

A Study of Health-Related Quality of Life in Children with Juvenile Idiopathic Arthritis

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Abstract

Background: Juvenile Idiopathic Arthritis (JIA) is one of the most common rheumatic disease of children and a major cause of chronic physical disability. Juvenile Idiopathic Arthritis (JIA) is not a single disease, It Is a group of diseases of unknown etiology, which are manifested by chronic joint inflammation. It is characterized by an idiopathic synovitis of the peripheral joints, associated with soft tissue swelling and effusion.

Aim: Aim of this study was to Assess the health related- Quality of life (HRQOL) in children with Juvenile Idiopathic arthritis. Detect the relationship between treatment satisfaction and maintenance of positive physical and psychosocial well- being.

Subject& Methods: 50 patient with JIA non complicated cases, 50 patient with JIA complicated cases and 50 apparently healthy control matched with age and sex matched children of the same social background by using Health Related Quality Of Life (HRQOL) questionnaire- Peds QL. version 3. arthritis module, (8- 12) years and children (12- 18) years children Questionnaire and parent- proxy Questionnaire include many items to measure the score physical, emotional, social, school and well being.

Results: Health Related Quality Of Life (HRQOL) of the patients varied according to the type and duration of the disease. According to child problems there was higher statistically significant rate with pain, daily activities and side effect of medications with poly and systemic type and less significant with feeling and school and according to parent problems show higher statistically significant with poor and moderate score in physical and social problems. Statistically difference between cases and control according to father education and occupation and no statistically significant difference between cases and control as regard mother occupation $P>0.05$. the frequency of JIA more in the female patient than male (2: 1) and the polyarticular type was most common type. Positive strong correlation and statistically significant between age and duration of the disease $P<0.001$. Also show systemic corticosteroid were (65.7%) highest frequency in polyarticular onset.

Conclusion: Children with more symptoms, polyarticular of JIA are poorer quality of life than oligoarticular. Early diagnoses and effective therapy of JIA have good prognoses and less complications. Quality of life in children with JIA depends on disease subtype and outcome.

دراسة نوعية الحياة عند الأطفال المصابين بالتهاب المفاصل

مقدمه: يعد مرض التهاب المفاصل الأكثر شيوعاً في الأطفال، كما يعد من أهم أسباب الإعاقة سواء على المدى القريب أو البعيد. ومازالت حتى الآن الأسباب وراء هذا المرض غير معلومة بصورة واضحة حيث أن هناك العديد من الأسباب الوراثية المركبة التي تتضمن تأثير العديد من الجينات المتعلقة بالمناعة والتهاب المفاصل الحثي مجهول السبب واحداً من أكثر الأمراض الرماتيزمية. هو مرض مزمن من خصائصه وجود التهاب مستمر في المفاصل والأعراض المحددة المصاحبه لالتهاب المفاصل هي: الأم والتورم وتقيد وصعوبة الحركة. وتجدر الإشارة الى ان التهاب المفاصل الروماتزمي لدى الأطفال قد يصيب مفصلاً واحداً او أكثر من مفاصل الجسم، كما انه قد يصيب جميع المفاصل لدى بعض اخر مما يؤدي الى انتفاخ العقد الليمفاوية وطفح في الجلد وارتفاع درجات الحرارة، وكما هو الحال في جميع اشكال التهاب المفاصل فالتهاب المفاصل الروماتزمي لدى الأطفال يمر بآفات حمود تختفي فيها اعراضه نهائياً وفترات اخرى تظهر فيها الاعراض. ان قياس نوعية الحياة كان يشكل تحدياً هماً بسبب عدم الاجماع على تعريف لها لكن منظمة الصحة العالمية عرفت على انها 'الاحساس الشخصي للفرد بمكانته في الحياة في حدود المنظوم الثقافي والنظم التقييميه التي يعيشها بالنسبه لاهدافه وتوقعاته ومعاييرها ومخاوفه' وهي تشمل منظورا متعدد الابعاد في المجالات البدنيه والاجتماعيه والنفسيه، ولقد اجريت هذه الدراسه في عيادة الحساسيه والمناعه للاطفال بمستشفى الاطفال الجامعي بجامعة عين شمس.

العيونه: المجموعه المختارة لهذه الدراسه تتكون من كل الاطفال المصابين بالالتهاب المفاصل الحثي في المرحله العمريه من (8- 16) سنه والذين يترددون على العياده الخارجيه بمستشفى الاطفال الجامعي بجامعة عين شمس.

الادوات: يتم في هذه الدراسه تقييم نوعية الحياه للاطفال المصابين بالالتهاب المفاصل باستخدام مقياس تقييم نوعية الحياه للاطفال المصابين بالالتهاب المفاصل الحثي اصداراً 4 ميزان رئيسي عام، تقرير نفس الطفل، تقرير والد الطفل. بعد مقارنه المجموع الكلي لمقياس نوعية الحياه للاطفال اصداراً 3، ميزان رئيسي عام لهؤلاء الاطفال المصابين مع الاطفال الاصحاء بنفس العمر وجد ان الاطفال المصابين بالالتهاب المفاصل الحثي يعانون من انخفاض ملحوظ في نوعية الحياه.

هدف الدراسه: تقييم نوعية الحياه في الاطفال المصابين بالالتهاب المفاصل، ودراسة قوة التقييم الذي يملأ بمعرفة الطفل ومقارنتها بالتقييم الذي يملأ بمعرفة أحد الوالدين وتأثيراته على نوعية حياة المريض وكل الأشخاص المحيطين به.

Introduction:

Juvenile Idiopathic Arthritis (JIA) is one of the most common rheumatic disease of children and a major cause of chronic physical disability.

It is characterized by an idiopathic synovitis of the peripheral joints, associated with soft tissue swelling and effusion (Rohr et.al., 2008 and Goldzweig et.al., 2011). The American college of Rheumatology criteria classify It as a category of diseases with three principle types of onset oligoarthritis, polyarthritis, and systemic onset disease.

The damage of the cartilaginous tissue is often irreversible and responsible for much of the morbidity (Meholjic- Fetahovic, 2005). Juvenile idiopathic arthritis Is the most common chronic rheumatic illness in children with a significant cause of both short and long term disabilities. In addition, premature mortality may occur from side effects of therapeutic regimens (Rohr et.al., 2008 and Goldzweig et.al., 2011). Quality Of Life is multidimensional. It includes social, physical, emotional and school functioning of the child (American College of Rheumatology, 2007).

Methodology**Patients:**

This study was conducted at rheumatology clinic, children hospital Ain Shams University.

All cases fulfilling the inclusion criteria were selected from Rheumatology clinic of Ain Shams University were included during a full calendar year (2017- 2018).

They were divided by different ways:

- ✧ First Method: age- children (8- 12) years. age- children (12- 18) years.
- ✧ Second Method: According to duration of treatment.

Then sub- sample of 150 persons will be selected as the following:

1. 50 persons from complicated cases.
2. 50 persons from non complicated cases.
3. 50 persons from the healthy control group

Controls:

Equal number of healthy age and sex matched children of the same social background were served as a control group.

1. The Inclusion Criteria:
 - a. All patients were diagnosed (age between 8- 18 years).
 - b. All patients fulfilled the JIA criteria.
2. The Exclusion Criteria:
 - a. Patients with inflammatory pathologies such as connective tissue disorders, ulcerative colitis and other chronic diseases.
 - b. Patients With Malignancy.
 - c. Patients receiving antipsychotic drugs.

Ethical Issue:

Written and oral consent were taken from the parents of the patients before insuring on the items of questions.

Methods:

1. Thorough History Taking Included:

- a. School performance, school failure, repeated grades, days of absence.
 - b. Onset, duration, severity, prognoses and disability.
 - c. Diagnosis, age of diagnosis.
 - d. Treatment details (Type duration)
 - e. Detailed general clinical examination including:
 - f. Heart, chest and neurological examinations.
 - g. Assessment of Health- related quality of life questionnaire for children and their parents and its Arabic version (Varni et.al. 2003). It is one of the international tools for assessment of HRQOL of children. This instrument provides both (child self-report) children; (8- 12) years and children (12- 18) years.
2. Peds QL version 3.0 arthritis module child Questionnaire and parent-proxy Questionnaire include 22 items as the following;
 - a. Problems with pain and hurt 4 items
 - b. Problems with daily activities 5 items
 - c. Problems with treatment 7 items
 - d. Problems with worry 3 items.
 - e. Problems with communication 3 items;
 - f. Assessment of (socioeconomic state (SES) Abd El Aziz El Shakhs (1995) which included; Father education and occupation and mother education and occupation and monthly income percapita according to EL- Shakhs (1995).
 3. Routine laboratory investigations:
 - a. Complete blood picture (CBC).
 - b. ESR.
 - c. ANA.
 - d. Rheumatoid Factor.
 4. Radiologic Investigations: Plain x- ray of the affected joints.

Statistical Analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were done:

1. Independent- samples t- test of significance was used when comparing between two means.
2. Chi square (χ^2) test of significance was used in order to compare proportions between qualitative parameters.
3. Pearson's correlation coefficient (r) test was used to assess the degree of association between two sets of variables.
4. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p- value was considered significant as the following:
5. Probability (P- value).
 - a. P- value <0.05 was considered significant.
 - b. P- value <0.001 was considered as highly significant.
 - c. P- value >0.05 was considered insignificant.

Results:

The characteristics age, sex and type of the disease in JIA cases and controls enrolled in this study were shown in table (1) which shows that the female patients were more than male patients and the most common type of JIA from complicated cases was polyarticular. (62%), followed by systemic onset type (38%) then periarticular type (22.5%).

There were statistically significant difference was found as regard profile of JIA cases, comparing the type of onset with age of onset, duration of illness, number of tender joints and number of swollen joints table (2).

Table (3): Comparison between Types of the JIA according to non-steroidal anti- inflammatory drugs (NSAID), steroids and methotrexate. Show Systemic corticosteroids were used by 23 cases (65.7%) with highest frequency in polyarticular onset cases, with statistical significance difference (p= 0.03).

Methotrexate was used by 11 cases (73.3%) with highest frequency in the systemic onset cases, with statistical significant difference (p< 0.001).

Table (4): Comparison between cases and control according to father and mother education and occupation show statistical significant difference between cases and control according to father education, occupation and mother education. Showed higher percentage of moderate and low education and occupation of father when compared to control group and no statistically significant difference between cases and control as regards mother occupation p> 0.05.

Table (5): Comparison between types of JIA disease and control group as regards problems with daily activities show There was statistically significant higher rate of daily activities function when compared with control group.

Table (6): Comparison between JIA group and control group as regards problems with communication. There was statistically higher rate with communication problems when compared with control group.

Table (7): Comparison between JIA groups and control group as regard problems with pain and hurt. There was statistically significant higher rate of problems with pain when compared with control group.

Table (8): Comparison between Types of JIA disease as regard child total score

This table shows statistically significant between types of JIA according to total child score. There was higher statistically significant rate with pain, daily activities and side effect of medication with polyarticular

Table (5) Comparison between types of JIA disease and control group as regards problems with daily activities as a parameter of Health- Related Quality of Life HRQOL)

Daily Activities	Complicated (N= 50)		Noncomplicated (N= 50)		Control (N= 50)		x ²	P- Value
	No.	%	No.	%	No.	%		
It is hard to turn on water faucets (no problem)	1	2.0%	0	0.0%	50	100.0%	207.402	<0.001**
It is hard to turn door handles (mild)	3	6.0%	28	56.0%	0	0.0%		
I have trouble eating with a fork and knife (moderate)	12	24.0%	4	8.0%	0	0.0%		
It is hard to write or draw with aspen or pencil (severe)	17	34.0%	18	36.0%	0	0.0%		
I have trouble carrying my school books (very severe)	17	34.0%	0	0.0%	0	0.0%		

There was high statistical significance of daily activities function and poor quality of life when compared with control group.

and systemic and less significant with feeling and school this is mostly due to family support.

Table (9) Comparison between Types of JIA disease as regard total parent score This table shows statistically significant between types of JIA according to total parent score with higher rate of poor and moderate score more in physical problem.

Table (1) The characteristics age, sex and types of onset in JIA cases and controls enrolled in this study.

Ch. Ch		Patients N= 100	Controls N= 50
Age Mean±Sd		13.78±2.71	13.72±2.61
Sex	Male N (%)	33	12
	Female N (%)	67	38
Types Of Disease	Polyarticular	31	
	Pauciarticular	50	
	Systemic	19	

Table (2) Profile of JIA cases, comparing the type of disease with age, duration of illness, number of tender joints and number of swollen joints.

Variable	Pauci Articular	Poly Articular	Systemic	P- Value
Age Mean±SD	4.00± 0.53	2.57±1.22	2.27±1.1	0.892
Duration Of Illness	2.68± 1.78	3.06±2.00	5.13±1.19	<0.001**
Number Of Tender Joints	3- 5	4- 5	4- 5	<0.001**
Number Of Swollen Joints	3- 5	4- 5	4- 5	<0.001**

Table (3) Comparison between Types of disease according to NSAID, steroid and methotrexate.

		Periarticular (n= 50)		Poly Articular (n= 35)		Systemic (n= 15)		x ²	P- Value
		No.	%	No.	%	No.	%		
NSAID	Not Used	5	5%	0	0.0%	0	0.0%	11.114	0.004*
	Used	45	95%	35	100.0%	15	100.0%		
Steroid	Not Used	15	30.0%	12	34.3%	8	53.3%	2.773	0.03
	Used	35	70.0%	23	65.7%	7	46.7%		
Methotrexate	Not Used	40	80.0%	8	22.9%	4	26.7%	31.47y.	<0.001**
	Used	10	20.0%	27	77.1%	11	73.3%		

Table (4) Comparison between cases and control according to father and mother education and occupation according to socioeconomic state (SES) El Shakhs.

		Cases (n= 100)		Control (n= 50)		x ²	P- Value	
		No.	%	No.	%			
Father	Education	Low	37	37.0%	5	10.0%	24.039	<0.001**
		Moderate	34	34.0%	10	20.0%		
		High	29	29.0%	35	70.0%		
	Occupation	Laborer Worker	37	37.0%	5	10.0%	24.039	<0.001**
		Employee	34	34.0%	10	20.0%		
		Prof. (doctor/ eng.)	29	29.0%	35	70.0%		
Mother	Education	Low	61	61.0%	5	10.0%	42.449	<0.001**
		Moderate	19	19.0%	10	20.0%		
		High	20	20.0%	35	70.0%		
	Occupation	Worker	50	50.0%	25	50.0%	0.000	1.000
		Housewife	50	50.0%	25	50.0%		

Table (6) Comparison between JIA group and control group as regards problem with communication as a parameter of Health- Related Quality of Life (HRQOL)

Communication	Complicated (N= 50)		Non- complicated (N= 50)		Control (N= 50)		x ²	P- Value
	No.	%	No.	%	No.	%		
It is hard for me to tell the doctors and nurses how I feel	15	30.0%	28	56.0%	50	100.0%	156.789	<0.001**
It is hard for me to ask the doctors and nurses questions	13	26.0%	4	8.0%	0	0.0%		
It is hard for me to explain my illness to other people	22	44.0%	18	36.0%	0	0.0%		

Table (7) Comparison between JIA group and control group as regard problems with pain and hurt as a parameter of Health- Related Quality of Life (HRQOL)

Pain And Hurt	Complicated (N= 50)		Non- complicated (N= 50)		Control (N= 50)		x ²	P- Value
	No.	%	No.	%	No.	%		
I ache or hurt in my joints and Or muscles	5	10%	5	10.0%	0	0.0%	238.636	<0.001**
I Hurt A Lot	5	10.0 %	5	10.0%	0	0.0%		
I have trouble sleeping because of pain in my joints and or muscles	20	40.0%	32	64.0%	0	0.0%		
I feel stiff in the morning or when I sit too long	20	40.0%	8	16.0%	0	0.0%		

Table (8) Child profile showing comparison between types of JIA disease as regards child total score of Health- Related Quality of Life (HRQOL).

Child Profile		Pauciarticular (n= 50)		Poly Articular (n= 35)		Systemic (n= 15)		x ²	P- Value
		No.	%	No.	%	No.	%		
Pain	Excellent	0	0.0%	0	0.0%	0	0.0%	58.730	<0.001**
	Good	5	10.0%	0	0.0%	0	0.0%		
	Moderate	32	64.0%	0	0.0%	0	0.0%		
	Poor	13	26.0%	35	100.0%	15	100.0%		
Daily Activities	Excellent	0	0.0%	1	2.9%	0	0.0%	43.124	<0.001**
	Good	28	56.0%	3	8.6%	0	0.0%		
	Moderate	4	8.0%	12	34.3%	0	0.0%		
	Poor	18	36.0%	19	54.3%	15	100.0%		
Treatment	Excellent	2	4.0%	1	2.9%	0	0.0%	29.147	<0.001**
	Good	26	52.0%	6	17.1%	0	0.0%		
	Moderate	6	12.0%	8	22.9%	0	0.0%		
	Poor	16	32.0%	20	57.1%	15	100.0%		
Side Effect Of Medication	Excellent	2	4.0%	8	22.9%	0	0.0%	26.086	<0.001**
	Good	22	44.0%	9	25.7%	0	0.0%		
	Moderate	10	20.0%	6	17.1%	2	13.3%		
	Poor	16	32.0%	12	34.3%	13	86.7%		
Communications	Excellent	2	4.0%	7	20.0%	0	0.0%	27.182	<0.001**
	Good	26	52.0%	8	22.9%	0	0.0%		
	Moderate	4	8.0%	8	22.9%	5	33.3%		
	Poor	18	36.0%	12	34.3%	10	66.7%		
Feeling	Excellent	2	4.0%	4	11.4%	0	0.0%	19.690	0.003*
	Good	24	48.0%	9	25.7%	0	0.0%		
	Moderate	6	12.0%	9	25.7%	3	20.0%		
	Poor	18	36.0%	13	37.1%	12	80.0%		
School	Excellent	2	4.0%	3	8.6%	0	0.0%	16.768	0.009*
	Good	28	56.0%	11	31.4%	1	6.7%		
	Moderate	8	16.0%	8	22.9%	7	46.7%		
	Poor	12	24.0%	13	37.1%	7	46.7%		
Total Score Child Profile	Mean±SD	12.64±5.62		14.86±5.13		19.73±1.39		F: 11.57	<0.001**
	Range	2-21		3-21		16-21			

JIA groups showed high statistical significance higher rate of moderate lower rate of good scores with school and feeling and poor scores with pain, daily activities and side effect of medication

Table (9) Parent profile showing, comparison between types of JIA disease as regards parent total score of Health Related Quality Of Life (HRQOL).

Parent Profile		Periarticular (n= 50)		Poly Articular (n= 35)		Systemic (n= 15)		x ²	P- Value
		No.	%	No.	%	No.	%		
Physical	Excellent	2	4.0%	0	0.0%	0	0.0%	27.585	<0.001**
	Good	26	52.0%	11	31.4%	0	0.0%		
	Moderate	0	0.0%	10	28.6%	4	26.7%		
	Poor	22	44.0%	14	40.0%	11	73.3%		
Emotional	Excellent	0	0.0%	0	0.0%	0	0.0%	20.174	<0.001**
	Good	26	52.0%	14	40.0%	0	0.0%		
	Moderate	0	0.0%	6	17.1%	2	13.3%		
	Poor	24	48.0%	15	42.9%	13	86.7%		

Parent Profile		Periarticular (n= 50)		Poly Articular (n= 35)		Systemic (n= 15)		x ²	P- Value
		No.	%	No.	%	No.	%		
Social	Excellent	4	8.0%	0	0.0%	0	0.0%	28.147	<0.001**
	Good	22	44.0%	13	37.1%	0	0.0%		
	Moderate	0	0.0%	9	25.7%	2	13.3%		
	Poor	24	48.0%	13	37.1%	13	86.7%		
School	Excellent	0	0.0%	2	5.7%	0	0.0%	27.981	<0.001**
	Good	28	56.0%	12	34.3%	0	0.0%		
	Moderate	10	20.0%	6	17.1%	1	6.7%		
	Poor	12	24.0%	15	42.9%	14	93.3%		
Well Being	Excellent	10	20.0%	6	17.1%	0	0.0%	17.357	0.008*
	Good	20	40.0%	11	31.4%	0	0.0%		
	Moderate	6	12.0%	4	11.4%	3	20.0%		
	Poor	14	28.0%	14	40.0%	12	80.0%		
Cognitive	Excellent	26	52.0%	7	20.0%	0	0.0%	43.351	<0.001**
	Good	16	32.0%	11	31.4%	0	0.0%		
	Moderate	6	12.0%	3	8.6%	5	33.3%		
	Poor	2	4.0%	14	40.0%	10	66.7%		
Total Score Parents Profile	Mean±SD	9.52±5.21		11.51±5.28		16.87±1.81		F: 13.05	<0.001**
	Range	2- 18		4- 18		12- 18			

Discussion:

Juvenile Idiopathic Arthritis JIA is the most common inflammatory arthritis worldwide with major individual and health service cost and characterized mostly by polyarticular inflammation, increased cytokine production and pannus development, which subsequently lead to the erosion of the cartilage and underlying bone (Song et al., 2012).

JIA is one of many chronic inflammatory diseases that predominate in females. The ratio of female: male patients ranges from 2: 1- 4: 1 except, for systemic onset type in which the sex ratio is equal. (Cassidy, 2001).

In this study as regard demographic characteristic of JIA patients found that 67 female patients 67% and 33 male patients 33%, it is observed in our sample that JIA is more prevalent in female than males. Female to male ration in our study 2.5: 1 as regard table (1).

In the current study, all patients received NSAIDs. (65.7%) of the studied group was receiving systemic corticosteroids with higher frequencies in the systemic and polyarticular cases more than periarticular (42.3% and 38.5 vs 18.2% respectively) with statistical significant difference (P= 0.04). Moreover, 30% of patients were receiving methotrexate with higher frequencies in the systemic and polyarticular cases more than periarticular (34.3% with statistical significant difference (P= 0.03).

Similar rates were noted in a study by Hossny et al., (2006) on JIA patients attending pediatric allergy and immunology clinic Ain Shams University. They found that all cases received NSAIDs, 70% received systemic corticosteroids, and 30% received methotrexate, while Cron et al. (1999), Alsufyani (2004) and Niehues and Lankisch.(2006) reported that methotrexate was the most common treatment prescribed for patients with JIA. This may be caused by lack of compliance of the patients.

HRQOL generally refers to how an individual feels about aspects of their life in relation to their health.

Study found that children with JIA has lower QOL when compared to normal healthy control.

There was lower QoL in arthritis module in female as regards physical and emotional appearance while lower QOL in males in cognitive problems and communication in current study table (8).

Girls reported a scientifically lower functioning in physical scale whereas boys had a lower QOL with regard to cognitive and emotional domains as reported by Landolt et al. (2006).

The current study evaluated the aspects of quality of life in children with JIA and who under treatment. the overall QOL has been found to be significantly lower than normal (as compared to normal historical control and normal control of Egyptians children).

The present study revealed that patient with systemic and polyarticular JIA have lower QOL compared to patients with Oligo arthritis.

The disease is divided into several subgroups, according to demographic characteristics, clinical features, treatment modalities and disease prognosis. In our study children with JIA in have lower quality of life than in healthy peers.

Study shows lower Ped- QL of children with JIA in relation to symptoms, severity and comorbidity.

Children with more symptoms, polyarticular of JIA are poorer quality of life than oligoarticular. Early diagnoses and effective therapy of JIA have good prognoses and less complications. This study also report lower Health Related Quality Of Life (HRQOL) compared to their healthy peers.

Quality of life in children with JIA depends on disease subtype, short term, long term disability and outcome. As the child's QOL decreases parental stress increases.

References:

1. Alsufyani K, Ortiz- Alvarez O, Cabral D, et al. (2004): The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. *J Rheumatol*; 31 (1): 179- 82.
2. Cassidy J; (2001): **Rheumatic Diseases of Childhood**. In: Kelley's

- Textbook of pediatric Rheumatology. 6th edition. Philadelphia: W. B. Saunders Company; (87): Pp. 1297- 1314.
3. Cron R, Sharma S. and Sherry D; (1999): Current treatment by United States and Canadian pediatric rheumatologists. *J Rheumatol* 26 (9): 20368. Cytokine- gene expression in rheumatoid arthritis. **J. Immunol.** 144: 3347- 3353.
 4. Goldzweig O, Hashkes PJ. Abatacept in the treatment of polyarticular JIA: development, clinical utility, and place in therapy. **Drug design, development and therapy.** 2011; 5:61.
 5. Hosney E, Abd EL- Hady H and Mabrouk R; (2006): The incidence of JRA in pediatric rheumatology diseases **Pediatr Allergy Immunol**; 11 (4): 250- 255.
 6. Landolt MA, Vollrath M, Niggli FK, Gnehm HE, Sennhauser FH. Health- related quality of life in children with newly diagnosed cancer: a one year follow- up study. **Health and quality of life outcomes.** 2006;4(1): 63.
 7. Meholic- Fetahovic A. (2005): Complex functional test in juvenile rheumatoid arthritis. **Med Arh**; 59 (6): 373.
 8. Meholic- Fetahovic A; (2005): Complex functional test in juvenile rheumatoid arthritis. **Med Arh**; 59 (6): 373.
 9. Niehues T and Lankisch P; (2006): Recommendations for the use of methotrexate in juvenile idiopathic arthritis. **Paediatr Drugs**; (6): 347- 56.
 10. Rohr P, Veit TD, Scheibel I, Xavier RM, Brenol JC, Chies JA, Kvitko K. Pediatric rheumatology GSTT1, GSTM1 and GSTP1 polymorphisms and susceptibility to juvenile idiopathic arthritis. **Clinical and experimental rheumatology.** 2008; 26:151- 5.
 11. Song G. Bae S. and Lee Y; (2012): The glutathione Stransferase M1 and P1 polymorphisms and rheumatoid arthritis: a meta- analysis. **Mol Biol Rep** (2012) 39: 10739- 10745.
 12. Varni JW, Sherman SA, Burwinkle TM, Dickinson PE, Dixon P. The PedsQL™ family impact module: preliminary reliability and validity. **Health and quality of life outcomes.** 2004; 2(1):55.