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THE HYPOTHALAMIC-PITUITARY AXIS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

322.01 – PAEDIATRICS AND NEONATOLOGY

Summary of Ph.D. thesis in medical sciences

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CONCEPTUAL RESEARCH MILESTONES

Timeliness and importance of the topic

Juvenile idiopathic arthritis (JIA) represents a group of inflammatory conditions characterized by chronic arthritis with various clinical forms of presentation [1, 2]. According to the International League against Rheumatism, 7 subtypes of JIA are distinguished depending on the degree and location of the inflammatory process, as well as the activity of biological markers [3].

Compromised development by growth retardation and delayed puberty are frequent complications observed in children with JIA, associated, in turn, with a marked negative impact on quality of life [4, 5]. As in the case of other complications of JIA, the impairment of growth process depends on the duration and activity of the disease, the most severe cases being recorded in patients with high values of long-lasting pro-inflammatory markers, for example, in the systemic and polyarticular subtypes of JIA [6]. The literature data on this subject remain brief and varied, as the incidence of growth retardation is estimated from 8 to 41%, some studies specifying only the severe forms of the disease, others reporting on all subtypes of JIA [7, 8]. In the same time, data on the incidence of puberty in these children are not clearly published [9].

Growth in children is a complex process, which can be influenced by multiple mechanisms, both systemic and local [10]. The inflammatory process mediated by pro-inflammatory cytokines, prolonged use of glucocorticosteroids (GCS) and nutritional disorders contribute to stunted growth and pubertal impairment [11, 12]. The chronic inflammatory process in children with JIA can cause flattening of the weight curve and accentuate growth retardation, while steroid treatment aimed at controlling inflammation involves growth impairment and excessive weight gain [13, 14]. Although the dysregulation of the GH/IGF1 axis is known, there are still insufficient data to elucidate systemic hormonal resistance on growth failure in children with JIA [15]. The cohort study conducted by Songyi et al. showed low serum levels of IGF-1 in the polyarticular and systemic forms of JIA compared to the control group, while the values remained within the normal range in the case of the oligoarticular form and the one associated with enthesitis. Decreased IGF-1 levels in these two forms reflect reduced pituitary function with GH deficiency or unresponsiveness to GH driven by chronic inflammation. At the same time, the same study finds weak to moderate-negative correlations in the comparative analysis of IGF-1 in relation to the basic parameters of disease activity [16].

The onset of puberty can be delayed by around 0.4-2.2 years compared to healthy children [17]. Some studies highlight that none of the adolescents with JIA have reached puberty stage 5 (according to Tanner) by the age of 16, although the onset of puberty occurred in physiological terms [9]. The pubertal growth spurt may be attenuated in patients with JIA and is usually very insignificant in the systemic form of the disease. At the same time, previous studies reflect the significant reduction of the target waist in adulthood in children with JIA [18].

In the conditions of optimizing the treatment tactics of JIA, with the use of biological treatment, an improvement in the velocimetry of growth is estimated, as well as a reduction of the long-term impact. The mechanism involved is not fully elucidated, the improvement being due to better control of the disease, reduction of GCS doses or both [13, 19].

Both growth itself and the onset of puberty are influenced by thyroid function. At the same time, thyroid hormones fluctuate considerably at different physiological ages of the child. Thyroid involvement can be functional, structural and/or autoimmune [20]. There are only a few studies evaluating the relationship between JIA and autoimmune thyroiditis [21]. Complex studies, in which all forms of involvement of the thyroid gland in JIA are reflected, are missing.

In the Republic of Moldova, studies that would address hormonal disorders with influence on growth and development in children with chronic diseases have not been carried out to date. Also, at the level of the Republic of Moldova, there is a lack of data on thyroid gland damage in the general pediatric population. Considering that the impact of the clinical consequences of the chronic inflammatory process starts from the early stages of the disease, the introduction of preventive auxological screening measures is necessary in children with JIA. These measures can detect developmental disorders at a very early stage, and over time, allow us to improve their therapeutic behavior.

These arguments are the basis for the need to carry out additional studies to identify and monitor risk factors affecting growth and puberty in children with JIA. The detailed study of hormonal axes and endocrine autoimmunity is an effective tool for optimizing therapeutic management.

The aim of the research is to study the impact of autoimmune inflammatory processes on the hypothalamic-pituitary axis in order to develop a diagnostic algorithm of endocrine comorbidities in juvenile idiopathic arthritis.

Research objectives:

1. Studying the pattern and velocimetry of growth according to age and gender, subtype, onset, duration and disease activity in juvenile idiopathic arthritis.
2. Evaluation of the influence of juvenile idiopathic arthritis on the process of pubertal development - clinical and serum, by determining the central and peripheral gonadal hormonal profile.
3. Analysis of the impact of juvenile idiopathic arthritis on hormonal and autoimmune thyroid changes with influence in the process of growth and puberty.
4. Development of the diagnostic algorithm of endocrine comorbidities in juvenile idiopathic arthritis.

The scientific novelty of the research:

For the first time, a prospective cohort study was carried out, aimed at the analysis of endocrine dysfunctions in juvenile idiopathic arthritis. The direction of the research concerned both the functional changes at the central and peripheral level, as well as the autoimmune implications at the level of the endocrine glands and their structural changes. We have based the interpretation of laboratory hormone analyzes based on percentiles by age and sex. Mathematically, we illustrated the interconnections between the endocrine system and the chronic inflammatory process in juvenile idiopathic arthritis. The data obtained allowed the identification, among the specific characteristics of the disease, of predictors for potential hormonal dysfunctions with implications on the growth and development of children. Based on the synthesis of our own data with those from the literature, we developed the diagnostic algorithm of endocrine comorbidities in juvenile idiopathic arthritis.

Theoretical significance:

The nature of JIA, the young age at onset, and the multiple medications required to manage it have multiple effects on patients' growth and development. The results of the study allow to facilitate the establishment of an early diagnosis of endocrine dysfunctions, to improve the individualized management of patients with juvenile idiopathic arthritis with complications for growth and development. Thus, understanding the nutritional problems associated with the diagnosis of JIA is important for their early identification and management to improve the health and prognosis of affected children.

Applicative value of the research: The results of the study elucidate clinical diagnostic dilemmas, encourage the correct use of diagnostic tests of endocrine dysfunctions and improve their interpretation in the pediatric population. Centile graphs of correct interpretation based on age and sex of laboratory results were developed. The results of the study were implemented in the practical activity of the rheumatology clinic within Mother and Child Healthcare Institute

from Chișinău. Also, the results obtained were used in the teaching process of the Department of Pediatrics within the USMF "Nicolae Testemițanu" and were used in the update of the PCN "Idiopathic juvenile arthritis in children".

Key words: juvenile idiopathic arthritis, children, growth, puberty, thyroid dysfunction, hypothalamic-pituitary-IGF axis, hypothalamic-pituitary-gonadal axis, hypothalamic-pituitary-thyroid axis, endocrine comorbidities, anti-pituitary antibodies.

RESEARCH METHODOLOGY

To achieve the goal, a cross-sectional descriptive observational study was planned, later continued by observational analytic cohort study. The children in the descriptive observational study were selected within the Rheumatology section of the IMSP Mother and Child Institute based on admission on the nominal lists.

The inclusion criteria were established as follows: children, the diagnosis of juvenile idiopathic arthritis established according to the ILAR/ACR criteria, the onset of the disease before the age of 16, the consent of parents and/or caregivers to the study, the consent of children older than 14 years.

The exclusion criteria were grouped as follows: children with other diffuse connective tissue diseases (systemic lupus erythematosus, acute rheumatic fever, systemic scleroderma, dermatomyositis/polymyositis, systemic vasculitis), endocrine pathologies (pituitary insufficiency, hypothyroidism, diabetes, etc.), refusal of parents/caregivers and/or the patient to participate in the study.

The required number of observation units included in the study (children with juvenile idiopathic arthritis with growth retardation/retardation and children with juvenile idiopathic arthritis without growth impairment) was determined based on the following formula:

$$n = \frac{1}{(1-f)} \times \frac{2(Z_\alpha + Z_\beta)^2 xP(1-P)}{(P_o - P_1)^2}$$

where:

Po = Children with juvenile idiopathic arthritis. According to the bibliographic data, in children with JIA, growth retardation occurs in the middle, in 35-40% of cases (P0=0.40).

P1 = Children with juvenile idiopathic arthritis. We assume that in the research group the value will be 80.0% (P1=0.80).

P = (P0 + P1)/2=0.6

Zα – the tabular value, when "α" – the significance threshold is 5%, then the coefficient Zα =1.96

Zβ – the tabular value, when "β" – the statistical power of the comparison of 90.0%, then the coefficient Zβ = 1.28

f = Proportion of subjects who are expected to drop out of the study for reasons other than the investigated effect q = 1/(1-f), f=10.0% (0.1).

Entering the data into the formula, it was obtained:

$$n = \frac{1}{(1-0.1)} \times \frac{2(1.96+1.28)^2 x0.625\, x0.375}{(0.45-0.80)^2} = 45$$

Thus, the research group for subsequent stages must include at least 45 children with JIA. Considering the variable physiological differences in the pediatric population, we aimed to include 45 prepubertal and 45 pubertal-aged children, respectively.

The research protocol was carried out using different methods depending on the stage of realization. Initially, methods of epidemiological observation and accumulation of informative data were applied. The method of accumulating informative data was carried out by both direct

and indirect methods. Of the direct ones, the method of observation, investigation, interview and long-term monitoring at 6 months, 12 months and 18 months are listed. For data management a complex patient examination questionnaire, made up of 129 questions, being structured into several sections: general data, diagnosis and disease history, auxology, pubertal evaluation, clinical evaluation, endocrine clinical features, laboratory data and imaging data.

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.

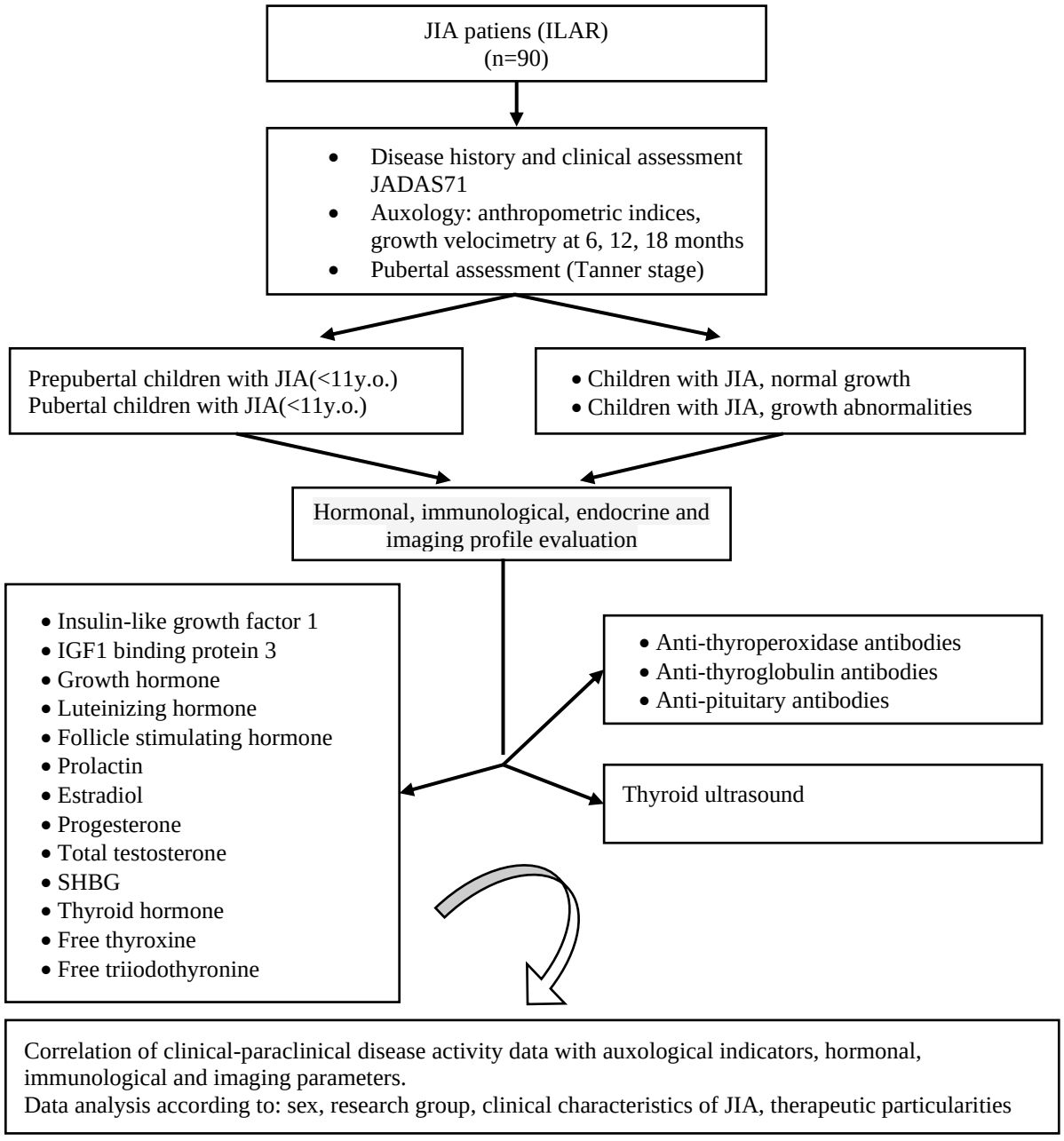


Figure 1. **Research design**

Note: JIA – juvenile idiopathic arthritis; ILAR - International League of Associations for Rheumatology; DAS28 - Disease activity score; JADAS71 - Disease activity score in JIA based on 71 joints; IGF1 - Insulin Growth Factor 1; SHBG - Sex hormone binding globulin.

SUMMARY OF THE CHAPTERS

CHAPTER 1 ("The current state of knowledge of JIA in children") includes a synthesis of the specialized literature related to the current diagnosis, classification and monitoring of JIA. We have described information about the development of diagnostic criteria used in pediatric rheumatology practice, with an emphasis on diagnostic criteria. We have reported current information on treatment options and their impact on growth and development in children with JIA [22–25]. In the subsection dedicated to the spectrum of complications, autoimmune diseases and endocrine comorbidities in juvenile idiopathic arthritis, the results of prospective, multicenter cohort studies that investigated the prognosis, treatment and influencing factors, but not the link between JIA and other types of autoimmune diseases, are analyzed. We developed at a theoretical level the impact of immunoendocrinology in chronic disease in children, on the JIA model. We also reviewed endocrine comorbidities in JIA with a study focus on diagnosis, monitoring and treatment options [26–28]. Although there are data in the literature regarding hypothalamic-pituitary-peripheral axis dysfunction as a whole in children and adolescents, there are no complex longitudinal epidemiological studies on it in juvenile idiopathic arthritis. The subchapters dedicated to the evaluation of the hypothalamic-pituitary-peripheral axes in JIA include the evaluation of both relevant clinical data and hormonal biomarkers associated with central and peripheral endocrine dysfunctions [6, 13, 29].

In **CHAPTER 2 ("Materials and methods of the research")** we have outlined the study design, eligibility criteria, patient investigation methods, programs and methods of statistical data processing and examination. In the prospective cohort study, 97 children underwent clinical, laboratory and imaging evaluation. In all research subjects, anamnestic data were collected, risk factors were assessed, specific laboratory tests were collected, and patients' evolution was prospectively monitored at 6, 12, and 18 months. Thus, the interdependence between the inflammatory process of juvenile idiopathic arthritis and the hormonal-dependent developmental consequences in these children was appreciated.

The data obtained through the evaluation of the subjects included in the research, were computer processed by the following methods: descriptive analysis, dispersion and correlational analysis, with the use of Office365 Microsoft Excel, Visual Studio Code; statistics and data science libraries NumPy, SciKit Learn, Altair. The conclusion of the differences between the average values of the studied parameters was estimated using the t-Student test and one-way ANOVA (one-way ANOVA test or simple ANOVA) in the case of parametric data. Values of $p<0.05$ were considered significant.

The degree of correlative association between the evaluated parameters was estimated by applying the correlation coefficient r (Pearson). To assess the predictive value of the researched parameters in the prognosis of chronic nutritional disorders, the ROC analysis was carried out with corresponding graphic representation and the calculation of the area/surface below the level of the ROC curve - AUC.

The statistical analysis of the laboratory data obtained in the research, then their comparison with those available from the international databases, were the basis for the elaboration of the centile graphs for the interpretation of the laboratory analyses. They were also the basis for the development of the diagnostic algorithm aimed at improving the diagnostic process of endocrine comorbidities in cohorts of children with chronic diseases.

CHAPTER 3 ("Peculiarities of the growth pattern and velocimetry in children with JIA") is made up of 4 subchapters, the first being dedicated to the description of the general study group, and the following ones present the growth disorders in children with JIA, both clinically, serologically, and through statistical analyzes of correlation of the clinical and hormonal values obtained with the specific characteristics of the disease.

The study included 97 children, including 52 patients in the cohort of prepubertal children (group L1 – prepubertal) and 45 patients in the cohort of pubertal children (group L2 – pubertal). The average age of patients in the general group is 10.66 years ± 4.53 years (Me=10.89 years, Q1=7.25 years, Q3=14.72 years). The average age at onset in the general study group is 6.73 years ± 4.08 years (Me=6.29 years, Q1=3.35 years, Q3=10.25 years). The average duration of the disease in the general group is 3.96 years ± 3.91 years (Me=2.93 years, Q1=0.62 years, Q3=6.29 years).

According to the gender distribution in the general group, we enrolled 54.63% girls (95% CI: 44.73%, 64.54%) compared to 45.36% boys (95% CI: 35.45%, 55.26%).

According to the ILAR classification, the most frequent subtype of onset of JIA, in the general study group, the oligoarticular form was found in 44.33% of cases (95% CI: 34.44%, 54.21%), followed by the polyarticular seronegative in 36.08% of cases (95% CI: 26.52%, 45.63%), and the systemic onset of JIA was diagnosed in 12.37% of cases (95% CI: 5.81%, 18.92%). According to the age, in the L1-prepuberty group we found the most frequent oligoarticular onset in 63.46% compared to the seronegative polyarticular onset (53.33%) in the L2-puberty group ($\chi 2 = 19.72$; gl=5; $p = 0.001$).

Clinical severity of JIA was quantified using several clinical tools (SVAD, EGBP, EGBM), including DAS28 activity scores and JADAS71 score. For the first time, we analyzed the incidence and distribution of reserved prognostic factors of JIA in a cohort of children.

The analysis of the forms of growth impairment revealed, among the children examined, 15.46% showed hypostatus (z score <-1.5 SD), and another 10.31% of them with a z score between -1.5 SD and -1.0 SD. In the case of weight assessment, undernutrition conditions were suspected in 20.62% of children with weight indices lower than -1.5SD for age and sex, and in 8.25% of them, nutritional disorders such as overweight were suspected and/or obesity. The analysis of the data obtained for BMI confirmed 30.93% of the children undernutrition and 9.28% of them - with overweight. For the first time, TPI was analyzed in children with JIA older than 10 years. Compared to the BMI, the undernutrition rate decreases statistically significantly in the general study group ($p<0.01$), as well as in boys ($p<0.01$). The results of the ROC curve analysis reveal that BMI remains a better predictor than TPI for nutritional status disorders in children with JIA.

According to age, sex and puberty (L1 and L2 research groups) we found the mean value of the waist at research enrollment lower (-0.336 SD ±1.03 SD) in children from L1 compared to subjects from the L2 group (- 0.252 SD ± 1.51 SD), where growth may already be influenced by the pubertal growth spurt. Boys, unlike girls, presented a negative value of SD for waist (-0.37 SD ±1.33SD versus -0.23 SD ± 1.23 SD) but without significant statistical differences (Z test=0.50, $p > 0.05$).

Depending on the age at the onset of the disease, lower values of the means of the standard deviations for weight and height are determined in those children with the onset of the joint syndrome before the age of 3 years compared to those with the onset after the age of 3 years (Z-test=- 0.96; $p>0.05$ for mass, and for waist - Z-test=-1.23; $p>0.05$; critical Z 1.95).

Depending on the JIA subtype (fig. 2), the Z score for weight assessment is statistically significantly lower in subjects with systemic onset of JIA both compared to subjects with oligoarticular onset ($p<0.05$) and compared to seronegative polyarticular onset ($p<0.05$). Z score for weight assessment is statistically significantly lower in subjects with systemic onset of JIA both compared to subjects with oligoarticular onset ($p<0.001$) and seronegative polyarticular onset ($p<0.01$).

Depending on the duration of the disease, it was found that the mean value of the waist in the group of children with a prolonged period of the disease (more than 1 month) was -0.42 SD ± 1.41 SD vs 0.01 SD ± 0 .80 SD in children with a newly established diagnosis (treatment <1 month), $p<0.05$.

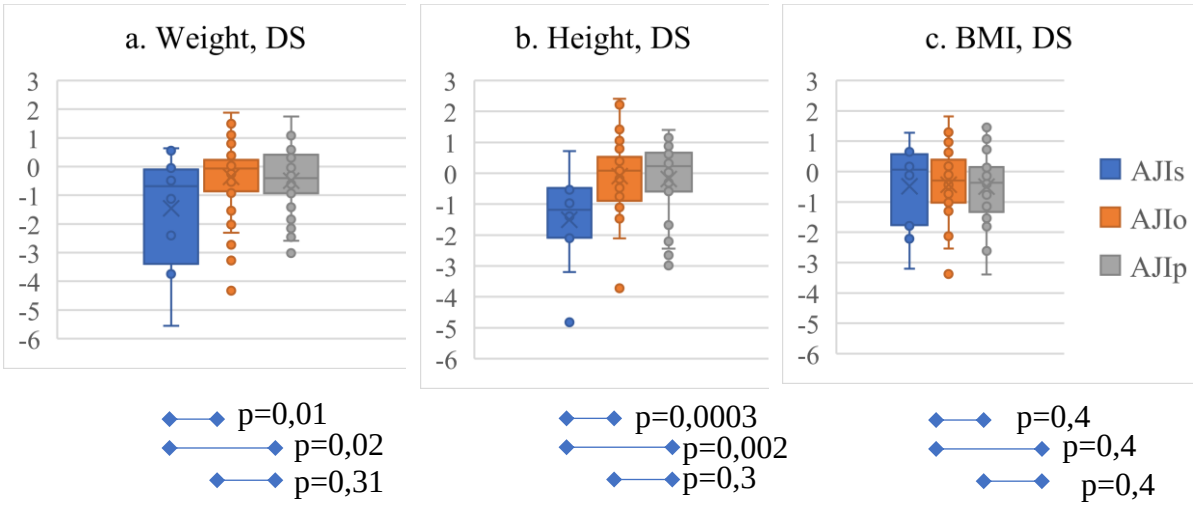


Figure 2. **Evaluation of anthropometric indicators (weight, height) and BMI according to JIA onset subtype, SD**

Depending on the use of GCS treatment. With a strong statistical significance (p<0.00001) it shows the average SD values for mass and for height among children who received treatment with GCS, Z-test=-3.96; p<0.00001; Critical Z 1.95.

Depending on the use of biological treatment. The assessment of growth according to the use of biological treatment revealed lower values in children who received biological treatment (-1.46 SD ± 1.78 SD) compared to those who were not subjected to biological treatment (Z-test=-3, 96; p<0.00001; critical Z 1.95). These registered statistically significant differences with considerable p-value values at all assessment points – 6, 12 and 18 months, in contrast to the dynamics of nutritional status at the same time intervals for clinical assessment, but without statistical significance between research groups. We consider these data insufficient, a limitation of the study being the summary number of patients who benefited from biological treatment.

For the first time, we present the evaluation data of the triponderal index (TPI) studied in a cohort of patients with a chronic rheumatic pathology, on the model of children with JIA. Thus, with a statistically significant difference, we observe that when TPI is applied, the rate of undernutrition and overweight, respectively previously known by applying BMI, decreases in the general study group ($\chi 2$ = 13.64; gl=3; p=0.003) and in the case of boys ($\chi 2$ = 11.34; gl=3; p=0.009).

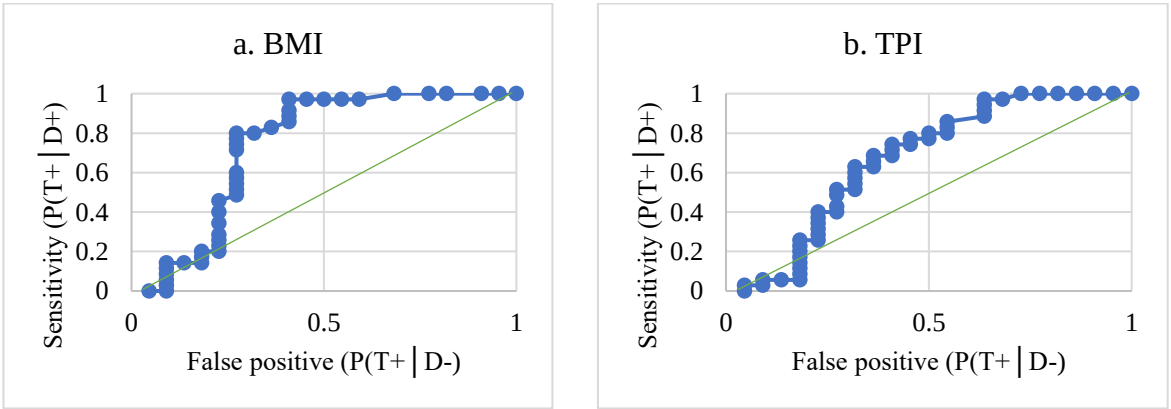


Figure 3. **ROC curve for BMI (a.) and TPI (b.) in children with JIA (>10 years)**

The comparative analysis of BMI versus TPI among girls did not reveal statistically significant differences ($\chi 2 = 3.11$; gl=3; $p>0.05$). The area under the ROC curve is insignificantly higher when evaluating BMI than in the case of TPI. The study findings suggest that BMI and TPI are significantly associated with nutritional disorders in children with JIA. However, BMI is a better predictor of nutritional disorders than TPI among children and adolescents aged 10–18 years (Fig.3).

Although, only 15.46% of children were clinically with compromised values of anthropometric indicators, in 41.24% of cases low serum values of insulin growth factor 1 (IGF1) were detected, of which 27.84% of cases with values corresponding to the centile range 0.1-5, and 13.40% of cases - with values lower than the 0.1 percentile. At the opposite pole, the serum values of IGF transport protein 3 (IGF-BP3) were in 43.30% of cases higher than the 90th percentile. Statistical analysis, based on the Pearson test, indicates an intensely positive correlation between these 2 variables (r=0.84).

Thus, we aimed to evaluate the incidence of central autoimmune damage in children with JIA and growth retardation. The evaluation of antipituitary antibodies was performed by the indirect immunofluorescence method. As a result, all the tests performed determined in 100% of cases negative results for the presence of antipituitary antibodies. Thus, we can conclude that the study carried out for the first time does not confirm the hypothesis of central hypothalamic-pituitary autoimmune dysfunction in children with JIA.

We applied the linear regression model in order to verify the prediction model of the analyzed parameters. Statistically significant correlation was found in the evaluation of the serum value of IGF1 against the age of the subjects and, respectively, the absolute values of the anthropometric indicators (table 1). The relationship between IGF1 levels and age is well documented in the literature. Our results are in agreement with those previously described in this field. Adjusting the interpretation of IGF1 values according to age, mass and height is essential for correct interpretation of the data.

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	***r^2***	***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/m^2)	0,48	0,23	15,52	2,85	5,44	**0,0000** (4,11E-07)	9,85; 21,18

Age at onset, likewise, correlates directly proportionally with IGF1, being considered as a potential predictor for growth disorders in children with JIA (r=0.47; p=0.0000). We also found a highly statistically significant, directly dependent correlation between the age of the research subjects and the serum value of IGF-BP3 (r=0.575). Compared to the anthropometric indicators, there is a statistically significant correlation, directly proportional both with mass (r=0.619), waist (r=0.616), and with the absolute value of BMI (r=0.517). In relation to the clinical, laboratory and activity indicators of JIA, no statistically significant correlations with IGF-BP3 were identified.

In **Chapter 4 („Pubertal development in juvenile idiopathic arthritis")**, we presented the impact of chronic autoimmune inflammatory processes on the JIA model on the hypothalamic-pituitary-gonadal axis in children, both through clinical manifestations, through

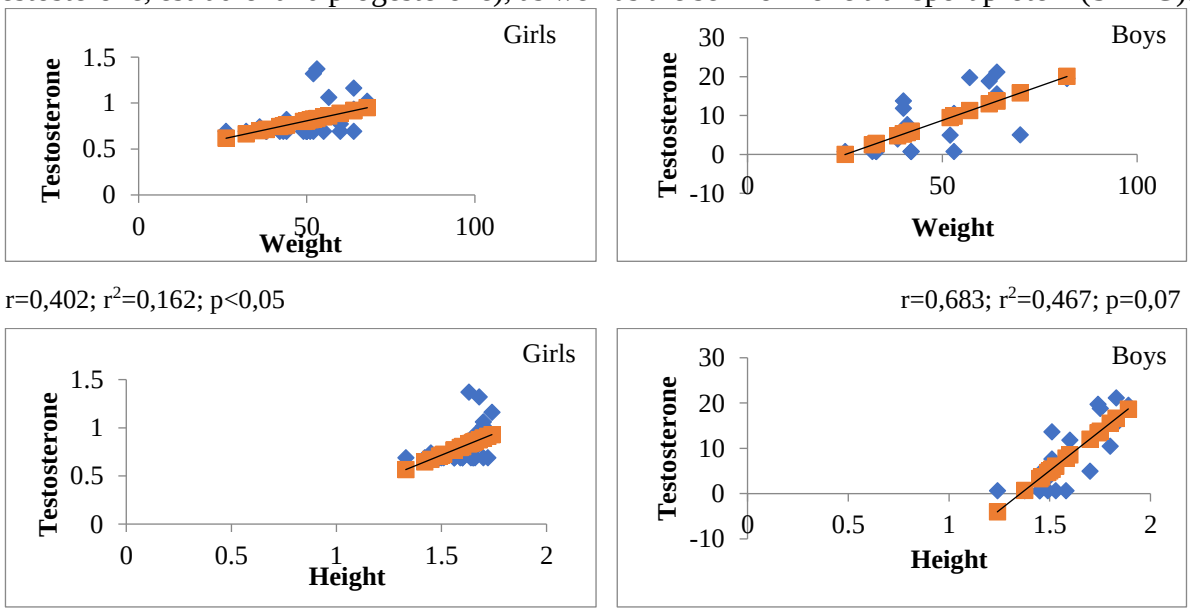
central and peripheral hormonal abnormalities, but also the correlations between them. We addressed the role of prolactin as a hormone as well as a proinflammatory mediator in JIA.

In proportion of 24.44% of children presented late onset of puberty. Depending on the gender, the late onset of puberty was found more frequently in boys in 36.84% of cases compared to the subgroup of girls in a proportion of 15.38% of cases ($\chi 2$ =2.73; GL=1; p=0, 09). At the remote follow-up, at intervals of 6, 12 and 18 months, puberty was assessed as slowly progressive in 26.67% of the participants in the general study subgroup, more frequently in the case of boys (36.84%) compared to the subgroup of girls (19.23%). Stagnant puberty was observed in 8.89% of cases among children, also with gender differences: in boys in a ratio of 15.79% compared to girls in 3.85% of cases ($\chi 2$ = 4.52; GL= 2; p=0.1).

Summarizing the puberty assessment components, Tanner stage at research enrollment in boys was significantly lower compared to girls (2.89±1.72 in boys versus 4.65±1.12 in girls; z= -3.54 ; p<0.0001). Pubertal assessment, in dynamics at 6, 12 and 18 months, shows persistent differences between the sexes.

Statistical analysis revealed that Tanner stage correlates strongly with anthropometric indicators and BMI (r >0.5) in both girls and boys. An inversely proportional correlation was found with JIA assessment indices, both the one reported by the patient/parent (EGB-P) and the one reported by the doctor (EGB-M). There were no statistically significant correlations with important laboratory indices in JIA monitoring (ESR and CRP), as well as statistically insignificant correlations with JIA severity scores (DAS28 and JADAS71).

In subchapter 2 of this section, the analysis of the results of the research carried out at the level of the hypothalamic-pituitary-gonadal axis was dedicated. Thus, hormones were evaluated both at the central level (LH, FSH and prolactin) and at the peripheral level (total testosterone, estradiol and progesterone), as well as the sex hormone transport protein (SHBG).



r=0,402; r^2=0,162; p<0,05

r=0,683; r^2=0,467; p=0,07

r=0,430; r^2=0,185; p>0,05

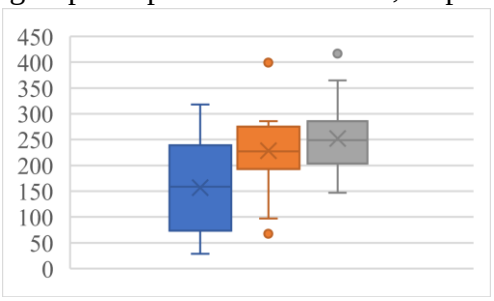
r=0,803; r^2=0,644; p<0,001

Figure 4. **Predictive value of anthropometric indices on serum total testosterone values in children with JIA according to gender**

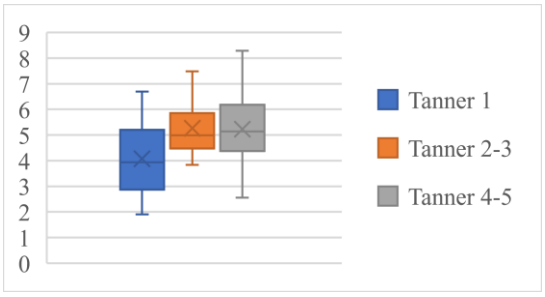
At the level of the pituitary glands, no major deviations were identified in the analyzes of the research subjects. In the group of girls, the analysis of peripheral hormones preferred by the female sex, estrogens and progesterone, did not reveal hormonal dysfunctions. In the case of boys, 28.89% of them have testosterone values between 2.5% and 50%. Serum testosterone values revealed significant statistical differences between girls and boys ($\chi 2$ = 25.01; gl=3;

p<0.00001). The secreted level of SH-BG is reduced to 11.5% of girls and 10.5% of boys. JIA activity indices (ESR and CRP) as well as disease activity scores (DAS28 and JADAS71) inversely correlated with pituitary and peripheral gonadal tropic hormone assays only in the boys assessment group. Unlike boys, only moderate direct correlation between estradiol and progesterone with JIA activity scores was found in girls.

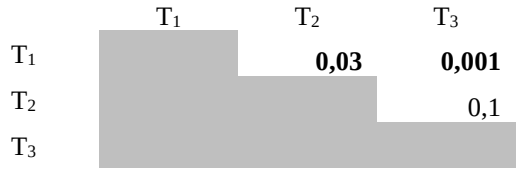
Depending on the developmental stages according to Tanner, significant differences were found for the growth pattern (figure 5). Thus, waist assessment in T1 subgroup subjects was more compromised with a mean height Z score of -1.28 ± 1.85 compared to T3 subgroup subjects with a mean value of +0.48 ± 0.78 (p <0.01). Also, statistically significant differences were found, including between the subjects of the T2 vs T3 group (p<0.01). The study of growth velocimetry according to Tanner stage revealed differences for the obtained values of IGF1 in subjects from the T1 subgroup compared to those from T2 (p<0.05); and between T1 and T3 – p<0.001. In the same way, statistical differences were also found for the average values of IGF-BP3 in the analyzed subgroups (p<0.05 being found only between the T1 subgroup compared to T2 and T3, respectively).



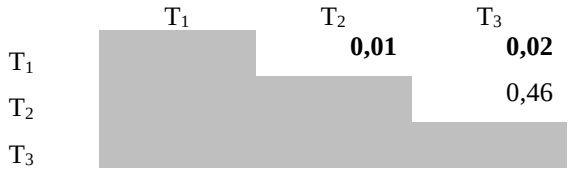
a. IGF1 mean values in research groups (ng/ml)



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



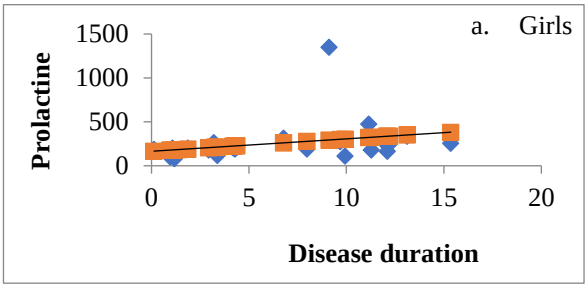
c. Statistical value of IGF1 between study subgroups (student t-test, p-value)



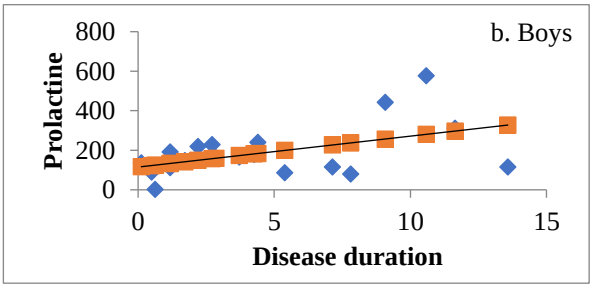
d. Statistical value of IGF-BP3 between study subgroups (student t-test, p-value)

Figure 5. **Evaluation of the hypothalamic-pituitary axis IGF1 (a) and IGF-BP3 protein (b) according to pubertal development and statistical significance (c, d)**

In subchapter 4 of the current compartment, we addressed the analysis of data regarding the potential inflammatory role of PRL in patients with JIA. Increased serum PRL values were identified in 9.28% of cases, more frequently found in girls (13.21%) compared to boys (4.55%), p<0.05. According to the JIA onset subtype, statistically significant differences were found between the subgroup of systemic JIA versus oligoarticular JIA (p<0.05) and systemic JIA versus seronegative polyarticular JIA (p<0.05).



r=0,279; r^2=0,078; p<0,05



r=0,475; r^2=0,226; p<0,01

Figure 6. **Predictive value of disease duration on serum prolactin values in girls (a.) and boys (b.) with JIA**

Depending on the age at the onset of the disease, the mean serum prolactin value was found to be the highest in those subjects with the onset of the disease up to 3 years, subsequently, in those with the onset between 3 and 10 years. Thus, comparative statistical significance was found between subjects with onset up to 3 years versus those with onset after 10 years ($p=0.002$), also between subjects with onset between 3 and 10 years versus those with onset after 10 years ($z=1.67$; $z_{critical}=1.64$, $p=0.04$). Depending on the therapeutic characteristics of JIA, we identified statistical differences between responder patients versus non-responders ($p<0.05$). Hyperprolactinemia correlates with disease duration with gender differences. Thus, a more intensely expressed prediction was identified in boys ($p<0.01$), compared to girls ($p<0.05$). As a function of disease activity, we observe a stronger directly proportional correlation represented in the L1-prepubertal versus L2-pubertal subgroup for both DAS28 and JADAS71. A moderate inverse correlation is found for boys versus girls also for DAS28 and JADAS71.

In **Chapter 5 ("Impact of thyroid hormonal changes on the growth process in JIA")** we reported the impact of autoimmune inflammatory processes in JIA on the hypothalamic-pituitary-thyroid axis both at the clinical, hormonal, autoimmune and imaging levels. Also, we have represented in tables and figures the evaluation of the HHT axis in JIA, as well as the correlations between the thyroid parameters and those specific to JIA.

Clinically, palmar erythema (54.63%), hypersweating (38.14%) and thermogenesis disorders (27.83%) were most frequently observed. Every fifth patient (20.61%) in the research group reported the presence of palpitations. The comparative analysis in the research subgroups, according to the distribution by age, revealed approximately the same distribution of the incidence of clinical manifestations ($\chi2 = 10.37$; $gl=5$; $p=0.06$), differences being registered according to the distribution by sex ($\chi2 = 15.008$; $gl=5$; $p=0.01$). In all 3 forms of JIA onset, every second subject included in the study had palmar erythema ($p<0.05$). Clinical manifestations of thyroid dysfunction according to treatment option as well as patient response showed the same distribution of clinical manifestations between subjects in comparison subgroups ($p>0.05$).

Hormonally, we identified significant differences between subjects of prepubertal L1 and pubertal L2 subgroups for mean serum TSH ($p<0.0001$), fT4 ($p<0.01$) and fT3 ($p<0.0001$) values. Our study clearly demonstrates the need for age- and sex-specific reference ranges (per% or SD) of serum TSH, fT4 and fT3 levels. According to the percentiles according to age and sex, the TSH values were higher than the 90th percentile in 11.34% of the cases, and in 11.4% of the cases values correspondingly lower than the 10th percentile were recorded. Thus, subclinical hypothyroidism with TSH values higher than the 90th percentile in the subgroup of prepubertal children was found in 15.38% of cases compared to 6.66% of cases in pubertal ones. Depending on the subtype of onset of the disease, significant statistical differences were found between the JIAs vs JIAo subjects – $p<0.05$; and between AJIo vs AJIp subjects – $p<0.01$.

Ultrasonographically, structural changes of the thyroid were identified. In 13.40% of cases, at least one ultrasound structural change was recorded, and in 11.34% of cases, 2 or more structural changes were detected. In 11.34% of the subjects included in the research, values of the thyroid gland volume lower than [-2 SDS] were recorded, and in 2.06 % of the cases the thyroid gland volume was estimated higher than [+2 SDS]. Thyroid gland volume is greater in the L2 group with a mean value of 7.35 cm3 versus 3.56 cm3 in the L1 group ($p<0.0001$). Depending on the subtype of onset of the disease, we revealed statistically significant differences only between oligoarticular and seronegative polyarticular onset of the disease ($p<0.01$).

Statistically, we demonstrated that there is a highly significant correlation (figure 7), directly dependent, between absolute and categorical values (per%) of TSH (r=0.936), fT4 (r=0.955), fT3 (r=0.752) and the estimated volume of the thyroid gland (r=0.446). The mean value of the estimated mean volume correlates moderately, inversely proportionally, with both fT3 (r= -0.341) and fT4 (r= -0.28), but does not correlate with the mean TSH value. In relation to the JIA characteristics, we identified a significant, inversely proportional correlation between absolute and categorical (per%) values of TSH and age categories, age at research enrollment, disease duration.

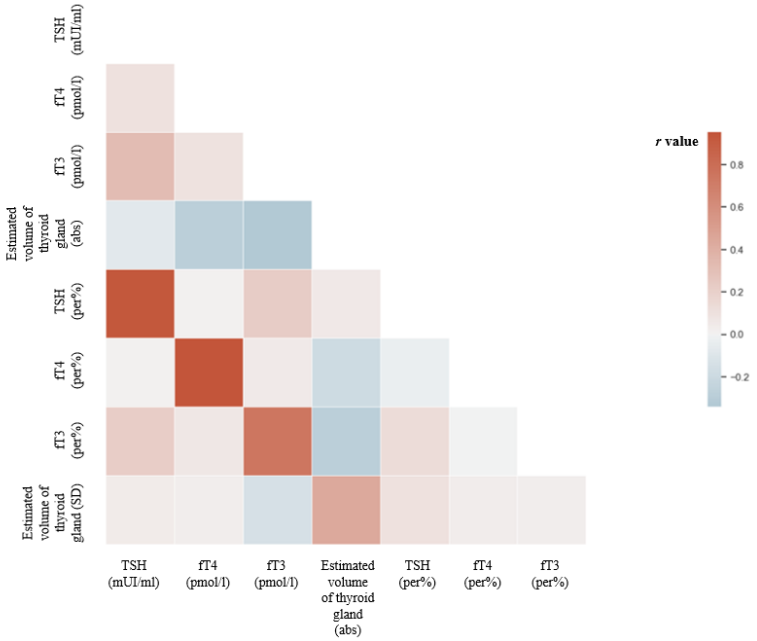


Figure 7. **Graphic representation of the correlations between the absolute and categorical values of the functional and structural parameters of the thyroid gland in children with JIA**

Also, a moderately significant correlation, indirectly proportional, was demonstrated between absolute and categorical values (per%) of TSH and anthropometric indicators - mass, waist, as well as BMI at research enrollment. Note the strong direct proportional correlation between the categorical values (per%) of TSH and thyroid hormones with the disease activity index DAS 28, respectively being r=0.936 between TSH per% and DAS 28; r=0.955 between fT4 per% and DAS 28 and respectively r=0.752 between fT4 per% and DAS 28. Correlations between thyroid parameters and JIA indices were also different according to gender.

In the **"Synthesis of research" chapter**, we included a comparative analysis of our own results with those from the specialized literature and the guidelines related to the pathology addressed, highlighting the similarities and differences found. The complex analysis allowed us to develop the diagnostic algorithm (figure 8) of endocrine comorbidities in JIA aimed at improving the management of these patients.

Regarding to growth evaluation and monitoring, we note that the data in the literature present similar studies, which correlate these cases with the long period until the diagnosis is established, respectively an intensely expressed inflammatory process, which affects the growth plate [10]. Anthropometric measurements are reliable, low-cost, non-invasive and can be performed without high-tech equipment by personnel with minimal training[13]. The data obtained by us are also comparable with similar studies published in recent years. Thus, the study by Mondal et al. (2014) report that comparative analysis between JIA onset subtypes

showed significant differences in assessment of height (p=0.011), weight (p=0.005) and growth velocity (p=0.005), but not in body mass index [28, 30].

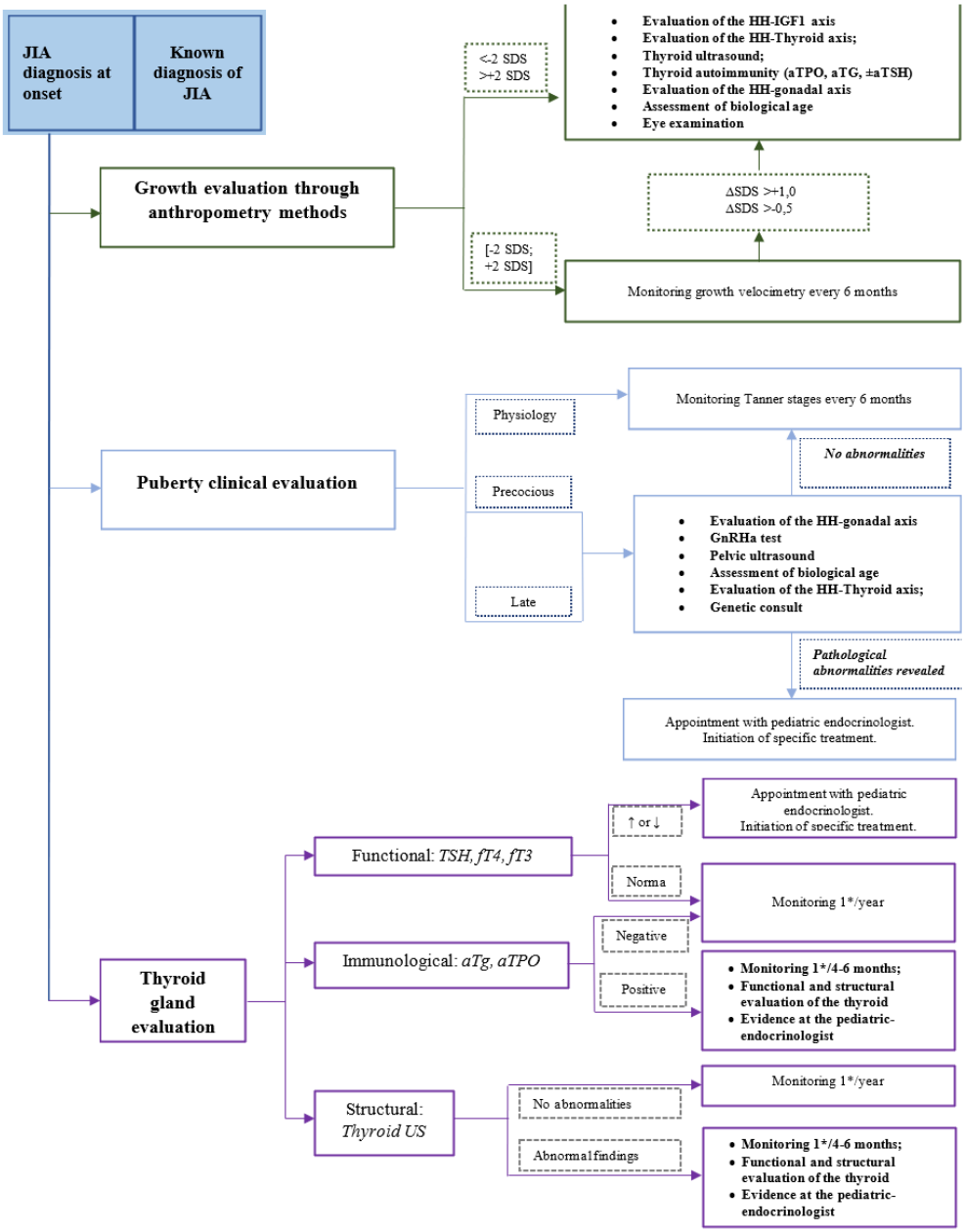


Figure 8. **Diagnosis and management of endocrine comorbidities in JIA**

Moreover, the addition of clinical variables with laboratory research could have accelerated the promptness in establishing the diagnosis and the appreciation of individualized treatment tactics for children with JIA. Currently, the most effective way to reduce growth retardation in children with chronic inflammation is to control the inflammation with currently available drugs while reducing the duration of treatment as well as the dose. It is also important to have an early diagnosis, as attempts to salvage bone growth in children must begin before epiphyseal closure [12]. In the diagnostic approach of the young and/or slow-growing child, serum IGF-1 is considered one of the essential components of the laboratory screening procedure, as the first indication for growth hormone deficiency [16].

Regarding to pubertal evaluation and monitoring, we have highlighted the assessment of pubertal status (by examining breast stage in girls and testicular volume in boys) should be incorporated into the routine care of adolescents with chronic disease [13, 31]. Similar to the data in our own study, some studies show the stages of puberty according to the age at which they were assessed. Hormonal changes have been associated with disease exacerbations and/or increased JIA activity [13, 32, 33]. According to the data from our study, not only the evaluation of the hormones of the H-H-G axis is important, but also their correct interpretation based on age and sex percentiles [34] . Further studies are needed to determine the exact mechanisms by which hypogonadism is related to JIA and the long-term effects of testosterone replacement on the prognosis of these patients. Screening by assessing PRL levels is suggested in children and adolescents with short stature and/or obesity, as they are at greater risk. Also, PRL is a neuroendocrine hormone that can cause inflammation [35, 36]. Targeted identification of hyperprolactinemia is important for appropriate management and follow-up.

Screening for thyroid comorbidities in patients with JIA is important for improving our understanding of the comorbidity associated with chronic autoimmune diseases [20, 21, 28]. Because thyroid disease is common and may present with nonspecific symptoms, thyroid function tests are one of the most requested laboratory investigations [37]. The frequency of thyroid dysfunction in children with chronic conditions is underestimated, mainly due to misinterpretation of results, values not being adjusted for age and sex. By ensuring optimal standards of care, all children with JIA would have the right to equitable access to the highest quality clinical care, based on current evidence and delivered by adequately resourced and experienced multidisciplinary teams.

GENERAL CONCLUSIONS

1. Autoimmune inflammatory processes in JIA are reflected on the hypothalamic-pituitary-GH/IGF axis in children by finding the incidence of growth retardation in 15.46% of cases (95% CI: 8.26%, 22.65%), malnutrition in 20.62% of cases (95% CI: 12.56%, 28.66%), and overweight in 9.28% of cases. Depending on the age, we found a lower mean value of DS for waist circumference in prepubertal children, and during puberty, the DS value for weight and BMI was more affected. Depending on sex, we observed more pronounced growth impairment in boys than in girls for height, weight, and BMI. Depending on the developmental stages according to Tanner, significant differences were found in the growth pattern. We observed the impairment of growth velocity in children with disease onset before 3 years of age ($p<0.05$ at 6, 12, and 18 months), with a long disease duration ($p<0.05$ at enrollment in the study), with systemic onset of JIA ($p<0.01$ vs. seronegative polyarticular onset, and $p<0.001$ vs. oligoarthritis), and with elevated proinflammatory activity ($p<0.01$ for DAS28 score). However, we note an improvement in growth towards 18 months of follow-up, indicating good disease control that allows the growth process to recover ($p<0.05$).
2. The impairment of the hypothalamic-pituitary-IGF1 axis was revealed through specific abnormalities of peripheral resistance – low serum values of IGF1 (41.24% of cases) and increased values of IGF-BP3 (43.30% of cases). Statistically, we found an intensely positive correlation between these two variables ($r=0.84$). Children with JIA do not present data of autoimmune involvement at the pituitary level. Active screening of growth disorders by serum evaluation of IGF1 and IGF-BP3 may contribute to the early detection of hypothalamic-pituitary-IGF1 axis damage and allow the optimization of therapeutic management.
3. Autoimmune inflammatory processes in JIA affecting the hypothalamic-pituitary-gonadal axis in children were clinically detected by late onset of puberty (24.44% of cases), slow progressive evolution (26.67% of cases), or stagnant puberty (8.89% of cases). By gender, the late onset of puberty was found more frequently in boys compared to girls. Six out of ten girls with JIA reported at least one menstrual cycle irregularity and menstrual dysfunction. The

pubertal evaluation over time at 6, 12, and 18 months denotes persistent differences between the sexes, but with positive dynamics of the Tanner stage in boys. Thus, there was a statistically significant reduction in the difference of average scores ($p<0.001$ at 6 months and 12 months, and $p<0.01$ at 18 months). Depending on the distribution by gender and form of disease onset, boys showed a lower score compared to girls only in the oligoarticular ($p<0.05$) and polyarticular seronegative ($p<0.05$) disease onset subtypes. The clinical assessment of pubarche and adrenarche, as well as the score obtained for the Tanner stage assessment, strongly correlate directly with age, age at disease onset, duration of disease evolution, and anthropometric indices, while an inversely proportional correlation was found with PtGA and PhGA.

4. Impairment of the hypothalamic-pituitary-gonadal axis was manifested as compromised serum testosterone levels in boys, with reduced levels of SH-BG observed in 11.5% of girls and 10.5% of boys. JIA activity indices (ESR and CRP), as well as disease activity scores (DAS28 and JADAS71), inversely correlated with pituitary and peripheral gonadal tropic hormone assays only in the boys' assessment group. Asymptomatic hyperprolactinemia was identified in 9.28% of cases. Depending on the subtype of JIA onset, hyperprolactinaemic states were predominant in systemic JIA forms. Depending on the age at disease onset, the mean serum prolactin value was found to be highest in subjects with disease onset before 3 years of age ($p=0.002$), followed by those with onset between 3 and 10 years of age ($p=0.04$). Hyperprolactinemia correlates with disease duration, with gender differences.

5. Autoimmune inflammatory processes in JIA affecting the hypothalamic-pituitary-thyroid axis in children were clinically manifested by palmar erythema, hyperperspiration, thermogenesis disorders, and palpitations. The clinical picture of thyroid dysfunction does not vary by age, sex, disease onset, treatment option, or patient response. On ultrasonographic examination, structural changes in the thyroid were identified. In 13.40% of cases, at least one ultrasound structural change was recorded, and in 11.34% of cases, two or more structural changes were observed.

6. In children with JIA, through the evaluation of thyroid function tests, we identified subclinical hypothyroidism in 15.38% of cases among prepubertal children and in 6.66% of cases among pubertal children. Serum concentrations of thyroid hormones and TSH vary significantly between individuals, and the application of age- and sex-specific reference ranges (percentiles or standard deviations) for thyroid function tests is indispensable. We demonstrated that there is a highly significant, directly proportional correlation between the absolute and categorical (percentile) values of thyroid function tests (TSH: $r=0.936$; fT4: $r=0.955$; fT3: $r=0.752$) and the estimated volume of the thyroid gland ($r=0.446$). Regarding the characteristics of JIA, we identified a significant inverse correlation between the absolute and categorical (percentile) values of TSH and the age categories, age at enrollment in the study, and disease duration. Additionally, a moderately significant, inversely proportional correlation was demonstrated between the absolute and categorical (percentile) values of TSH and anthropometric indicators—weight, waist circumference, as well as BMI at enrollment in the study. It is also noteworthy that there is a strong directly proportional correlation between the categorical (percentile) values of TSH and thyroid hormones with the disease activity index DAS 28 ($r=0.936$ between TSH per% and DAS 28; $r=0.955$ between fT4 per% and DAS 28; and, respectively, $r=0.752$ between fT4 per% and DAS 28).

PRACTICAL RECOMMENDATIONS:

1. Apply the algorithm developed based on this study for the active screening of endocrine complications and comorbidities in patients with JIA to improve diagnosis, enhance treatment response and outcomes, and thus ensure timely access to quality care.

2. At the level of primary care: (a) Evaluate anthropometric indices, nutritional status, and pubertal development systematically every 6 months in children with JIA; (b) Upon identifying growth and/or pubertal disorders, patients with JIA should be referred to a specialist (pediatric rheumatologist, pediatric endocrinologist) for confirmation or exclusion of complications related to the underlying disease.
3. At the level of specialized care: (a) Evaluate hormonal profiles (hypothalamic-pituitary-peripheral axes) according to the patient's age and sex; (b) Interpret the results of the requested laboratory tests according to reference values based on percentiles or standard deviations appropriate for the patient's age and sex.
4. At the research level, continue the study of autoimmune pathologies with molecular genetic research to identify risk factors for the development of long-term complications based on genetic predisposition and proinflammatory activity triggered in juvenile idiopathic arthritis.

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LIST OF SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

of Mrs. EREMCIUC Rodica, PhD graduate, Department of Pediatrics, made for her doctoral thesis in medical sciences on the theme "Hypothalamic-pituitary axis in juvenile idiopathic arthritis in children", doctoral program 322.01 Pediatrics and Neonatology, "Nicolae Testemițanu" State University of Medicine and Pharmacy from the Republic of Moldova

Scientifical publications

- **Chapter in monography:**

1. **Eremciuc R**. Dereglările sistemului endocrin în afecțiunile reumatice. În *Reumatologie pediatrică.* Revenco N., Chișinău: Tipografia ”Reclama”; 2018, pp. 61-83 p. ISBN 978-9975-58-147-9.

- **Chapter in textbook:**

2. Revenco N., **Eremciuc R.** Patologia sistemului endocrin. În *Pediatrie ediția a II-a*. Revenco N., Chișinău: Tipografia ”Reclama”; 2020, pp. 955-986. ISBN 978-9975-58-259-9.

- **Chapter in course support:**

3. **Eremciuc R.** Creșterea și dezvoltarea copiilor. În *Nursing pediatric.* Revenco N, Chișinău: Tipografia ”Taicom”; 2021, pp. 53-95. ISBN 978-9975-58-257-5.

- **Articles in scientific journals abroad**

✓ **articles in ISI, SCOPUS and other international databases**

4. **Eremciuc R.**, Gaidarji O., Nikitina I., Revenco N. Thyroid Hormones Interpretation in Children with Juvenile Idiopathic Arthritis. In: *6th International Conference on Nanotechnologies and Biomedical Engineering IFMBE Proceedings Springer, Cham.* 2023; 6 (91): 487-495. ISSN 16800737 ; DOI: 10.1007/978-3-031-42775-6_52
5. Revenco N., Cracea A., **Eremciuc R.**, et al. The clinical and paraclinical efficacy of tocilizumab in juvenile idiopathic arthritis. In: Archives of the Balkan Medical Union. 2021, 56(2):185-192. ISSN 1584-9244. https://doi.org/10.31688/ABMU.2021.56.2.07.
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- **Articles in accredited national scientific journals:**

✓ **articles in category B journals**

7. Revenco N., **Eremciuc R.**, Afectarea hepatică în maladiile autoimune sistemice la copii (revista literaturii), În: *Sănătatea publică, economie și management în medicină*. 2017 4(74): 122-126. ISSN 1729-8687
8. **Eremciuc R.**, Revenco N. Particularitățile creșterii la copiii de vârstă prepubertară cu artrită juvenilă idiopatică. În: *Buletin de perinatologie*. 2020, 3(88): 60-64. ISSN 1810-5289
9. Revenco N., Cracea A., **Eremciuc R.**, et al. Tratamentul cu preparatul Tocilizumab la pacienții cu artrită juvenilă idiopatică – eficiența clinică și paraclinică. În: *Buletin de perinatologie*. 2021, 2(91): 6-10. ISSN 1810-5289.

- **Articles in international scientific collections:**

10. **Eremciuc R.**, Revenco N., Cracea A., et al. Corelațiile dintre volumul estimat al glandei tiroide și indicii artritei juvenile idiopatice. În: *Concepte actuale în practica*

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- **Articles in the proceedings of scientific conferences:**

  ✓ **national with international participation**

  11. **Eremciuc R.**, Revenco N. Height velocity and pubertal development in patients with juvenile idiopathic arthritis. În: *Materialele Conferinței naționale cu participare internațională Bienala Chișinău-Sibiu "Managementul interdisciplinar al copilului", ediția a V-a.* Chișinău, Republica Moldova, 2022; pp.24-31. ISBN 978-9975-58-274-2.
  12. Revenco N., Cracea A., **Eremciuc R.**, et al. Eficiența clinică și paraclinică a preparatului Golimumab în artrita juvenilă idiopatică. În: *Materialele Conferinței naționale cu participare internațională Bienala Chișinău-Sibiu "Managementul interdisciplinar al copilului", ediția a V-a.* Chișinău, Republica Moldova, 2022; pp.11-16. ISBN 978-9975-58-274-2.
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  ✓ **national**

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- **Summaries/abstracts/theses in the works of national and international scientific conferences**

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- **Invention patents, patents, registration certificates, materials for invention salons**

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58. Revenco N., **Eremciuc R.** Aplicarea metodei de evaluare și interpretare a volumului glandei tiroide estimat ecografic la copii. Certificat de inovator RM MS nr. 6175, 15.01.2024

- **Participation with communications at scientific forums:**

✓ **international**

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✓ **national**

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95. **Eremciuc R.** Hormonal predictors in juvenile idiopathic arthritis. *29th European Paediatric Rheumatology Congress*, 28.09-01.10.2023, Rotterdam, Netherlands.

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EREMCIUC Rodica

THE HYPOTHALAMIC-PITUITARY AXIS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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