DR GIORGIO CIPRANDI (Orcid ID : 0000-0001-7016-8421)

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PTX3 and D-dimer in children with asthma: a real-world study.

Amelia Licari[1], Gianluigi Marseglia[1], Mara De Amici[1], Giorgio Ciprandi[2]

[1] Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy;
[2]Allergy Clinic, Villa Montallegro, Genoa, Italy

Corresponding Author:
Giorgio Ciprandi
Via P. Boselli 5,
16146, Genoa, Italy
gio.cip@libero.it

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To the Editor,

Global Initiative for Asthma (GINA) document defines asthma as a multifaceted disease, usually characterized by chronic airway inflammation (htpp://www.ginasthma.org). Pathophysiological characteristics of asthma are: bronchial hyperresponsiveness, airway infiltration by inflammatory cells, and remodelling. Asthma treatment is targeted to achieve the best control of symptoms and risk factors. Anti-inflammatory agents are the most common medications used, since inflammation is the grounds of asthma. In children, the most common phenotype/endotype is represented by type2 immune response, characterized by eosinophilic infiltration. Moreover, the best tailored therapy is identified by precision

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medicine, i.e. the assessment of biomarkers useful to define specific phenotype/endotype. In this regard, Gao and colleagues investigated the role of pentraxin 3 (PTX3) to distinguish the eosinophilic asthma from non-eosinophilic one (1). They evaluated PTX3 both at plasmatic and bronchial (i.e. sputum) level. Plasmatic concentrations were not different in the two asthma subgroups, whereas sputum PTX3 levels were higher in non-eosinophilic asthma. Moreover, there is an intriguing link between inflammation and coagulation pathways. Actually, allergen challenge is generally accompanied by the extravasation of plasma, platelet aggregation, and activation of the coagulation cascade in the lung interstice and bronchoalveolar compartment, with increased levels of tissue factor, thrombin, and fibrinogen, what explains how fibrinogen cleavage products can be generated after allergen exposure. In addition, platelet activating factor (PAF) is a potent inflammatory mediator able to induce eosinophilic inflammation. Therefore, it has been collected a body of evidence supporting a direct involvement of coagulation pathway in allergic asthma, mainly concerning the possibility that asthma may be associated with enhanced thrombin generation and impaired fibrinolysis, which might in turn contribute to thromboembolic events. In this regard, D-dimer has been used as reliable biomarker of fibrinolysis. Indeed, it has been reported that asthma may be associated with reduced fibrinolytic activity (2).

On the basis of this background, we aimed to evaluate the validity of both plasma PTX3 and serum D-dimer as potential biomarker in a group of 121 children (71 males, 50 females, mean age 11.6+3.2 years) with allergic asthma and compared them with a well-matched group of healthy children (32 males, 31 females, mean age 10.7+2.6 years). The study was approved by the Ethics Committee and parents signed an informed consent. PTX3 was measured by immunoassay (R&D Systems, Minnesota, USA) as well as D-dimer (Cusabio, Milan, Italy). Asthma diagnosis was performed according to GINA document. Clinical data,

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including control asthma grade, asthma severity, and medication use, and lung function were evaluated in all children.

Figure 1A shows the plasma PTX3 levels, 1B the peripheral eosinophil number, and 1C the serum D-dimer levels in both groups. There were significant differences for all biomarkers, as their concentrations were always higher in asthmatics than in normal children. However, PTX3 levels did not correlate with lung function, asthma control grade, severity of asthma, symptom severity, and inhaled corticosteroid dosage as well as with both eosinophil number and serum D-dimer values. Equally, serum D-dimer levels did not correlate with any considered parameters.

About PTX3, our findings were consistent with a previous study showing increased sputum PTX3 levels in children with asthma (3). Moreover, sputum PTX3 positively correlated with atopy and asthma severity, but negatively with lung function; thus, the authors concluded that sputum PTX3 could be a candidate biomarker to evaluate airway inflammation and remodelling in childhood asthma. Also, our study confirmed a previous report showing increased PTX3 levels in patients with severe asthma compared with normal controls (4). However, Schwingel and colleagues reported that asthmatic patients had PTX3 levels comparable to normal subjects, whereas patients with COPD had higher values than both asthmatic and healthy subjects (5). Therefore, the real role of PTX3 as biomarker for asthma is still controversial and further studies should be conducted to clarify this issue.

On the other hand, our findings concerning D-dimer evaluation confirmed previous studies showing increased D-dimer levels in non-allergic asthma (6). However, the current findings were conflicting with other studies that reported negative outcomes. Experimental rhinovirus

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infection induced procoagulant changes in the airways of asthmatics through an increased activity of tissue factor-exposing microparticles, but serum D-dimer levels were not different between asthmatics and normal subjects both before and after virus exposure (7). The same group reported that loss of the asthma control after suspension of inhaled steroids did not increase haemostatic activation, including D-dimer assessment, in asthmatics (8). Moreover, asthma exacerbations did not increase D-dimer levels in asthmatic children, even though protein C significantly diminished during exacerbation episodes (9). Finally, it has been reported that in steroid-naïve asthma clot retraction rate (CRR) negatively correlated with FeNO, but positively with FEV_1, so these data were consistent with the hypothesis that asthma may be associated with decreased CRR and reduced fibrinolytic potential, even if D-dimer levels did not differ between asthmatic patients and healthy volunteers (2). Therefore, also the reliability of the D-dimer is still debated and further should be conducted to define its real role in asthma.

The present study has some limitation, including the lack of complete coagulation pathway evaluation and of inflammatory mediators. However, it included a group of asthmatic children visited in clinical practice, so representative of the real-world population of children with asthma. Notably, the 1year follow-up of these subjects confirmed the current outcomes (data not shown).

In conclusion, PTX3 and D-dimer could be considered useful to demonstrate the presence of a low-grade inflammatory status and a low-grade fibrinolytic activity in children with asthma, but could not be able to detect significant associations with asthma severity and asthma control, so cannot be considered as reliable biomarkers for asthma management.

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Figure Legend

Figure 1 = quadrant A: levels of Pentraxin 3 in normal children and in asthmatic children; quadrant B: number of peripheral eosinophils in normal children and in asthmatic children; quadrant C: levels of D-dimer in normal children and in asthmatic children.

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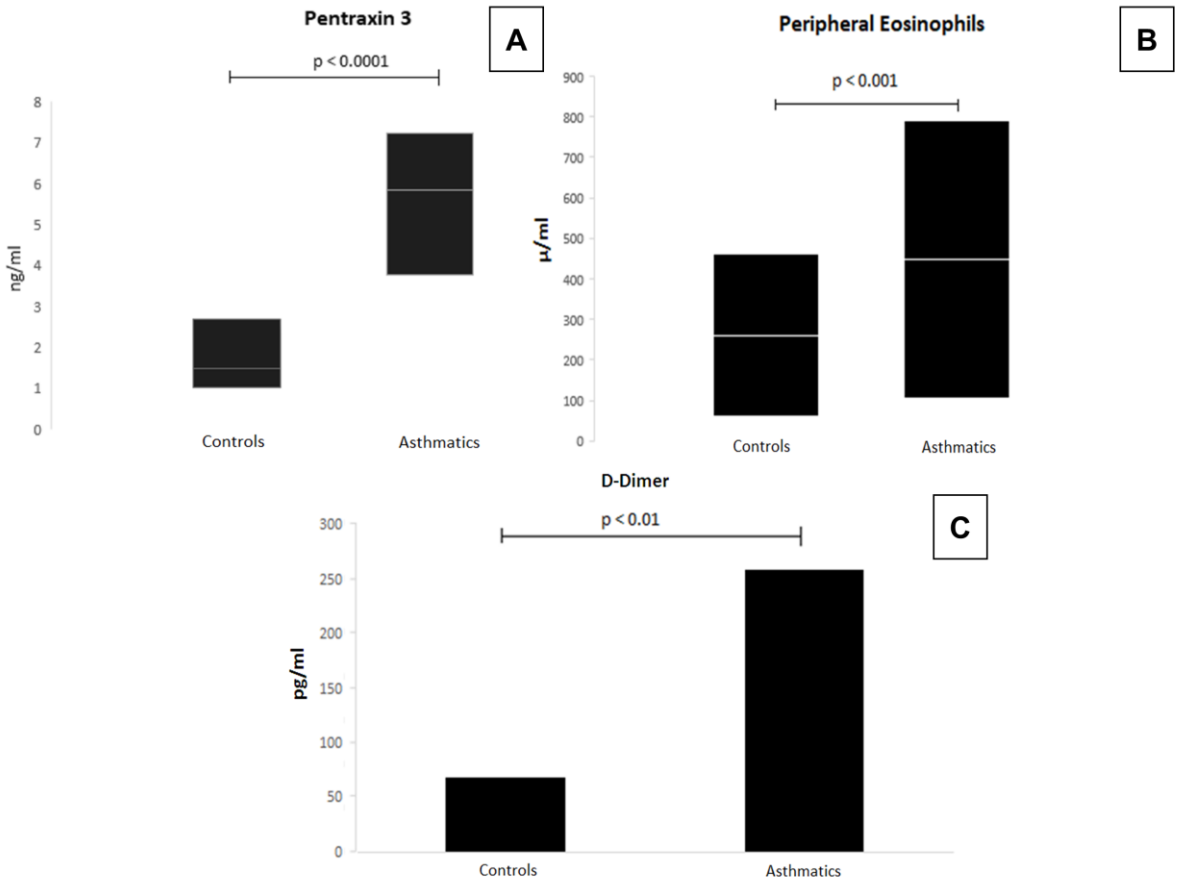

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