U.D.C.: 616.43-053.6-07:616-036.12
DOI: https://doi.org/10.52692/1857-0011.2025.2-82.06

ALGORITHM FOR MONITORING PHYSICAL AND PUBERTAL DEVELOPMENT IN CHILDREN WITH CHRONIC DISEASES

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Summary.
Children with chronic diseases frequently present growth disorders and delayed puberty, complications that negatively impact general health status and quality of life. **Aim of the study**: to elaborate a diagnostic algorithm for endocrine comorbidities in pediatric chronic diseases, using juvenile idiopathic arthritis as a model.

According to the study design, children with juvenile idiopathic arthritis were included, in whom growth parameters, pubertal development, and endocrine function were assessed using age- and sex-specific percentiles. The investigations comprised anthropometric indices, Tanner staging, hormonal analyses, and ultrasound, integrated with clinical disease activity scores. Based on the obtained results and current literature data, a structured algorithm for auxological and pubertal monitoring was developed.

The study confirmed that growth delay, delayed or abnormal puberty, and endocrine comorbidities are frequent in children with chronic inflammatory diseases. Significant correlations were identified between growth velocity, pubertal progression, hormonal profiles, and disease activity. The proposed algorithm integrates anthropometric, pubertal, endocrine, and imaging evaluations, allowing early detection of developmental disorders and supporting individualized management.

Conclusions: The algorithm provides a practical framework for the systematic evaluation of physical and pubertal development in children with chronic diseases. Its implementation may improve early detection of growth and endocrine disorders, support therapeutic decisions, and optimize the long-term prognosis.

Keywords: chronic disease; children; growth monitoring; puberty; endocrine dysfunction; diagnostic algorithm; auxology.

Rezumat. Algoritm de monitorizare a dezvoltării fizice și pubertare la copii cu boli cronice.
Copiii cu boli cronice prezintă frecvent tulburări de creștere și pubertate întârziată, complicații care afectează negativ starea generală de sănătate și calitatea vieții. **Scopul studiului**: elaborarea unui algoritm diagnostic pentru comorbiditățile endocrine în bolile pediatrice cronice, utilizând artrita idiopatică juvenilă drept model.

Conform designului cercetării, au fost incluși copii cu artrită idiopatică juvenilă, la care s-au evaluat parametrii de creștere, dezvoltarea pubertară și funcția endocrină prin percentile specifice vârstei și sexului. Investigațiile au cuprins indici antropometrici, stadializarea Tanner, analize hormonale și ecografie, integrate cu scorurile clinice de activitate a bolii. Pe baza rezultatelor obținute și a datelor din literatura de specialitate, a fost elaborat un algoritm structurat de monitorizare auxologică și pubertară.

Studiul a confirmat că întârzierea creșterii, pubertatea întârziată sau anormală și comorbiditățile endocrine sunt frecvente la copiii cu boli inflamatorii cronice. S-au evidențiat corelații între viteza de creștere, progresia pubertară, profilurile hormonale și activitatea bolii. Algoritmul propus integrează evaluările antropometrice, pubertare, endocrine și imagistice, permițând identificarea precoce a tulburărilor de dezvoltare și facilitând managementul individualizat.

Concluzii: Algoritmul oferă un cadru practic pentru evaluarea sistematică a dezvoltării fizice și pubertare la copiii cu boli cronice. Implementarea lui poate îmbunătăți depistarea precoce a tulburărilor de creștere și endocrine, sprijinind deciziile terapeutice și optimizând prognosticul pe termen lung.

Cuvinte cheie: boală cronică; copii; monitorizarea creșterii; pubertate; disfuncții endocrine; algoritm diagnostic; auxologie.

Резюме. Алгоритм мониторинга физического и пубертатного развития у детей с хроническими заболеваниями.
У детей с хроническими заболеваниями часто отмечаются нарушения роста и задержка полового созревания, что отрицательно влияет на общее состояние здоровья и качество жизни. **Цель исследования**: разработка диагностического алгоритма для эндокринных коморбидностей при хронических заболеваниях у детей, используя ювенильный идиопатический артрит в качестве модели.

Согласно дизайну исследования, были включены дети с ювенильным идиопатическим артритом, у которых оценивались параметры роста, половое развитие и эндокринная функция с использованием возрастных и половых перцентилей. В исследование вошли антропометрические показатели, стадирование по Таннеру, гормональные анализы и ультразвуковое исследование, интегрированные с клиническими шкалами активности болезни. На основе полученных данных и анализа литературы был разработан структурированный алгоритм мониторинга роста и полового развития.

Исследование подтвердило, что задержка роста, позднее или аномальное половое созревание и эндокринные коморбидности часто встречаются у детей с хроническими воспалительными заболеваниями. Были выявлены значимые корреляции между скоростью роста, прогрессией полового созревания, гормональными профилями и активностью болезни. Предложенный алгоритм объединяет антропометрические, пубертатные, эндокринные и инструментальные оценки, позволяя выявлять нарушения развития на ранних стадиях и обеспечивая индивидуализированный подход к лечению.

Выводы: Алгоритм представляет собой практическую основу для систематической оценки физического и полового развития у детей с хроническими заболеваниями. Его внедрение может улучшить раннюю диагностику нарушений роста и эндокринных функций, поддержать терапевтические решения и оптимизировать долгосрочный прогноз.

Ключевые слова: хроническое заболевание; дети; мониторинг роста; пубертат; эндокринные дисфункции; диагностический алгоритм; ауксология.

Introduction.

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of inflammatory conditions defined by chronic arthritis and diverse clinical manifestations [1, 2]. According to the International League of Associations for Rheumatology, seven subtypes are recognized, classified by the extent and location of inflammation as well as specific biological markers [3].

Growth retardation and delayed puberty are among the most frequent complications in children with JIA, with significant consequences for health and quality of life [4, 5]. The severity of growth impairment depends largely on disease duration and activity, being most pronounced in patients with persistently elevated pro-inflammatory markers, especially in systemic and polyarticular subtypes [6]. Reported prevalence of growth retardation varies widely, from 8% to 41%, reflecting differences in disease subtype selection and outcome measures across studies [7, 8]. By contrast, the true incidence of delayed puberty remains insufficiently documented [9].

Normal growth is a complex process influenced by systemic and local mechanisms [10]. In JIA, chronic inflammation driven by cytokines, long-term glucocorticosteroid (GCS) therapy, and nutritional disturbances are key contributors to impaired growth and pubertal delay [11, 12]. Inflammatory burden may flatten weight curves and exacerbate stunting, while GCS use, though effective in controlling inflammation, further compromises growth and promotes excess weight gain [13, 14]. Dysregulation of the GH/IGF-1 axis has been described, yet mechanisms of hormonal resistance in growth failure are not fully clarified [15]. In a cohort study, Songyi et al. demonstrated reduced IGF-1 levels in systemic and polyarticular JIA, with values preserved in oligoarticular and enthesitis-related subtypes. These findings indicate impaired pituitary function or reduced GH responsiveness under chronic inflammation, with weak to moderate negative correlations between IGF-1 and disease activity [16].

Puberty is also affected, with onset delayed by 0.4–2.2 years compared to healthy peers [17]. In some cohorts, none of the adolescents with JIA reached Tanner stage 5 by age 16, despite a physiologic onset of puberty [9]. The pubertal growth spurt may be blunted, particularly in systemic JIA, and adult height is often reduced compared with target expectations [18]. Advances in therapy, especially biologics, appear to improve growth velocity and mitigate long-term impact, likely through better disease control and reduced GCS exposure [13, 19].

Thyroid function is another determinant of growth and puberty. Thyroid hormone levels vary physiologically with age, while thyroid involvement in JIA may be functional, structural, or autoimmune [20]. Only limited research has explored the link between JIA and autoimmune thyroiditis [21], and comprehensive studies of thyroid involvement in JIA are lacking.

In Moldova, the last studies conducted provide valuable data on growth and endocrine disturbances in children with chronic diseases and permit us to design a diagnostic algorithm for monitoring these conditions. Furthermore, national data on thyroid pathology in the general pediatric population are still limited. Given that consequences of chronic inflammation begin early, preventive auxological screening in children with JIA is essential. Early identification of growth and developmental impairment may allow timely therapeutic adjustments and improve long-term outcomes.

Taken together, these considerations highlight the need for in-depth studies to identify and monitor risk factors impacting growth and puberty in JIA. A detailed assessment of hormonal axes and endocrine autoimmunity represents a valuable strategy for optimizing disease management and improving the quality of life of affected children.

The aim of the research is to develop a diagnostic algorithm for endocrine comorbidities in chronic pediatric diseases, using juvenile idiopathic arthritis as a model.

Methods.

To achieve the research aim, a cross-sectional descriptive observational study was initially conducted, which was later extended into an analytic observational cohort study. Children for the descriptive study were selected from the Rheumatology section of the IMSP Mother and Child Institute, based on admission records from nominal lists.

Inclusion criteria were: children diagnosed with juvenile idiopathic arthritis (JIA) according to ILAR/ACR criteria, disease onset before 16 years of age, and written informed consent from parents and/or caregivers. Children older than 14 years also provided their own consent.

Exclusion criteria included: children with other diffuse connective tissue diseases (systemic lupus erythematosus, acute rheumatic fever, systemic scleroderma, dermatomyositis/polymyositis, systemic vasculitis), known endocrine pathologies (pituitary insufficiency, hypothyroidism, diabetes, etc.), or refusal of participation by parents, caregivers, or the child.

The required sample size was calculated to ensure sufficient statistical power. Based on bibliographic data, growth retardation in children with JIA occurs in approximately 35–40% of cases ($P_0 = 0.40$). Assuming an expected prevalence of 80% in the research group ($P_1 = 0.80$) and an average proportion $P = 0.60$, the sample size formula was applied with $\alpha = 0.05$ ($Z\alpha = 1.96$), $\beta = 0.10$ ($Z\beta = 1.28$), and an anticipated dropout rate of 10% ($f = 0.10$, $q = 1/(1-f)$). The calculation indicated that at least 45 children with JIA should be included. To account for physiological variability, the study aimed to include 45 prepubertal and 45 pubertal-aged children.

Study methods varied by stage. Initially, epidemiological observation and data accumulation methods were employed. Direct methods included clinical observation, investigation, structured interviews, and longitudinal follow-up at 6, 12, and 18 months. Data were collected using a comprehensive patient examination questionnaire of 129 items, organized into sections covering general information, diagnosis and disease history, auxology, pubertal evaluation, clinical and endocrine features, laboratory results, and imaging data. This structured approach enabled integration of anthropometric, hormonal, and imaging parameters to support the development of the diagnostic algorithm.

Results.

The study demonstrated that autoimmune inflammatory processes in juvenile idiopathic arthritis (JIA) profoundly disrupt multiple hypothalamic-pituitary axes, leading to measurable impairments in growth patterns, pubertal development, and endocrine function, with variability depending on age, sex, disease subtype, and activity level.

Growth and GH/IGF-1 Axis: Growth retardation was observed in 15.46% of children (95% CI: 8.26–22.65%), malnutrition in 20.62% (95% CI: 12.56–28.66%), and overweight in 9.28% of cases. Prepubertal children showed lower mean DS for waist circumference, while during puberty, weight and BMI were more affected. Growth impairment was more pronounced in boys than girls across height, weight, and BMI. Differences were also significant according to Tanner stage.

By JIA subtype (Figure 1), the Z score for weight was significantly lower in children with systemic onset compared to those with oligoarticular onset ($p < 0.05$) and seronegative polyarticular onset ($p < 0.05$). Similarly, significant differences were observed with even stronger statistical significance for weight Z scores in systemic JIA versus oligoarticular ($p < 0.001$) and seronegative polyarticular onset ($p < 0.01$).

Low serum IGF-1 levels were found in 41.24% of children, and elevated IGF-BP3 in 43.30%. A strong positive correlation existed between these markers ($r=0.84$). No autoimmune involvement at the pituitary level was detected. A linear regression model was applied to assess the predictive relationship of the analyzed parameters. A statistically significant correlation was observed between serum IGF-1 levels and both the age of the subjects and the corresponding absolute anthropometric measurements (Table 1).

Therefore, adjusting IGF-1 interpretation for age, weight, and height is essential to ensure accurate evaluation of growth and endocrine status. Active hormonal screening may enable early identification of hypothalamic-pituitary-IGF1 axis dysfunction.

Hypothalamic-Pituitary-Gonadal Axis: Late onset, slow progression, or stagnant puberty occurred in 24.44%, 26.67%, and 8.89% of children, respectively, with delayed puberty more frequent in boys. In girls, menstrual irregularities were reported

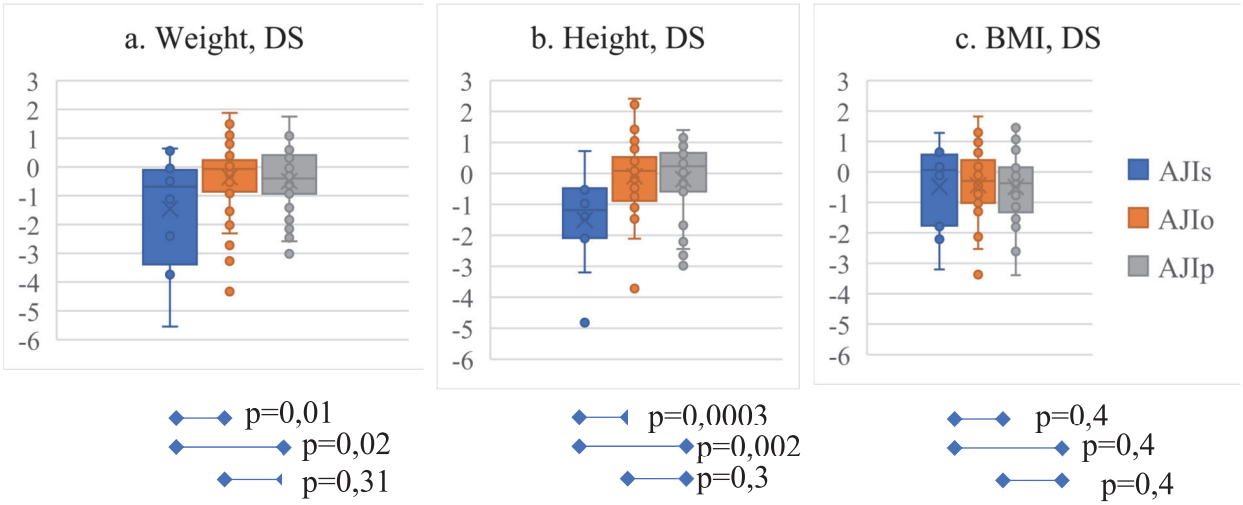
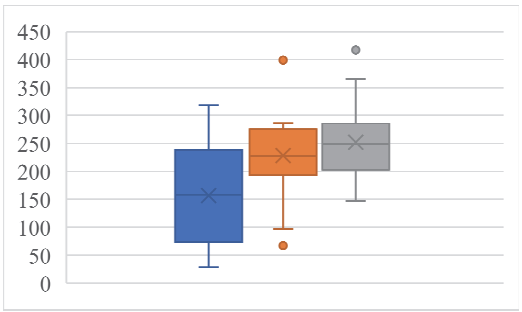


Figure 1. Evaluation of anthropometric indicators (weight, height) and BMI according to JIA onset subtype, SD

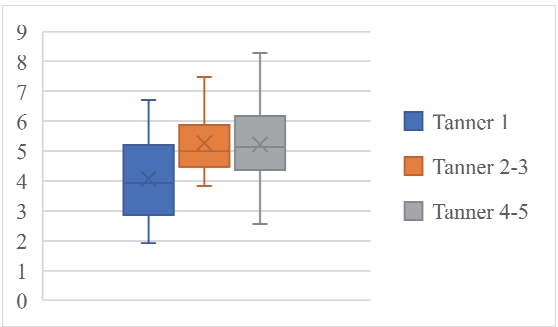
Table 1.

Evaluation of the influence of anthropometric indicators on the serum value of IGF1 by the method of logistic regression

Parameter	*Statistical indicator*						
	r	***r²***	***ß***	***ES***	***t stat***	***p***	***IÎ 95%***
Age (years)	0,67	0,44	13,48	1,53	8,79	**0,0000** (6,15E-14)	10,43; 16,52
Weight (kg)	0,69	0,48	3,76	0,4	9,37	**0,0000** (3,67E-15)	2,96; 4,56
Height (m)	0,72	0,53	255,6	24,6	10,36	**0,0000** (2,74E-17)	206,7; 304,64
BMI (kg/m²)	0,48	0,23	15,52	2,85	5,44	**0,0000** (4,11E-07)	9,85; 21,18



a. IGF1 mean values in research groups (ng/ml)



b. IGF-BP3 mean values in research groups (µg/ml)

	T_1	T_2	T_3
T_1		**0,03**	**0,001**
T_2			0,1
T_3			

c. Statistical value of IGF1 between study subgroups (student t-test, p-value)

	T_1	T_2	T_3
T_1		**0,01**	**0,02**
T_2			0,46
T_3			

d. Statistical value of IGF-BP3 between study subgroups (student t-test, p-value)

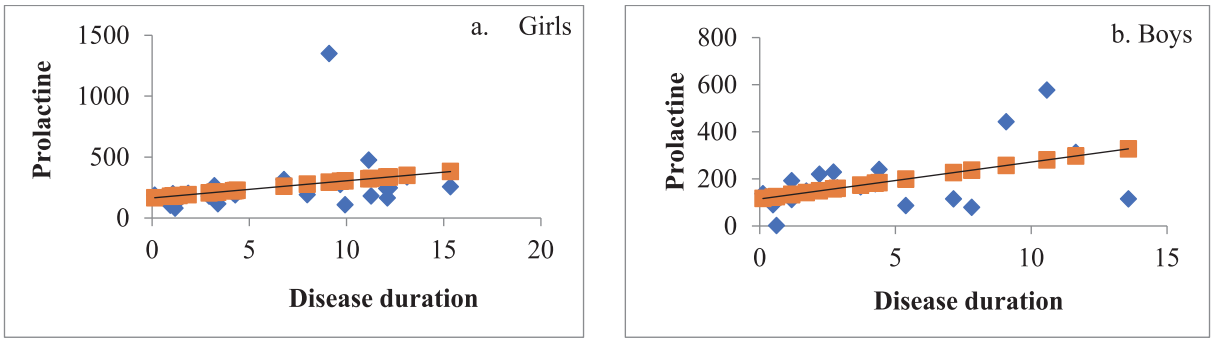
Figure 2. Evaluation of the hypothalamic-pituitary axis IGF1 (a) and IGF-BP3 protein (b) according to pubertal development and statistical significance (c, d)

in 60% of cases. Tanner stage progression over 6–18 months showed sex-based differences, with significant improvement in boys ($p<0.001$–0.01). Boys had lower Tanner scores than girls in oligoarticular and polyarticular seronegative subtypes ($p<0.05$).

Analysis according to Tanner developmental stages revealed significant differences in growth patterns (Figure 2). Growth velocity analysis by Tanner stage demonstrated that IGF-1 levels were significantly lower in the T1 subgroup compared to T2 ($p < 0.05$) and T3 ($p < 0.001$). Similarly, mean IGF-BP3 values differed significantly across the subgroups, with T1 showing lower levels compared to T2 and T3 ($p < 0.05$).

Elevated serum PRL levels were detected in 9.28% of cases, occurring more frequently in girls (13.21%) than in boys (4.55%, $p < 0.05$). When analyzed according to JIA onset subtype, statistically significant differences were observed between systemic JIA and oligoarticular JIA ($p < 0.05$), as well as between systemic JIA and seronegative polyarticular JIA ($p < 0.05$). Hyperprolactinemia correlates with disease duration with gender differences. Thus, a more intensely expressed prediction was identified in boys ($p<0.01$), compared to girls (figure 3).

Hypothalamic-Pituitary-Thyroid Axis: In children with JIA, evaluation of thyroid function tests revealed subclinical hypothyroidism in 15.38% of



$r=0,279$; $r^2=0,078$; $p<0,05$ $r=0,475$; $r^2=0,226$; $p<0,01$

Figure 3. Predictive value of disease duration on serum prolactin values in girls (a.) and boys (b.) with JIA

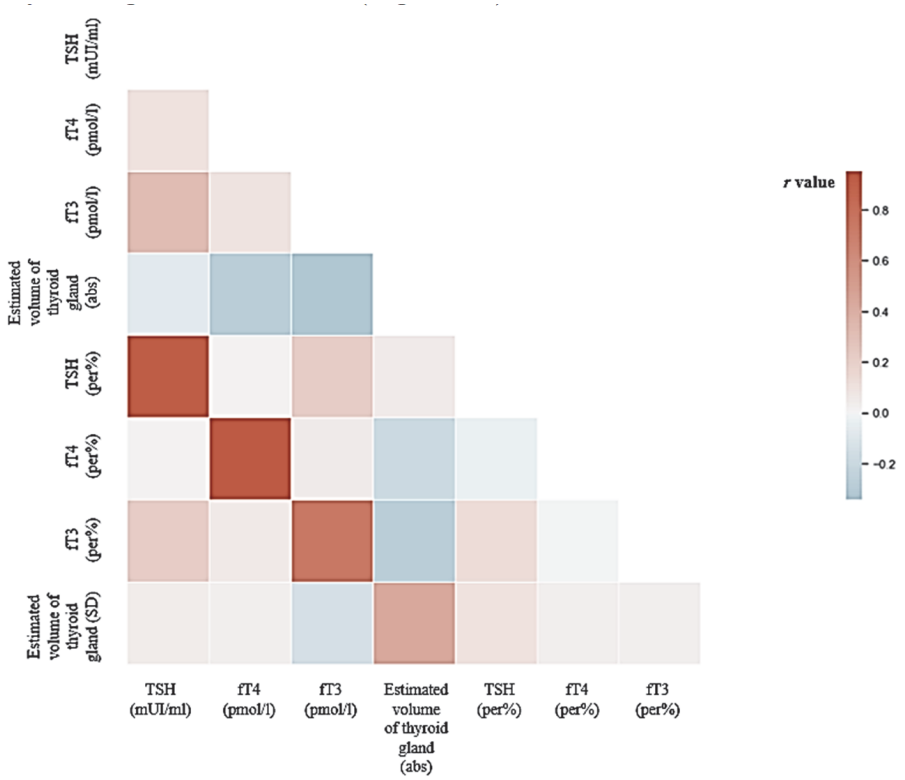


Figure 4. Graphic representation of the correlations between the absolute and categorical values of the functional and structural parameters of the thyroid gland in children with JIA

prepubertal children and 6.66% of pubertal children. Serum levels of thyroid hormones and TSH showed significant inter-individual variability, highlighting the necessity of using age- and sex-specific reference ranges (percentiles or standard deviations) for accurate interpretation. We observed a highly significant, directly proportional correlation between both absolute and percentile-based thyroid function test values and estimated thyroid gland volume (figure 4).

Regarding JIA characteristics, a significant inverse correlation was identified between TSH values and age categories, age at study enrollment, and disease duration. Additionally, a moderately significant, inversely proportional correlation was found between TSH values and anthropometric parameters, including weight, waist circumference, and BMI at enrollment. Importantly, categorical (percentile) TSH and thyroid hormone values were strongly directly correlated with disease activity as measured by DAS28.

These findings provided the evidence base for constructing a stepwise diagnostic algorithm for endocrine comorbidities in children with JIA, integrating growth, pubertal, and thyroid assessments.

Discussion.

The comparative analysis of our findings with existing literature and clinical guidelines underscores the complexity of endocrine comorbidities in children with juvenile idiopathic arthritis (JIA) and highlights the necessity of a structured diagnostic and monitoring approach.

The integration of our data with previous studies allowed us to develop a stepwise diagnostic algorithm (Figure 5) aimed at optimizing patient management.

Growth evaluation remains a cornerstone of monitoring in JIA, as confirmed by both our study and prior reports. Delays in diagnosis and prolonged inflammatory activity are consistently associated with growth plate impairment [10]. Anthropometric measurements are reliable, low-cost, and non-invasive, making them feasible for routine clinical practice with minimal training [13]. Our results align with other studies, who observed significant differences in height, weight, and growth velocity between JIA subtypes, although BMI was not affected [22, 23]. These findings reinforce the importance of early identification and timely intervention, as controlling inflammation while minimizing steroid exposure is critical to preserving growth potential before epiphyseal closure [12]. Serum IGF-1 remains an essential laboratory marker for detecting GH axis disturbances and guiding individualized management [16].

Pubertal monitoring is equally important, with routine assessment of breast stage in girls and testicular volume in boys recommended for adolescents with chronic disease [13, 24]. Our analysis, consistent with other studies, emphasizes that hormonal changes often correlate with disease activity [13, 25, 26]. Correct interpretation of H-H-G axis hormones using age- and sex-specific percentiles is necessary for accurate clinical decision-making [27]. Screening for hyperprolactinemia is advised in children with growth delay or obesity, given its role in inflammation and potential impact on pubertal progression [28, 29].

Thyroid screening is another critical component of endocrine evaluation in JIA. Thyroid dysfunction may present with subtle or nonspecific symptoms, and age- and sex-adjusted reference ranges are essential for accurate interpretation [20, 21, 22, 30]. Systematic thyroid evaluation can enhance early detection and ensure equitable access to high-quality, evidence-based care delivered by multidisciplinary teams.

Overall, these findings highlight the value of a comprehensive diagnostic algorithm that integrates growth, pubertal, and thyroid assessments, providing a practical framework for early identification and individualized management of endocrine comorbidities in children with JIA.

Conclusions.

The stepwise diagnostic algorithm provides a practical and standardized framework for monitoring physical and pubertal development in children with chronic inflammatory diseases. By integrating anthropometric measurements, Tanner staging, hormonal assessments, and imaging, it enables early detection of endocrine comorbidities, guides individualized management, and supports timely therapeutic decisions. Its application in clinical practice can improve growth and developmental outcomes, enhance the quality of care, and promote consistent monitoring across different healthcare settings.

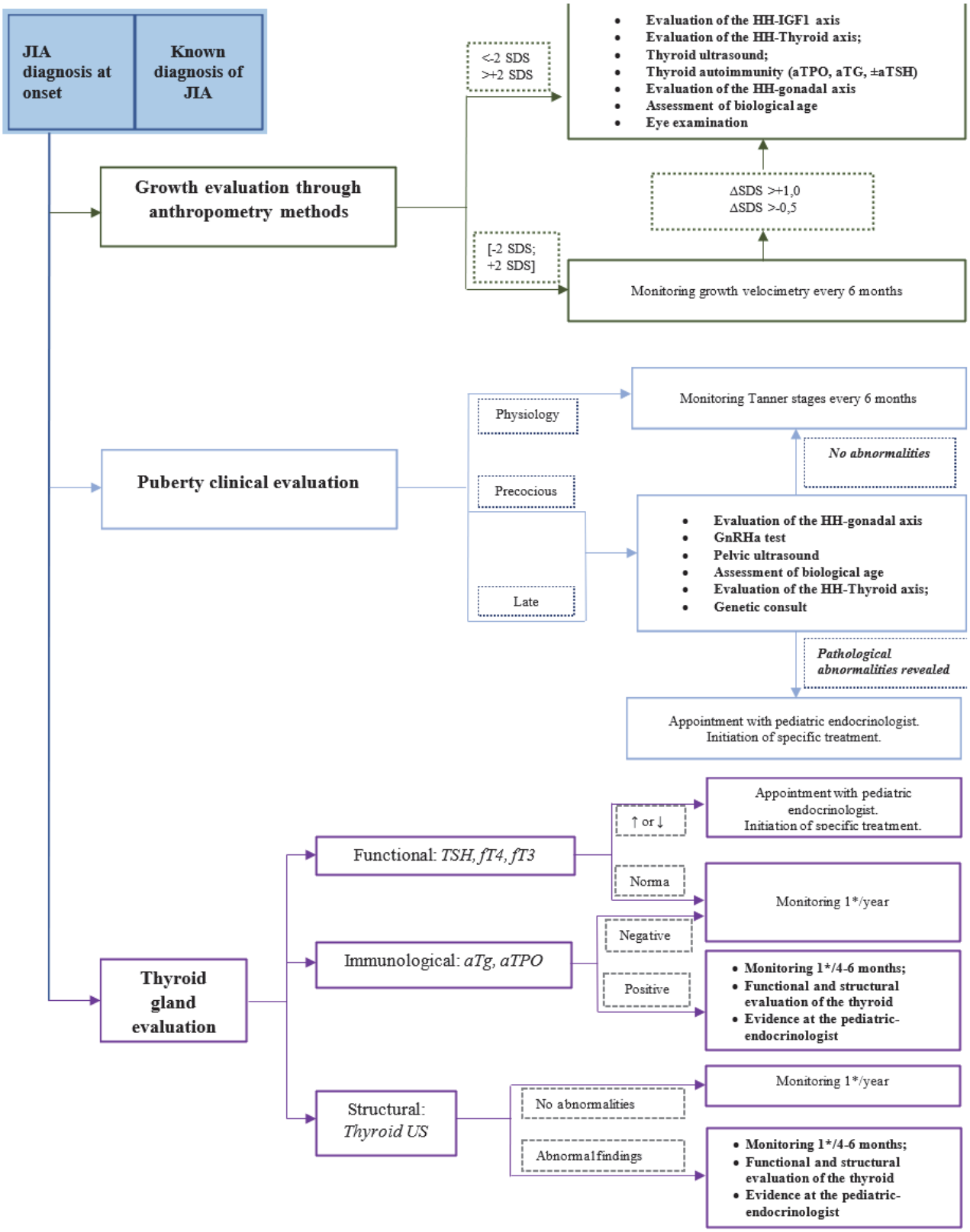


Figure 5. Diagnosis and management of endocrine comorbidities in JIA

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Conflict of interest: The authors declare that they have no conflicts of interest.

Ethics approval: The study carried out was positively approved by the University's Research Ethics committee of the State of Medicine and Pharmacy "Nicolae Testemițanu", by the minutes no. 53 of April 12, 2018.

Authors' contributions: Both authors conceived and conducted the study, participated in study design, carried out the literature review, performed the statistical analysis, proposed the presented algorithm, and drafted the manuscript. NR provided critical guidance throughout the research process, and revised the manuscript for important intellectual content.