# A Study of Serum S100A4 in Patients with Systemic Onset Juvenile Idiopathic Arthritis in Relation to Disease Activity, Joint Destruction and Macrophage Activation Syndrome

### Chesis

Submitted For Partial Fulfillment of Master Degree in Pediatrics

### By

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Thanks are one emotion that flow directly from the heart and it is very wonderful feeling that never goes away.

First and foremost, Thanks are due to **ALLAH** the most merciful and the mightiest to whom I relate my success in achieving any work in my life.

I would like to express my sincere gratitude and deepest appreciation to **Prof. Dr. Khaled Salah Awwad.** Professor of Pediatrics, Ain Shams University, for his kindness, precious advice, continous encouragement and guidance throught out the preparation of this work.

I am deeply greatfull to **Prof. Dr. Sahar Samir Abdel Maksoud**, Professor of Clinical Pathology, Ain

Shams University for her guidance and help in this work.

I really express my gratitude to **Dr. Hanan Mohamed Abd El-Jateef**, Lecturer of Pediatrics, Ain
Shams University, for her support, attention and supervision throw out this work.

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# **List of Abbreviations**

Abb.	Full term
ACPA	Anti citrullinated protein antibody
ACR	American College of Rheumatology
ALT	Alanine aminotransferase
ANAs	Antinuclear antibodies
AST	Aspartate aminotransferase
CAPS	Cryopyrin-associated autoinflammatory
	syndromes
CBC	Complete blood count
CD	Cluster of differentiation
CMV	Cytomegalovirus
CRP	C-reactive protein
CTLs	Cells and cytotoxic T lymphocytes
CTLs	Cytotoxic T-lymphocytes
CyA	Cyclosporin A
DAS28	Disease activity score of 28 joint
DIRA	Deficiency of IL-1Ra
DITRA	Deficiency of IL-36Ra
DMARD	Disease-modifying antirheumatic drug
EBV	Epstein barr virus
EGFR	Epidermal growth factor receptor
ELISA	Enzyme linked immunosorbent assay
ER	Endoplasmic reticulum
ERA	Early rheumatoid arthritis
ESR	Erythrocyte sedimentation rate
EULAR/ACR	European League Against Rheumatism/
	American College of Rheumatology
GC	Guanylate cyclase
HLA	Human leukocyte antigen
HLH	Hemophagocytic lymphohistiocytosis
HMGB1	Mobility group protein B1
IFN	Interferon

Abb.	Full term	
IL	Interleukin	
IL-18BP	Interleukin 18 binding protein	
IL-1Ra	Interleukin-1 receptor antagonist	
	protein	
IL-1RN	IL-1 receptor antagonist gene	
ILAR	International League of Associations for	
	Rheumatology	
JIA	Juvenile Idiopathic Arthritis	
LAR	Leukocyte common antigen-related	
LCMY	Lymphocyte choriomengitis virus	
MAP	Microfibrill-associated glycoprotein	
MAS	Macrophage activation syndrome	
M-CSF	Macrophage-colony-stimulating factor	
MetAP2	Methionine aminopeptidase 2	
MKD	Mevalonate kinase deficiency	
MMPs	Matrix metalloproteinases	
Mts1	Metastasin	
MTX	Methotrexate	
NBD	Nucleotide binding domain	
NK	Natural killer cells	
NMMHC	Non-muscle myosin heavy chain	
NMMHC	Non muscle myosin heavy chain	
NSAIDs	Nonsteroidal anti-inflammatory drugs	
OA	Osteoarthritis	
P2X7	p2x purinoceptor 7	
PRINTO	Pediatric rheumatology international	
	trials organization	
RA	Rheumatoid arthritis	
RAGE	Receptor for advanced glycation	
	endproducts	
RANKL	Receptor activation of nuclear factor-ê B	
	ligand	
S100A8	Protein S100A8	

# List of Abbreviations

Abb.	Full term
SDAI	Simplified disease activity index
SF	Synovial fluid
sIL2Rá	Soluble IL 2 receptor subunit á
sJIA	Systemic juvenile idiopathic arthritis
SPSS	Statistical package for social science
Th1	T helper lymphocyte 1
TLR	Toll like receptors
TMJ	Tempromandibular joint
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
TRAPS	TNF receptor-associated periodic
	syndrome
VEGF	Vascular endothelial growth factor
WBC	White blood cell

### Introduction

Juvenile idiopathic arthritis (JIA) is the most common inflammatory rheumatic disease in childhood, affecting one in 1000 children (*Duurland and Wedderburn*, 2014). JIA is characterized by severe joint inflammation in one or more joints, which persists for at least six weeks, with disease onset before the age of 16 years. This heterogeneous group of diseases can be divided into several subtypes on the basis of clinical symptoms, medical history, and abnormalities in laboratory measures (*Ravelli and Martini*, 2007).

Approximately 10% of children with systemic JIA develop overt clinical features of macrophage activation syndrome (MAS), a life-threatening condition characterized by fever, organomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and coagulopathy, among other findings (*Martini*, 2012). The mortality rate for children hospitalized with systemic JIA and MAS is estimated to be as high as 6%, but may even be higher based on estimates from case series (*Bennetti et al.*, 2012).

NK cells and cytotoxic T lymphocytes (CTLs) cells may be directly involved in induction of apoptosis of activated macrophages and T cells during the contraction stage of the immune response (*Kagi et al.*, 1999). Cytotoxic cells dysfunction leads to persistent expansion of T cells and macrophages and escalating production of proinflammatory cytokines explaining largely the clinical findings during the acute phase of MAS (*Alexei and Grom*, 2010).

Rheumatoid arthritis (RA) is characterized at the synovial lining hyperplasia, angiogensis and mononuclear cell infiltrates in which there may be an imbalance between growth and death of fibroblast-like synoviocytes (*Fan et al.*, 2010). A failure of apoptotic pathways may explain these pathological changes in RA synovial tissues (*Smith et al.*, 2010).

S100A4 is a Ca-binding protein that regulates cell growth, survival, and motility (*Erlandsson et al.*, 2013).

The abundant expression of S100A4 in rheumatoid arthritis contributes to the invasive growth of joint tissue and bone damage (*Erlandsson et al.*, 2013).

High level of S100A4 was associated with severe radiographic changes (*Erlandsson et al.*, 2012).

Persistently high S100A4 level predicted poor treatment outcome and S100A4 may thus represent promising biomarker for assessing treatment response in patients with RA (*Senolt et al.*, 2015).

### Aim of the Work

This work aims to study the value of measuring the serum level of S100A4 in relation to the disease activity, degree of joint destruction and evolution of macrophage activation syndrome (MAS) in patients with systemic onset juvenile idiopathic arthritis (SoJIA).

### Chapter (I):

# Systemic Juvenile Idiopathic Arthritis

### **Definition and Epidemiology:**

Systemic juvenile idiopathic arthritis (sJIA, formerly called Still's disease or systemic juvenile rheumatoid arthritis) is officially classified as a heterogeneous form of arthritis in childhood. SJIA is a subset of JIA that includes patients with characteristic daily (quotidien) fever spiking to more than 39°C (102.2°F) for 2 weeks or greater in association with arthritis of 1 or more joints (*Petty et al.*, 2001).

SJIA accounts for approximately 10 to 20 % of all cases of JIA. It typically affects both sexes equally and may present in children as young as one year of age or younger. Patients with sJIA fall into the category of systemic arthritis in the 2004 when the International League of Associations for Rheumatology (ILAR) proposed classification of the childhood arthritides (*Nigrovic*, 2014).

JIA is the most common chronic rheumatic disease in childhood with an incidence of 1 in 1000. Up to 1/3 of children are reported to have active disease progressing