

**Estimation of 25 Hydroxyvitamin D level and Vitamin D deficiency in Juvenile Idiopathic Arthritis (JIA) patients and its relation to disease activity.**

*Thesis*

***Submitted in Partial Fulfillment for the Master Degree in Rheumatology and Rehabilitation***

***By***

***Radwa Abd-El Halim Mohamed***

M.B., B.Ch. Faculty of Medicine Cairo University

*Supervised by*

**Professor Dr. Abir Mohamed Nabil**

Assistant Professor of Rheumatology and Rehabilitation, Faculty of medicine, Cairo University.

**Professor Dr. Rasha Mahmoud El Refai**

Lecturer of Rheumatology and Rehabilitation, Faculty of medicine, Cairo University.

**Professor Dr. Sahar Abd El –Atty Sharaf;**

Professor of Clinical and Chemical Pathology, Faculty of medicine, Cairo University.

**Faculty of Medicine**

**Cairo University**

**2014**

# *Acknowledgement*

*Foremost, I thank Allah the most graceful and the most merciful for all his blessings and for being able to complete this work.*

*It gives me a great pleasure to express my deepest gratitude and cordial feeling to Prof. Dr. Abir Mohamed Nabil, Assistant Professor of Rheumatology and Rehabilitation, Faculty of Medicine, Cairo University. I am greatly indebted to her for suggesting this work and for her valuable guidance, continuous encouragement and discussion, It has been a great honor to proceed this work under her supervision.*

*I am also so grateful to Prof. Dr. Rasha Mahmoud El Refai, Lecturer of Rheumatology and Rehabilitation, Faculty of Medicine, Cairo University. I shall not forget her sincere guidance, valuable help and the concern she paid to the subject of this thesis.*

*I would like also to express my great thanks to Prof. Dr. Sahar Abd El-Atty Sharaf, Professor of chemical pathology, Faculty of Medicine, Cairo University. I am thankful for her close*

*supervision, continuous help and guidance in the course of this study.*

*I would like to thank my colleagues and all the staff members of the Rheumatology and Rehabilitation department, Faculty of Medicine, Cairo University, who continuously encouraged me throughout this study.*



## **Abstract**

**Objectives and Aim of the work:** The aim of this study was to determine the level of vitamin D and to examine the relation between serum levels of 25(OH)D and disease activity in patients with JIA.

**Patients and Methods:** 31 patients with Juvenile idiopathic arthritis (JIA) fulfilling the ILAR criteria for classification of JIA and 30 healthy individuals who served as controls participated in this study. All JIA patients were subjected to full history taking, clinical examination and laboratory investigations including assessment of serum level of 25(OH)D<sub>3</sub>.

**Results:** High prevalence of vitamin D deficiency and insufficiency among Egyptian JIA patients (42%) was found. There is a statistically significant difference in serum vitamin D level between the number of the patients of the 2 JIA groups receiving vitamin D supplements ( $P=0.003$ ). There is also a statistically significant difference on comparing the mean levels of 25(OH)D among the patients of the 2 JIA groups according to the dietary vitamin D intake ( $P=0.025$ ) and highly significant difference according to the total vitamin D intake ( $P<0.001$ ). On comparing between serum levels of 25(OH)D (ng/ml) according to drug intake, we found a statistically significant difference on comparing the patients taking and not taking NSAIDs ( $P=0.011$ ). Also on dividing the JIA patients into 2 groups according to the vitamin D level, there is a significant relation between the number of patients receiving NSAIDs ( $P=0.027$ ) and hydroxychloroquine ( $P=0.036$ ) on one side and vitamin D level on the other side. No statistically significant relation was detected including the disease activity score JADAS-27.

**Conclusion:** Egyptian Juvenile Idiopathic Arthritis (JIA) patients have high prevalence of vitamin D deficiency, but is not correlated to disease activity score JADAS-27.

### **Key words**

Juvenile idiopathic arthritis-25(OH) vitamin D

# **CONTENTS**

|                                                               | <b>Page</b> |
|---------------------------------------------------------------|-------------|
| <b>INTRODUCTION AND AIM OF THE WORK</b>                       | <b>1</b>    |
| <b>REVIEW OF LITERATURE</b>                                   |             |
| <b>Vitamin D</b>                                              | <b>4</b>    |
| <b>Vitamin D and autoimmune diseases</b>                      | <b>33</b>   |
| <b>The role of vitamin D in Juvenile Idiopathic Arthritis</b> | <b>52</b>   |
| <b>PATIENTS AND METHODS</b>                                   | <b>60</b>   |
| <b>RESULTS</b>                                                | <b>69</b>   |
| <b>DISCUSSION</b>                                             | <b>93</b>   |
| <b>SUMMARY</b>                                                | <b>101</b>  |
| <b>CONCLUSION</b>                                             | <b>104</b>  |
| <b>RECOMMENDATIONS</b>                                        | <b>105</b>  |
| <b>REFERENCES</b>                                             | <b>106</b>  |
| <b>ARABIC SUMMARY</b>                                         |             |

## **LIST OF TABLES**

|                   |                                                                                                                           | <b>Page</b> |
|-------------------|---------------------------------------------------------------------------------------------------------------------------|-------------|
| <b>Table (1)</b>  | Selected food sources of vitamin D according to USDA 2009.                                                                | <b>14</b>   |
| <b>Table (2)</b>  | Classification of childhood arthritis.                                                                                    | <b>52</b>   |
| <b>Table (3)</b>  | Summary of the differences among the schemata.                                                                            | <b>53</b>   |
| <b>Table (4)</b>  | Exclusion for each category of Juvenile Idiopathic Arthritis.                                                             | <b>56</b>   |
| <b>Table (5)</b>  | The characteristics of the JIA patients.                                                                                  | <b>70</b>   |
| <b>Table (6)</b>  | The clinical data of the JIA patients.                                                                                    | <b>72</b>   |
| <b>Table (7)</b>  | The laboratory data of the JIA patients.                                                                                  | <b>74</b>   |
| <b>Table (8)</b>  | JADAS-27 of the studied group and its individual components.                                                              | <b>75</b>   |
| <b>Table (9)</b>  | Drug therapy of JIA patients.                                                                                             | <b>75</b>   |
| <b>Table (10)</b> | Serum level of 25(OH)D in JIA patients and controls.                                                                      | <b>76</b>   |
| <b>Table (11)</b> | Comparison between patients versus controls according to the level of serum 25(OH)D.                                      | <b>78</b>   |
| <b>Table (12)</b> | Value of vitamin D intake among JIA patients.                                                                             | <b>79</b>   |
| <b>Table(13)</b>  | Correlation of serum 25(OH)D with various demographic, laboratory and clinical data of JIA patients.                      | <b>79</b>   |
| <b>Table(14)</b>  | Comparison between serum level of 25(OH)D (ng/ml) and various clinical manifestations among JIA patients under study.     | <b>80</b>   |
| <b>Table(15)</b>  | Comparison between serum level of 25(OH)D (ng/ml) and various laboratory data among JIA patients under study.             | <b>81</b>   |
| <b>Table(16)</b>  | Comparison between serum levels of 25(OH)D(ng/ml) according to drug intake among JIA patients under study.                | <b>81</b>   |
| <b>Table(17)</b>  | Comparison between of serum level of vitamin D and various demographic data among the 2 JIA groups under study.           | <b>83</b>   |
| <b>Table (18)</b> | Comparison between the number of patients among the 2 JIA groups as regards sex and seasonal effect of sample collection. | <b>84</b>   |

|                   |                                                                                                                                  |           |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>Table (19)</b> | Comparison between the number of patients among the 2 JIA groups as regards their various clinical data.                         | <b>86</b> |
| <b>Table (20)</b> | Comparison between the number of patients among the 2 JIA groups as regards various laboratory data.                             | <b>87</b> |
| <b>Table (21)</b> | Comparison between serum level of vitamin D among the 2 JIA groups under study according to various laboratory data.             | <b>87</b> |
| <b>Table (22)</b> | Comparison between the serum level of vitamin D among the 2 JIA groups under study according to their scoring system (JADAS-27). | <b>88</b> |
| <b>Table (23)</b> | Comparison between the number of patients in the 2 JIA groups according to their various treatment.                              | <b>89</b> |
| <b>Table (24)</b> | Comparison between the number of the patients in the 2 JIA groups according to their intake of vitamin D supplements.            | <b>90</b> |
| <b>Table (25)</b> | Comparison between the serum level of vitamin D among the 2 JIA groups under study according to their Vitamin D intake.          | <b>90</b> |

## **LIST OF TABLES**

|                   |                                                                                                                           | <b>Page</b> |
|-------------------|---------------------------------------------------------------------------------------------------------------------------|-------------|
| <b>Table (1)</b>  | Selected food sources of vitamin D according to USDA 2009.                                                                | 14          |
| <b>Table (2)</b>  | Classification of childhood arthritis.                                                                                    | 52          |
| <b>Table (3)</b>  | Summary of the differences among the schemata.                                                                            | 53          |
| <b>Table (4)</b>  | Exclusion for each category Juvenile Idiopathic Arthritis.                                                                | 56          |
| <b>Table (5)</b>  | The characteristics of the JIA patients.                                                                                  | 70          |
| <b>Table (6)</b>  | The clinical data of the JIA patients.                                                                                    | 72          |
| <b>Table (7)</b>  | The laboratory data of the JIA patients.                                                                                  | 74          |
| <b>Table (8)</b>  | JADAS-27 of the studied group and its individual components.                                                              | 75          |
| <b>Table (9)</b>  | Drug therapy of JIA patients.                                                                                             | 75          |
| <b>Table (10)</b> | Serum level of 25(OH)D in JIA patients and controls.                                                                      | 76          |
| <b>Table (11)</b> | Comparison between patients versus controls according to the level of serum 25(OH)D.                                      | 78          |
| <b>Table (12)</b> | Value of vitamin D intake among JIA patients.                                                                             | 79          |
| <b>Table(13)</b>  | The correlation of serum 25(OH)D with various demographic, laboratory and clinical data of JIA patients.                  | 80          |
| <b>Table(14)</b>  | Comparison between serum level of 25(OH)D (ng/ml) and various clinical manifestations among JIA patients under study.     | 80          |
| <b>Table(15)</b>  | Comparison between serum level of 25(OH)D (ng/ml) and various laboratory data among JIA patients under study.             | 81          |
| <b>Table(16)</b>  | Comparison between serum levels of 25(OH)D(ng/ml) according to drug intake among JIA patients under study.                | 82          |
| <b>Table(17)</b>  | Comparison between of serum level of vitamin D and various demographic data among the 2 JIA groups under study.           | 83          |
| <b>Table (18)</b> | Comparison between the number of patients among the 2 JIA groups as regards sex and seasonal effect of sample collection. | 85          |

|                   |                                                                                                                                  |    |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------|----|
| <b>Table (19)</b> | Comparison between the number of patients among the 2 JIA groups as regards their various clinical data.                         | 87 |
| <b>Table (20)</b> | Comparison between the number of patients among the 2 JIA groups as regards various laboratory data.                             | 88 |
| <b>Table (21)</b> | Comparison between serum level of vitamin D among the 2 JIA groups under study according to various laboratory data.             | 88 |
| <b>Table (22)</b> | Comparison between the serum level of vitamin D among the 2 JIA groups under study according to their scoring system (JADAS-27). | 89 |
| <b>Table (23)</b> | Comparison between the number of patients in the 2 JIA groups according to their various treatment.                              | 90 |
| <b>Table (24)</b> | Comparison between the number of the patients in the 2 JIA groups according to their intake of vitamin D supplements.            | 91 |
| <b>Table (25)</b> | Comparison between the serum level of vitamin D among the 2 JIA groups under study according to their Vitamin D intake.          | 91 |

## **LIST OF ABBREVIATIONS**

|                      |                                                            |
|----------------------|------------------------------------------------------------|
| <b>µg</b>            | <b>Microgram.</b>                                          |
| <b>1,25(OH)2D3</b>   | <b>1,25 dihydroxyvitamin D.</b>                            |
| <b>1,25(OH)D-VDR</b> | <b>1,25 dihydroxyvitamin D-Vitamin D receptor complex.</b> |
| <b>24,25(OH)D</b>    | <b>24,25 dihydroxyvitamin D.</b>                           |
| <b>25(OH)D</b>       | <b>25 hydroxyvitamin D.</b>                                |
| <b>ACCP</b>          | <b>Anticyclic citrullinated peptide antibodies.</b>        |
| <b>ACR</b>           | <b>American college of rheumatology.</b>                   |
| <b>AI</b>            | <b>Adequate Intake.</b>                                    |
| <b>ALT</b>           | <b>Alanine aminotransferase.</b>                           |
| <b>ANA</b>           | <b>Antinuclear antibody.</b>                               |
| <b>Anti U1 RNP</b>   | <b>Anti U1-ribonuclear protein antibodies.</b>             |
| <b>Anti-sm</b>       | <b>Anti-smith antibodies.</b>                              |
| <b>APCs</b>          | <b>Antigen presenting cells.</b>                           |
| <b>AS</b>            | <b>Ankylosing spondylitis.</b>                             |
| <b>ASBMR</b>         | <b>American Society for Bone and Mineral Research.</b>     |
| <b>AST</b>           | <b>Aspartate aminotransferase.</b>                         |
| <b>BASDAI</b>        | <b>Bath Ankylosing Spondylitis Disease Activity Index.</b> |
| <b>BD</b>            | <b>Behcet's Disease.</b>                                   |
| <b>BDCAF</b>         | <b>Behcet's Disease Current Activity Form.</b>             |
| <b>BMC</b>           | <b>Bone mineral content.</b>                               |
| <b>BMD</b>           | <b>Bone mineral density.</b>                               |
| <b>BMI</b>           | <b>Body mass index.</b>                                    |
| <b>C</b>             | <b>Complement.</b>                                         |

|                        |                                                          |
|------------------------|----------------------------------------------------------|
| <b>Ca<sup>++</sup></b> | <b>Calcium.</b>                                          |
| <b>CAMP</b>            | <b>cyclic Adenosine Mono Phosphate.</b>                  |
| <b>CBC</b>             | <b>Complete blood count.</b>                             |
| <b>Cm</b>              | <b>Centimeter.</b>                                       |
| <b>CRP</b>             | <b>C-reactive protein.</b>                               |
| <b>CTDs</b>            | <b>Connective Tissue Diseases.</b>                       |
| <b>CYP27A1</b>         | <b>25 hydroxylase enzyme.</b>                            |
| <b>CYP27B1</b>         | <b>1 alpha hydroxylase enzyme.</b>                       |
| <b>D<sub>2</sub></b>   | <b>Vitamin D<sub>2</sub> Ergocalciferol.</b>             |
| <b>D<sub>3</sub></b>   | <b>Vitamin D<sub>3</sub> Cholecalciferol.</b>            |
| <b>DAS-28</b>          | <b>Disease activity score -28.</b>                       |
| <b>DBP</b>             | <b>Vitamin D binding protein.</b>                        |
| <b>DC</b>              | <b>Dendritic cells.</b>                                  |
| <b>DM</b>              | <b>Dermatomyositis.</b>                                  |
| <b>DMARDs</b>          | <b>Disease modifying antirheumatic drugs.</b>            |
| <b>DNA</b>             | <b>Deoxyribonucleic acid.</b>                            |
| <b>DRIs</b>            | <b>Dietary Reference Intakes.</b>                        |
| <b>Ds</b>              | <b>Double stranded.</b>                                  |
| <b>Ds DNA Abs</b>      | <b>Double stranded deoxyribonucleic acid antibodies.</b> |
| <b>DV</b>              | <b>Daily Value.</b>                                      |
| <b>DXA</b>             | <b>Dual x-ray absorptiometry.</b>                        |
| <b>ELISA</b>           | <b>Enzyme Linked Immunosorbant Assay.</b>                |
| <b>ESR</b>             | <b>Erythrocyte sedimentation rate.</b>                   |
| <b>EULAR</b>           | <b>European League Against Rheumatism.</b>               |
| <b>FLSs</b>            | <b>Fibroblast Like Synoviocytes.</b>                     |
| <b>FNB</b>             | <b>Food and Nutrition Board.</b>                         |

|                         |                                                               |
|-------------------------|---------------------------------------------------------------|
| <b>Hb</b>               | <b>Haemoglobin.</b>                                           |
| <b>HLA-B27</b>          | <b>Human leucocytic antigen.</b>                              |
| <b>HLA-DRB1*1501</b>    | <b>Histocompatibility gene.</b>                               |
| <b>HSP</b>              | <b>Heat Shock Proteins.</b>                                   |
| <b>IBD</b>              | <b>Inflammatory bowel disease.</b>                            |
| <b>IDBP</b>             | <b>Intracellular D binding protein.</b>                       |
| <b>IF gamma</b>         | <b>Interferon gamma.</b>                                      |
| <b>IFN-γ</b>            | <b>Interferon gamma.</b>                                      |
| <b>Ig</b>               | <b>Immunoglobulin.</b>                                        |
| <b>Ig A RF</b>          | <b>Immunoglobulin A Rheumatoid Factor.</b>                    |
| <b>Ig M RF</b>          | <b>Immunoglobulin M Rheumatoid factor.</b>                    |
| <b>IJD</b>              | <b>Inflammatory joint disease.</b>                            |
| <b>IL</b>               | <b>Interleukin.</b>                                           |
| <b>ILAR</b>             | <b>International League of Associations for Rheumatology.</b> |
| <b>IRF-8</b>            | <b>Interferon Regulatory Factor 8.</b>                        |
| <b>IU</b>               | <b>International units.</b>                                   |
| <b>JADAS-27</b>         | <b>Juvenile arthritis disease activity score.</b>             |
| <b>JAS</b>              | <b>Juvenile ankylosing spondylitis.</b>                       |
| <b>JCA</b>              | <b>Juvenile chronic arthritis.</b>                            |
| <b>JIA</b>              | <b>Juvenile idiopathic arthritis.</b>                         |
| <b>JPsa</b>             | <b>Juvenile psoriatic arthritis.</b>                          |
| <b>JRA</b>              | <b>Juvenile rheumatoid arthritis.</b>                         |
| <b>Kg</b>               | <b>Kilogram.</b>                                              |
| <b>Kg/m<sup>2</sup></b> | <b>Kilogram per meter square.</b>                             |
| <b>M</b>                | <b>Meter.</b>                                                 |
| <b>MCTD</b>             | <b>Mixed connective tissue disease.</b>                       |

|               |                                                             |
|---------------|-------------------------------------------------------------|
| <b>Mg</b>     | <b>Milligram.</b>                                           |
| <b>MHAQ</b>   | <b>Modified health assessment questionnaire.</b>            |
| <b>MI</b>     | <b>Milli-liter.</b>                                         |
| <b>MMP</b>    | <b>Matrix Metalloprotease.</b>                              |
| <b>MS</b>     | <b>Multiple sclerosis.</b>                                  |
| <b>Ng/ml</b>  | <b>Nanogram per milliliter.</b>                             |
| <b>NHANES</b> | <b>National Health and Nutrition Examination Survey.</b>    |
| <b>Nmol/l</b> | <b>Nanomol per liter.</b>                                   |
| <b>NSAIDs</b> | <b>Nonsteroidal anti-inflammatory drugs.</b>                |
| <b>PAD</b>    | <b>Peripheral artery disease.</b>                           |
| <b>PM</b>     | <b>Polymyositis.</b>                                        |
| <b>PTH</b>    | <b>Parathyroid hormone.</b>                                 |
| <b>RA</b>     | <b>Rheumatoid arthritis.</b>                                |
| <b>RDA</b>    | <b>Recommended Dietary Allowance.</b>                       |
| <b>RF</b>     | <b>Rheumatoid factor.</b>                                   |
| <b>RNA</b>    | <b>Ribo Nucleic Acid.</b>                                   |
| <b>RR</b>     | <b>Rapid Response.</b>                                      |
| <b>RXR</b>    | <b>Retinoid X Receptor.</b>                                 |
| <b>SD</b>     | <b>Standard deviation.</b>                                  |
| <b>SLE</b>    | <b>Systemic lupus erythematosus.</b>                        |
| <b>SLEDAS</b> | <b>Systemic Lupus Erythematosus Disease Activity Score.</b> |
| <b>SPAP</b>   | <b>Systolis Pulmonary Artery Pressure.</b>                  |
| <b>SPF</b>    | <b>Sun Protection Factor.</b>                               |
| <b>SS</b>     | <b>Sjogren's Syndrome.</b>                                  |
| <b>SSc</b>    | <b>Systemic sclerosis.</b>                                  |
| <b>TGF-B</b>  | <b>Transforming Growth Factor B.</b>                        |

|                                |                                                    |
|--------------------------------|----------------------------------------------------|
| <b>TH</b>                      | <b>T helper cells.</b>                             |
| <b>TLC</b>                     | <b>Total leucocytic count.</b>                     |
| <b>TLRs</b>                    | <b>Toll like receptors.</b>                        |
| <b>TNF-<math>\alpha</math></b> | <b>Tumor necrosis factor alpha.</b>                |
| <b>Tregs</b>                   | <b>T regulatory cells.</b>                         |
| <b>UCTD</b>                    | <b>Undifferentiated Connective Tissue Disease.</b> |
| <b>UL</b>                      | <b>Tolerable Upper Intake Level.</b>               |
| <b>US</b>                      | <b>United states.</b>                              |
| <b>USDA</b>                    | <b>United States food and Drug Adminstration.</b>  |
| <b>UV</b>                      | <b>Ultraviolet.</b>                                |
| <b>UVA</b>                     | <b>Ultraviolet A.</b>                              |
| <b>UVB</b>                     | <b>Ultraviolet B.</b>                              |
| <b>UVR</b>                     | <b>Ultraviolet rays.</b>                           |
| <b>VAS</b>                     | <b>Visual analogue scale.</b>                      |
| <b>VDR</b>                     | <b>Vitamin D Receptor.</b>                         |
| <b>VDRE</b>                    | <b>Vitamin D Responsive Elements.</b>              |
| <b>VDR<sub>mem</sub></b>       | <b>Vitamin D receptor membrane.</b>                |
| <b>VDR<sub>nuc</sub></b>       | <b>Vitamin D receptor nucleus.</b>                 |
| <b>WBC</b>                     | <b>White blood cells.</b>                          |