

# YKL-40 is a reliable biomarker in children pathology

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**Abstract:** In a world where inflammatory diseases, allergies, and non-communicable diseases increase, biomarkers offer a new picture of human pathology. YKL-40 is studied especially in adult pathology. Regarding children and the involvement of this protein in pediatric pathology, there is still much to be studied, but more and more interesting aspects are being revealed.

**Keyword:** YKL-40, children

## Introduction:

YKL-40 (chitinase-3-like protein 1) is a novel biomarker for a large number of pathological conditions, inflammation and allergic diseases. This chitinase-like protein belongs to the chitinases family and is a protein encoded by the CHI3L1 gene. Chitinases are enzymes responsible for the degradation of chitin "the second most abundant biopolymer on Earth".(1,2) Several chains of chitooligomeri result from this degradation, with lower molecular weight. (1)

As strange as it may seem, the human body contains only a small quantity of chitin, but hosts more genes encoding different human chitinases. The role of these chitinases is as a defensive mechanism against parasites and fungi that might contain chitin. (1)

Human chitinases are included in the 18-glycosyl-hydrolases family. Based on their activity they are divided into "true chitinases" and "chitinase-like proteins". This last category includes YKL-40 which plays a significant role in human pathologies such as asthma and COPD, recurrent wheezing, atopic dermatitis, cancer, urinary tract infections, brain trauma, and diabetes mellitus. (1)

YKL-40 has a molecular weight of 40 kDa, a single polypeptide chain of 383 amino acids, and an isoelectric point of 7.6. It is one of the best-characterized molecules, considered pro-inflammatory cytokine and it is secreted by a wide range of cells, such as macrophages, epithelial cells, neutrophils, chondrocytes, synoviocytes, vascular smooth muscle cells, fibroblasts, cancer cells, and stem cells. (1,3,4,5) YKL-40 high expression is observed in cells with high cellular activity. (6)

YKL-40 has very complex functions implicated in the pathological state:

- role in cell proliferation and differentiation (7)
- inflammation (3,7)
- protection against apoptosis (7)
- stimulation of angiogenesis (7)
- regulation of extracellular tissue remodeling (3,7)
- metastasis potential (7)
- inhibits injury (8)
- increase fibro-proliferative repair and tissue scarring (8)
- regulation of the innate immune responses (9)
- cell proliferation (10)
- peritumoral inflammation. (10)

Studies on adults reveal the variability of YKL-40 concentration. This may vary due to physiological factors as well as environmental ones. This aspect is detailed as follows: (5,7,8,11,12,13)

<i>Correlation</i>	<i>Without correlation</i>
Age – highly correlated	BMI - no correlation
Diurnal variation - higher concentrations from 10 a.m. to 10 p.m.	Inflammatory markers - C reactive protein
Stable for healthy subjects for short term and long term -3years	Gender
	Physical exercise

Table 1. Variability of YKL-40

**YKL-40 and children disease:**

The studies carried out on children regarding YKL-40 are more and more numerous. They address the most diverse aspects of the child's pathology, which makes this biomarker a valuable one in the diagnosis and monitoring of pediatric diseases. The range of diseases is very large, from respiratory disease to atherosclerosis, cancers, and urinary tract infection.

*Asthma and recurrent wheezing* - this biomarker is mainly related to neutrophilic inflammation and macrophagic activation in asthma and is not associated with biomarkers of eosinophilic inflammation. (9,14) YKL-40 values in preschool children cannot predict which subjects will develop asthma at school age. (4,15), but asthmatic children have significantly higher expression of YKL-40 (8), and the serum levels were increased with asthma severity. (9) In children, this biomarker is correlated to severe-therapy-resistant asthma,(4) and no relationship between YKL-40 levels and lung function was noticed. (9,14)

*Atopic rhinitis* – levels of YKL-40 were lower when compared to control group. (8)

*Pneumonia* – YKL-40 serum levels were significantly higher for children with pneumonia, without a remarkable difference between viral pneumonia, bacterial pneumonia, or co-infection. The levels of BALF were significantly higher in bacterial pneumonia versus viral pneumonia and higher compared to serum levels. Based on these results it is considered that YKL-40 can accelerate tissue injury by acting as a pro-inflammatory cytokine. (3)

For viral pneumonia, the higher the percentage reduction of YKL-40, the shorter the hospital stay. This conclusion is not be drawn either for bacterial pneumonia or co-infections. The reduction of YKL-40 is an independent risk factor for ICU admission, sepsis onset, and mechanical ventilation. (3)

For hypersensitivity pneumonitis, YKL-40 is correlated with prognosis, mortality risk, and severity index. (3)

*Bronchopulmonary dysplasia* – this severe condition affects preterm children, due to early mechanical ventilation and induces chronic inflammation of the lung, leading to impaired lung function. YKL-40 levels are higher for newborns with bronchopulmonary dysplasia. These levels are not affected by neonatal morbidity and are "indicative of structural lung disease at ten years of age".(4) Studies comparing YKL-40 in asthma versus bronchopulmonary dysplasia show that serum levels are significantly higher in bronchopulmonary dysplasia. (9,16)

*Dyslipidemia and atherosclerosis* – recent studies show that YKL-40 levels are significantly higher in children with dyslipidemia, regardless of BMI. This marker is not related to total cholesterol and LDL-Cholesterol is negatively correlated to HDL-Cholesterol and positively correlated to triglyceride levels. (5)

*Urinary tract infection* - the levels of urinary YKL-40 are elevated in febrile young children with UTI and appears that children with febrile UTI have significantly higher values compared to febrile children with other infections. (17,18,19)

*Cancer* – multiple studies on adult patients show that the levels of this protein are elevated in the serum or plasma of patients with different types of cancer. In children, studies are fewer and less consistent. YKL-40 is involved in carcinogenesis in different cellular processes. Studies on acute lymphoblastic leukemia in children reveal that serum YKL-40 levels are higher compared with children without leukemia and it is associated with the survival of children with ALL. (10)

*COVID-19* – YKL-40 is associated with lung disease, therefor it is related to the recent pandemic experience of COVID-19. The serum levels of this protein are higher in COVID-19 patients compared to a control group and significantly higher for severe forms of the disease. It is correlated with ICU admission and multiple organ failure.(20) It is considered a neurodegeneration marker that keeps high values in COVID-19 survivors and a potential liaison with psychoactive disorders, delirium, and atypical dementias is proposed. (21). No studies are available for children, COVID-19 and YKL-40 until this date.

**Conclusion:**

YKL-40 is a reliable biomarker for multiple pathological conditions in children. There still are aspects to be discovered. They might offer a new perspective on children's diseases and efficient monitoring.

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