Metabolic Phenotypes in Asthmatic Adults

Subjects: Respiratory System
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Bronchial asthma is a chronic respiratory disease that belongs to all ages. Transforming involves chronic airway inflammation and symptoms of varying magnitude over time, which include dyspnea, chest tightness, and coughing. It has a high prevalence, high morbidity and considerable levels of mortality. According to the Global Initiative for Asthma (GINA), “Asthma is a heterogeneous disease with different underlying pathological processes. Recognizable groups of demographic, clinical and/or pathophysiological characteristics are called 'asthma phenotypes'. In fact, several studies show that various asthma subtypes may be reflected in external manifestations of the disease, which are designated as “phenotypes”, and may involve clinical and inflammatory characteristics, among others. However,

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1. Overview

Bronchial asthma is a chronic disease that affects individuals of all ages. It has a high prevalence and is associated with high morbidity and considerable levels of mortality. However, asthma is not a single disease, and multiple subtypes or phenotypes (clinical, inflammatory or combinations thereof) can be detected, namely in aggregated clusters. Most studies have characterized asthma phenotypes and groups of phenotypes using mainly clinical and inflammatory parameters. These studies are important because they can have clinical and prognostic implications and can also help define personalized treatment approaches. In addition, several metabolomics studies have helped to better define the metabolic characteristics of asthma, using electronic noses or targeted and non-targeted approaches. In addition to discriminating between asthma and a healthy state, metabolomics can detect the metabolic signatures associated with some asthma subtypes, namely, eosinophilic and non-eosinophilic phenotypes or the obese asthma phenotype, and this can be very useful in application to the site of attendance. In addition, metabolomics also discriminates between asthma and other “phenotypes” of chronic obstructive airway diseases, such as chronic obstructive pulmonary disease (COPD) or Asthma-COPD Overlap (OAC). However, there are still several aspects that need to be further investigated in the context of asthma phenotypes in properly designed, homogeneous and multicentric studies, using appropriate tools and integrating metabolomics in a multilevel approach. namely, eosinophilic and non-eosinophilic phenotypes or the obese asthma phenotype, and this can be very useful in the application at the point of care. In addition, metabolomics also discriminates between asthma and other “phenotypes” of chronic obstructive airway diseases, such as chronic obstructive pulmonary disease (COPD) or Asthma-COPD Overlap (OAC). However, there are still several aspects that need to be further investigated in the context of asthma phenotypes in properly designed, homogeneous and multicentric studies, using appropriate tools and integrating metabolomics in a multilevel approach. namely, eosinophilic and non-eosinophilic phenotypes, or the obese asthma phenotype, and this can be very useful in point-of-care application. In addition, metabolomics also discriminates between asthma and other “phenotypes” of chronic obstructive airway diseases, such as chronic obstructive pulmonary disease (COPD) or Asthma-COPD Overlap (OAC). However, there are still several aspects that need to be further investigated in the context of asthma phenotypes in properly designed, homogeneous and multicentric studies, using appropriate tools and integrating metabolomics in a multilevel approach. such as chronic obstructive pulmonary disease (COPD) or asthma-COPD overlap (COC). However, there are still several aspects that need to be further investigated in the context of asthma phenotypes in properly designed, homogeneous and multicentric studies, using appropriate tools and integrating metabolomics in a multilevel approach. such as chronic obstructive pulmonary disease (COPD) or asthma-COPD overlap (COC). However, there are still several aspects that need to be further investigated in the context of asthma phenotypes in properly designed, homogeneous and multicentric studies, using appropriate tools and integrating metabolomics in a multilevel approach.

2. Bronchial asthma

Bronchial asthma is a chronic respiratory disease that affects individuals of all ages. It usually involves chronic airway inflammation and symptoms of variable magnitude over time, which include dyspnoea, chest tightness, and cough[1]. It has a high prevalence, high morbidity and considerable levels of mortality[2]. According to the Global Initiative for Asthma (GINA), “Asthma is a heterogeneous disease with different underlying pathological processes. Recognizable groups of demographic, clinical and/or pathophysiological characteristics are often referred to as 'asthma phenotypes'[1]. In fact, several studies have shown that various asthma subtypes can be reflected in external manifestations of the disease, which are referred to as “phenotypes”. ”, and may involve clinical and inflammatory features, in addition to others[3]. However, since asthma phenotypes do not imply any specific underlying pathophysiological mechanisms, asthma can also be classified into subtypes known as “endotypes”[4], which are based on specific pathophysiological mechanisms at cellular and molecular levels[5][6][7].

The detection of biomarkers is necessary to obtain more robust definitions of asthma phenotypes or endotypes[8][9][10]. This further helps to classify patients and may allow for a more tailored therapeutic approach for each phenotype or endotype[11]. Although different types of biomarkers have been described, metabolic pathways also have components that are different between a healthy state and disease, and which may also be relevant as asthma biomarkers. Thus, the complete analysis of small molecules such as amino acids, lipids, organic acids and nucleotides through metabolomic studies carried out in different biological samples - exhaled air condensate (EBC), peripheral blood or urine - can be very important in the management of asthma in diagnosis, monitoring, personalized treatment and prognosis, but many issues still need to be addressed. In fact, more specifically, metabolomics-associated biomarkers can be very useful for understanding the pathophysiology of asthma, as well as several other aspects of the disease, including the prediction of exacerbation and response to treatment.

Metabolomics uses high-throughput analytical techniques that are combined with bioinformatics to obtain a complete and detailed overview of various metabolites in biological sources, thus being able to characterize health status and disease-related metabolic signatures. Fast and targeted metabolomics and non-targeted metabolomics are the two main study strategies in the field of metabolomics[12][13]. Both provide important information about changes in metabolism and quantification of metabolites in many chronic pathological environments, with applications in the diagnosis, pathophysiology and treatment of diseases, including asthma[14]. If, on the one hand, targeted metabolomics is concerned only with identifying and quantifying partially or totally the predefined metabolites of interest, the untargeted strategy offers much more comprehensive results regarding the identification and quantification of metabolites, since it does not restrict the analysis to previously defined target molecules[12]. The latter is possibly the best way to characterize a disease from a metabolic point of view and identify new biomarkers [12][15]. However, the untargeted metabolomic strategy can be problematic because it identifies a wide range of metabolites that can be difficult to interpret and constitute a confounding factor. In fact, identification and validation of relevant metabolites using undirected metabolomics requires careful analysis, as only a subset of all metabolite characteristics can be positively attributed to a molecular structure[16][17]. Furthermore, a high level of big data computational analysis is crucial for an adequate and standardized analysis and interpretation of results that can avoid or significantly minimize the possibility of producing erroneous results[16][18][19][20]. This is very important because the metabolome can be influenced or confused by many aspects such as age, sex, circadian rhythm, medications and other xenobiotics, microbiota, physical exercise, diet or even air pollution, both in healthy states and in diseases. In addition, sample source and types, sample collection and storage aspects, analytical procedure aspects as well as data analysis also influence the results. Finally, external validation using results from different patient cohort samples is crucial to make the results robust and generalizable; however, this aspect is absent in many studies.

Methodologically, metabolomics strategies can be supported by several techniques, namely nuclear magnetic resonance (NMR) "spectroscopy"[21], liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC) -MS) [20][22]. LC-MS has possibly been the most used technique as it offers greater sensitivity in identifying metabolites[15][23]. In any case, NMR is also an extremely useful technique, and the best and most complete metabolomic approach would likely involve a combination of both the techniques. In fact, the joint use of LC-MS and NMR (LC-NMR-MS systems) allows the combination of high throughput (via NMR) with high sensitivity and resolution levels (via LC-MS)[24][25].

Electronic nose (eNose) devices can be used for global characterization of metabolites, detecting complex mixtures of Volatile Organic Compounds (VOCs) in exhaled breath and providing associated respiratory impressions of such mixtures. eNose technologies are cheaper, non-invasive, and provide faster features, allowing early detection of metabolite changes compared to conventional methods based on analytical chemistry[26][27][28][29].

In the specific context of respiratory diseases, eNoses can detect changes in VOC mixtures in asthma[30][31][32], COPD[33][34][35], as well as in several other respiratory diseases, including cystic fibrosis or tuberculosis[36][37][38][39]. Dual-technology eNoses are similar to conventional chemical identification approaches in that they have chemical analysis capabilities that allow them to identify VOCs as disease-specific biomarkers[30][31][32][33][34][35]. Finally, in this context, the use of Application-specific database libraries of VOC biomarkers may favor early disease detection[29][40][41].

Overall, several metabolomics studies, focusing on small molecule metabolites in urine, peripheral blood or EBC, including VOCs, have shown that the expression of metabolites can discriminate between (a) asthmatic and non-asthmatic individuals[32][42][43][44][45][46][47][48][49][50][51]; (b) asthmatic patients and patients with chronic obstructive pulmonary disease (COPD)[52]; (c) asthma exacerbations and stable asthma[53], (d) severe and non-severe asthma[54][55][56][57][58], (e) different asthma phenotypes[59][60][61] and (f) evaluation of treatment responses and effects, including responsiveness or not to corticosteroids[13].

Most studies on biomarkers and phenotypes have been carried out mainly in children and non-elderly asthmatic adults. In fact, phenotyping studies in elderly asthmatics are scarce and, as far as we know, no metabolomic approach has been used in this subgroup of patients. This constitutes a great knowledge gap, as, in the last twenty years, there has been an evident increase in the percentage of the elderly population[62]. In addition, asthma is not always easy to diagnose or treat in these patients, due to multiple comorbidities, polypharmacy, partially different clinical manifestations, less awareness of symptoms, medication non-compliance, or other problems[62][63]. Thus, having metabolomic biomarkers that can increase the diagnostic, prognostic and therapeutic capacity in the approach of personalized medicine becomes of great importance in all age groups, especially in the elderly.

3. Conclusions

[64][65][66]

Several studies have shown that metabolomics can help distinguish between asthma and a healthy state, between severe and non-severe asthma, and between asthma and other chronic obstructive respiratory diseases. In particular, and as mentioned earlier in this review and also reviewed in depth by others[49][64][65][66], some metabolic pathways appear to be altered more consistently in asthma than in a healthy state.

Furthermore, it also seems clear that some of the inflammatory phenotypes of asthma (eg, eosinophilic asthma) may be preferentially associated with certain metabolic signatures. However, fully demonstrable and reproducible asthma-related metabolic "phenotypes" cannot be robustly defined, with the possible exception of obesity-related asthma, which may constitute an endotype of its own and also involve a clearer metabolic phenotype with characteristics specific underlyings - that is, a "metabolic endotype".

Thus, it is now probably more appropriate to mention the metabolic signatures of asthma than the actual metabolic phenotypes or endotypes. In any case, the situation will be better clarified once some of the future challenges are resolved. This may involve aspects such as the actual definition of clear molecular metabolic phenotypes, based on integrated, multi-level and unbiased cluster analyses. In addition, proper assessment of the reliable relationships between metabolic phenotypes and integrated groups of multiparameter asthma phenotypes will be relevant in the hope that non-invasive and timely assessment of the metabolic aspects of asthma can accurately reflect the specificities of various clustered asthma of phenotypes and endotypes. For this to occur, more multicentric multinational metabolic studies are needed, using the same techniques and similar targeted and non-targeted approaches. In addition, the reproducibility of asthma metabolic signatures needs to be better defined in different scenarios, as well as over time, in further longitudinal studies, so that the limits of variability and stability are understood for the most relevant metabolites and pathways. In addition, at least some additional aspects that can affect the expression of asthma and the metabotypes related to the asthma phenotype should also be studied, namely the nutritional aspects [so that the limits of variability and stability are understood for more metabolites and pathways. relevant. In addition, at least some additional aspects that can affect the expression of asthma and the metabotypes related to the asthma phenotype should also be studied, namely the nutritional aspects [so that the limits of variability and stability are understood for more metabolites and pathways. relevant. In addition, at least some additional aspects that may affect the expression of asthma and the metabotypes related to the asthma phenotype should also be studied, namely nutritional aspects[67], metabolic aspects associated with the microbiome[68] or air pollution parameters[69][70].

Further research is warranted and the integration of metabolomics with multifunctional and multifunctional parameters, with subsequent algorithm-based analysis, based on "big data" artificial intelligence (AI), can allow for a more complete and complete analysis of phenotype global/integrative clusters not only of asthma, but also in the context of chronic

obstructive respiratory diseases, thus allowing for greater diagnostic yield, personalized approaches and prognostic capacity.

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