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Thyroid Disorders and Anti-Thyroid Antibody Level in Juvenile Idiopathic Arthritis in Children

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Abstract

Background: Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease in children and is recognized as an autoimmune condition. Autoimmune thyroid disorders are known to co-occur with rheumatologic diseases, yet their association in pediatric JIA remains underexplored. **Objective:** To investigate the prevalence of thyroid disorders and anti-thyroid antibody levels in children diagnosed with JIA. **Methods:** This cross-sectional analytical study included 70 children with JIA (Group I) and 35 age- and sex-matched healthy controls (Group II), conducted at BSMMU from April 2021 to March 2022. Thyroid function tests (FT3, FT4, TSH) and anti-thyroid antibodies (anti-TG and anti-TPO) were measured using chemiluminescent immunoassay. Statistical analysis was performed using SPSS 26.0, with significance set at $p < 0.05$. **Results:** TSH levels were significantly higher in the JIA group compared to controls ($p = 0.015$), while FT3 and FT4 levels did not differ significantly. Anti-TG and anti-TPO antibodies were significantly elevated in JIA patients ($p = 0.006$ and $p = 0.013$, respectively). Subclinical hypothyroidism was observed in 12.9% of JIA patients, all of whom were antibody positive. Antibody-positive patients had significantly higher TSH and lower FT3 and FT4 levels compared to antibody-negative patients. **Conclusion:** Children with JIA exhibit a higher prevalence of subclinical hypothyroidism and elevated anti-thyroid antibodies compared to healthy peers. Routine screening for thyroid dysfunction may be warranted in this population for early identification and management.

Keywords

Juvenile Idiopathic Arthritis, Thyroid Dysfunction, Anti-Thyroid Antibodies, Subclinical Hypothyroidism, Autoimmunity

1. Introduction

Juvenile Idiopathic Arthritis (JIA) is the most prevalent chronic rheumatic disease in the pediatric population. It is a multifactorial autoimmune condition characterized by persistent joint inflammation of unknown origin, diagnosed using the International League of Associations for Rheumatology (ILAR) criteria [1]. While global incidence varies widely, estimates in developed countries range from 16 to 150 per 100,000 children [2]. In Bangladesh, a study from a semi-urban region reported a point prevalence of 60.5 per 100,000 children [3].

The pathogenesis of JIA is complex, involving genetic predisposition and environmental triggers that lead to an aberrant immune response. The chronic inflammation resulting from this autoimmune insult primarily affects the synovial membrane, leading to joint destruction and systemic manifestations [4].

Children with autoimmune diseases such as JIA have a higher risk of developing additional autoimmune disorders, including autoimmune thyroid diseases. Studies in adult populations have established a strong association between autoimmune rheumatic diseases and thyroid dysfunction; however, limited research exists in pediatric cohorts. Notably, JIA has been shown to share susceptibility loci with other autoimmune conditions, suggesting a common immune-pathological basis [5].

In recent years, several studies have demonstrated a higher prevalence of autoimmune thyroiditis and subclinical hypothyroidism in children with JIA. A U.S.-based cohort study revealed that 19% of JIA patients had coexisting autoimmune conditions, including autoimmune thyroiditis [6]. Similarly, Italian research has reported a 10.1% prevalence of autoimmune thyroid disease in JIA patients [7]. Alpigiani MG found an association of endocrine autoimmunity in young patients with JIA, showing 14% had autoimmune thyroiditis back in 2002 [8].

Despite emerging global data, the prevalence and clinical significance of thyroid dysfunction and anti-thyroid antibodies in children with JIA remain underexplored in Bangladesh. This study aims to assess thyroid function and the presence of anti-thyroid antibodies in Bangladeshi children with JIA.

2. Materials and Methods

This cross-sectional observational study was conducted at the Pediatric Rheumatology Clinic and Inpatient Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from April 2021 to March 2022.

A total of 70 children diagnosed with JIA (Group I), according to ILAR classification, were enrolled and compared with 35 age and sex-matched apparently healthy controls from pediatric ward/OPD (Group II). Children were excluded, if they were on thyroid hormone therapy, had a history of thyroid surgery, malignancy, radiotherapy, or declined consent. Sample size was determined by using a formula in a cross-sectional study, and it was 95. Due to financial constraints, a sample 70 was taken.

Ethical approval was obtained from the Institutional Review Board (IRB) of

BSMMU, registration no: 3365. Written informed consent was obtained from participants or their guardians prior to enrollment.

Demographic information, disease subtype, and duration were recorded using a structured questionnaire. Clinical evaluations were followed by laboratory investigations.

Thyroid function was assessed through free tri-iodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) levels. Autoimmune screening included anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibody levels. Blood samples were collected from patients with aseptic precautions in a red cap vacutainer sterile test tube, and about 5 mL of blood was collected. This blood was allowed to clot, then centrifuged at 6000 - 7000 rpm for 10 minutes, and serum was collected in a microcentrifuge tube and stored at 4˚C. The serum was then put on the IMMULITE 2000 XPI machine to perform the test. It took around 80 minutes to get the results of the chemiluminescent immunoassay from the Department of Microbiology and Immunology, BSMMU.

Reference values are Serum FT_3—1.4 - 4.2 pg/ml, Serum FT_4—0.8 - 1.8 ng/dl, Serum TSH—0.70 - 5.70 mIU/L, Serum anti-TPO Antibody—≤40 IU/mL, Serum anti-TG antibody—≤35 IU/mL. Thyroid function was categorized as euthyroid, subclinical hypothyroid, overt hypothyroid, or hyperthyroid based on these parameters.

Statistical analyses were performed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation and compared using independent t-tests or Mann-Whitney U tests. Categorical data were analyzed using chi-square tests. A p-value < 0.05 was considered statistically significant.

3. Results

Among the enrolled 70 children with Juvenile Idiopathic Arthritis (JIA) and 35 age- and sex-matched healthy controls, the mean age of JIA patients was 10.82 ± 3.89 years, compared to 9.44 ± 3.43 years in the control group (p = 0.092). Males were slightly predominant in both groups, and no statistically significant difference in age or sex distribution was observed (p = 0.890). (Table 1)

Table 1. Distribution of the study subjects according to demographic characteristics in JIA patients (group I) and the comparison group (Group II).

Parameter	Group I (n = 70)	Group II (n = 35)	P-value
Age (years)	10.82 ± 3.89	9.44 ± 3.43	[a]0.092
Sex			
Male	37 (52.9%)	19 (54.3%)	
Female	33 (47.1%)	16 (45.7%)	[b]0.890
M/F ratio	1.1:1	1.2:1	

Data were expressed as mean ± SD, number and percentage; P-value was calculated from [a]Unpaired t-test and [b]Chi-square test.

Thyroid function analysis revealed that TSH levels were significantly higher in the JIA group than in controls (3.29 ± 2.27 vs. 2.30 ± 0.81 mIU/L; p = 0.015). However, FT3 and FT4 levels did not differ significantly between the groups (p = 0.314 and p = 0.403, respectively). Anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies were significantly elevated in JIA patients (p = 0.006 and p = 0.013, respectively), indicating a greater prevalence of thyroid autoimmunity in this group. (Table 2)

Table 2. Laboratory parameters among study subjects.

	Group I (n = 70)	Group II (n = 35)	P-value
FT3 (pg/ml)	2.89 ± 0.38	2.96 ± 0.31	[a]0.314
FT4 (ng/dl)	1.61 ± 0.46	1.54 ± 0.33	[a]0.403
TSH (mIU/L)			
Mean ± SD	3.29 ± 2.27	2.30 ± 0.81	
Median	2.56	2.24	[b]0.041*
IQR	1.65 - 3.98	1.75 - 2.98	
Anti-TG Antibody (IU/ml)			
Mean ± SD	37.9 ± 69.9	13.47 ± 2.02	
Median	14.7	13.50	[b]0.006*
IQR	13.3 - 18.5	11.8 - 15.0	
Anti-TPO Antibody (IU/ml)			
Mean ± SD	55.9 ± 155.5	5.48 ± 1.29	
Median	6.27	5.4	[b]0.013*
IQR	5.1 - 8.4	4.7 - 6.6	

Data were expressed as mean ± SD and median; P-value was calculated from [a]Unpaired t-test and [b]Mann-Whitney test; *significant.

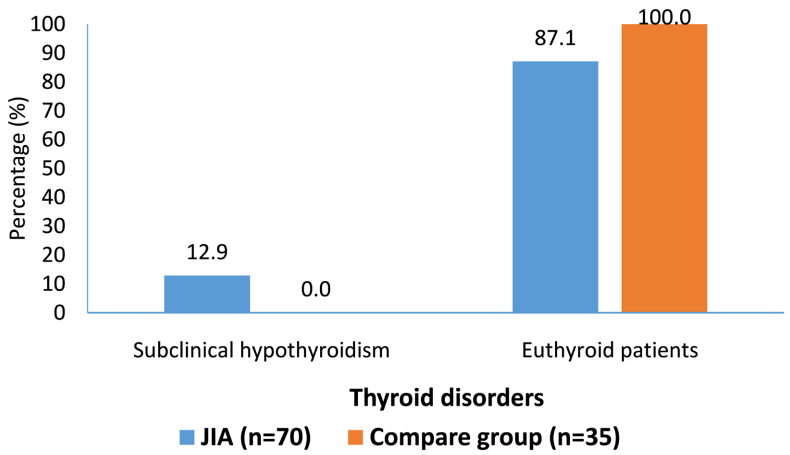

Figure 1. Bar diagram showing the distribution of thyroid disorders between JIA patients and the comparison group.

Subclinical hypothyroidism was identified in 12.9% (n = 9) of JIA patients, while none of the controls exhibited thyroid dysfunction ($p < 0.05$). (Figure 1) All nine JIA patients with subclinical hypothyroidism were positive for both anti-TG and anti-TPO antibodies. No significant differences were observed in age or sex distribution between the subclinical hypothyroid and euthyroid JIA subgroups ($p = 0.414$ and $p = 0.424$, respectively).

Subclinical hypothyroidism was most common in the oligoarticular subtype (33.3%), followed by systemic JIA (16.7%). Thyroid dysfunction was present across multiple subtypes, though differences between them were not statistically significant. (Figure 2)

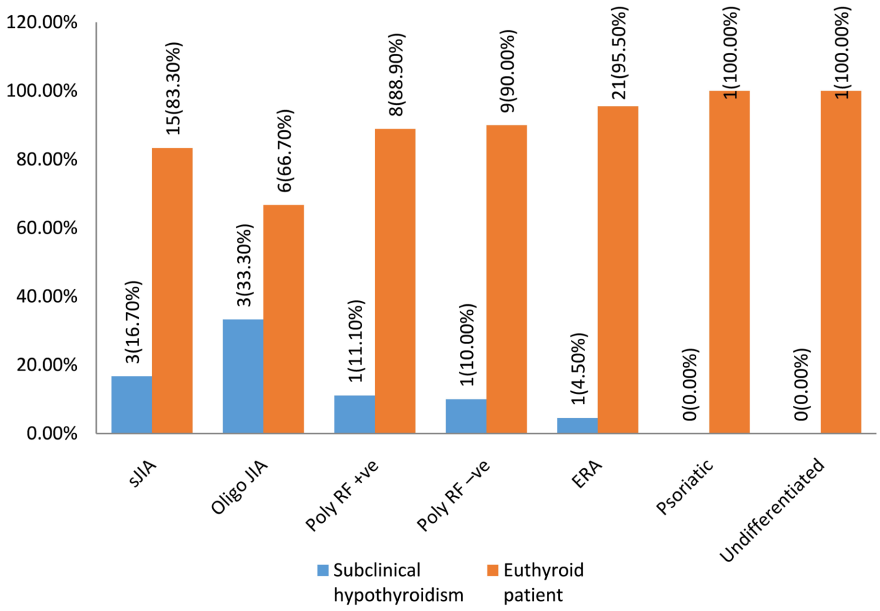

Figure 2. Bar diagram showing thyroid hormone status in different JIA subtypes (n = 70).

Table 3. Frequency of thyroid antibodies in JIA patients in relation to thyroid function (n = 70).

Parameters	Subclinical hypothyroidism (n = 9)	Euthyroid (n = 61)	p-value
Anti-TG Antibody (IU/ml)			
Mean ± SD	193.6 ± 103.8	14.9 ± 3.88	
Median	130.5	14.7	<0.001*
IQR	114.8 - 259	12.7 - 16.2	
Anti-TPO Antibody (IU/ml)			
Mean ± SD	386.9 ± 258.9	7.11 ± 4.63	
Median	286.0	6.10	<0.001*
IQR	220.9 - 503	5.03 - 7.3	

Data were expressed as mean ± SD and median; P-value was calculated from the Mann-Whitney test; *significant.

The mean anti-TG antibody and anti-TPO antibody were significantly increased in subclinical hypothyroidism patients compared with euthyroid patients ($p < 0.001$). (Table 3)

JIA patients with positive anti-TG or anti-TPO antibodies had significantly lower FT3 and FT4 levels and higher TSH levels than those without antibodies ($p < 0.001$ for FT3 and TSH; $p = 0.034$ for FT4). (Table 4, Table 5). Comparison between groups showed that only JIA patients had subclinical hypothyroidism and antibody positivity; all controls remained euthyroid and antibody-negative.

Table 4. Thyroid hormone status in relation to Anti-TG antibody in JIA patients (n = 70).

Parameters	−Ve anti-TG (n = 61) Mean ± SD	+Ve anti-TG (n = 9) Mean ± SD	P value
FT3 (pg/ml)	2.96 ± 0.31	2.37 ± 0.55	[a]<0.001*
FT4 (ng/dl)	1.61 ± 0.42	1.31 ± 0.32	[a]0.034*
TSH (mIU/L)			
Mean ± SD	2.52 ± 1.15	8.45 ± 0.61	
Median	2.32	8.62	[b]<0.001*
IQR	1.62 - 3.75	8.09 - 8.99	

Data were expressed as mean ± SD, median and IQR; P-value was calculated from [a]Unpaired t-test; [b]Mann-Whitney test; *significant.

Table 5. Thyroid hormone status in relation to Anti-TPO antibody in JIA patients (n = 70).

Parameters	−Ve Anti-TPO (n = 61) Mean ± SD	+Ve Anti-TPO (n = 9) Mean ± SD	P value
FT3 (pg/ml)	2.96 ± 0.31	2.37 ± 0.55	[a]<0.001*
FT4 (ng/dl)	1.61 ± 0.42	1.31 ± 0.32	[a]0.034*
TSH (mIU/L)			
Mean ± SD	2.52 ± 1.15	8.45 ± 0.61	
Median	2.32	8.62	[b]<0.001*
IQR	1.62 - 3.75	8.09 - 8.99	

Data were expressed as mean ± SD, median and IQR; P-value reached from [a]Unpaired t-test; [b]Mann-Whitney test; *significant.

4. Discussion

In this cross-sectional observational study, the mean age of JIA patients was 10.82 years, which is comparable to findings reported in previous studies [9], suggesting consistency in the age of onset of JIA across different populations. Interestingly, we observed a male predominance in our cohort, which contrasts with most international literature reporting a higher incidence in females [6] [7]. A similar male predominance was noted in a previous study conducted in Bangladesh [10],

which reported a male-to-female ratio of 2:1. This trend in our sample may be attributed to the higher proportion of Enthesitis-Related Arthritis (ERA) subtype, which is known to be more common in males. These findings highlight the importance of regional epidemiological variations and the need for subtype-specific analysis in JIA research.

This study demonstrates a significant association between Juvenile Idiopathic Arthritis (JIA) and autoimmune thyroid dysfunction in the pediatric population. Our findings demonstrate that children with JIA are at increased risk of developing thyroid abnormalities, particularly subclinical hypothyroidism, and show a higher prevalence of anti-thyroid autoantibodies compared to age- and sex-matched healthy controls. This reinforces the concept of shared autoimmunity and the potential for multi-organ involvement in children with rheumatologic conditions [5].

One of the most prominent observations was the significantly elevated serum thyroid-stimulating hormone (TSH) levels in JIA patients, despite the absence of significant differences in FT3 and FT4 levels between groups. This hormonal pattern is indicative of subclinical hypothyroidism, a condition characterized by an early stage of thyroid failure, where the gland is still able to produce sufficient hormone to maintain normal metabolic function, but under increased pituitary stimulation [11]. The presence of subclinical hypothyroidism in 12.9% of the JIA cohort, compared to none in the control group, underscores the potential clinical relevance of routine thyroid screening in this population.

Importantly, all patients diagnosed with subclinical hypothyroidism tested positive for both anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies. These autoantibodies are hallmark markers of autoimmune thyroiditis, such as Hashimoto's thyroiditis, and are frequently associated with future progression to overt hypothyroidism [12]. Their presence supports an autoimmune etiology for the thyroid dysfunction observed in our JIA cohort. Notably, neither the healthy controls nor euthyroid JIA patients showed antibody positivity, which strongly suggests a direct link between thyroid autoimmunity and disease state in JIA.

Our findings align with previous studies, such as Harel *et al.* (2006) [9], which reported similar patterns of increased antithyroid antibody prevalence and TSH elevation in children with JIA. Additionally, studies from Italy, Türkiye and Germany have documented autoimmune thyroid disease in up to 10% of JIA patients, reinforcing the need for vigilance in clinical monitoring [7] [9] [13]-[15].

Interestingly, although thyroid abnormalities were detected across various JIA subtypes, no significant intergroup differences were found, except in FT4 levels. This suggests that the risk of thyroid involvement is not restricted to a particular subtype but may be a general feature of the autoimmune milieu present in JIA. The presence of thyroid dysfunction in oligoarticular, polyarticular, and systemic JIA subtypes also mirrors findings from international studies, indicating a global consistency in disease behavior despite geographic and ethnic differences [6].

The clinical implications of our findings are significant. Subclinical hypothy-

roidism, if left unrecognized, can progress to overt hypothyroidism and contribute to growth retardation, fatigue, cognitive impairment, and poor quality of life in children [16]. Moreover, thyroid dysfunction may complicate the management of JIA, potentially interacting with medications such as corticosteroids or methotrexate, which themselves can impact endocrine function. Early detection and timely intervention may therefore improve both rheumatologic and endocrine outcomes.

This study also raises important considerations for clinical practice. Given the relatively high rate of thyroid autoimmunity and dysfunction, routine screening for thyroid function and antibody levels should be considered in all children diagnosed with JIA, even in the absence of overt symptoms. This could be particularly valuable at baseline and during follow-up evaluations, especially in patients presenting with fatigue, weight gain, or growth delay.

Despite its strengths, this study has some limitations. Being a single-center study with a modest sample size limits generalizability. Additionally, the cross-sectional design precludes assessment of the temporal relationship between JIA onset and thyroid dysfunction. Longitudinal studies are needed to establish causality, evaluate the progression of subclinical thyroid disease, and determine the long-term impact of early thyroid dysfunction on disease activity and quality of life in JIA.

In summary, our study contributes to the growing body of evidence linking autoimmune thyroid disease to JIA. It emphasizes the need for an integrated approach in managing children with rheumatologic disorders, one that considers not just joint involvement but the broader systemic autoimmune burden.

5. Conclusion

This study confirms a higher prevalence of subclinical hypothyroidism and positive anti-thyroid antibodies in children with JIA compared to healthy peers. The presence of thyroid autoantibodies was strongly associated with altered thyroid function. These findings underscore the importance of routine thyroid screening in JIA patients to enable timely intervention.

6. Limitation

Single-center study.

7. Recommendation

- Multi-centered large sample size studies are needed for better evaluation.
- Follow-up and evaluation of the cases are needed for a clear understanding of the consequences of thyroid function in JIA patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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