Airway Inflammation, Diagnosis, Perception of Asthma, and Sputum Zinc Levels in a Community Cohort.

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Abstract

Induced sputum examination (IS), an established research tool to measure airway inflammation (AI), is normally confined to specialised institutions and selected populations with airway disease, especially asthma. This thesis examines the role of IS in the diagnosis of asthma in a community.

The first study explores the accepted definitions of asthma, the utility of IS, and another marker of AI, exhaled nitric oxide (eNO), in establishing the diagnosis of asthma. The findings confirm that symptoms, variable airflow obstruction and airway hyper-responsiveness (AHR) are inter-linked in the definition of asthma. Bronchodilator reversibility (BDR), used traditionally, remains the most specific test to aid a diagnosis of asthma in the community. The results favour a tailored approach in the diagnosis of asthma using BDR initially, then selecting a test, either eNO or IS depending on the clinical scenario. The usefulness of AHR with hypertonic saline to diagnose asthma is equivocal given the moderate sensitivity and poor specificity of the test documented within. If a global assessment of AI is required, an eNO measurement is recommended initially, given its ease of use. Sputum examination is useful in delineating the subtype of AI present.

Dyspnoea is a cardinal symptom in asthma. Studies have shown a correlation between AI measured by IS and an altered perception of dyspnoea (POD) in selected subjects with asthma. The aim of the second and third studies was to determine if a similar relationship exists in subjects with and without AHR from a community sample. In both groups, increasing POD was related to worsening lung function and increased BMI. Increased POD was also associated with poorer psychosocial and economic outcomes in subjects with AHR. In the context of previous research, these results illustrate

that heightened POD itself, rather than asthma, is associated with these outcomes. Sputum eosinophilia was not associated with an altered POD in subjects with and without asthma.

There has been mounting research establishing the role of zinc as an immunomodulator in asthma. Mouse models have demonstrated that zinc deficiency is associated with airway eosinophilia. Two pools of zinc exist in the body: largely fixed, enzyme-bound zinc, and free or labile zinc, the biologically active component. With zinc deficiency, it is the latter pool that is preferentially depleted. Our laboratory has developed a novel method, Zinquin fluorometry, allowing measurement of labile zinc in body fluids. The final two studies demonstrate that IS lends itself to labile zinc measurements. Zinquin fluorometry was optimised to measure free pools of zinc in sputum. It was then used to quantify labile sputum zinc concentrations in subjects with and without asthma. Lower zinc concentrations were found in the sputum of subjects with asthma and a significant association noted between lower zinc concentrations and worsening asthma severity.

From a community perspective, these findings suggest that while IS has a limited role in diagnosing asthma, it lends itself to measurement of airway zinc. This work has been conducted in a cross-sectional community cohort where relationships were explored. Ongoing research is required to establish causal links conclusively.

Declaration

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Abbreviations

AHR: airway hyper-responsiveness

AE: airway epithelium

AI: airway inflammation

BAL: brochoalveolar lavage

BDI: baseline dyspnoea index

BDR: bronchodilator reversibility

BMI: body mass index measured as weight in kilograms(kg) divided by height in metres squared(m^2);

CDF: cation diffusion facilitator

COPD : chronic obstructive pulmonary disease

ECP: eosinophil cation protein

eNO: exhaled nitric oxide

Eo: eosinophil

ESAHR: episodic symptoms and airway hyper -responsiveness

ESDBDR: episodic symptoms and bronchodilator reversibility

FEV_1: forced expiratory volume in one second

FVC: forced vital capacity

GP : general practitioner

HS: hypertonic saline

IQR: interquartile range

IS: induced sputum examination

L: litres

µL: microlitres

NWAHS : North West Adelaide Health Study

OVA: ovalbumin

PC_{20}: provocation concentration causing 20 percent fall in FEV_1 from baseline

PEF: peak expiratory flow

POD: perception of dyspnoea

ppb: parts per billion

SABA: short acting beta 2 agonist

SD: standard deviation

SF-36: short form 36 quality of life questionnaire

SRDD: self reported doctor diagnosis

TCC: total cell count

TH1: T helper 1

TH2: T helper 2

Zn : zinc

ZIP: ZRT/IRT –related protein