CASE REPORT

Intisari Sains Medis 2024, Volume 15, Number 1: 245-249
P-ISSN: 2503-3638, E-ISSN: 2089-9084

Intisari Sains Medis

Published by Intisari Sains Medis

Low Free Thyroxine (FT4) in critically ill juvenile systemic lupus erythematosus: a diagnostic approach

Elien Yuwono[1*], Ketut Dewi Kumara Wati[1], I Made Arimbawa[1]

[1]Department of Child Health, Medical School of Universitas Udayana / Prof. Dr. I G.N.G Ngoerah Hospital, Denpasar, Bali.

*Corresponding author:
Elien Yuwono;
Department of Child Health, Medical School of Universitas Udayana / Prof. Dr. I G.N.G Ngoerah Hospital, Denpasar, Bali;
elienyuwono.ey@gmail.com

Received: 2024-01-03
Accepted: 2024-02-19
Published: 2024-03-15

ABSTRACT

Introduction: Thyroid dysfunction was frequent in systemic lupus erythematosus (SLE) patients, which may present as euthyroid, hypothyroid, or hyperthyroid states. Critical conditions have a higher chance of euthyroid sick syndrome due to alterations in the hypothalamic-pituitary-thyroid (HPA) axis. Renal impairment was associated with an increased risk of low FT4 due to proteinuria followed by thyroid loss.

Case Description: We reported one patient, a 15-year-old girl, who complained of shortness of breath and revealed acute respiratory distress syndrome, valve regurgitation, and pericardial effusion. She also felt joint pain over the leg and odor urination. Further evaluation showed non-scaring alopecia, pyuria, proteinuria >0.5 gram/24 hours, urinary cast, and acute kidney injury stage failure. ANA (IF) pattern: scattered with titer 1:100, ANA profile indicated Smith (Sm) antigen (+) and C3 108.3 mg/d, which fulfilled Systemic Lupus International Collaborating Clinics (SLICC) 2015 and European League Against Rheumatism (EULAR) 2019 criteria for SLE. On the fourth day of treatment, the patient had acute confusion, hypothermia, and sinus bradycardia, while the investigation of FT4 hormone was 0.45 ng/dL, TSH 2.39 ulu/ml, which revealed euthyroid sick syndrome. After treatment with a high dose of methylprednisolone, cyclophosphamide, rituximab, levothyroxine, a phosphodiesterase inhibitor, and a diuretic, she deteriorated and passed away.

Conclusion: The higher prevalence of thyroid dysfunction in juvenile SLE patients necessitates further attention. Lupus nephritis, increased creatinine level, detection of Smith (Sm) antigen, and critical condition were also at higher risk of low FT4 in juvenile SLE patients. This condition may have a worsened prognosis with prompt diagnosis and treatment.

Keywords: euthyroid sick syndrome, *systemic lupus erythematosus*, free thyroxine, juvenile.

Cite This Article: Yuwono, E., Wati, K.D.K., Arimbawa, I.M. 2024. Low Free Thyroxine (FT4) in critically ill juvenile systemic lupus erythematosus: a diagnostic approach. *Intisari Sains Medis* 15(1): 245-249. DOI: 10.15562/ism.v15i1.1926

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic illness characterized by extensive inflammation and the presence of autoantibodies that damage several organ systems. The condition is characterized by the buildup of autoantibodies and immune complexes, which causes tissue destruction. SLE is caused by three processes: complement insufficiency, interferon- (IFN-) overproduction, and apoptotic damage pathways. Approximately 15–20% of SLE patients present with the symptoms before the age of 18 and are associated with higher disease activity, more severe organ manifestations, and increased morbidity.[1]

Numerous studies also have reported an association between SLE and thyroid disease with a wide range of variability. Conflicting findings exist regarding whether hyperthyroidism, hypothyroidism or euthyroid is more commonly associated with SLE. Despite that, it is reported that hypothyroidism and autoimmune thyroiditis appear to be more prevalent in SLE patients with overlap syndrome, with the prevalence of hypothyroidism in SLE ranging between 15% to 19%.[2,3] Furthermore, some clinical evidence suggests that there was a link between the severity of these two disorders; for instance, patients with coexisting SLE and thyroid dysfunction exhibited an extended duration of SLE disease activity compared to those with SLE alone.[4,5] Patients with subclinical hypothyroidism showed that delays in treating subclinical hypothyroidism can cause SLE remission to be delayed.[6] Furthermore, in critical conditions that can occur transient alterations in the hypothalamic-pituitary-thyroid (HPA) axis lead to euthyroid sick syndrome. Low total T3 and free T3 levels with low or normal T4 and thyroid-stimulating hormone (TSH) levels are the most common hormone patterns in euthyroid sick syndrome.[7] Renal dysfunction in SLE was associated with an increased risk of low FT4 due to proteinuria, the urine loss of thyroid hormones bound to different binding proteins such as thyroxine-binding globulin (TBG), albumin, pre-albumin, and transthyretin. In addition, patients with SLE who carried the Sm

antigen were also more likely to have hypothyroidism (p 0.05), implying an immunological relationship between the two disorders.[4]

The term "euthyroid sick syndrome," also known as "nonthyroidal illness syndrome," refers to a reduction in free serum thyroid hormones without a concurrent increase in TSH, which is commonly seen in critically ill individuals and may contribute to greater mortality. A study by Antonelli et al., euthyroid sick syndrome was also observed to be higher in SLE patients than in control.[7] As the clinical symptoms of hypothyroidism can be vaguely similar to the manifestations of SLE, delays in the diagnosis and treatment of hypothyroidism can occur. The impact of the pro-inflammatory immune state induced by SLE on thyroid function remains uncertain. The present study reported on a critical patient presenting with concurrent SLE, renal dysfunction, and positive Smith (Sm) antigen, which may be associated with a decrease in FT4.

CASE REPORT

A 15-year-old female presented at the emergency room with a recent onset of a non-productive cough persisting for a week accompanied by acute dyspnea. Concurrently, the patient also reported diffuse lower extremity pain with limited range of motion and localized warmth. The onset of joint pain was noted two months prior and subsequently worsened within the last 10 days, resulting in functional impairment requiring ambulatory assistance. Notably, the patient had experienced hair loss for the past month and an oral ulcer 2 weeks prior, as shown in Figure 1. Additionally, she reported cloudy and malodorous urine for the past 2 weeks without any abdominal discomfort or diminished urine output. Fever, headache, redness on the cheeks were denied.

Upon initial evaluation, her blood pressure was 105/70 mmHg (P50th), and her heart rate was 74 beats/minute, regular and adequate. She was alert with a respiratory rate of 32 breaths/minute and a body temperature of 36.9℃. Further assessment revealed non-scarring alopecia, mucosal ulcer, tachypnea without rales, wheezing, and tenderness in both ankles. Her body

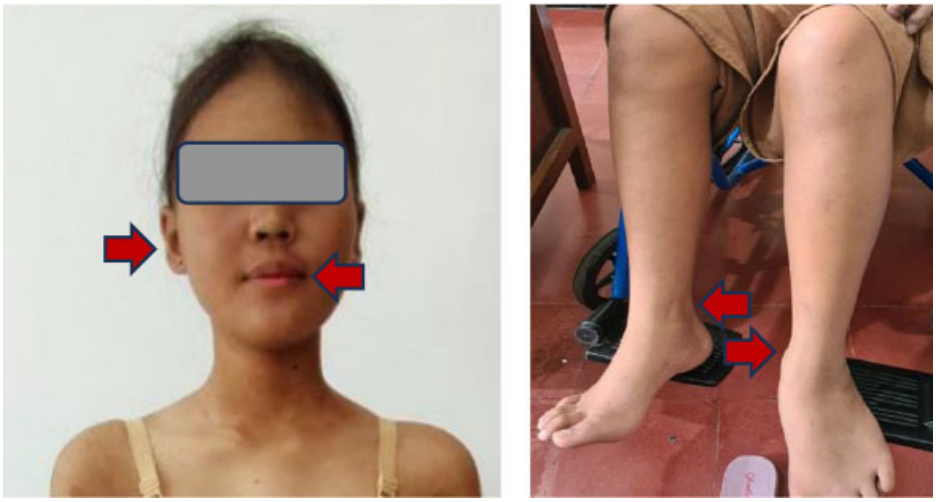


Figure 1. Clinical manifestations consistent with classic SLE such as non-scarring alopecia, oral ulcer, arthritis.

weight was 55 kg, and her body mass index (BMI) was 21.48 indicating good nutrition status. Laboratory investigation showed white blood cell count (WBC) of 8.68 x10^3/µL, haemoglobin level (Hb) of 11.7 g/dL, platelets at 282x10^3/ul with kidney function showed blood urea nitrogen (BUN) 32.10 mg/dL, creatinine serum 3.62 mg/dL with glomerular filtration rate 24.3 ml/min/1.73m^2 revealing Acute Kidney Injury (AKI) stage failure with hyperuricemia (uric acid 12.69 mg/dl). Urinalysis revealed leukocytes (4+) 300 mg/dL, proteinuria (3+) 300 mg/dL (1-2 gram/day), hematuria (blood (3+)). Liver function tests were normal, with SGOT 23.80 U/L SGPT 32.90 U/L and albumin 3.15 g/dL. Electrolytes were normal (potassium 3.55 mmol/L, sodium 157 mmol/L, chloride 131.6 mmol/L and calcium 10.2 mg/dL). Blood gas analysis revealed pH 7.36, pCO_2 27 mmHg, pO_2 92 mmHg, HCO_3 15.30 mmol/L revealed compensated metabolic acidosis. Further investigation revealed ANA (IF) pattern: speckled with titer 1:100, ANA profile revealed Sm (Sm) antigen (+) and C3 108.3 mg/dL. She fulfilled nine criteria for the diagnosis of SLE based on Systemic Lupus International Collaborating Clinics (SLICC) 2015 criteria, including non-scarring frank alopecia (1), oral ulcer (1), arthritis (1), pericarditis (1) and positive ANA-IF titer(1), positive anti-Sm antibodies (3) and proteinuria >+3 (1).

On the fourth day of treatment, the patient's dyspnea getting worse and chest radiograph revealed signs of pulmonary

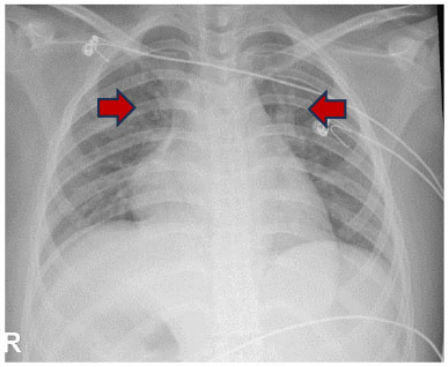
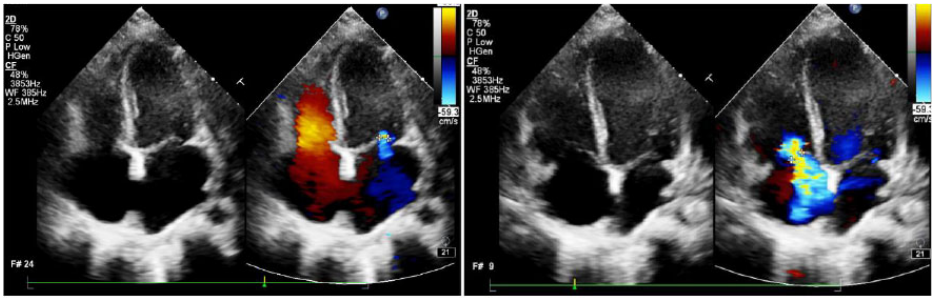


Figure 2. Chest radiograph revealed of pulmonary congestion.

congestion, as showed in Figure 2. Echocardiography findings indicated group 1 pulmonary hypertension, along with severe tricuspid regurgitation (TR), moderate mitral regurgitation (MR), and mild pericardial effusion as showed in Figure 3. The patient also exhibited acute confusion, hypothermia, sinus bradycardia prompting further investigation revealed FT4 and TSH levels were 0.45 ng/dL and 2.39 uIu/ml then diagnosed as euthyroid sick syndrome. Treatment consisting of non-invasive ventilation, antibiotic, high dose of methylprednisolone, cyclophosphamide, rituximab, dobutamine, phosphodiesterase inhibitor, diuretic, intravenous insulin, xanthine oxidase, levothyroxine, multivitamins, mycophenolate sodium (MPS), and hydroxychloroquine (HCQ) were implemented. Nonetheless, her condition deteriorated and she passed away on the eighteenth day of treatment.



(a) (b)

Figure 3. Echocardiography revealed pulmonary hypertension group 1, moderate mitral regurgitation (a) and severe tricuspid regurgitation (b).

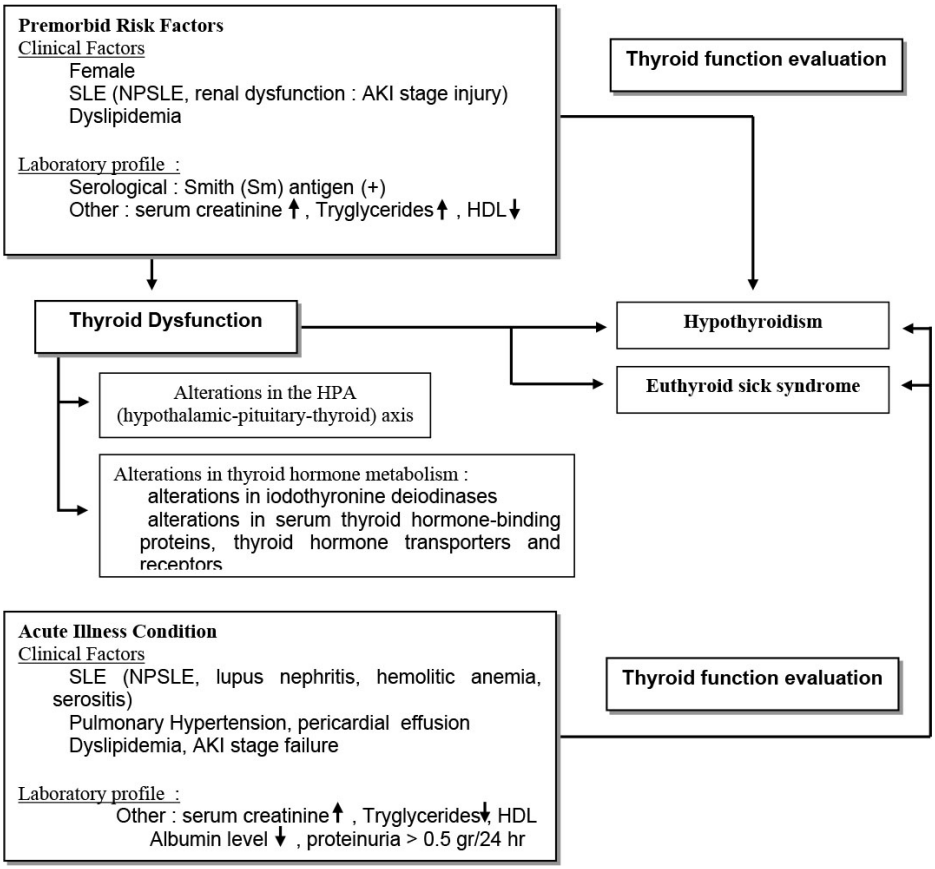


Figure 4. Low FT4 in Critically Ill Juvenile SLE : Diagnostic Approach.

DISCUSSION

Systemic lupus erythematosus (SLE) is a self-sustaining autoimmune illness characterized by a complex combination of dysregulated apoptotic clearance, elevation of the innate and adaptive immune systems, complement activation, immune complex formation, and tissue inflammation.[2,8,9] This patient came with clinical symptoms consistent with classic SLE, such as arthritis, oral ulcer, and non-scarring alopecia two months prior. She had also experienced cloudy and malodorous urination with renal function tests indicating AKI stage failure. Urinalysis showed leukocyturia, proteinuria, and hematuria, revealing a possibility for lupus nephritis. The presence of protein in urine indicates glomerular damage while renal biopsy shows immune-complex-mediated nephritis with complement deposition. Renal involvement affects 50-75% of pediatric SLE patients, with over 90% developing lupus nephritis within two years of diagnosis.[10] Patient also had non-productive cough with shortness of breath and pulmonary congestion from chest radiograph. Echocardiography showed signs of pulmonary hypertension along with pericardial effusion, indicating pericarditis.

Systemic lupus erythematosus (SLE) is diagnosed using the clinical and laboratory criteria provided in the most recent SLICC 2015 classification. In this case, patient scored nine out of 16 SLICC 2015 criteria which definitive SLE. Additionally, the EULAR and the American College of Rheumatology (ACR) introduced new classification criteria in 2019, requiring a minimum score of 10 for a patient to be classified as having SLE, in this case patient scored 22 at initial diagnosis, which including fever (2), non-scarring frank alopecia (2), oral ulcer (2), arthritis (6), proteinuria > 0.5 gr/day (4) and positive anti-Sm antibodies (6). On the fourth day of treatment, patient exhibited neurophychiatric symptoms, acute confusion also leukopenia, with evaluation of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score was 20 (organic brain syndrome (8), pericarditis (2), arthritis (4), mucosal ulcer (2), alopecia (2), fever (1), leukopenia (1) while proteinuria was improved.[8-11]

Thyroid dysfunction was common in SLE patients, which may present as euthyroid, hypothyroid or hyperthyroid states. A study investigated hypothyroidism is the most frequent thyroid disorder in lupus patients. Primary hypothyroidism affects 15% to 19% of lupus patients, which is much higher than the overall population's rate of roughly 4.6%.[4] In comparison to healthy controls, people with lupus had a higher prevalence of hypothyroidism in all age groups. This study found that the increased prevalence is greatest in patients under the age of 20 (odds ratio [OR] 8.38; 95% confidence interval [CI] 2.71-26.01), and female patients with SLE are more likely to have both clinical and subclinical hypothyroidism than male patients.[4] A recent meta-analysis has shown that hypothyroidism appeared to have a higher prevalence among SLE patients (OR 2.93; $p<0.05$).[12]

SLE patients with low free thyroxine (FT4) and normal TSH levels in critical condition, revealed euthyroid sick syndrome, which can be affected by variety of factors, such as severity of the inflammation condition, deprivation of

calories and renal dysfunction. According to, study by Jingyi et al, revealed that lupus nephritis was retained as an independent risk factor for low FT4 or hypothyroidism, which prevalence of hypothyroidism in lupus nephritis patient was 39.4% versus 17.2% in SLE without lupus nephritis patient (p <0.001), also increased creatinine level was associated with incidence of hypothyroidism in SLE patient (p 0.025).[6] Renal dysfunction can cause clinical and subclinical hypothyroidism due to thyroid hormone urinary loss, starvation, and iodine deficiency. Lupus nephritis were at higher risk of low FT4 due to proteinuria, which is urine loss of thyroid hormones bound to different binding proteins such as TBG, albumin, prealbumin, and transthyretin and in this study was also revealed that 24 hour urine protein was significantly higher in the SLE-hypothyroidism group.[6] In addition, study by Klionski et al, patients with SLE with Smith (Sm) antigen were also more likely to exhibit low free thyroxine and hypothyroidism (p<0.05).[4] In this case, patient in critical condition diagnose with juvenile SLE, female gender with renal dysfunction (proteinuria and increased creatinine level), positive Smith (Sm) antigen, which can raised the risk of low free thyroxine. The premorbid risk factor also the acute illness condition which contribute in thyroid dysfunction can be seen in Figure 4.

The term "euthyroid sick syndrome" (ESS), also known as "non-thyroidal illness syndrome" (NTIS) or "low T3-(/T4-) syndrome," refers to a drop in free serum thyroid hormones without a rise in thyroid stimulating hormone (TSH).[6] It is caused by transient alterations in the hypothalamic-pituitary-thyroid axis and this is a common occurrence in critically ill patients, and it is associated with a number of serious consequences, including sepsis, multiple organ failure, prolonged mechanical ventilation, an extended stay in the intensive care unit (ICU), and higher death.[7,13] Changes in thyroid hormone parameters reported in euthyroid sick syndrome are assumed to be a response to systemic sickness via a variety of distinct channels, a compensatory mechanism in response to the oxidative stress of acute illness, or pro-inflammatory cytokines.[7] In this case, patient exhibited hypothermia and sinus bradycardia on the fourth day of treatment, with thyroid function test revealed low free thyroxine (FT4), normal TSH level, which can be manifestation of euthyroid sick syndrome with threatening condition.

Hypothyroidism is a distinct condition resulting from low levels of thyroid hormone. Primary and secondary (central) hypothyroidism are the two main types. Primary hypothyroidism is a disorder in which the thyroid gland itself does not produce enough thyroid hormone. Secondary or central hypothyroidism, on the other hand, is distinguished by normal thyroid gland activity, with the underlying illness arising in the pituitary gland or hypothalamus.[11-14] Given the potential for mild and nonspecific manifestations, it is crucial to maintain a suspicion for hypothyroidism. Not all patients will exhibit classic features such as cold intolerance, puffiness, decreased sweating, constipation, weight gain, poor growth velocity, short stature, dry skin, bradycardia, and myxedema. Laboratory findings such as anemia and dyslipidemia may aid the diagnosis. To comprehensively assess the presence of autoimmune thyroid diseases, it is important to include laboratory testing for anti-thyroid antibodies, specifically thyroid peroxidase antibodies and/or antithyroglobulin antibodies. In this case, pasien with hypothyroid symptoms, which can be manifestation of euthyroid sick syndrome then have been treated with levothyroxine orally and showed slightly hemodynamic improvement before then deteriorated and anti-thyroid antibodies test had not been performed yet.

Regarding the management of SLE patients with hypothyroidism, immunosuppressants, particularly glucocorticoids, continue to hold significant therapeutic value. Given that the underlying pathogenesis of hypothyroidism in SLE individuals is largely attributed to autoimmunity, the anti-inflammatory and immunosuppressive properties of glucocorticoids further enhance their efficacy in this context. Glucocorticoids exert their therapeutic effects in hypothyroidism by downregulating the expression of proinflammatory cytokines including TNF-α, IL-8, and IL-6, while simultaneously upregulating the expression of anti-inflammatory proteins such as IL-10.[15] This is supported by a study that found that there was an inverse correlation between the administration of glucocorticoids and the prevalence of hypothyroidism.[6] In the event that standard-of-care treatment fails, rituximab is regarded as an option in cases of high-activity SLE including the kidneys, the central nervous system, and hematological symptoms. Rituximab, an IgG1-k monoclonal antibody with affinity for the surface CD-20 antigen of B-lymphocytes, causes B-cell depletion and inhibits the creation of plasma cells, the production of autoantibodies, and intercellular cooperation with B-lymphocytes.[16] In this case, on the fourth day of treatment, the patient's dyspnea worsened, chest radiograph revealed signs of pulmonary congestion, and the patient also exhibited acute confusion as a manifestation of neuropsychiatric lupus in the central nervous system accompanied by leucopenia while evaluation of proteinuria was improved. Treatment consisting high dose of methylprednisolone pulse dose for 3 days, continued with cyclophosphamide 500 mg per time intravenously followed by rituximab on the sixth day of treatment, were implemented to decrease SLE disease activity.

Thyroid hormones play a vital role in regulating lipoprotein metabolism, exerting a wide range of physiological effects. Consequently, the concentrations of thyroid hormones have a notable impact on plasma lipid and lipoprotein levels. In autoimmune thyroiditis (AIT), the changes in lipid profile progressively worsen as hypothyroidism advances, leading to dyslipidemia in patients with overt hypothyroidism.[17,18] In this case, patient has diagnosed with metabolic syndrome and dyslipidemia since four months prior with triglyceride level >100 and HDL level < 40 mg/dl**, t**herefore it is crucial to monitor lipid profile levels in individuals with low free thyroxine (FT4) and SLE**.**

This case presentation has certain limitations that should be acknowledged. Firstly, the evaluation of thyroid

antibodies, specifically anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO), was not performed. Additionally, important factors such as the patient's iodine status history were not documented, which could potentially contribute to the development of hypothyroidism. SLE patients with low free thyroxine (FT4) levels in critical condition, can be caused by euthyroid sick syndrome, which can be affected by variety of factors, such as severity of the inflammation condition, deprivation of calories and renal dysfunction.

CONCLUSION

Higher prevalence of thyroid dysfunction in juvenile SLE patients necessitates further attention. Lupus nephritis, increased creatinine level, detection of Smith (Sm) antigen and critical condition were also at higher risk of low FT4 in juvenile SLE patients. With prompt diagnosis and treatment, this illness may have a worse prognosis.

ACKNOWLEDGEMENTS

The authors received no specific grants from any funding agency in the public, commercial, or non-for-profit sectors.

CONFLICT OF INTEREST

The author stated there is no conflict of interest in this study.

FUNDING

None.

CONSENT FOR PUBLICATION

The informed consent was given verbally to all patients.

AUTHOR CONTRIBUTION

All author contribute equally for preparing this manuscript.

REFERENCES

1. Charras A, Smith E, Hedrich CM. Systemic Lupus Erythematosus in Children and Young People. Curr Rheumatol Rep. 2021 Feb 10;23(3):20.
2. Pan L, Lu MP, Wang JH, Xu M, Yang SR. Immunological pathogenesis and treatment of systemic lupus erythematosus. World J Pediatr. 2020 Feb;16(1):19-30. doi: 10.1007/s12519-019-00229-3.
3. Lin WY, Chang CL, Fu LS, Lin CH, Lin HK. Systemic lupus erythematosus and thyroid disease: A 10-year study. J Microbiol Immunol Infect. 2015 Dec;48(6):676-83. doi: 10.1016/j.jmii.2014.03.004.
4. Klionsky Y, Antonelli M. Thyroid Disease in Lupus: An Updated Review. ACR Open Rheumatol. 2020 Feb;2(2):74-78. doi: 10.1002/acr2.11105
5. Antonelli A, Fallahi P, Mosca M, Ferrari SM, Ruffilli I, Corti A, et al. Prevalence of thyroid dysfunctions in systemic lupus erythematosus. Metab Clin Exp 2010; 59:896e900.
6. Ni J, Li J, Wang Y, Guan L, Lin H, Zhang L, Zhang H. Systemic Lupus Erythematosus Patients With Related Organic Damage Are at High Risk of Hypothyroidism. Front Endocrinol (Lausanne). 2022 Jul 15;13:920283. doi: 10.3389/fendo.2022.920283.
7. Radwa Shamma *et al.* (2023) 'Association between Systemic Lupus Erythematosus and Autoimmune Thyroid Dysfunction in Pediatric Population Cross Sectional Study, Single Center Experience', pp. 1–14.
8. Chiewchengchol D, Murphy R, Edwards SW, Beresford MW. Mucocutaneous manifestations in juvenile-onset systemic lupus erythematosus: a review of literature. Pediatr Rheumatol 2015;13:1-9
9. Chaudhary SN, Rahman SA, Islam MI, Begum S, Talukdar MK, Ansari MIH, Hasan M. Thyroid Functions and Thyroid Auto-Antibodies in Pediatric Systemic Lupus Erythematosus Patients: A Study from Bangladesh. Am J Clin Exp Med. 2015;3(5):207-212
10. Patil N, Rehman A, Jialal I. Hypothyroidism. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519536/
11. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Againts Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis & Rheumatology. 2019; 0 (0) : 1-13.
12. Luo W, Mao P, Zhang L, Yang Z. Association between systemic lupus erythematosus and thyroid dysfunction: a meta-analysis. Lupus. 2018 Nov;27(13):2120-2128.
13. Radwa Shamma *et al.* (2023) 'Association between Systemic Lupus Erythematosus and Autoimmune Thyroid Dysfunction in Pediatric Population Cross Sectional Study, Single Center Experience', pp. 1–14.
14. Patil N, Rehman A, Jialal I. Hypothyroidism. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519536/
15. Strehl C, Buttgereit F. Unraveling the Functions of the Membrane-Bound Glucocorticoid Receptors: First Clues on Origin and Functional Activity. Ann N Y Acad Sci (2014) 1318:1–6.
16. Trindade, V. C. *et al.* (2021) 'An Update on the Management of Childhood-Onset Systemic Lupus Erythematosus', *Pediatric Drugs*, 23(4), pp. 331–347. doi: 10.1007/s40272-021-00457-z.
17. Vukovic R, Zeljkovic A, Bufan B, Spasojevic-Kalimanovska V, Milenkovic T and Vekic J (2019) Hashimoto Thyroiditis and Dyslipidemia in Childhood: A Review. Front. Endocrinol. 10:868.
18. Yulistiawati F, Awalia. A case report of a woman with SLE and lupus enteritis as the first manifestation of active systemic lupus erythematosus. Bali Med J. 2023;12(2):1321-237.