According to serum lipid profile, AR patients were divided into dyslipidemia group (n = 84) and normal lipid profile group (n = 66). Abnormal serum lipid profile (TG ≥ 150 mg/dL and/or TC ≥ 200 mg/dL) was found in 84 patients (56%). Twenty-eight AR patients suffered from elevated LDL-C, while 56, 27, and 28 AR patients suffered from elevated TC, elevated TG and low HDL, respectively. Single lipid profile abnormality occurred in 22 patients while 62 had combined lesions (Fig. 1).

Risk factors associated with dyslipidemia

Univariate analysis of dyslipidemia and both demographic and disease-specific characteristics showed a statistically significant relationship between dyslipidemia and both VAS score and sensitization to hay dust and mixed mites. There was no statistical significance between dyslipidemia and age, gender, associated allergic disorders, sensitization to other aeroallergens, and
RQLQ score. Sensitization to hay dust and mixed mites significantly increased risk of dyslipidemia among AR patients by 4.21 and 3 folds respectively, while sensitization to wool, mixed pollens, mixed molds and cockroaches, comorbid bronchial asthma, perennial AR, and intermittent moderate/severe AR non-significantly increased risk of dyslipidemia (Table 2). The dyslipidemia group showed significantly more severe symptoms of AR as compared to the normal lipid profile group. Although QoL was lower in AR patients with dyslipidemia, the difference did not reach a statistical significance (Table 3).

Assessing relation between dyslipidemia and laboratory data of AR patients revealed that AR patients with dyslipidemia had significantly higher serum total IgE and IL-17A levels in comparison to AR patients with normal lipid profile (Table 4).

Multivariate analysis of factors associated with dyslipidemia showed that higher serum total IgE level, higher serum IL-17A level, and sensitization to hay dust and mixed mites were significant independent risk factors for dyslipidemia that significantly increased the risk of dyslipidemia among AR patients by 1.004, 1.062, 4.057, and 3.652, respectively ($P < 0.05$) (Table 5).

**DISCUSSION**

Although the etiology of atopy is unclear, immunological and environmental factors have been implicated. Dyslipidemia is 1 factor that modulates the immune response by promoting Th2 and Th17 polarization, establishing a state of chronic inflammation.\textsuperscript{12}

Our findings indicated that dyslipidemia was prevalent among AR patients, where LDL-C showed the highest level followed by TC. These findings are concordant with available

| Characteristics | AR patients (n = 150) |
|-----------------|----------------------|
| **Gender, n (%)** |                      |
| Female          | 62 (41.3)            |
| Male            | 88 (58.7)            |
| **Age, years**  |                      |
| Mean ± SD       | 32.19 ± 8.05         |
| **BMI (kg/m²)** |                      |
| Mean ± SD       | 21.815 ± 2.275       |
| **Symptoms, n (%)** |                  |
| Runny nose      | 95 (63.3)            |
| Sneezing        | 68 (45.3)            |
| Nasal obstruction | 110 (73.3)        |
| Post nasal drips | 46 (30.7)           |
| Itchy nose      | 19 (12.7)            |
| Cough           | 53 (35.3)            |
| Eye symptoms    | 23 (15.3)            |
| **ARIA classification** |                 |
| Mild Intermittent | 2 (1.3)               |
| Moderate to severe intermittent | 1 (0.7)           |
| Mild persistent | 54 (36)              |
| Moderate/severe Persistent | 93 (62)            |
| **SPT, n (%)**  |                      |
| House dust      | 78 (52)              |
| Cotton dust     | 25 (16.7)            |
| Wool            | 32 (21.3)            |
| Mixed molds     | 28 (18.7)            |
| Animal danders  | 61 (40.7)            |
| Mixed pollens   | 83 (55.3)            |
| Hay dust        | 35 (23.3)            |
| Cockroach       | 37 (24.7)            |
| Mixed mites     | 70 (46.7)            |
| **VAS score**\textsuperscript{b} |       |
| Mean ± SD       | 5.897 ± 1.325        |
| **RQLQ score**\textsuperscript{c} |            |
| Mean ± SD       | 4.363 ± 0.896        |

Table 1. Basic characteristics of study population a. SPT, skin prick test b. VAS visual analogue scale c. RQLQ rhinoconjunctivitis quality of life questionnaire
| Characteristics                             | AR patients (n = 150) |       |       |       |       |
|--------------------------------------------|-----------------------|-------|-------|-------|-------|
|                                            |                       | COR<sup>c</sup> | (95% CI)<sup>d</sup> |       |       |
|                                            |                       |       |       |       |       |
|                                            | Dyslipidemia group n = 84 |       |       |       |       |
| Gender, no (%)                             |                       |       |       |       |       |
| Female                                     | 36 (58.1)             | 26 (41.9) | 1.15 (0.6-2.22) |       |       |
| Male                                       | 48 (54.5)             | 40 (45.5) | 1 (reference) | 0.669 |       |
| Age (years), no (%)                        |                       |       |       |       |       |
| 16–30 years                                | 36 (58.1)             | 26 (41.9) | 1.15 (0.6-2.22) |       |       |
| >30–52 years                               | 48 (54.5)             | 40 (45.5) | 1 (reference) | 0.669 |       |
| SPT, no (%)<sup>a</sup>                    |                       |       |       |       |       |
| House dust                                 | 42 (53.8)             | 36 (46.2) | 0.83 (0.44-1.59) | 0.58  |       |
| Animal dander                              | 31 (50.8)             | 30 (49.2) | 0.7 (0.36-1.35) | 0.29  |       |
| Cotton dust                                | 12 (48)               | 13 (52) | 0.68 (0.29-1.6) | 0.377 |       |
| Wool                                       | 21 (65.6)             | 11 (34.4) | 1.67 (0.74-3.76) | 0.216 |       |
| Mixed pollens                              | 50 (60.2)             | 33 (39.8) | 1.47 (0.77-2.82) | 0.244 |       |
| Mixed molds                                | 19 (67.9)             | 9 (32.1) | 1.85 (0.78-4.42) | 0.161 |       |
| Hay dust                                   | 28 (80)               | 7 (20) | 4.21 (1.7-10.42) | 0.001 |       |
| Cockroach                                  | 23 (62.2)             | 14 (37.8) | 1.4 (0.65-3) | 0.384 |       |
| Mixed mites                                | 49 (70)               | 21 (30) | 3 (1.53-5.9) | 0.001 |       |
| ARIA classification<sup>b</sup>            |                       |       |       |       |       |
| Mild Intermittent                          | 2 (100)               | 0 (0) | ∞ | 0.495 |       |
| Moderate/severe intermittent               | 1 (100)               | 0 (0) | ∞ | ∞ | 0.495 |
| Mild persistent                            | 34 (63)               | 20 (37) | 1.66 (0.84-3.3) | >0.999 |       |
| Moderate/severe Persistent                 | 47 (50.5)             | 46 (49.5) | 1 (reference) | 0.144 |       |
| Associated allergies, no (%)              |                       |       |       |       |       |
| None                                       | 54 (50.9)             | 51 (49.1) | 1 (reference) | 1.96 (0.93-4.12) | 0.202 |
| Allergic conjunctivitis                    | 29 (69)               | 14 (31) | 1.96 (0.93-4.12) | 0.202 |       |
| Atopic dermatitis                          | 1 (50)                | 1 (50) | 0.94 (0.06-15.5) | >0.999 |       |
| Seasonal AR                                |                       |       |       |       |       |
| Perennial                                  | 48 (56.5)             | 37 (43.5) | 1.05 (0.55-2) | 1 (reference) | >0.999 |
| Seasonal                                   | 36 (55.4)             | 29 (44.6) | 0.94 (0.06-15.5) | >0.999 |       |

Table 2. Comparison of clinical characteristics between dyslipidemia group and normal lipid profile group among AR patients.  
<sup>a</sup>SPT, skin prick test  
<sup>b</sup>ARIA, Allergic Rhinitis and its Impact on Asthma  
<sup>c</sup>COR, Crude Odds Ratio  
<sup>d</sup>CI, confidence interval, p < 0.05 is statistically significant, p ≤ 0.001 is statistically highly significant
LDL-C has been found to increase adhesion, diapedesis, and macrophage trapping with upregulation of TNF-α and IL-1 which in turn induce a state of chronic inflammation.\(^\text{15}\)

AR patients with dyslipidemia showed significantly more severe AR symptoms as compared to AR patients with normal lipid profile. This is partially in line with previous studies.\(^\text{5,16,17}\) Dyslipidemia promotes Th2 and Th17 cytokine profile release (IL-6, IL-1, IL-4, and IL17)\(^\text{12}\) and also downregulates IL-10.\(^\text{18}\) All these factors promote and exacerbate a state of chronic inflammation which in turn exacerbates AR symptoms.

Intermittent AR (either mild or moderate/severe) non-significantly increased the risk of dyslipidemia. Conversely, La Mantia et al found significantly higher serum lipids in patients with moderate/severe AR, particularly those with intermittent symptoms as compared with patients with mild disease.\(^\text{5}\) However, the difference in cytokine pattern between persistent and intermittent AR could be explained since elevated levels of proinflammatory cytokines are seen in both disease entities. Nonetheless, they are more pronounced in intermittent AR, indicating a higher degree of inflammation and disturbed lipid levels.\(^\text{19}\) An alternative explanation could be the impact of steroid therapy on lipoprotein metabolism both in acute and chronic dosing.

The current study showed a statistically significant relationship between presence of dyslipidemia and sensitization to hay dust and mixed mites, increasing the risk of dyslipidemia by 4.21 and 3 folds respectively. These data are consistent with Vinding et al who showed that both HDL-C and TG levels were associated with aeroallergen sensitization among children with allergic airway diseases.\(^\text{20}\) However, Schäfer et al noted a negative linear association between TC and LDL levels and the frequency of atopic sensitization and AR incidence. Conversely, a positive linear association was detected between HDL levels and AR severity.

| Laboratory parameters | AR patients (N = 150) | p-value |
|-----------------------|-----------------------|---------|
| Total IgE (IU/mL)     |                       |         |
| Mean ± SD             | 179.204 ± 134.619     | 0.042   |
| Range                 | 12.5-531              |         |
| IL-17A (pg/mL)        |                       |         |
| Mean ± SD             | 46.19 ± 8.403         | 0.018   |
| Range                 | 32-68                 |         |

Table 4. Comparison of laboratory characteristics between dyslipidemia group and normal lipid profile group among AR patients p < 0.05 is statistically significant.
and atopic sensitization and AR incidence, although no significance was detected after adjustment for covariates.\textsuperscript{21} Fessler et al reported that increase in TC and non-HDL-C increased the risk of atopy, yet this association was race specific.\textsuperscript{22}

Similar findings were reported by Fenger et al who tested the hypothesis that metabolic biomarkers associated with adipose tissue dysfunction, namely serum TG and HDL levels could be predictive of wheezing and AR, independent of obesity. The study group reported that increased TG and low HDL were significantly associated with wheezing, with more pronounced association in individuals without rhinitis symptoms than patients with symptoms.\textsuperscript{23}

The relation between dyslipidemia and atopic sensitization can be explained by the mechanism of how lipoproteins take part in the pathogenesis of allergy mechanisms. In other words, dyslipidemia induces a shift toward an immunologic Th2-oriented response and then enhances allergic inflammation, which has been found in mice.\textsuperscript{5,24} Total serum cholesterol (HDL-C and HDL-C) may also potentiate eosinophilic inflammation in those with genetic susceptibility for atopy, with a significant correlation between serum cholesterol and elevated inflammatory markers. Authors also found that the administration of pravastatin decreased pulmonary allergic inflammation. A similar anti-inflammatory effect of statins at varying doses has been demonstrated in other animal studies indicating its therapeutic potential in asthma.\textsuperscript{25}

Limitation

We are aware of the relatively small sample size of our study population, and large scale multi-center studies should be performed to further elucidate the importance of measuring serum lipid profile in AR patients. Additionally, longitudinal studies might serve to better understand the causal relationship between dyslipidemia and AR where we could determine whether AR is preceded by dyslipidemia or the other way round. The role of IL-17A as a biomarker of AR severity and its role in dyslipidemia should be further elucidated.

CONCLUSION

In summary, high total IgE, high IL-17A, and sensitization to hay dust and mixed mites were closely related to dyslipidemia in AR patients. These results highlight the need for routine screening programs for serum lipid profile in AR patients with appropriate intervention programs aiming at risk factor reduction.

ABBREVIATIONS

Allergic rhinitis, AR; immunoglobulin E, IgE; T helper, Th; Interleukin, IL; skin prick test, SPT; Allergic Rhinitis and its Impact on Asthma, ARIA; Visual analogue scale, VAS; quality of life, QOL; rhinoconjunctivitis quality of life questionnaire, RQLQ; total cholesterol, TC; total triglycerides, TG; high density lipoproteins-cholesterol, HDL-C; low density lipoproteins-cholesterol, LDL-C; American College of Cardiology/American Heart Association, ACC/AHA; enzyme-linked immunosorbent assay, ELISA; adjusted odds ratios, AORs; Crude

Table 5. Logistic regression to risk factors of dyslipidemia among AR patients  

| Risk factors                          | β    | p-value | AOR\textsuperscript{a} | Lower | Upper   |
|--------------------------------------|------|---------|-------------------------|-------|---------|
| Total IgE(IU/mL)                      | 0.004| 0.020   | 1.004                   | 1.001 | 1.007   |
| IL-17A (pg/mL)                       | 0.060| 0.014   | 1.062                   | 1.012 | 1.114   |
| Sensitization to hay dust            | 1.400| 0.005   | 4.057                   | 1.543 | 10.671  |
| Sensitization to mixed mites         | 1.295| 0.001   | 3.652                   | 1.696 | 7.867   |

\textsuperscript{a} AOR, adjusted odds ratio \textsuperscript{b} CI, confidence interval, p < 0.05 is statistically significant, p ≤ 0.001 is statistically highly significant.
Odds Ratio, COR; confidence intervals, CIs; body mass index, BMI.

Author contributions
All authors contributed equally to the development of the paper. All authors approved the final version.

Availability of data and materials
Data and material are available.

Ethical approval
The study was approved by the institutional review board (IRB), Faculty of medicine, Zagazig University. In addition, the Research Ethics Committee at Ain Shams University approved the study. An informed written consent was obtained from all participants at the time of recruitment.

Authors' consent for publication
Each author listed in the manuscript had seen and approved the submission of this version of manuscript and takes full responsibility for it.

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