Coexistence of obesity and asthma determines a distinct respiratory metabolic phenotype

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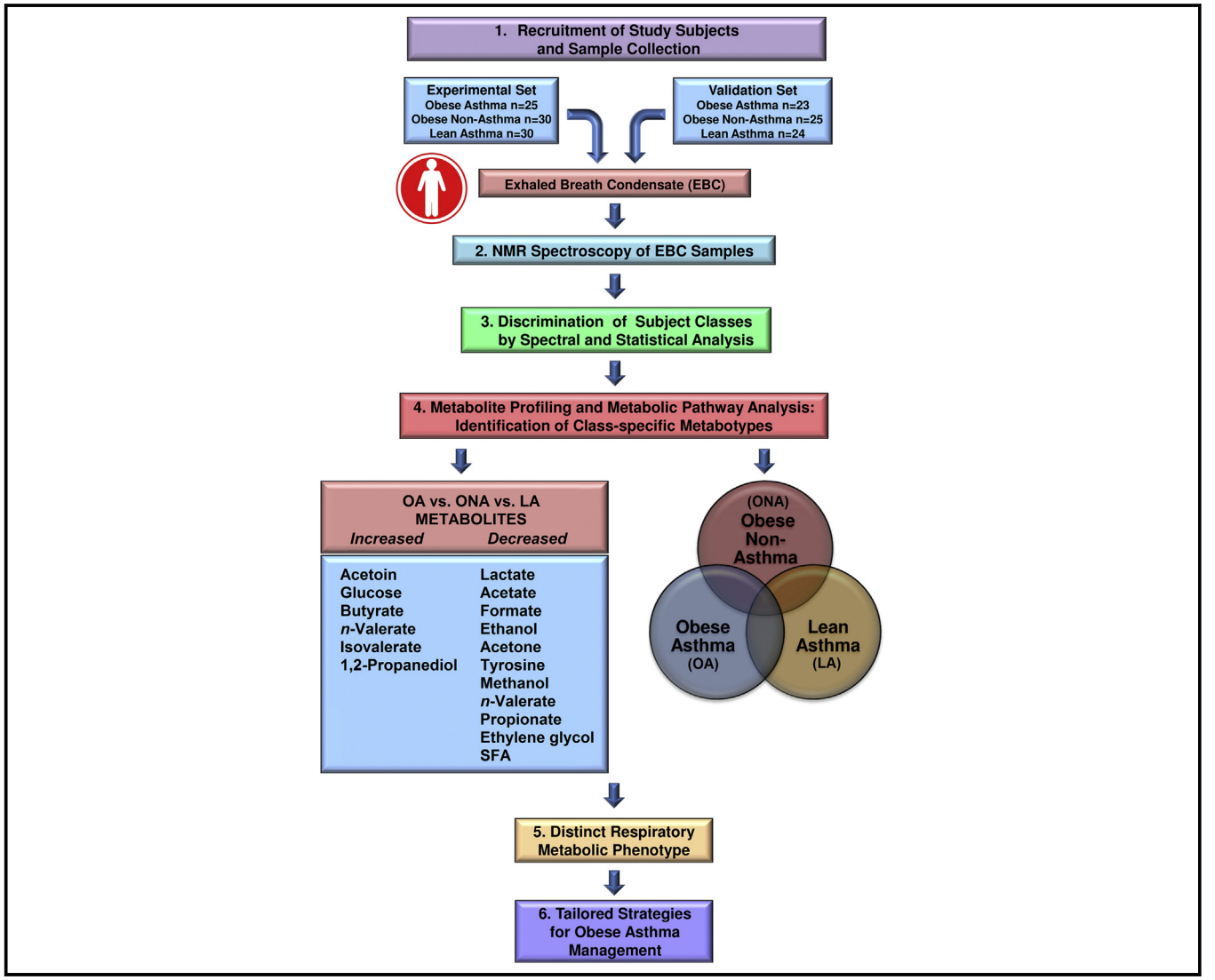
GRAPHICAL ABSTRACT



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Background: Epidemiologic and clinical evidence supports the existence of an obesity-related asthma phenotype. No distinct pathophysiologic elements or specific biomarkers have been identified thus far, but increased oxidative stress has been reported.

Objective: We aimed at verifying whether metabolomics of exhaled breath condensate from obese asthmatic (OA) patients, lean asthmatic (LA) patients, and obese nonasthmatic (ONA) subjects could recognize specific and statistically validated biomarkers for a separate "asthma-obesity" respiratory metabolic phenotype, here defined as "metabotype."

Methods: Twenty-five OA patients, 30 ONA subjects, and 30 mild-to-moderate LA age-matched patients participated in a cross-sectional study. Nuclear magnetic resonance (NMR) profiles were analyzed by using partial least-squares discriminant analysis, and the results were validated with an independent patient set.

Results: From NMR profiles, we obtained strong regression models that distinguished OA patients from ONA subjects (quality parameters: goodness-of-fit parameter $[R^2] = 0.81$ and goodness-of-prediction parameter $[Q^2] = 0.79$), as well as OA patients from LA patients ($R^2 = 0.91$ and $Q^2 = 0.89$). The all-classes comparison ($R^2 = 0.86$ and $Q^2 = 0.83$) indicated that OA patients possess a respiratory metabolic profile fully divergent from those obtained in the other patient groups. We also identified specific biomarkers for between-class separation, which are independent from clinical bias. They are involved in the methane, pyruvate, and glyoxylate and dicarboxylate metabolic pathways.

Conclusions: NMR-based metabolomics indicates that OA patients are characterized by a respiratory metabolic fingerprint fully different from that of patients independently affected by asthma or obesity. Such a phenotypic difference strongly suggests unique pathophysiologic pathways involved in the pathogenesis of asthma in adult obese subjects. Furthermore, the OA metabotype could define a strategy for patient stratification based on unbiased biomarkers, with important diagnostic and therapeutic implications. (J Allergy Clin Immunol 2017;139:1536-47.)

Key words: *Obesity, asthma, phenotype, nuclear magnetic resonance, metabolomics, profiling, exhaled breath condensate, biomarkers*

Abbreviations used

BMI:	Body mass index
1D:	One-dimensional
2D:	2-dimensional
EBC:	Exhaled breath condensate
FVC:	Forced vital capacity
GINA:	Global Initiative for Asthma
HSQC:	Heteronuclear single quantum coherence
LA:	Lean asthmatic
NMR:	Nuclear magnetic resonance
OA:	Obese asthmatic
ONA:	Obese nonasthmatic
OPLS:	Orthogonal projections to latent structures
OPLS-DA:	Orthogonal projections to latent structures–discriminant analysis
OSC:	Orthogonal signal correction
PLS-DA:	Partial least-squares discriminant analysis
Q^2:	Goodness-of-prediction parameter
R^2:	Goodness-of-fit parameter
ROS:	Reactive oxygen species
SCFA:	Short-chain fatty acid
TOCSY:	Total correlation spectroscopy
TSP:	Sodium 3-trimethylsilyl (2,2,3,3-$^2H_4$)propionate

Asthma affects more than 350 million subjects worldwide.[1] Both clinical features and underlying pathophysiologic processes indicate that asthma is a heterogeneous disease, phenotypes of which depend on complex genetic traits, inflammatory status, comorbidities, age, time of onset, and demographic characteristics.[2,3] A phenotype consistently suggested in unbiased cluster analyses is the "asthma-obesity" phenotype,[4,5] which deserves particular attention given the increasing incidence worldwide of both conditions. Several epidemiologic studies corroborate the association between asthma and obesity,[6,7] with the latter found to be a risk factor for incident asthma and affecting its severity, control, and medication response.[8,9]

Several factors (genetic, epigenetic, mechanical, and inflammatory) might contribute to a distinct asthma phenotype occurring in the context of obesity.[10] Obesity is currently viewed as an inflammatory state,[8,11] and the inflammatory milieu found in obese asthmatic (OA) patients, both systemically and in the lungs, also supports the existence of a distinct and specific obese asthma phenotype related to the age of onset and the type of underlying inflammation.[11] In fact, obesity associated with late-onset asthma displays features that indicate the occurrence of non-T_H2, oxidative stress–driven inflammation, such as low fraction of exhaled nitric oxide, low eosinophil counts and IgE levels, and poor response to glucocorticoid therapy.[9,11,12] In this context increased secretion from adipose tissue of the proinflammatory adipokine leptin, as well as reduction in secretion of the anti-inflammatory adipokine adiponectin, might contribute to the development of asthma by skewing airway inflammation toward the mentioned molecular phenotype.[13,14]

The definition of obesity as a determinant of an independent asthma phenotype will be more conclusive with the identification of reliable biomarkers applicable in diverse clinical settings. Exhaled breath condensate (EBC) is a simple and noninvasive matrix by which several inflammatory biomarkers have been identified within the volatile compartment of the lung epithelial lining fluid,[15] offering potential applications for diagnosis and long-term follow-up. Currently, nuclear magnetic resonance (NMR)–based metabolomics of EBC are widely used for metabolic profiling.[16,17] It unambiguously recognizes biomarkers that separate healthy subjects from children with asthma,[18] adults with chronic obstructive pulmonary disease,[19] and adults with other pulmonary diseases.[20-22] We recently reported that obese patients present a specific respiratory metabolic phenotype ("metabotype") that differentiates them from the corresponding control population of lean asthmatic (LA) patients and nonasthmatic subjects, respectively.[23,24]

In the present study we investigate whether the additional presence of asthma changes the profile of obese subjects by comparing the metabotype of obese asthmatic (OA) patients with that of LA patients and obese nonasthmatic (ONA) subjects. To further test the hypothesis that asthma in obese subjects holds a specific molecular phenotype, we searched for metabolites that