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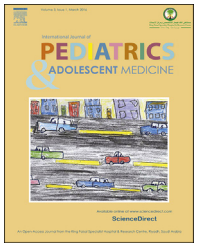

ORIGINAL RESEARCH ARTICLE

# Coexistence of endocrinopathies in children with rheumatic diseases

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Q3 **KEYWORDS**
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Autoimmune thyroiditis;
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**Abstract** *Objective:* To examine the frequency of endocrinopathies in children with systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA).
*Methods:* A cross-sectional study was conducted in Saudi children with SLE and JIA who were seen at King Faisal Specialist Hospital and Research Center, Riyadh, between September 2013 and April 2015. All enrolled patients completed the clinical evaluation, which included information about a family history of autoimmune disease, growth parameters and tanner stage, as well as the following assessments: vitamin D profile (parathyroid hormone and 25-OH vitamin D levels), TSH, FT4 and total T3, thyroglobulin antibodies, thyroperoxidase antibodies, random blood sugar, $Hb_{A1C}$, $IGF_1$, $IGF_{BP-3}$, LH, and FSH.
*Results:* A total of 42 patients, 22 with JIA and 20 with SLE, were included in the study. The mean participant age was 12.2 ± 5.3 years with a mean disease duration of 3.2 ± 3.4 years. Female gender was predominant (17 SLE, 13 JIA) in the patient population. Fifteen patients (35.7%) presented with a family history of autoimmune disease. The most frequently detected endocrinopathies were vitamin D insufficiency (35%) and thyroid disease (31%). Eight JIA patients and 7 SLE patients exhibited low vitamin D levels; 10 patients presented with hyperparathyroidism. Thyroid dysfunction was observed in 13 patients (8 SLE, 5 JIA), and 2 patients were found to be euthyroid (normal TSH, FT4) with positive thyroid autoantibodies. Furthermore, 7 patients presented with subclinical hypothyroidism (high TSH, normal FT4), and 4 patients presented with overt hypothyroidism (high TSH, low FT4). Seven patients (4 SLE and 3 JIA) presented with short stature due to growth hormone insufficiency (low $IGF_1$, $IGF_{BP-3}$). Two patients exhibited delayed puberty accompanied by low LH levels. Diabetes mellitus was more frequently observed in patients with JIA (4 patients) than in patients with SLE (1 patient).
*Conclusion:* Our findings demonstrated that coexistence of endocrinopathies is not uncommon in children diagnosed with JIA and SLE. Abnormal thyroid function occurs frequently and at a similar rate in children diagnosed with SLE and JIA. Thus, screening for endocrinopathies, namely thyroid disease, during the assessment of childhood SLE and JIA is worth consideration.

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## 1. Introduction

Autoimmunity plays a role in many inflammatory disorders including rheumatic diseases. Although the exact etiology of systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA) remains undefined, multiple etiologic factors including genetic, environmental and hormonal factors might contribute to immune dysregulation and pathogenesis [1]. Growing evidence has indicated that vitamin D deficiency may be associated with an increased susceptibility of developing autoimmune diseases [2]. Furthermore, patients who have been diagnosed with autoimmune disorders have a higher probability of being affected by a second autoimmune disorder. Endocrinopathies have been frequently described in patients with autoimmune rheumatic diseases such as SLE and Sjögren's syndrome [3–5]. Interestingly, there is evidence suggesting that JIA shares many susceptibility loci with other autoimmune diseases [6].

Autoimmune endocrinopathies frequently overlap with autoimmune rheumatic diseases; the prevalence of various autoantibodies in patients with SLE and rheumatoid arthritis is not uncommon, indicating the importance of screening patients with SLE and systemic rheumatic diseases for the coexistence of other autoimmune diseases [7,8]. The presence of endocrinopathies in patients with autoimmune diseases has primarily been described in adult patients. Reports of the coexistence of endocrinopathies and childhood autoimmune diseases, namely childhood SLE and JIA, are scarce. Interestingly, some of the associated autoimmune disorders occur at a subclinical level, and the appearance of clinical manifestations may emerge late in the disease course [9,10].

In this study, we examined the frequency of selected endocrinopathies in children with SLE and JIA. We compared the results from children diagnosed with SLE to children diagnosed with JIA. We elucidated the impact of endocrinopathies on disease activity of childhood SLE.

## 2. Methods

A cross-sectional study was conducted on Saudi children diagnosed with SLE and JIA who were followed at King Faisal Specialist Hospital and Research Center, Riyadh, between September 2013 and April 2015. All enrolled patients were 14 years or younger. All SLE patients met the criteria of SLE diagnosis according to the Systemic Lupus International Collaborating Clinic classification criteria for systemic lupus erythematosus, and all patients diagnosed with JIA met the diagnostic criteria of the International League of Associations for Rheumatology [11,12]. All patients were assessed for demographic data and disease duration. Patients completed a clinical assessment that addressed family history of autoimmune disease, growth parameters and tanner stage and were evaluated for the following laboratory values: vitamin D profile (parathyroid hormone and 25-OH vitamin D levels), TSH, FT4 and total T3, thyroglobulin antibodies (TgA), thyroperoxidase antibodies (TPOA), random blood sugar, $Hb_{A1C}$, $IGF_1$, $IGF_{BP-3}$, LH, FSH and Celiac disease panel. We considered vitamin D insufficiency to be an autoimmune disease regardless of the underlying cause or coexistence with endocrinopathies, or the sequence of the disease or the current treatment. The standard range in Saudi Arabia for total 25-OH vitamin D levels established by liquid chromatography-tandem mass spectrometry is 13–76 nmol/l, and the optimal concentration should exceed 75 nmol/l. We diagnosed patients with vitamin D insufficiency if the 25-OH vitamin D level was below 75 nmol/l. Additionally, we considered patients to have diabetes mellitus if the $Hb_{A1C}$ value was greater than 0.065. Q4

Complement (C3, C4) levels, anti-double-stranded DNA (anti-ds DNA) antibody and anti-nuclear antibody (ANA) were included in the analysis of patients with SLE. We also calculated the disease activity score using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [13].

All collected data were handled anonymously, and patient confidentiality was protected. Additionally, all collected data were acquired through routine clinical care. Informed consent was obtained from the parents of pediatric patients. The proposal was approved by the Research Affairs Council at KFSHRC.

## 3. Statistical methods Q5

SAS 9.2 (SAS Institute Inc., Cary, NC, USA) software was used for statistical analysis. The variables were compared using 2-sample *t*-tests, chi-square tests and Fisher's exact tests. The results are expressed as the mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Regression analysis was carried out to examine the influence of the variables on outcome measures. A $P$ value of $<.05$ was considered statistically significant.

## 4. Results

A total of 42 Saudi children, 22 with JIA and 20 with SLE, were included in the current study. The mean age was 12.2 ± 5.3 years with a mean disease duration of 4.2 ± 5.4 years. Female gender was predominant (17 SLE, 13 JIA). All SLE patients presented with multiple organ involvement and a mean SLEDAI score of 6 ± 5.6. Overall, nephritis (61%) was the most frequently detected major organ condition; none of the SLE patients exhibited renal impairment. Patients exhibited an elevated ANA with a mean value of 965

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