# Serum Neopterin Level in Children with Juvenile Idiopathic Arthritis

*Thesis*

*Submitted for Partial Fulfillment of Master Degree in Pediatrics*

*By*

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Sara Mohammed

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# List of Abbreviations

| | |
|---|---|
| **ACR** | American College of Rheumatology |
| **ADHD** | Attention deficit hyperactive disorder |
| **ANA** | Antinuclear antibody |
| **bDMARD** | Biological disease-modifying anti-rheumatic drugs |
| **CAD** | Coronary Acute Disease |
| **CMI** | Cell-mediated immunity |
| **CRP** | C-reactive protein |
| **CS** | Corticosteroids |
| **csDMARD** | Conventional synthetic disease-modifying antirheumatic drugs |
| **CVD** | Cardiovascular disease |
| **CSF** | Cerebrospinal fluid |
| **DMARD** | Disease-modifying antirheumatic drugs |
| **EBV** | Epstein-Barr virus |
| **ELISA** | Enzyme-Linked Immunosorbent Assay |
| **EPTB** | Extrapulmonary tuberculosis |
| **ESR** | Erythrocyte sedimentation rate |
| **EULAR** | European League Against Rheumatism |
| **Hb** | Hemoglobin |
| **HDLC** | High density lipoprotein cholesterol |
| **HF** | Heart Failure |
| **HFpEF** | HF with preserved left ventricular ejection fraction |
| **HIV** | Human Immunodeficiency Virus |
| **HLH** | Hemophagocytic lymphohistiocytosis |

| | |
|---|---|
| **IBD** | Inflammatory Bowel Disease |
| **IDO** | Indoleamine 2,3 dioxygenase |
| **IFN** | Interferon |
| **IL** | Interleukin |
| **IL-1ra** | IL-1 receptor antagonist |
| **ILAR** | International League of Associations for Rheumatology |
| **JIA** | Juvenile idiopathic arthritis |
| **MAS** | Macrophage activation syndrome |
| **MTX** | Methotrexate |
| **NSAIDs** | Nonsteroidal anti-inflammatory drugs |
| **PLT** | Platelet |
| **QFT-G** | QuantiFERON-TB-Gold |
| **RA** | Rheumatoid arthritis |
| **SC** | Subcutaneous |
| **SDAI** | Simplified Disease Activity Index |
| **SLE** | Systemic lupus erythematosus |
| **SoJIA** | Sysytemic onset juvenile idiopathic arthritis |
| **TB** | Tuberculosis |
| **TCZ** | Tocilizumab |
| **TH1** | T helper 1 |
| **TLC** | Total leucocytic count |
| **TNFi** | Tumor necrosis factor inhibitor |

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# Introduction

Juvenile idiopathic arthritis (JIA) is generally considered a clinical syndrome involving several disease subsets, with a number of inflammatory flows, leading to an eventual common pathway in which persistent synovial inflammation and associated damage to articular cartilage and underlying bone are present **(Shady et al., 2015).**

Many biological therapies are now available for patients with rheumatoid arthritis (RA) who have an inadequate response to synthetic disease modifying anti-rheumatic drugs (DMARDs) especially methotrexate **(Viatte et al., 2012).**

The 2015 American College of Rheumatology (ACR) treatment guideline addresses the use of DMARDs, biologics, tofacitinib, and glucocorticoids in early and established RA. It is also recommended to use various treatment approaches in frequently encountered clinical scenarios, including treat-to-target, switching between therapies, tapering of therapy, the use of biologics and DMARDs in high-risk RA patients **(Singh et al., 2016).**

Neopterin is a pyrazino-pyrimidine compound that is synthesized by monocytes and macrophages in response to

interferon (IFN) which is produced by activated T-cells. It is a marker of cellular immune response, and levels are elevated in conditions of T-cell or macrophage activation, including autoimmune diseases such as systemic lupus erythematosus and JIA **(Shady et al., 2015).**

Neopterin is found at increased levels in biological fluids from individuals with inflammatory disorders. Due to its capacity to increase hemeoxygenase-1 content, it has been proposed as a protective agent during cellular stress **(Ghisoni et al., 2016).**

Neopterin is a biologically stable metabolite, which gives an advantage of its detection in assessing the activity of the immune response **(Dudina et al., 2014).** An association between CRP and ESR levels as well as neopterin concentrations has been shown already earlier in patients with many diseases such as cardiovascular disease and malignancies as well as in patients with RA **(Kurz et al., 2011).**

Neopterin is accepted as an immunologic marker and an indicator of activation of the immune system **(Tuncer et al., 2015).** Neopterin levels in patients with active RA are noted to be accentuated **(Arshadi et al., 2013).**

# Aim of the Work

This study aims to assess serum level of neopterin in patients with Juvenile Idiopathic Arthritis (JIA) in relation to the disease activity, severity and response to conventional and biological therapy.

# Neopterin

Neopterin is a marker of immune activation, which is produced by monocyte/macrophages in response to inflammation **(Oweira et al., 2016).** It is accepted that neopterin is an immunologic marker and an indicator of activation of the immune system **(Tuncer et al., 2015).**

Neopterin is a valuable biomarker of cell mediated immunity. It is a pyrazino-pyrimidine compound belonging to the class of pteridine with a molecular weight of 253D. It is produced before the onset of symptoms in adverse conditions, like chronic infection **(Shubhangi et al., 2015).**

Neopterin is a reliable marker in the assessment of the rate of IFN-γ production. Levels of neopterin increase in direct proportion with the level of interferon. Therefore, estimation of neopterin is helpful in the monitoring of the activity of IFN-γ inducible inflammation **(Chuang et al., 2016).**

Neopterin is an unconjugated pteridine, which has a potential function in the inflammation process **(Palabiyik et al., 2016).** Neopterin is a prognostic indicator for cell-mediated immunity (CMI) and chronic infection **(Shubhangi et al., 2015).**

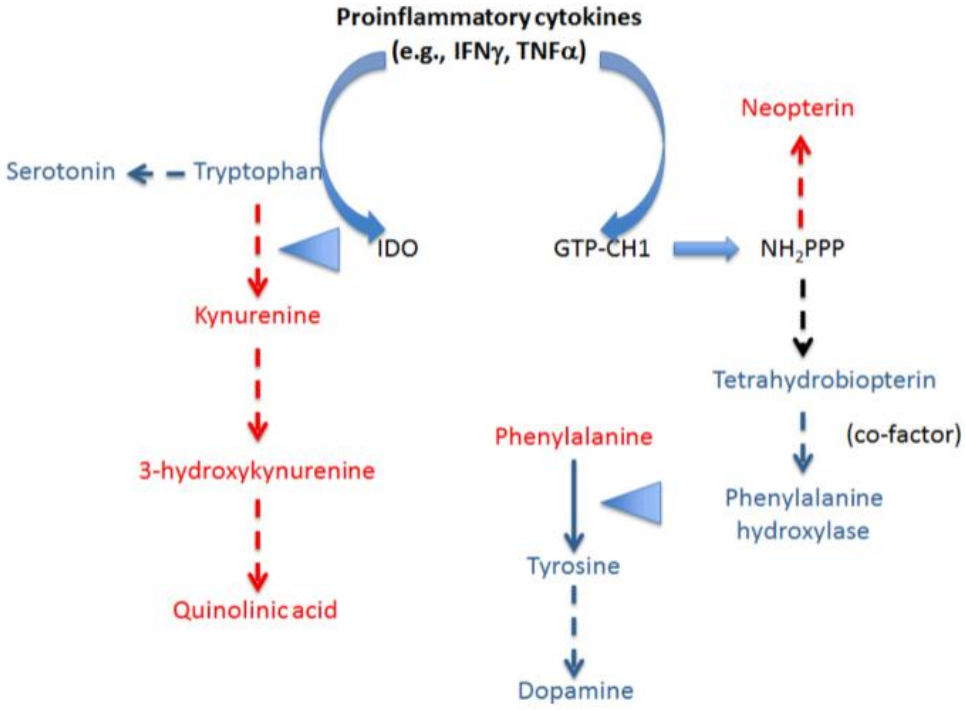


**Figure (1):** Role of proinflammatory cytokines and their effects on enzymatic pathways responsible for tryptophan degradation and neopterin formation. Abbreviations: CH1, cyclohydrolase 1; IDO, indoleamine 2,3 dioxygenase; IFN-γ, interferon-γ, NH2PPP, 7,8-dihydroneopterin triphosphate; TNF-α, tumor necrosis factor-α **(Capuron et al., 2011).**

Increased serum neopterin concentration is a sensitive marker of activation of cell-mediated immunity and T cell activation. Increased neopterin levels in body fluids of patients are observed in diseases with activated cell mediated (=TH1-type) immune response such as malignant tumors, allograft rejection, autoimmune disorders, or virus infections, also neopterin concentrations

increase in neurodegenerative diseases and during pregnancy **(Zeng et al., 2016).**

Estimation of neopterin levels may also be helpful in following the evolution of specific inflammatory conditions (e.g., systemic inflammatory diseases, autoimmune diseases, viral infection, renal transplant rejection, and nephritic syndrome) **(Zeng et al., 2016).**

Levels of neopterin increase in biological fluids of individuals with inflammatory disorders. Due to its capacity to increase hemeoxygenase-1 content, it is considered as a protective agent during cellular stress **(Ghisoni et al., 2016).**

Elevated neopterin concentration in biological body fluids is an indicator of cellular innate immune response **(Volgger et al., 2016).**

Neopterin also has an important role in the modulation of processes mediated by oxygen radicals and in the activation of the reactive oxygen species **(Shubhangi et al., 2015).**

High neopterin levels are associated with conditions of increased production of reactive oxygen species, thereby neopterin is also an indicator for oxidative stress due to activation of immune system **(Chuang et al., 2016).**

Neopterin levels increase in cerebrospinal fluid and plasma during immune system activation or as a result of damage, or infection **(Ghisoni et al., 2015).**

It was indicated that both oxidative stress and inflammation are important processes in the destruction of synovial tissue in rheumatoid arthritis patients. Systemic inflammatory markers, oxidative stress, and neopterin levels are related to the severity of the disease in rheumatoid arthritis **(Shahmohamadnejad et al., 2015).**

Articular inflammation causes activation and proliferation of the synovial lining, expression of inflammatory cytokines, and B cell activation with autoantibody production. Altered cytokine and signal transduction pathways and inhibition of programmed cell death contribute to synoviocyte- and osteoclast-mediated cartilage and bone destruction **(Ozkan et al., 2012).**

Auto reactive T cells in JIA produce different types of cytokines which cause subsequent activation of innate immunity cells, where neopterin is synthesized from guanosine triphosphate by macrophages **(Arshadi et al., 2013).**

Among all variable mechanisms, Tryptophan degradation, IDO activity, and neopterin pathway could be