



# Serum Interleukin 13 Level in Steroid Sensitive Nephrotic Syndrome

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## Abstract

**Background:** There are studies indicating the relationship between interleukin 13 and pathogenesis of nephrotic syndrome. To find this relationship, we measured serum IL13 concentration in acute and remission phases in children with steroid sensitive nephrotic syndrome.

**Methods:** The serum of 15 patients was achieved for measurement of IL-13 in two phases: acute phase and remission phase. To this end, we used Biofarm ELIZA kites.

**Results:** The mean concentration of serum IL-13 was  $430 \pm 279$  ng/mL (227-960 ng/mL) before starting steroid treatment. The mean concentration of serum IL-13 was  $428 \pm 259$  ng/mL (215.6-960 ng/mL) after 4 weeks of steroid treatment. The difference between pre and post treatment of serum IL-13 levels was not significant ( $P = 0.91$ ).

**Conclusions:** We showed serum IL13 does not significantly decrease after steroid treatment. Although the role of IL13 in increasing glomerular permeability has been shown in previous studies, the local IL13 may be more important than the systemic form. It also can be postulated that mediators other than IL13 also have primary roles in pathogenesis of proteinuria. However, we need more studies to determine the role of IL13 in the pathogenesis of nephrotic syndrome.

**Keywords:** Interleukin-13, Nephrotic Syndrome, Children, Acute and Remission Phases

## 1. Background

Minimal change disease (MCD) is the most common cause of nephrotic syndrome in children. The pathogenesis of minimal change nephrotic syndrome is not completely clear, but it is probably due to the imbalance between T helper 1 and T helper 2 cells. It appears that activation of T helper 2 lymphocytes has an important role in pathogenesis of MCD (1-3). Cytokines of T helper 2 cells that have some possible roles in the induction of proteinuria include IL4, IL10, and especially IL13. Interleukin 13 may alter glomerular permeability and induce proteinuria in patients with MCD (4).

To our knowledge, there is one study on the measurement of serum IL-13 concentration in nephrotic syndrome. Hence, to further determine the relationship between serum IL13 and steroid sensitive nephrotic syndrome, we assessed serum IL13 before and after 4 weeks of steroid treatment in children with nephrotic syndrome who responded to steroid.

## 2. Methods

In this prospective study, 15 children with steroid sensitive nephrotic syndrome admitting to Ali asghar children hospital were recruited. All patients presented with edema, hypoalbuminemia, hyperlipidemia, and significant proteinuria ( $> 40$  mg/m<sup>2</sup>/h). All patients were treated with 60 mg/m<sup>2</sup>/day steroid. We defined remission as disappearance of proteinuria and edema after treatment. Steroid sensitive idiopathic nephrotic syndrome (SSNS) was defined as the response to 4-week daily prednisone since the onset of the disease.

All patients less than 1 year old, those with systemic manifestations, hypertension, gross hematuria, renal dysfunction, and steroid resistance were excluded. We did not have any control group in this study. Serum interleukin 13 was measured in all patients in acute and remission phases (before and after steroid treatment) by Biofarm Eliza kites.

### 2.1. Statistical Analysis

SPSS version 18 software (SPSS, Inc, Chicago, IL, USA) was used for statistical analysis. The descriptive results are expressed as means  $\pm$  standard deviation. To compare pre and post treatment of serum interleukin 13, we used

Wilcoxon Signed-rank test. All P values less than 0.05 were considered statistically significant.

### 3. Results

Initially, 29 patients with idiopathic nephrotic syndrome were included in this study. Six patients were excluded because of steroid resistance. We excluded eight patients because their parents were not consent to participate in this research program. Finally, 15 children with SSNS were assessed for serum IL-13. Nine patients (60%) were male. The mean age was  $72 \pm 53$  months (13 -168 months).

The mean concentration of serum IL-13 was  $430 \pm 279$  ng/mL (227 - 960 ng/mL) before starting steroid treatment. The mean concentration of serum IL-13 was  $428 \pm 259$  ng/mL (215.6 - 960 ng/mL) after 4 weeks of steroid treatment. The difference between pre and post treatment serum IL-13 level was not significant ( $P = 0.91$ ). Serum IL-13 concentration increased in 6 patients (positive rank), decreased in 7 patients (negative rank), and did not change in 2 patients after treatment with steroid. The decrease in serum IL-13 level was not significant in 7 patients mentioned above.

### 4. Discussion

The association between minimal change disease and atopy has been shown before. Additionally, allergic events can induce proteinuria in patients with MCD. As T-helper-2 lymphocytes are key cells during atopy and allergic events, a possible role for these cells can be considered in the pathogenesis of MCD. There is evidence that Interleukin 13, the key cytokine produced by T helper 2 cells, may play some roles in the pathogenesis of MCD. Kimata et al. showed increased production of IL13 by T cells and increased expression of IL13 receptors by B cells in MCD patients for the first time. Some more recent studies have shown that T helper 2 lymphocytes express more IL13 during the acute phase of MCD and this expression reduces during remission (1, 3, 5). Some investigators also have shown that visceral podocytes express more IL4 and IL13 receptors during the acute phase of MCD (4).

Jose et al. showed that IL3 induces proteolysis at the basolateral surface of visceral podocytes in glomeruli. Thus, IL13 may injure glomerular visceral cells and increase glomerular permeability (4). Moreover, recent studies have shown that IL-13 induces the expression of CD80 by podocytes, resulting in proteinuria and epithelial cell foot process effacement (6, 7).

To our knowledge, there is one study assessing the serum IL-13 levels in patients with MCD. In this study, the

authors found higher levels of serum IL-13 in patients with acute MCD in comparison with a control group. This result confirms previous studies showing the increased expression of IL-13 by T helper 2 cells in children with acute nephrotic syndrome. The important finding of this study is that serum IL-13 levels increased significantly after treatment with steroid in patients with steroid sensitive nephrotic syndrome ( $166.36 \pm 53.19$  vs  $61.89 \pm 24.18$  pg/mL,  $n = 15$ ,  $P = 0.027$ ) (8).

We did not have any control group in our study, but IL13 levels in our patients in the acute nephrotic syndrome phase was significantly higher than the amounts in the control group of Tain et al. study.

We also showed that serum IL13 level increased in 6 patients, did not changed in 2, and reduced in 7 after treatment with steroid in comparison with pretreatment levels. Totally, the mean serum level of IL-13 was not different statistically before and after steroid treatment in our study ( $430 \pm 279$  ng/mL vs  $428 \pm 259$  ng/mL).

The increased expression of IL-13 gene in CD4+ and CD8+ cells in acute nephrotic syndrome has been shown by previous studies (3). We also know that steroid can suppress the production of IL-13 by CD4+ cells rather than by CD8+ lymphocyte (3). This can confirm our finding that serum IL-13 did not reduce in SSNS patients after steroid treatment. Previous studies have also shown that IL-13 induces CD80 expression in podocytes, and CD80 is the key mediator for inducing proteinuria. It is supposed that nephrotic syndrome has two steps: the first step is increased serum IL13 level and then CD80 in cytoplasm of podocytes and the second step is inadequate silencing of CD80 by insufficient release of soluble CTLA-4. Thus, nephrotic syndrome can start with an increase in IL13 production but its remission may depend on the CD80/CTLA-4 ratio not on the level of serum IL-13. Additionally, the effect of IL-13 on podocytes may be local depending on the IL-13 level in the region and its receptors expression. However, we need more studies to determine the precise role of IL13 in the pathogenesis of MCD. More information about IL13 role may help us to treat MCD patients more specifically.

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