

Putative roles of circulating resistin in patients with asthma, COPD and cigarette smokers

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Abstract. *Aims:* To investigate the hypothesis that circulating resistin reflects the degree of pulmonary inflammation, this study explores putative roles of resistin in patients with acute and stable inflammatory obstructive airway diseases and cigarette smokers.

Methods: We determined complements C3, C4, fasting resistin, insulin, glucose and lipid profile; calculated insulin resistance (homeostasis model assessment (HOMA-IR) in patients with acute asthma exacerbation ($n = 34$); stable asthma ($n = 26$) and stable chronic obstructive pulmonary disease (COPD; $n = 26$), cigarette smokers ($n = 81$), and healthy control subjects ($n = 42$). We determined the associations between these variables and pulmonary function tests.

Results: Patients with COPD, acute and stable asthma had significantly higher resistin and insulin than control subjects. Resistin, insulin, HOMA-IR, FEV1% and FEV1/FVC were significantly ($p < 0.05$) different between patients with acute asthma compared with stable asthma and COPD; smokers had similar levels of resistin, C3 and C4 as patients with asthma and COPD. In smokers, patients with asthma or COPD, resistin showed significant inverse correlations with FEV1%; FEV1/FVC% and positive significant correlations with BMI and HOMA-IR. Logistic regression showed that resistin is associated ($p < 0.05$) with inflammatory obstructive airways disease – odds ratio (OR) = 1.22 and smoking OR = 1.18.

Conclusion: Resistin may be a disease activity marker and may contribute to insulin resistance in smokers, asthma and COPD.

Keywords: Asthma, chronic obstructive pulmonary diseases, insulin resistance, resistin, smokers

1. Introduction

Resistin, also called adipose tissue-specific secretory factor (ADSF) or Found in Inflammatory Zone (FIZZ3) is a hormone, which is secreted by adipose tissue cells in mouse [1] but has been shown to be produced by monocytes with increased expression as the monocytes mature into macrophages in humans [2]. Although results have been controversial, studies on resistin have focused mainly on its potential role in obesity-related insulin resistance with studies showing lack of association [3,4] and others showing significant associa-

tions between resistin, insulin resistance and Type 2 diabetes [5,6].

Much less controversial is the association of resistin with inflammatory conditions and several studies have shown association of resistin with inflammatory factors such as $\text{TNF}\alpha$, IL-6 and C-reactive protein (CRP) [6–8]. Resistin has been linked to several inflammation-related diseases like atherosclerosis, arthritis [9] and recently to inflammatory lung diseases [10,11]. Larochelle et al. found patients with asthma to have higher levels of resistin compared to normal controls and those levels were increased with disease severity in an asthmatic cohort [10].

Some published studies have shown that resistin's association with inflammatory markers appeared independent of Body Mass Index (BMI) [12] though other studies showed significant BMI-dependent association with insulin resistance and factors linked with obesity

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and inflammation in patients with type 2 diabetes [6, 13]. Hypoxia, especially in the expanding adipose-tissue of obese subjects, has been shown to cause dys-regulated production of adipokines and could affect resistin levels [14,15]. In patients with obstructive inflammatory airway disease, it is unclear whether the determinants of circulating resistin are obesity related factors such as insulin resistance or the degree of inflammation. Therefore, the present study was designed to test the hypothesis that circulating resistin reflects the degree of pulmonary inflammation in patients with acute and stable inflammatory obstructive airway disease (asthma and chronic obstructive pulmonary disease (COPD) as well as subjects who smoke cigarettes and, therefore, likely to have airway inflammation. The study also aimed at evaluating the determinants and associations of resistin as well as complements C3 and C4 which have been shown to play key roles in the induction or amplification of airways inflammation in airways diseases such as asthma and chronic obstructive airways disease [16–18].

2. Patients, materials and methods

2.1. Subjects

Five main groups of patients were recruited for this study – group 1 subjects with acute asthma exacerbation ($n = 26$), group 2 subjects with stable chronic asthma ($n = 34$), group 3 consisted of patients with stable COPD ($n = 26$) and group 4 consisted of subjects who smoke ($n = 81$; consisting of 42 subjects who smoke cigarettes and 39 subjects who smoke Sheesha (hubble-bubble or hooka – a traditional method of smoking tobacco leaves in the Middle East and Indian subcontinent) and group 5 were apparently healthy non-smoking subjects ($n = 42$). Acute and stable asthma were defined and managed according to the National Heart, Lung and Blood Institute Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication number 08-4051, 2007. [19]. The COPD patients were identified by using the NHLBI/WHO Global Initiative for chronic obstructive lung disease (GOLD) Workshop Summary [20]. The subjects were interviewed by a trained nurse or a physician and details of current and past medical histories, drug history and nature of therapy and smoking status were recorded. Patients with stable asthma were maintained on low to moderate dose inhaled steroid (beclomethasone or budesonide up to 200 μg /

day increasing to moderate dose of up to 400 $\mu\text{g}/\text{day}$; alternatively, some patients were maintained on fluticasone 250 $\mu\text{g}/\text{day}$ increasing to 500 $\mu\text{g}/\text{day}$ as required) plus long acting inhaled bronchodilators when indicated. While COPD patients were mainly on short or long acting bronchodilators. Severely hypoxic patients requiring mechanical ventilation were excluded from the study. In groups 1–3 and control subjects other exclusion criteria included smoking, use of oral steroids or statins and presence of any other concurrent inflammatory disease at the time of recruitment for the study. Six of the patients in group 3 had never smoked and all the other patients were ex smokers. Group 4 subjects were apparently healthy subjects who smoke and who are not on any medication. All the participating subjects gave informed voluntary consent to participate in the study according to the protocol approved by the local ethics committee and in accordance with the ethical standards of the Helsinki declaration.

Fasting (defined as eight hours or longer since the last meal before specimen collection) blood samples were collected from all participating subjects. Patients with asthma exacerbation had their blood samples collected before commencement of therapy. All anthropometric measurements were made by trained observers using standard techniques (World Health Organisation. Measuring obesity: classification and distribution of anthropometric data. Copenhagen: WHO, 1989. (Nutr UD, EUR/ICP/NUT 125) [21] with the participant wearing light clothes without shoes. Height (to the nearest 0.1 cm) was determined by use of a stadiometer, and weight (to the nearest 0.1 kg) was determined by use of a standardized standing beam balance and from these the body mass index (BMI) was calculated as weight (kg) divided by the height (m) squared.

2.2. Spirometry

Spirometry (Using the Jaeger Masterlab (version 4.34, GmbH, Germany) was done on all patients with asthma (acute and stable), COPD as well as cigarette smokers. The system was calibrated for body temperature and pressure of saturated gas and volume and as per American Thoracic Society Standards (ATS) [22].

3. Laboratory methods

3.1. Inflammatory markers

Levels of complement C3 and C4 were assayed on the Beckman IMMAGE[®] (Beckman Corporation, Brea, CA, USA) immunochemistry analyser.

3.2. Resistin

Fasting plasma resistin was measured using an enzyme-linked immunoassay (ELISA) kit (BioVendor, Brno, Czech Republic) with a limit of detection of 0.20 ng/ml. The inter- and intra-assay coefficients of variation on pooled plasma specimen with resistin concentration of 6.8 ng/mL were 3.4% and 5.2% respectively.

3.3. Other assays

Fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), and creatinine were analyzed on an automated analyzer (Beckman LX20, Beckman Corporation, Brea, CA, USA). The low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula [23].

Fasting serum insulin was determined with the Immulite 1000 automated immunoassay system (DPC, Los Angeles, USA). Insulin resistance was calculated using the homeostasis model assessment (HOMA) formula using a calculator downloaded from <http://www.dtu.ox.ac.uk/index.html?maindoc=/publications/> [24]. The HOMA calculator also gives estimates of steady state beta cell function (%B) and insulin sensitivity (%S).

3.4. Statistical methods

Statistical analyses were performed using the Statistical Package for Social Sciences version 14 for windows (SPSS Inc. Chicago, USA). Distributions of continuous variables were tested for normality. Relationships between continuous variables were assessed using Pearson correlation coefficient. Study population characteristics and anthropometric and laboratory measurements were presented as mean and 95% confidence intervals (CI). Comparison between two groups was performed with the unpaired student *t*-test and the Kruskal-Wallis analysis of variance was used to determine the differences between more than two groups. The associations of resistin with obstructive airways disease, insulin resistance and smoking were examined by binary logistic regression analysis that included age, BMI, glucose, insulin and HOMA-IR as potential confounders. Values of $p \leq 0.05$ were considered to be statistically significant.

4. Results

4.1. General

Table 1 summarises the results from the various study groups. The subjects were matched for BMI and fasting glucose but patients with COPD were older than control subjects because, for logistic reasons and local factors, we were unable to recruit older age-matched healthy controls. Patients with acute and stable asthma and those with COPD had significantly higher resistin and insulin than control subjects (Fig. 1). Kruskal-Wallis analysis of variance shows that resistin ($p = 0.019$), insulin ($p = 0.03$), HOMA-IR ($p = 0.02$), FEV1% ($p = 0.002$) and FEV1/FVC ($p < 0.0001$) were significantly different when patients with acute asthma were compared to those with stable asthma and COPD but the inflammatory markers C3 and C4 were not. Subjects who are smokers had similar levels of the inflammatory markers C3 and C4 with patients with asthma and COPD and these were significantly higher than in control subjects.

4.2. Correlations of resistin

In control subjects, resistin showed modest correlation with BMI ($r = 0.27$; $p = 0.045$) but did not show significant correlations with insulin, HOMA-IR and other metabolic variables.

In patients with asthma or COPD, resistin showed significant inverse correlations with FEV1% ($r = -0.41$; $p = 0.01$) and FEV1/FVC% ($r = -0.33$; $p = 0.04$). Resistin also showed significant correlations with BMI ($r = 0.31$; $p = 0.046$); insulin ($r = 0.31$, $p = 0.03$) HOMA-IR ($r = 0.42$, $p = 0.027$) and C3 ($r = 0.32$, $p = 0.046$) but did not show significant correlations with complement C4 and glucose. However, in this group, BMI also showed significant correlations with C3 ($r = 0.33$; $p = 0.008$); insulin ($r = 0.51$; $p < 0.0001$); glucose ($r = 0.28$; $p = 0.028$). Figure 2 shows the correlation of resistin with C3 in patients with acute asthma.

The mean (95% CI) smoking pack years in the cigarette smokers was 21.9 (6.8–37.0) pack years. In these subjects, resistin also showed significant inverse relationships with FEV1% ($r = -0.28$; $p = 0.04$); FEV1/FVC% ($r = -0.26$; $p = 0.04$); BMI ($r = -0.31$, $p = 0.04$) and HDL cholesterol ($r = -0.38$; $p = 0.03$) and significant positive correlation with HOMA-IR ($r = 0.27$, $p = 0.03$).

Table 1
Characteristics of the subjects. Results are mean (95% confidence interval)

Parameter	Controls	Acute asthma	Stable asthma	COPD	Smokers
Age (years)	41.4 (36.8–47.1)	51.9 (45.7–58.1)*	46 (39.5–52.5)	68.0 (64.6–71.5)**	37.8 (36.2–39.4)
BMI (kg/m ²)	26.7 (25.0–28.4)	27.9 (25.0–30.8)	25.9 (23.4–28.4)	21.1 (18.7–23.4)	26.9 (25.9–28.0)
Fasting Glucose (mmol/L)	5.2 (4.7–5.7)	5.6 (5.1–6.0)	5.2 (4.7–5.7)	5.8 (5.2–6.4)	5.5 (5.4–5.6)
Fasting Insulin μ IU/ml	5.3 (4.1–6.3)	17.8 (10.5–25.2)***	19.6 (11.5–27.7)***	10.7 (5.6–15.7)**	5.9 (5.3–6.4)
HOMA-IR	1.3 (0.9–1.7)	2.3 (1.6–2.9)*	2.3 (1.4–3.2)**	1.6 (0.8–2.3)	1.9 (1.3–2.6)*
Total Cholesterol (mmol/L)	4.3 (4.0–4.6)	3.5 (3.1–3.8)	3.9 (3.5–4.4)	3.5 (3.0–4.0)	5.2 (5.0–5.4)*
Triglycerides (mmol/L)	1.3 (1.1–1.5)	1.1 (0.9–1.2)	1.6 (1.4–1.9)*	1.0 (0.8–1.2)	1.6 (1.4–1.8)*
HDL Cholesterol (mmol/L)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.7 (0.6–0.9)	0.9 (0.7–1.1)	1.0 (1.0–1.1)
LDL Cholesterol (mmol/L)	2.8 (2.5–3.0)	2.1 (1.8–2.3)	2.5 (2.1–2.8)	2.1 (1.7–2.4)	3.7 (3.5–3.9)
Resistin (ng/mL)	4.2 (3.7–4.8)	6.9 (5.1–8.7)**	4.6 (3.0–6.2)*	8.1 (3.8–12.4)**	8.9 (7.0–10.8)**
Complement C3 g/L	0.9 (0.8–0.9)	1.5 (1.3–1.6)**	1.7 (1.5–1.8)**	1.4 (1.3–1.4)**	1.4 (1.1–1.7)**
Complement C4 g/L	0.3 (0.2–0.3)	0.4 (0.4–0.5)*	0.4 (0.4–0.4)*	0.4 (0.3–0.5)*	0.4 (0.3–0.5)*
FEV1%	Not Done	53 (44–62)	74 (62–86)	44 (32–57)	90.4 (87.7–93.1)
FEV1 / FVC%	Not Done	64 (57–72)	85 (75–94)	54 (43 - 64)	89.3 (88.0–90.7)

***Difference from control group is significant at the 0.0001 level (2-tailed).

**Difference from control group is significant at the 0.001 level (2-tailed).

*Difference from control group is significant at the 0.05 level (2-tailed).

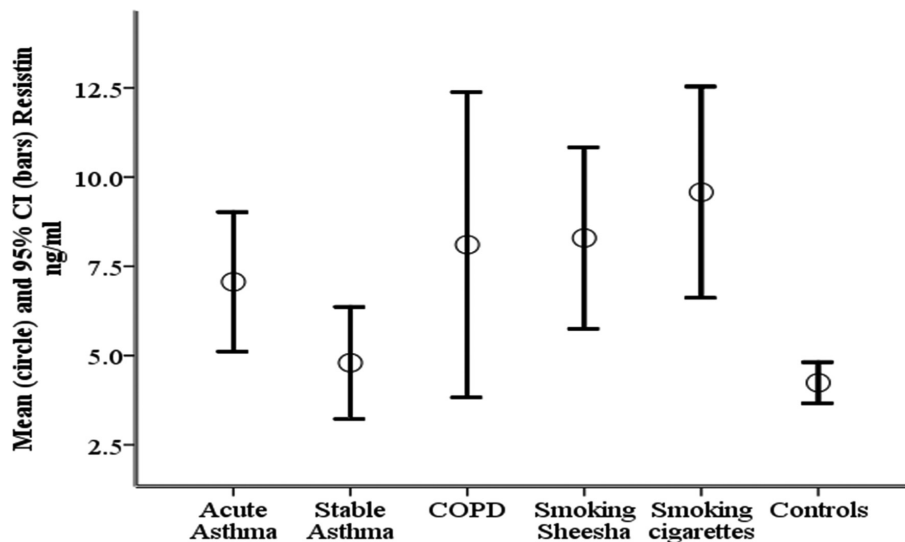


Fig. 1. Error bar plots showing serum resistin in the different groups of subjects studied. The circles in the middle of the error bars represent the mean and the bars represent the 95% confidence interval (CI). COPD = chronic obstructive pulmonary disease.

4.3. Regression analyses

On binary logistic regression with obstructive airways disease (asthma or COPD) as the dependent variable, resistin was significantly associated with inflammatory obstructive airways disease odds ratio (OR) and (95% confidence interval (CI) = 1.22 (1.12–1.33) $p = 0.001$. However when the confounding effects of age, BMI, glucose, insulin and HOMA-IR were included in the model, the association became insignificant, OR (95% CI) = 1.12 (0.93–1.31); $p = 0.12$. However, resistin was significantly associated with smoking, OR (95% CI) = 1.18 (1.10–1.28); $p < 0.0001$ and this as-

sociation remained significant when confounding factors (age, BMI, glucose, insulin and HOMA-IR) were included in the model, OR (95% CI) = 1.2 (1.04–1.42).

5. Discussion

In this study we have shown that resistin is significantly higher in patients with inflammatory obstructive airways disease compared to control subjects. We have also shown that smoking is associated with higher resistin and inflammatory markers C3, C4. Our finding of higher resistin, C3 and C4 in smokers is novel as

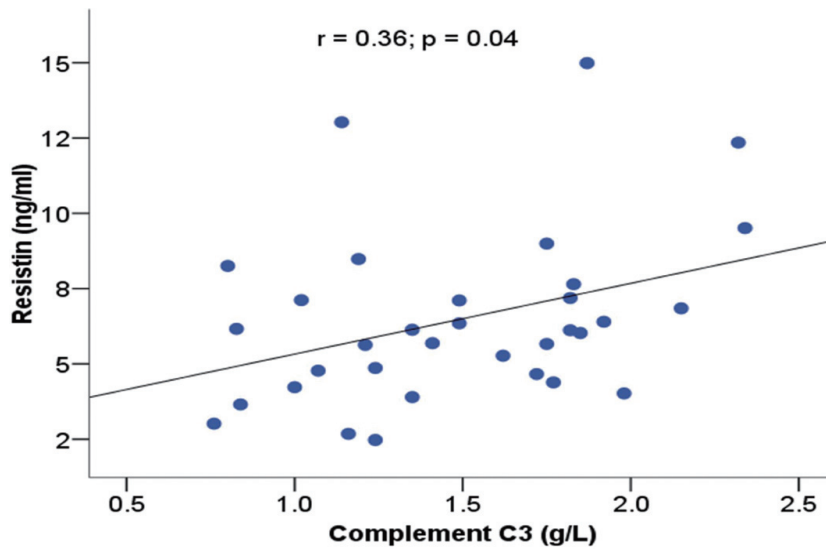


Fig. 2. Scatter plot showing the relationship between resistin and complement C3 in patients with acute asthma exacerbation. Line through the scatter points is regression based fit line showing the trend of the data.

we are not aware of previous studies showing this phenomenon. This finding suggests that smoking produces the same types of effect as inflammatory obstructive airways diseases.

The finding that resistin is increased in subjects with pulmonary inflammation confirms earlier studies [10, 11]. Although, initially identified as a protein, secreted by adipocytes with potential roles in adipose tissue differentiation and insulin resistance, several studies have now confirmed that resistin is associated with inflammation [7–9]. In fact, one of the resistin-like molecules (RELM), RELM α was originally found in inflammatory zones in a murine model of experimental asthma [25]. It is now believed that the predominant producer of resistin in humans are macrophages [26] but whether resistin is simply a marker of inflammation or an active promoter of airway inflammation and even lung remodeling in humans remains a matter of conjecture. There are reports which suggest that resistin plays a role in promoting airway inflammation in a murine animal model [27]. In the study by Mishra et al. [27] intrathecal administration of RELM-beta resulted in dose-dependent increased accumulation of macrophages and goblet cell hyperplasia. The correlation of resistin with complement C3 (Fig. 2) supports the fact that the role of resistin in this experimental model of allergic airway inflammation is similar to what occurs in humans. We have also shown that smoking and inflammatory obstructive airways disease share similar responses with regards to resistin, C3 and C4. This is not surprising

because smoking may affect airway function in similar ways due to its toxic and pro-inflammatory effects [28].

Resistin probably contributes to the higher insulin and HOMA-IR in patients with inflammatory airways disease and smokers. The high insulin levels (Table) in relation to acute asthma exacerbation, chronic stable asthma and COPD could be explained in terms of the effects of intermittent hypoxia (as occurs in acute asthmatics) versus chronic hypoxia (COPD patients) on glucose metabolism. It is known that acute exposure to hypoxia at high altitudes [29–31] results in worsening of glucose tolerance; whereas sustained exposure to hypoxia at high altitude is not associated with persistent abnormalities in glucose homeostasis [30] partly because chronic high altitude exposure stimulates glucose production but increases peripheral insulin sensitivity. Moreover, for a given level and duration of exposure, the systemic and cellular responses that affect glucose homeostasis are more potent with intermittent than with sustained hypoxia [32] which might explain the high and variable levels of insulin (Table) in patients with asthma and COPD. This could also explain the higher HOMA-IR observed in patients with asthma compared to controls and patients with COPD. The observation of significantly higher HOMA-IR in smokers (Table 1) is in agreement with the well known association of smoking with insulin resistance [33]. The correlation of resistin with HOMA-IR in smokers suggests that resistin may be a contributory factor to the insulin resistant state. Apart from the cross-sectional design which can not prove “the cause and effect relationships”, the only

other limitation of this study is that we did not do *a priori* sample size calculations for detection of differences in HOMA-IR resistin concentrations in the different subgroups. However, *a posteriori* calculations showed that the power to detect differences between the controls and other subgroups at an alpha error of 0.05 was as high as 0.80 for HOMA-IR and 0.85 for resistin.

In conclusion, this study has confirmed and extended earlier observations that showed resistin to be a marker of pulmonary inflammation. Our results suggest that smoking and conditions with pulmonary inflammation are accompanied by higher resistin which contributes to an insulin resistant state. The higher resistin in smokers is independent of the BMI and degree of insulin resistance and may be a key player linking smoking, insulin resistance and cardiovascular disease.

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