

Free Kappa Light Chain in Bronchial Asthma; Review Article

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Abstract

Background: Polyclonal immunoglobulin free light chains (FLC) were found elevated in various biological fluids in a number of chronic inflammatory diseases. Urinary FLC concentrations, which correlate with the degree of systemic inflammation, are elevated in patients with chronic inflammatory rheumatic disease; serum FLC concentrations, correlating with disease activity, were found elevated in patients with systemic lupus erythematosus (Bramlage et al., 2016). A previous study showed elevated serum κ , but not λ , Ig FLCs in both atopic and nonatopic asthma patients compared with healthy control subjects. FLC are active ubiquitous molecules that are able to trigger and/or participate in inflammatory processes through the antigen-specific activation of mast cells.

Aim: To compare FLC- κ serum level in both asthma patients and healthy control. To compare FLC- κ serum levels in mild to moderate and severe asthma patients. To compare FLC- κ serum levels in atopic and non atopic asthma patients. To assess diagnostic value of FLC- κ in asthma patients.

Conclusion: Serum FLC- κ levels were significantly higher in patients with bronchial asthma than in healthy controls. Furthermore, serum FLC- κ levels increased progressively with increasing asthma severity, being highest among patients with severe asthma. Moreover, ROC curve analysis demonstrated excellent diagnostic performance of serum FLC- κ levels. All these findings suggest that serum FLC- κ may represent a promising biomarker for diagnosis and assessment of asthma and may reflect the inflammatory burden and severity of the disease.

Keywords: *bronchial asthma; free light chains; kappa light chain; biomarkers; mast cells; inflammation*

Introduction

Several inflammatory and immune cells, including mast cells, dendritic cells, eosinophils, T cells and neutrophils are involved in the pathophysiology of asthma. In particular, mast cells contribute to asthma airway inflammatory processes through immunoglobulin (Ig) E-dependent or non-IgE-dependent mechanisms. Mast cells are elevated in bronchial biopsies in both atopic and nonatopic adults with asthma and airway submucosal glands in asthma, and the extent of degranulation of these cells is directly related to disease severity (Galli et al., 2020).

Polyclonal immunoglobulin free light chains (FLC) were found elevated in various biological fluids in a number of chronic inflammatory diseases. Urinary FLC concentrations, which correlate with the degree of systemic inflammation, are elevated in patients with chronic inflammatory rheumatic disease; serum FLC concentrations, correlating with disease activity, were found elevated in patients with systemic lupus erythematosus (Bramlage et al., 2016).

A previous study showed elevated serum κ , but not λ , Ig FLCs in both atopic and nonatopic asthma patients compared with healthy control subjects. FLC are active ubiquitous molecules that are able to trigger and/or participate in inflammatory processes through the antigen-specific activation of mast cells (Napodano et al., 2019).

One of the major complications in the pathophysiology of asthma is airway remodeling. Identification of non-invasive biomarkers of airway inflammation and remodelling is a priority in asthma research (Global Initiative for Asthma, 2023).

Biological Characteristics of Free Light Chains

I. Characteristics of free light chains:

Braber et al. (2012) found in mice that FLCs can increase after inflammatory stimuli such as smoke exposure through NF- κ B activation. They are normally present in body fluids, including serum, cerebrospinal fluid, urine, and synovial fluid.

About 500 mg of free light chains (FLCs) are produced daily and cleared mainly by the kidneys. Normal urinary excretion is approximately 1–10 mg per 24 hours, while serum levels increase in renal failure (Table5) (Esparvarinha et al., 2017).

Table (5): Reference range for serum-free light chain

(Esparvarinha et al., 2017)

Polyclonal hypergammaglobulinemia	Renal failure	Healthy persons	Parameter
19.6 (4.3–273)	43.8 (3–251)	7.3 (0.8–34.7)	κ FLC, mg/L
28.8 (8.5–307)	38.0 (1.0–251)	12.4 (2.7–37.4)	λ FLC, mg/L
0.55 (0.38–1.18)	1.12 (0.37–3.17)	0.59 (0.26–1.65)	Ratio

FLCs may retain antigen-binding activity but usually with lower affinity than intact antibodies. They exist as monomers or dimers and are involved in immune signaling, inflammation, and coagulation. Elevated FLC levels are associated with autoimmune diseases, inflammation, and disease relapse (Damelang et al., 2024).

Clinical Significance and Inflammatory Mechanisms

Clinical significance of FLCs:

FLCs can contribute to inflammation by activating mast cells and preventing neutrophil apoptosis. Changes in FLC levels in body fluids such as blood, urine, and cerebrospinal fluid (CSF) may indicate various diseases. Therefore, measuring FLC concentrations can be useful for disease diagnosis and prognosis (Ferraro et al., 2020) (Figure 10).

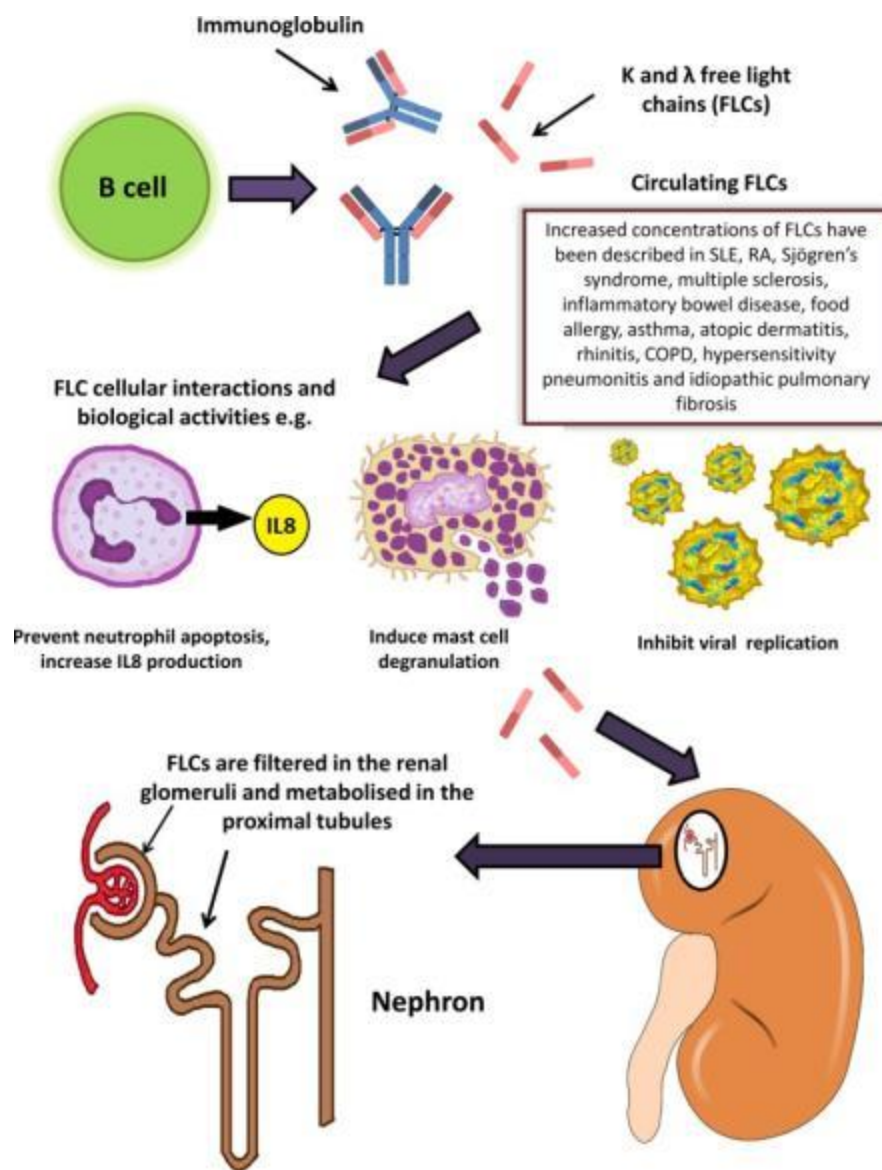


Figure (10): Free light chain production, biological interactions and metabolism.

(Brebner and Stockley, 2013)

Normally, plasma cells produce small amounts of FLCs that are cleared by the kidneys. Elevated FLCs indicate abnormal plasma cell or immune activity and are useful for diagnosing, monitoring, and assessing treatment response in conditions such as multiple myeloma, monoclonal gammopathies, and autoimmune diseases (Bradwell et al., 2020).

II. The effect of FLCs on mast cells:

A newly identified IgE-independent, antigen-specific hypersensitivity pathway shows that immunoglobulin free light chains (Ig-FLCs) can activate mast cells and trigger inflammation. Ig-FLC-induced mast cell activation is characterized by granule release and degranulation channels similar to those seen in anaphylaxis. Although the receptor responsible for Ig-FLC-mediated activation remains unknown, evidence suggests that this process may

involve Fc receptors, with effective mast cell activation requiring cross-linking of Fc receptor-bound immunoglobulins (El Ansari et al., 2022).

Paired Ig-like receptors (PIR-A and PIR-B) regulate immune cell activation. PIR-A promotes mast cell activation through Fc γ signaling, while PIR-B inhibits activation by recruiting phosphatases (SHP-1/SHP-2) via ITIMs (Ong et al., 2021).

Mast cells release inflammatory mediators such as TNF and macrophage inflammatory protein-2 (MIP-2), which recruit immune cells like neutrophils. Their activation can also occur through T-cell interactions and complement-dependent pathways (Esparvarinha et al., 2017).

During repeated antigen exposure, plasma cells produce complete antibodies and excess free light chains (FLCs). These FLCs can bind mast cells through surface receptors and contribute to mast cell activation upon re-exposure (Esparvarinha et al., 2017).

Kraneveld et al. (2005) found elevated kappa free light chains (FLCs) in asthma patients, suggesting increased polyclonal B-cell activity. FLCs can activate mast cells through surface protein crosslinking, causing degranulation and leukotriene release (Figure 11).

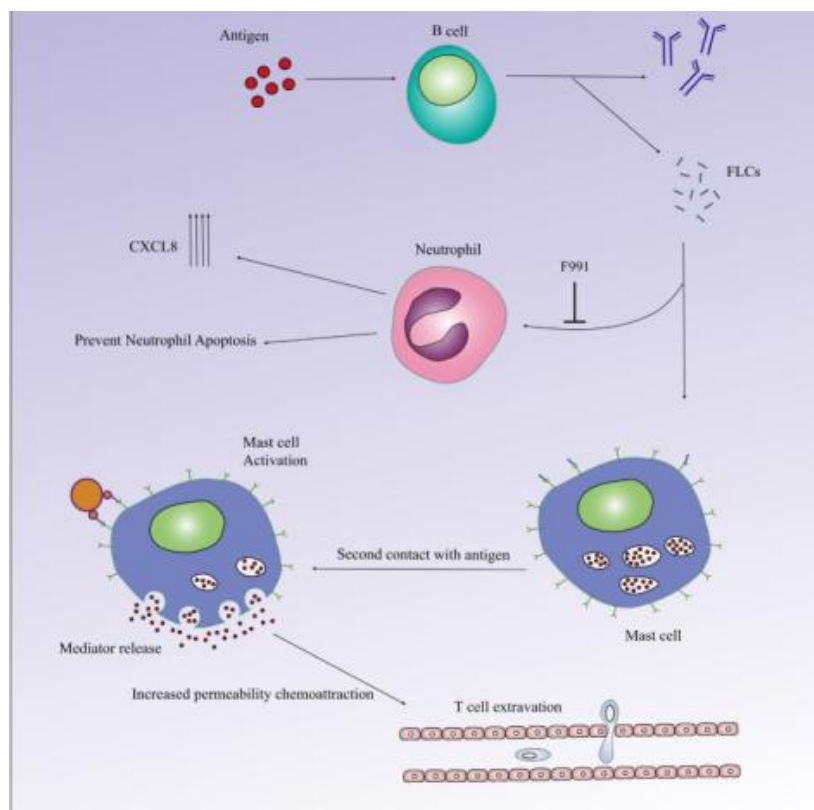


Figure (11): Immune response causing a hypersensitivity reaction intermediated via FLCs and mast cells (Esparvarinha et al., 2017).

Lambda (λ) light chains more effectively suppress autoreactive B-cell responses than kappa (κ) chains. The F991 antagonist blocked hypersensitivity responses in mice, suggesting that FLC levels can indicate adaptive immune system activity

Free Light Chains as Biomarkers of Disease Activity

III. Polyclonal free light chains as biomarkers for disease activity:

Elevated FLCs are found in many inflammatory and autoimmune diseases, including SLE, rheumatoid arthritis, Sjögren's syndrome, asthma, and multiple sclerosis. FLC levels may reflect disease activity and progression (Gudowska-Sawczuk & Mroczko, 2023).

Gottenberg et al. (2007) showed that FLCs concentration correlate with rheumatoid arthritis activity and B-cell activation. Due to their shorter half-life, FLCs may better reflect current disease activity than total IgG or gamma globulin levels.

A study of 710 early arthritis patients showed that elevated polyclonal FLCs correlate with rheumatoid arthritis activity (DAS28), with similar associations observed in SLE

Hopper et al. (1989) found that increased urinary FLC levels occurred 4–8 weeks before clinical relapse in SLE patients. A larger study of 75 patients showed that serum FLC levels correlated with SLE disease activity scores (SLEDAI).

FLCs may help monitor B-cell activity and treatment response. Studies show that Rituximab therapy reduces FLC levels in patients who respond clinically, including those with rheumatoid arthritis and SLE. Larger studies are needed to confirm the role of FLC monitoring in inflammatory diseases (Stathopoulos and Dalakas, 2022).

Increased serum FLC levels may predict early diabetic nephropathy and are elevated in chronic kidney disease because of impaired renal clearance (Sorvor et al., 2022).

IV. Free light chains and hypersensitivity reactions:

In 2002, Redegeld et al. (2002) demonstrated that free light chains can elicit immediate hypersensitivity responses in sensitised mice and described how in vitro cross-linking of free light chains and mast cell surface proteins can induce degranulation.

F991 is a 9-mer peptide that blocks FLC activity by targeting the light-chain binding site of Tamm-Horsfall glycoprotein. It reduces airway obstruction, hyperresponsiveness, and inflammation in asthma models and inhibits mast cell activation in inflammatory diseases (Fisher, 2022).

V. Free light chain interaction with neutrophils:

FLCs can inhibit neutrophil apoptosis, potentially promoting inflammation. Elevated FLC levels in end-stage renal disease may contribute to the chronic pro-inflammatory state observed in these patients (Cohen & Hörl, 2012).

Braber et al. (2012) demonstrated that FLCs contribute to COPD inflammation by activating neutrophils and increasing IL-8 production. Blocking FLCs with F991 reduced neutrophil lung infiltration and inflammatory responses.

Measurement of Free Light Chains

VII. Measurement of free light chains:

Traditional FLC detection methods using electrophoresis and immunofixation have limited sensitivity. Highly sensitive nephelometric immunoassays targeting hidden FLC epitopes improved detection and enabled accurate reference ranges for serum FLC levels and κ/λ ratios (Giles and Karunanithi, 2024).

Methods are generally categorized into automated immunoassays, electrophoretic techniques, and emerging mass spectrometry protocols.

A. Automated Immunoassays:

These are the gold standard for clinical FLC measurement because they are approximately three orders of magnitude more sensitive than electrophoresis (Jenner, 2024). They use antibodies that specifically target "hidden" epitopes on light chains that are only exposed when the chain is free and not bound to a heavy chain.

Nephelometry: Measures the light scattered by antigen-antibody complexes. The N Latex FLC assay is a common example using monoclonal antibodies.

Turbidimetry: Measures the reduction in light intensity due to the formation of these complexes. The Freelite assay is a widely used turbidimetric method that utilizes polyclonal antisera to recognize the high diversity of light chains (Jenner, 2024; Messiaen et al., 2017).

Sandwich ELISA: The Sebia FLC ELISA uses polyclonal anti- κ and anti- λ antibodies to measure free light chains. It offers advantages such as reduced antigen excess interference and improved consistency compared with the Freelite assay.

B. Electrophoretic Methods:

These methods were historically the primary way to detect "Bence-Jones proteins" (monoclonal FLCs in urine), but they are significantly less sensitive than serum immunoassays.

Serum Protein Electrophoresis (SPEP): Often insensitive for FLCs as they are typically present in low concentrations in the serum.

Immunofixation Electrophoresis (IFE): Used to confirm the presence and type (clonality) of a light chain, but it remains a qualitative or semi-quantitative tool rather than a precise measurement of concentration (Jenner, 2024).

C. Mass Spectrometry (MS):

Advanced mass spectrometry methods such as mass spectrometry immunofixation (MASS-FIX) or matrix-assisted laser desorption/ionization (MALDI-TOF) provide highly sensitive detection of monoclonal FLCs by directly identifying unique protein signatures. They can detect low-level disease and non-secretory myeloma that may be missed by conventional assays (Jenner, 2024).

FLC assays have limitations, including batch variation, non-linear dilution, and antigen excess, which can cause falsely low results. Accurate interpretation requires awareness of assay limitations and close collaboration between laboratory specialists and clinicians

Free Kappa Light Chain in Asthma

A cross-sectional observational study measured serum κ and λ immunoglobulin free light chains (FLCs) in 54 asthma patients of varying severity and 20 healthy controls to assess their relationship with inflammation. Serum κ and λ FLCs were significantly elevated in severe asthma patients compared to mild asthma and healthy subjects, correlated with blood eosinophil and neutrophil counts, CRP levels, and were higher in eosinophilic versus non-eosinophilic patients, but were independent of atopy or serum IgE. FLC levels were negatively associated with lung function (FEV_1 and FEV_1/FVC), suggesting that serum Ig FLCs may serve as novel biomarkers of inflammation in severe asthma, warranting further investigation (Basile et al., 2023).

In a cohort of 79 asthmatic patients and 40 healthy controls, serum free light chains (FLCs) were analyzed in relation to asthma severity and clinical parameters. FLC- κ levels were significantly elevated in asthmatics, and the FLC- κ /FLC- λ ratio differed markedly from controls, while FLC- λ levels negatively correlated with FEV_1 . Additionally, the FLC- κ /FLC- λ ratio was negatively associated with Sino-nasal outcome test (SNOT-22) scores, and FLCs correlated with sensitization to *Staphylococcus aureus* enterotoxins. These findings support the potential role of FLCs as

biomarkers in asthma, with FLC- κ and the κ/λ ratio reflecting qualitative disease presence, and FLC- λ indicating clinical severity (Caruso et al., 2024).

In a murine model of nonatopic asthma, the LC antagonist peptide F991 prevented airway obstruction, hyperresponsiveness, and inflammation, while passive immunization with antigen-specific LCs triggered mast cell-dependent bronchoconstriction.

Moreover, elevated serum free κ LC levels were observed in adult asthma patients compared to healthy controls, highlighting their potential role in asthma pathogenesis and suggesting that pharmacologic inhibition of LC-induced mast cell activation may offer a promising therapeutic approach (Kraneveld et al., 2005).

In a study of 547 patients with α_1 -antitrypsin deficiency (A1ATD) and 327 patients with usual COPD, circulating combined free light chains (cFLCs) measured by the FreeLite® assay were stable over repeated measurements and inversely correlated with renal function. Higher cFLC levels were observed in patients with chronic bronchitis and airway bacterial colonisation, while the association with lung function was weak after adjusting for age and renal function. Importantly, cFLC levels above the normal range (>43.3 mg/L) were significantly associated with increased mortality in both A1ATD and COPD cohorts, suggesting cFLCs could serve as a potential biomarker for risk stratification in these populations (Hampson et al., 2016).

Increased FLC levels can be detected in patients suffering from several immunological disorders. For example, it has been shown that antigen-specific FLCs mediate hypersensitivity-like responses. Importantly, these hypersensitivity-like responses in the lung could be initiated by adoptive transfer of allergen specific FLC. This suggests that these FLCs may be important in the pathophysiology of asthma as well as other non-IgE-mediated inflammatory diseases. Furthermore, the FLC antagonist, F991, completely inhibited both the early- and late-phase of dinitrofluorobenzene (DNFB)-induced pulmonary hypersensitivity in a mouse model of non-atopic asthma (Douwes et al., 2002).

The role of IgE and FLCs in allergic and non-allergic diseases has been extensively reviewed and it underlines a possible role for targeting FLC biology in the development of novel therapeutic approaches in these diseases. Since F991 has demonstrated remarkable biological activity in several animal models of disease this needs to be translated into human clinical trials (Redegeld and Wortel, 2008).

In a 2-year prospective study of 63 stable male COPD patients, serum combined free light chains (cFLCs) were measured to evaluate their potential as a biomarker for exacerbation risk. Patients with low cFLC levels (below mean-SD) experienced a significantly shorter time to their first exacerbation. Multivariate analysis showed that both low cFLC and reduced FEV1 % predicted were independently associated with increased risk of COPD exacerbations, suggesting that low cFLC may serve as a novel B-cell-related biomarker for predicting exacerbation risk in COPD (Tanimura et al., 2020).

In a 6-months retrospective, observational study of fifteen adults with uncontrolled severe asthma, Kappa free light chains (FLCs), which have been proposed as novel biomarkers in severe asthma, showed a significant mean reduction after switching to dupilumab. The study performed correlation analyses to explore the relationships among baseline biomarkers. Blood eosinophil counts and total IgE levels exhibited a robust correlation with kappa FLCs. These strong correlations reinforce the potential utility of these biomarkers in predicting and monitoring response to treatment. Moreover, elevated baseline levels of type 2 inflammatory markers, particularly blood eosinophils, eosinophil cationic protein (ECP), total IgE, and serum free light chains (FLCs), appear to be associated with a more favorable response, highlighting their potential role as predictive tools in guiding individualized treatment strategies

Conclusion

Serum FLC- κ levels were significantly higher in patients with bronchial asthma than in healthy controls. Furthermore, serum FLC- κ levels increased progressively with increasing asthma severity, being highest among patients with severe

asthma. Moreover, ROC curve analysis demonstrated excellent diagnostic performance of serum FLC- κ levels. All these findings suggest that serum FLC- κ may represent a promising biomarker for diagnosis and assessment of asthma and may reflect the inflammatory burden and severity of the disease.

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