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Ph.D. Thesis - Summary

GROWTH DISORDERS IN CHILDREN LIVING IN IODINE DEFICIENCY AREAS IN SIBIU COUNTY

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THESIS CONTENT

INTRODUCTION

Growth and developmental disorders in children are one of the most common situations in which the parent seeks specialized medical advice.

Due to the multiple and complex metabolic roles, thyroid hormones intervene in the growth and development of the human body starting from the intrauterine period, later postnatal, so that any dysfunction of the thyroid gland can lead to notable consequences that can occur in the newborn or child.

According to World Health Organization (WHO), more than 2 million people in Europe are affected by iodine deficiency (91).

Iodine deficiency is a major public health problem, especially for newborns, children, and adolescents, being one of the most important causes of preventable mental and somatic disorders in childhood.

MOTIVATION OF THE THESIS

Population health is considered an important part of the sustainable development process, being the main vehicle for economic and social progress. It has been estimated that at least a quarter of the global population's health problems are attributed to environmental factors (131).

Iodine is a microelement found in nature, having as an essential role, the participation in all the stages of formation of thyroid hormones, thus being involved in all their actions. The decisive stage of brain development in the human species is represented by the fetal period and the first three years postnatal. An eventual iodine deficiency that appeared in this critical period, will lead to alterations, often irreversible, in the development of the nervous system and the brain, the clinical consequence being the appearance of mental retardation (199).

World statistics show that 1.6 billion people worldwide are at risk of being affected by iodine deficiency, with iodine deficiency disorders affecting approximately 50 million children worldwide, and 100000 children with cretinism are born each year (174).

Growth disorders in children, with an emphasis in this paper on the presence of small stature, can have multiple pathological endocrine or non-endocrine causes. Among the endocrine causes, it is considered an important aspect to monitor the occurrence of growth retardation following a thyroid dysfunction, namely thyroid failure, having as a triggering factor iodine deficiency.

RESEARCH OBJECTIVES

Iodine deficiency can lead to dysfunction of the thyroid gland which results in its secretory insufficiency, namely hypothyroidism. At present, research in the field has shown that we continue to face problems related to iodine deficiency in certain areas and geographical regions around the world and our country (39,146,163).

The first objective of our research was to evaluate, from an auxological point of view, the school population aged between 6 and 14, students of middle schools in several localities of Sibiu County.

The second objective of this study refers to children detected with growth retardation in the group of children initially measured, and we wanted to investigate them from a clinical, paraclinical, and imaging point of view.

The final objective of the research was the elaboration of a diagnostic algorithm regarding the detection of the causes of small stature and the elaboration of a brochure, which would later be distributed to the family doctors and the medical staff within the school medicine office.

At the same time, we wanted to develop an electronic application that can be accessed from any electronic device with an internet connection. The role of this application will be to help doctors, but also parents, quantify in advance any problems related to the growth and development of children.

ETHICAL CONSIDERATIONS

The entire study was carried out with the consent of the Sibiu County School Inspectorate, school principals, and teachers of institutions where we conducted the research, and by acknowledging and signing the Informed Consent Form by the parents of children included in this project, they have the right to withdraw their child at any time they wish, from participating in research.

The research was carried out in full compliance with the rules of ethics and medical ethics. All the forms regarding the agreements of the institutions involved, respectively the informed consent of the parents are attached in the annexes of the paper.

PART I

CURRENT STATE OF KNOWLEDGE

I.1. IODINE DEFICIENCY IN NATURE

I.1.1. General notions

Iodine is a trace element found everywhere in nature, in a considerable amount at soil level, between 50 and 9000 µg/kg, but also in sea and ocean water; atmospheric air has an iodine content of 0.5 µg/L (199).

The most important sources of iodine in human nutrition are shellfish and sea fish. Meat, eggs, milk, and dairy products have a variable iodine content, depending on the amount of iodine in the feed, and the iodine content of the feed, as well as cereals and vegetables, depends on the iodine concentration of the soil in which they grew (170).

The only proven role of this trace element in the human body is its contribution to all stages of thyroid hormone biosynthesis.

I.1.2. Epidemiology of iodine deficiency

By 1990 a small number of countries, such as Switzerland, the United States, Canada, several Scandinavian countries, and some regions of Australia, received a sufficient supply of iodine, making iodine deficiency a major global public health problem that needed to be combated (127).

In 1993, the WHO estimated that 97 million people in Europe were suffering from iodine deficiency (10).

In Romania, a national strategy on the eradication of iodine deficiency disorders has been developed, called "National Strategy for the Elimination of Iodine Deficiency Disorders by Universal Iodization of Salt for Direct Human Consumption and Bread Manufacturing for 2004-2012", this pathology being considered at that time, one of the major public health problems in our country (174).

I.1.3. Patophysiology

The most important source of iodine in the diet remains iodized salt, iodine being rapidly absorbed, in a percentage of over 90%, in the stomach and duodenum, and eliminated from the circulation through the thyroid and kidney, thyroid clearance being variable depending on the iodine intake (4,118,202).

Due to the hypothalamic-pituitary-thyroid axis that reacts to low iodine intake through a series of pathophysiological changes, increased TSH secretion causes at the morphological level the appearance of thyroid hypertrophy, so affected individuals will typically have goiter, hypothyroidism in some cases, and newborns and children, mental and somatic disorders can occur, especially in severe cases, up to endemic cretinism (60).

In 2007, international organizations represented by WHO, UNICEF, and ICCIDD published certain recommendations on iodine intake by setting appropriate daily doses for different age groups such as 90 µg/day in children aged 0-5 years; 120 µg/day in children between 6-12 years; 150 µg/day in adults and children over 12 years (186).

I.1.4. Clinical findings of insufficient iodine intake

The spectrum of clinical manifestations due to insufficient iodine intake is varied, depending on the age group and the period in which this deficiency occurs and manifests itself: in the fetal period can lead to miscarriage, birth defects, stillbirth; in the newborn causes the appearance of a goiter associated with hypothyroidism and small stature, endemic cretinism; in children and adolescents may appear goiter associated with thyroid failure, delayed somatic development with or without impairment of the intellect; and in adults, the appearance of a goiter associated with hypothyroidism and impaired intellect in certain cases is also noted (186).

I.1.5. Evaluation of iodinated status

There are four essential methods for determining iodine status, namely: urinary iodine, thyroid volume (Tvol), serum TG and serum TSH (203).

I.1.5.1. Urinary iodine

Determining the concentration of urinary iodine in a urine sample is the first recommendation to monitor the iodine status of an individual (186).

Depending on the median urinary iodine determined in school-age children, the WHO formulated a classification of iodine intake in: optimal (100-199 µg/L), mild deficiency (50-99 µg/L), moderate deficiency (20-49 µg/L), severe deficiency (<20 µg/L) and excess iodine (>300 µg/L) (186).

I.1.5.2. Thyroid volume

There are two methods for measuring Tvol: inspection of the anterior cervical region accompanied by palpation of the thyroid gland, respectively thyroid ultrasonography.

According to the WHO, hypertrophy of the thyroid gland (goiter) is classified in 3 degrees as follows: grade 0 - thyroid that is not visible at the neck and is not felt on palpation; grade 1 - the thyroid can be highlighted by palpation, but without being visible in the anterior cervical region with the neck in a normal position; grade 2 - thyroid visible and palpable obviously in the neck, which is in a normal position (189).

Numerous studies have been performed to determine Tvol in children, by age and sex; for the age group 6-15 years the most representative being the ThyroMobil project carried out in Europe, following which certain reference tables could be compiled (10,45,190).

I.1.5.3. TSH, FT4

Thyroid hormone dosages, respectively the determination of TSH and free thyroxine (FT4), are not specific indicators of iodine status; usually in people with iodine deficiency, TSH may increase and FT4 may decrease, but there are many situations in which they remain within the normal reference range (204).

I.1.5.4. Serum thyroglobulin

TG is the most important protein that is part of the thyroid gland, synthesized exclusively at its level, and which is a more sensitive indicator in assessing the status of iodine, compared to TSH and FT4 (201). In iodine-deficient areas, serum TG increases due to excessive stimulation by TSH, following thyroid gland hypertrophy (86).

I.1.6 Treatment and prevention of iodine deficiency

The most important strategy for the prevention of endocrine pathology related to iodine deficiency, adopted worldwide, is the universal iodization of salt for human consumption; a strategy that proved to be extremely effective, on 2007 over 90% of the population consumed iodized salt (186).

Adjunct to the primary strategy for the prevention of iodine deficiency disorders, iodine can also be administered in the form of tablets containing potassium iodide, iodine-containing oil, iodized water (155).

I.2. GROWTH DISORDERS

I.2.1. Physiological growth

The physiological growth of a child is represented by the ensemble and the progression of the changes at the level of the anthropometric indices represented by: height, body mass, cranial perimeter, wingspan; compatible with the standards set for a given population. The progression of children's growth and development is interpreted and established according to the genetic potential of each child (95).

A height beyond the limits corresponding to the age and sex of the child in question, according to national standards, available for each state, or international; whether it is too small or, on the contrary, too great, it can be the alarm signal of a condition which, discovered in time, can benefit from an appropriate treatment (19).

GH formed and released from the anterior pituitary gland is the main promoter of growth in most organs and tissues of the human body (24). Along with GH, thyroid hormones also play an important role in the ossification processes of the human body, they are essential in the development and maintenance of bone mass, in linear growth, but also the effective healing of possible fractures (70).

Thyroid failure in childhood, which may be a consequence of iodine deficiency during this period, can stop growth by delaying bone formation and mineralization, a proper hormone replacement can effectively combat all these skeletal changes (142).

I.2.2. Growth assessment indicators

In assessing the growth and development of children, a series of parameters are used, the most important of which are the anthropometric ones represented by height and body mass, comparing the results with those of a reference population (healthy children of the same age and sex) recommended by WHO or the Center for Disease Prevention and Control (CDC), these are represented by: height-related body mass and age-related height (173).

In medical practice, if we refer to the short stature, we can say that any child with a height lower than -2DS (standard deviations) compared to the average for the age group, race, and sex to which he belongs must be suspected of suffering from a growth disorder, the degree of suspicion increasing inversely proportional to the child's height (19,23,34,200).

Along with height, another important parameter is the determination of body mass, then the calculation of BMI (body mass index); and the staging of children's nutritional status will be based on BMI percentages, according to the WHO 2010 classification (187).

I.2.3. Pathological growth

Short stature is defined as a height of more than two standard deviations below the average corresponding to a certain age group and sex, or as a height of fewer than three percentiles compared to the average of that age (14).

The causes that lead to this change are multiple, and according to the European Society of Pediatric Endocrinology (ESPE), they fall into three broad categories, namely: primary causes, secondary causes, and idiopathic short stature (122,194).

I.2.4. Evaluation of short stature

The first step in assessing short stature is to perform a detailed history of the child and his parents and complete medical history. Following the anamnesis, a complete objective clinical examination must be performed by the attending physician, with an emphasis on the presence or absence of any type of dysmorphic change (35).

After obtaining, by repeated and as accurate measurements as possible, the child's height and body mass, these will be interpreted by comparing them with the corresponding values in the growth nomograms, specific to the patient's population, nomograms that are available for several states of the world (14).

The next step in assessing short children is to perform paraclinical examinations to rule out or confirm a specific cause. The main examinations are represented by: general paraclinical examinations (hemoleukogram, inflammatory markers, renal and hepatic function), screening for celiac disease, hormonal determinations, such as thyroid hormonal dosages, and those on the somatotropic axis (30).

I.2.5 Endocrine causes of short stature

The most important and most common endocrine causes in the medical practice of stature hypotrophy are represented by GH deficiency and its variants, congenital or juvenile hypothyroidism, hypercorticism, and puberty or early sexualization.

PART II

PERSONAL CONTRIBUTION

II.1. STUDY NO. 1: DETERMINATION OF AUXOLOGICAL PARAMETERS OF CHILDREN FROM DIFFERENT AREAS OF SIBIU COUNTY

II.1.1. Introduction

Evaluation of children’s auxological parameters, respectively by periodically determining their height and body mass, is an important factor in maintaining the health of a population, by detecting as early as possible any growth and development disorders that may occur, and subsequently by treating them accordingly.

II.1.2. Materials and methods

The target population is represented by children aged between 6 and 14, from schools located in Sibiu County. We determined the height and body mass of 1946 children, 52.16% being female (N=1015) and 47.84% male (N=931), from seven localities of Sibiu County, which we have divided into two distinct geographical areas: the submontane area (Jina, Poiana Sibiului, Rîul Sadului, and Gura Rîului) and the hilly area (Cisnădie, Sadu, Șeica Mare).

We visited the seven localities mentioned above, between October 2013 and December 2013, and we performed specific measurements to determine the auxological parameters, represented by height and body mass, of students of grades 0-VIII.

The methods used to measure children's anthropometric indices were as follows: determination of height using a thaliometer with a slider fixed to the wall; determination of body mass using a correctly calibrated scale; assessment of weight status by BMI calculation using the following formula:

$$BMI=\text{body mass(kg)}/\text{height}^2\text{(m)}$$

The measurements were performed with an accuracy of 0.1 cm for the height and 0.1 kg for body weight, all children being dressed in light clothes, without shoes, and in rooms with a normal temperature.

The children were divided according to sex and age categories as follows: category 6 years (72 ÷ 83 months); 7 years (84 ÷ 95 months); 8 years (96 ÷ 107 months); 9 years (108 ÷ 119 months); 10 years (120 ÷ 131 months); 11 years (132 ÷ 143 months); 12 years (144 ÷ 155 months); 13 years (156 ÷ 167 months); 14 years (168 ÷ 179 months).

In evaluating and comparing the indices obtained, for height we used the growth nomograms specific to Romania (Pașcanu 2016), those published by Prader (1989), as well as the international ones accepted and published by WHO (2007); and for weight status we used the calculation of BMI and its reporting to internationally accepted standards and published by the WHO (2007), as well as to the new national standards published in the same study conducted for our country in 2016 (125,135,187).

The data obtained were initially processed with the help of the Excel program version 2016 and later the statistical analysis was performed with the help of the Minitab program version 2018.

II.1.3 Results

The group of children evaluated includes 1946 schoolchildren, of which a number of 1015 were female (52.16%) and a number of 931 were male (47.84%), with a total of 403 children (20.71%) from the urban area, of which 213 girls and 190 boys; respectively a total of 1543 children (79.29%) from rural areas, of which 802 girls and 741 boys.

Regarding the geographical areas, from the submontane area came a number of 1035 children (53.19%) of which 538 girls and 497 boys, and from the hilly area came a number of 911 children (46.81%) of which 477 girls and 434 boys.

Comparing the values obtained for height, body mass and BMI, with the three references studied (Romania, WHO, Prader), we obtained statistically significant differences ($p<0.05$) for each of the three parameters, for both sexes.

II.1.4. Discussions

The most useful tool for determining the health of a population is represented by evaluation by determining the anthropometric indices, of which the most important being the height and body mass of individuals in a community (177).

Therefore, we evaluated the anthropometric indices of children from schools located in different geographical areas of Sibiu County, hilly and submontane, comparing the results obtained with the reference ones for the Romanian population, with the WHO nomograms accepted internationally, as well as with the references established by Prader in 1989 for Swiss children.

We noticed that the results of the averages obtained, for males, are below the values published for Romania for all age categories, as well as below those published by Prader for the age categories 6,7,8,9,10 years; and above the values obtained by Prader for the age groups 11,12,13 and 14 years; and above the values published by the WHO at all ages (6-14 years).

Regarding the body mass and the BMI of the evaluated boys, the differences are bigger between the averages obtained and those published in Romania and WHO, in all age categories, keeping the same trend as in the case of heights, the evaluated children having averages of body mass, respectively of the BMI, lower than those published for Romanian boys, but higher than those recognized internationally by the WHO.

For the female sex, comparing the results obtained for height, with those published in 2016 for our country, we observe, at all age categories, lower average values compared to the references for Romania. Compared to Prader's references to Switzerland, the girls evaluated had averages of lower heights in the age groups 6,7 and 8 years; and higher height averages in the 9 to 14 age group.

Analyzing the average body mass of the evaluated girls compared to the standards accepted for Romania, lower averages are observed compared to the reference ones for our country. Compared to WHO standards, the average body mass of the evaluated girls has a higher value for all age groups (6-9 years).

Regarding the BMI values obtained in the evaluated girls, the differences between the averages, both with those published for Romania and with those published by the WHO, are smaller, in a negative sense compared to the girls in our country and in a positive sense compared to the standards. WHO.

Studies on the anthropometric indices of children in our country have been conducted over time, studies that have shown an acceleration of the phenomenon of increasing the averages of auxological indices during 1950-1978, especially at puberty, because between 1978 and 1985 to observe a plateau phase (109).

II.1.4. Conclusions

1. The target population was 1946 children, of whom 52.16% (N=1015) were female and 47.84% (N=931) were male, between 6 and 14 years of age.
2. 79.29% (N=1543) of children came from rural areas, and 20.71% (N= 403) from urban areas, 53.19% (N=1035) being residents of localities in the submontane area and 46, 81% (N=911) coming from localities of the hilly area.
3. The minimum height measured for boys was 111.8 cm and for girls it was 105.6 cm, while the maximum height for males was 185.3 cm and for females 178.9 cm.
4. Regarding body weight, we obtained a minimum value of 17.6 kg in males, and a maximum value of 72.2 kg, and in girls, the minimum value of body mass was 15.2 kg, and the maximum of 72.1 kg.
5. The minimum BMI obtained in males was 13 kg/m2, the maximum being 23.6 kg/m2; for females we calculated a minimum BMI of 12.4 kg/m2, and a maximum of 26 kg/m2.
6. We detected statistically significant differences (p value<0.05) between our data compared to the references for Romania, with those published by Prader and by the WHO, both for height, body mass, and BMI.
7. The measured children had on average higher heights than the Prader and WHO nomograms, and lower compared to the references for Romania.
8. The measured children had on average a body mass and a BMI higher than the WHO standards but lower than those proposed for our country.
9. Periodic assessment of children's growth and development by determining anthropometric indices is an essential component for detecting growth disorders that may occur during childhood.

II.2. STUDY NO. 2: PREVALENCE OF SHORT STATURE AND EVALUATION OF WEIGHT STATUS IN A LOT OF CHILDREN FROM DIFFERENT AREAS OF SIBIU COUNTY

II.2.1 Introduction

Short stature is one of the most common situations in which the parent seeks specialized medical advice. It is defined as a heightt less than 2DS or below the 3rd percentile, compared to the average height for the same age and sex. The initial assessment of a child with short stature suspicion includes a history and a thorough clinical examination, by making serial measurements of height and body mass, determining growth rate, bone age and parental height (14).

II.2.2 Materials and methods

We evaluated by determining the height and body mass, then the BMI calculation, a number of 1946 children: 1015 girls and 931 boys, by specific measurement methods, between October 2013 and December 2013, residents of the two distinct geographical areas: submontane and hilly.

We used the growth nomograms used in current practice in Romania during the period in which we made the measurements (2013), namely those published by Prader in 1989 for the population of Switzerland, with which we determined children of short stature, this being defined as and a height equal to or less than 2DS compared to the average height for the same age and sex (214).

By calculating the BMI, we detected children with altered weight status, the underweight, overweight and obese; and with the help of nomograms provided by the WHO (2007), we interpreted the values obtained (187).

The data were initially processed in the Excel program version 2016, later, the statistical data processing was performed with the Minitab program version 2018.

II.2.3 Results

From the total of 1946 children evaluated, by comparing their heights with the reference ones in the growth nomograms established by Prader, we obtained a total of 1821 children

(93.58%) with a height above -2DS, and a total of 125 children (6.42%) of short stature, with a height lower than -2DS compared to the corresponding average for age and sex.

Among the children of short stature, 106 (84.80%) were male and the remaining 19 (15.20%) were female. The distribution of children by geographical area is shown in Table 2.3.1, together with the p-value obtained when applying the corresponding statistical test.

Tab. 2.3.1: Distribution of children (boys / girls) of small stature in the two geographical areas

	Children with short stature (H<-2DS)			
	Boys		**Girls**	
Hilly area	44	41.51%	7	36.84%
Submontane area	62	58.49%	12	63.16%
TOTAL	106		19	
p-value=0.70				

The p-value is calculated using the Chi-Square test

We determined by BMI calculation, the weight status of the 1946 schoolchildren included in the study, obtaining the following results: 1727 of the children (88.75%) fall to a normal weight corresponding to the age and sex category to which they belong, 57 (2.93%) have a BMI below the 5th percentile which falls into the category of underweight status, 106 (5.45%) were found to be overweight, and 56 (2.88%) had a BMI value over the 95th percentile, which places them in the obesity category.

Depending on the area of origin of the children, in table 2.3.2, we represented their weight status and their distribution according to sex and geographical area, and the p values obtained from the application of statistical tests in table 2.3.3.

Tab. 2.3.2: Distribution of children (boys / girls) according to weight status, in the two geographical areas

		Hilly area			Submontane area		
		No.	%	Total	No.	%	Total
Boys	Underweight (BMI<p5)	9	2.07%	434	17	3.42%	497
	Normai weight (p5≤BMI≤p85)	380	87.56%		444	89.34%	
	Overweight (p85<BMI≤p95)	32	7.37%		26	5.23%	
	Obese (BMI>p95)	13	3.00%		10	2.01%	
Girls	Underweight (BMI<p5)	16	3.36%	477	15	2.79%	538
	Normal weight (p5≤BMI≤p85)	410	85.95%		493	91.64%	
	Overweight (p85<BMI≤p95)	29	6.08%		19	3.53%	
	Obese (BMI>p95)	22	4.61%		11	2.04%	

Tab. 2.3.3: P values obtained in children (boys / girls) depending on weight status

Children's (boys/girls)	p-value
Underweight (BMI<p5)	0.19
Normal weight (p5≤BMI≤p85)	0.76
Overweight (p85<BMI≤p95)	0.58
Obese (BMI>p95)	0.44

The p-values were calculated with the Chi-Square Test

II.2.4 Discussions

The results of our study showed a prevalence of short stature, among schoolchildren aged between 6 and 14 years selected from schools in certain localities of Sibiu County, equal to 6.42%, most of them, namely 86.8%, being male. Analyzing the data obtained in relation to the geographical areas of residence, there is a higher prevalence, over 50%, of short stature in children living in localities in the submontane area, both females (63.16%) and sex male (58.49%), compared to those living in the hilly area.

Studies that have looked at the prevalence of short stature in children have been conducted in several countries around the world. A recent study published in June 2020, which assessed children aged 6-11 in Egypt, concluded that 17% of schoolchildren assessed were short (52). Using the growth nomograms proposed by the WHO, children and adolescents aged 5 to 17 years in Saudi Arabia were assessed, with the prevalence of short stature in boys being 12.1% compared to 10.9% in girls (112).

Similar results to those obtained by us, were published for a group of children aged 6 to 16 in Turkey, where a short stature prevalence of 5.7% was obtained, another study conducted in South Africa obtains a prevalence between 5% and 7% of short stature among children and adolescents aged between 5 and 20 years (67.85).

There has been a marked decrease in the prevalence of short stature in Asia from 49% in 1990 to 28% in 2010, while in Africa this incidence has stagnated since 1990, with recent studies showing a declining incidence of stature. globally so far, including in Africa (41).

In the United States, the largest study on physical development of children, by measuring their height and weight, found a percentage of 2.07% of American children with short stature (96,216).

Studies on the prevalence of obesity among children and adolescents have been conducted worldwide, but in our country, data on this issue are not sufficient, although several papers have been published in the literature on the weight status of children in Romania (13,32,133,178).

Compared to our results, significantly higher values of the incidence of overweight were detected and published by Barbu et al. in 2016 (13), for a group of 866 children aged between 6 and 18 years, where 31.6% of them were overweight and obese, and 11.4% were obese, compared to the criteria WHO.

Data published in 2009 for a large group of children, namely 7904, aged between 6 and 18, from 20 schools in Cluj-Napoca, also show a higher prevalence of overweight and obesity (178).

A meta-analysis published in 2016, which included studies conducted in different regions of Romania, between 2006 and 2015, and which followed a total of 25092 children aged 6 to 19 years, enrolled in 11 studies obtained, compared to the WHO criteria, a prevalence of underweight status of 5%, slightly higher than the value obtained by us of 2.92%, and a prevalence of overweight and obesity of 28.3%, significantly higher than our value of 8.33% (32).

Internationally, studies in multiple European countries show an increasing trend in the incidence rate of overweight and obesity in children (101). In Germany, data published over time revealed a 50% increase in overweight in children between 1985 and 1997, as well as a doubling of the obesity incidence rate in the last 3 years since the study was published, 2003-2006 (88,215).

Studies conducted in the UK show a tripling of the prevalence of overweight and obesity in the last 30 years, with an increase from 9.4% (in 1974) in male children to 22.8% (in 1998) and 32, 7% (in 2007); and for girls there was an increase from 12.1% (in 1974) to 26.3% (in 1998) and 29.2% (in 2007) (37).

In Central Europe, the prevalence of overweight and obesity among Polish schoolchildren increased from 6.5% (in 1971) to 15.5% (in 2000), a trend that is also observed by other Central and Eastern European countries (107).

II.2.5 Conclusions

1. Out of the total of 1946 children evaluated, 6.42% were detected with short stature, compared to the growth nomograms proposed by Prader.
2. Of the children found to be short, 84.8% were male and the remaining 15.2% were female.
3. The largest number of children detected with short stature belong to the age group 8 years, namely a number of 37 children (boys=32, girls=5).
4. A higher percentage of children of short stature come from the submontane area, compared to the hilly area, both boys (58.49%) and girls (63.16%).
5. According to WHO standards, 88.75% of the total children evaluated were normal-weight, 2.92% of the children were underweight, 8.33% were overweight and obese (5.45% and 2.88%, respectively), with a 1:1 boys/girls ratio.
6. The data obtained on the prevalence of obesity are below the average values in our country and in Europe.
7. There was a higher incidence of overweight and obesity in children in the hilly area than in the submontane area, both in females (10.37% in the hilly area and 7.24% in the submontane area) and males (10.69% in the hilly area, 5.57% in the submontane area).
8. Early detection of growth and developmental disorders in children is an important first step in maintaining the health of a population.

II.3. STUDY NO. 3: DETERMINATION OF URINARY IODINE IN CHILDREN WITH SHORT STATURE FROM DIFFERENT AREAS OF SIBIU COUNTY

II.3.1. Introduction

Iodine deficiency has been considered a public health problem that, according to recent studies, remains today one of the major causes of preventable mental retardation, affecting approximately 50 million children worldwide, annually 100,000 of children being diagnosed with endemic cretinism (121,171,185).

Urinary iodine remains today the most useful method of determining iodine status in an individual, and is the first recommendation in monitoring iodine nutrition (186).

Currently there are many methods for determining the concentration of iodine in urine, the most commonly used method being the Sandell-Kolthoff reaction, spectrophotometric, potentiometric methods but also by inductively coupled plasma mass spectrometry (ICP-MS) (99).

II.3.2. Materials and methods

Following the anthropometric determination and the processing of the obtained data, we found a number of 125 children, out of the 1946 evaluated, who showed short stature. Of these, a number of 112 children were included in this study, those from whom we obtained the prior consent of the parents, respectively were present at school on the day we collected the urine samples; 66 children from the submontane area, respectively 46 children from the hilly area.

To determine the urinary iodine, we collected urine samples in accordance with the rules for collecting biological samples, which were then transported in appropriate conditions, to be processed in the laboratory of the Faculty of Medicine and Pharmacy in Sibiu.

The laboratory analysis of the collected iodine was performed using an adapted titrimetric method, using the European Pharmacopoeia ed. 8.0. (16).

According to the median urinary iodine determined in school-age children, the WHO formulated a classification of iodine intake in: optimal, mild, moderate, severe or excess iodine deficiency (186).

The data obtained were initially processed in the Excel program version 2016, later the statistical interpretation was performed with the Minitab program version 2018.

II.3.3. Results

Of the 112 patients included in the study, 66 came from the submontane area (53 boys and 13 girls), respectively 46 patients came from localities located in the hilly area (39 boys and 7 girls).

Applying the descriptive statistics for the obtained data results an average of iodides for the hilly area of 112.74 µg/l, a median of 108.43 µg/l, For the submontane area, the values obtained are lower, with an average of 79.28 µg/l, a median of 77.34 µg/l.

By applying the non-parametric Mann-Whitney test to compare the values obtained for the two groups of subjects, coming from the specified geographical areas; we obtained a value p<0,0001, statistically significant.

The distribution of patients according to iodine nutrition, according to the WHO classification, by sex and area of origin, is represented in Table 3.3.1, together with the p values obtained from the application of the corresponding statistical tests.

Tab. 3.3.1: Distribution of patients according to iodine nutrition according to WHO classification, by sex and area of origin and p values obtained

	Hilly area				**Submontane area**				
	Boys		**Girls**		**Boys**		**Girls**		**p-value**
Iodine nutrition	No. patients	%	No. patients	%	No. patients	%	No. patients	%	
Severe deficit	0	0.00%	0	0.00%	2	3.77%	2	15.38%	-
Moderate deficit	2	5.13%	0	0.00%	11	20.75%	6	46.15%	1
Mild deficit	13	33.33%	2	28.57%	19	35.85%	5	38.46%	0.55
Optimal intake	23	58.97%	5	71.43%	21	39.62%	0	0.00%	**0.04**
More than adequate	1	2.56%	0	0.00%	0	0.00%	0	0.00%	-
Excess	0	0.00%	0	0.00%	0	0.00%	0	0.00%	-
	39		7		53		13		

The p values are calculated with the Chi-square test

II.3.4. Discussions

The results of this study showed a statistically significant difference ($p<0,0001$) between the values of urinary iodine concentration of the two groups of patients, aged between 6 and 12 years, residents of the two distinct geographical areas of Sibiu County.

We found a statistically significant difference (p value = 0.04) between the two areas, related to the number of children in whom the values of urinary iodine concentration were within the optimal range of iodine nutrition according to the WHO classification.

In the specialized literature were published multiple studies that followed the evolution of iodine deficiency in Sibiu County, in 2003 the data published by Dr. Stanciu and Prof. Totoianu (163) identified an average value of iodine in schoolchildren in Gura Rîului of 39.53 µg/l. Later in 2009, Dr. Rusu and Prof. Totoianu (146) published a similar study that showed an average value of iodides, in the same locality, of 45.69 µg/l.

Similar results to those obtained in this study were published in 2013 by Prof. Kun et al. (87), which determined the concentration of urinary iodine in 135 children aged between 6 and 14 years from three localities located in mountainous regions of Mureș County, obtaining an average value of iodides of 85.37 µg/l, with a median of 74.88 µg/l, a value similar to that found in our study.

In our country, studies on iodine deficiency were conducted in other geographical regions, such as the one published in 2015 by Dr. Nuță et al. (121), which determined the concentration of urinary iodine in a group of 241 children aged between 6 and 7 years, students of some schools in Bucharest. This study highlighted a percentage of 15% of children with iodine deficiency based on iodide values, which demonstrates the effectiveness of prophylactic methods established to combat iodine deficiency disorders.

Globally, the prevalence of low iodine intake in school-age children fell from 36.5% (285 million) in 2003, to 31.5% (266 million) in 2007 and to 29.8% (241 million) in 2011, with global progress from 2003 to 2011, which, however, depends heavily on each region (7).

II.3.5. Conclusions

1. We determined the concentration of urinary iodine in 112 children detected with short stature, with an average age of 9 years, 41.07% (N = 46) of them being residents of the hilly area and 58.93% (N = 66) belonging localities included in the submontane area.
2. The average value of iodide in patients in the hilly area is 112.74 µg/l with a median of 108.43 µg/l, statistically significant values ($p<0,0001$) higher than those obtained for the submontane area, in which the average iodide was 79.28 µg/l, with a median value of 77.34 µg/l.
3. Among male children, 33.46% of the hilly area had iodine deficiency compared to 60.37% of those living in the submontane area.
4. Among female children, 28.57% of the hilly area had iodine deficiency, values much lower than those obtained for girls in the submontane area, where all had values of urinary iodine concentration below 100 µg/l.
5. In a single male patient from the hilly area, we obtained a value of iodide higher than 200 µg/l, having an iodinated intake more than adequate.
6. Iodine deficiency remains a global public health problem, although the methods of prophylaxis adopted have significantly improved iodine deficiency disorders

II.4. STUDY NO. 4: INVESTIGATION OF SHORT STATURE IN CHILDREN FROM DIFFERENT AREAS OF SIBIU COUNTY

II.4.1. Introduction

Growth disorders in children, respectively short stature, is a fairly common reason for seeking consultation at the endocrinology office.

The causes of stature retardation are very varied, the most common being represented by normal variants of short stature, as well as other pathological causes of which an important role is played by endocrine causes (1,147).

Among the endocrine causes of short stature are: thyroid insufficiency (hypothyroidism), pituitary dysfunction that causes GH deficiency and Cushing's syndrome or excess glucocorticoids (1).

In 2016, a prevalence of short stature due to a certain pathological cause between 1.3% and 19.8% was reported, depending on the referral criteria of the patients (150).

II.4.2. Materials and methods

Children detected with short stature were evaluated clinically and paraclinically by performing endocrine clinical examination, specific hormonal determinations and thyroid ultrasound.

The collection of biological samples was carried out in appropriate conditions, subsequently their values being determined by specific laboratory methods.

Clinical examination by palpation of the thyroid gland was performed by the same examiner, and the degree of goiter in each patient was found. We used the goiter staging proposed by the WHO which classifies thyroid gland hypertrophy into three degrees (189).

For thyroid ultrasonography we used a Versana Premier ultrasound from General Electric Healthcare with a linear probe with a frequency of 6-10 MHz.

Thyroid volume (Tvol) was calculated according to the following calculation formula proposed by Brunn et al. (4) where: the volume of each thyroid lobe (mL) = anteroposterior diameter (cm) x mediolateral diameter (cm) x craniocaudal diameter (cm) x 0.479; and the total thyroid volume represents the sum of the volumes of both thyroid lobes (25,207). The calculated values were compared with those published in 1997 by Delange et al. (45), recognized by the WHO as reference values, but also with those obtained and published 7 years later in 2004 (207).

The data obtained were initially processed in the Excel program version 2016, later we performed the statistical analysis using the program Minitab version 2018.

II.4.3. Results

Out of the total of 56 children investigated, 24 children come from the hilly area, of which 18 (75%) were boys and 6 (25%) were girls; 32 children are residents of the localities located in the submontane area, of which a number of 24 (75%) boys and 8 (25%) girls.

In table 4.3.3 we represented the means and standard deviations of the evaluated parameters, within the two groups of subjects distributed according to the geographical area of origin, as well as the p values obtained after applying the appropriate statistical tests to compare the data.

Tab. 4.3.3: The values obtained by comparing the data according to the two geographical areas by applying the corresponding statistical tests

Parameters	Hilly area	Submontane area	p value
No. patients	24	32	-
Age [years]	8.17(±1.83)	8.53(±1.76)	0.38
Height [cm]	123.38(±9.08)	124.74(±9.14)	0.43
Body mass [kg]	23.79(±5.44)	24.44(±4.58)	0.4
BMI [kg/m^2]	15.42(±1.60)	15.58(±1.38)	0.73
Urinary iodine [µg/l]	**113.43(±31.18)**	**77.23(±42.57)**	**0.001**
TSH [µUI/ml]	**2.13(±0.89)**	**2.77(±0.91)**	**0.026**
FT4 [ng/dl]	**1.40(±0.23)**	**1.19(±0.23)**	**0.003**
GH [ng/ml]	2.27(±1.00)	2.17(±0.98)	0.987
IGF-1 [ng/ml]	190.90(±70.00)	181.20(±68.60)	0.71

Data are expressed as mean ± standard deviation.
The p values are obtained after applying the Mann-Whitney test

We performed the clinical examination of the subjects, with emphasis on the endocrine clinical examination, by palpating the thyroid gland; and we found statistically significant differences (p value = 0.045) between the two groups in terms of the presence of goiter.

Regarding the thyroid volume, we obtained statistically significant differences ($p<0.05$ value) between the values calculated for the subjects of the two distinct geographical areas.

We aimed to verify the correlations between Tvol obtained according to sex, in relation to age and anthropometric indices of the subjects included in the study, respectively to correlate Tvol with their height and body mass. Positive Pearson correlation indices were obtained, with $p<0,0001$ values in all statistically analyzed situations.

II.4.4. Discussions

In this study we investigated possible endocrine causes of short stature, which occurred in a number of 125 children of the 1946 previously evaluated from an auxological point of view.

Comparing the values of the parameters followed within the two groups of subjects, a statistically significant difference ($p<0.05$) is observed for iodide and thyroid hormone dosages (TSH and FT4), for the rest of the parameters the differences being statistically insignificant.

Global studies on the relationship between iodine deficiency, thyroid function and child growth have reported different results. Ziemmermann et al. (206) published in 2007 a paper comprising in fact three interventional studies conducted on 71 children (7-10 years) from Morocco, 310 children (10-12 years) from Albania and 188 children (5-14 years) from South Africa, children from iodine-deficient areas who subsequently received iodine-based supplements for a period of 6 months in the first and second studies, and for 10 months in the third, following the dynamics urinary iodine concentration, thyroid hormone and IGF-1 and IGFBP-3 levels, before and after iodine supplementation (206).

In the first two studies, statistically significant increases were observed after iodine supplementation, both in the levels of iodide and thyroid hormones and IGF-1 along with IGFBP-3, and in the study in South Africa the values of iodine and IGF- 1 and IGFBP-3 increased significantly after iodine supplementation, but not total thyroxine values, where an increase was observed, but statistically insignificant (206).

Among the endocrine causes of stature retardation, hypothyroidism remains one of the leading causes of short stature after GH deficiency, a study conducted in Columbia and published in 1995, shows the positives effects of thyroid hormones on growth, after L-Thyroxine administration, in children with mild thyroid dysfunction (71).

A recent study published in 2019 on the etiology of short stature in a group of 100 children with stature deficit below -2DS in Bangladesh found 12 children who were diagnosed with hypothyroidism and 8 children with GH deficiency. (82).

In 2017, Hussein et al. (77) published the results of an observational study conducted in Egypt between 2012 and 2015, which looked at 637 children, who looked at the causes of the stature deficit of these children, of whom 26% were of endocrine origin, with GH (45.2% of cases) followed by primary hypothyroidism (34.9%).

Regarding thyroid volume, the values obtained in our study after applying the appropriate statistical tests are statistically insignificant compared to the reference ones published in 2004 by Ziemmermann et al. (207), both for children in the hilly area and for those residing in the localities of the submontane area, for all ages of the subjects included in the study and according to their sex ($p = 0.695$, $p = 0.491$, $p = 0.177$, $p = 0.238$), but they are statistically significantly different for children in the hilly area compared to the 1997 WHO references ($p = 0.009$, $p = 0.007$), for all ages and for both sexes.

II.4.5 Conclusions

1. A number of 56 children (boys = 42, girls = 14) with an average age of 9 years, detected with short stature, 24 of them from the localities in the hilly area and 32 children residents in submontane areas, were investigated clinically, paraclinically, and imagistically.
2. Following laboratory investigations, statistically significant differences ($p<0.05$) are observed between the mean values of iodide, TSH and FT4.
3. At the clinical examination of the thyroid gland we found the presence of grade I goiter in 33.33% of the resident children of the hilly area, statistically significant ($p = 0.045<0.05$) lower than that obtained in children in the submontane area of 59.38% for the presence of grade I goiter; 6.24% had grade II goiter from this geographical region.
4. Regarding the thyroid volume calculated following the thyroid ultrasound, statistically significant differences ($p<0.05$) were found between the values obtained in children in the hilly area compared to those in the submontane area, for the age groups 6-9 years , and insignificant statistics ($p>0.05$) for children aged 11 and 12 years.
5. Thyroid volume values are positively correlated with age ($r = 0.901$, $r = 0.851$, $r = 0.931$, $r = 0.846$), height ($r = 0.891$, $r = 0.810$, $r = 0.809$, $r = 0.788$) and body mass ($r = 0.894$, $r = 0.751$, $r = 0.707$, $r = 0.602$).
6. Of the 56 children evaluated, 4 were found to have endocrine causes of stature deficiency, 2 of them being diagnosed with primary hypothyroidism and another 2 children being diagnosed with GH deficiency.
7. Iodine deficiency is still present in schoolchildren living in localities in sub-mountain areas, the average iodide being 77.23 µg/l, lower than the normal value of over 100 µg/l.
8. Iodine deficiency is still a serious public health problem, which is why efforts to combat iodine deficiency must continue.

II.5. PROPOSAL FOR ASSISTANT MEANS OF AUXOLOGICAL ASSESSMENT AND DETECTION OF GROWTH DISORDERS IN CHILDREN

II.5.1. Introduction

Maintaining the proper health of children, as well as ensuring that they reach their growth and development potential, are mandatory requirements for the sustainable development of a society (131,184).

We aim to contribute to improving the quality of life of children, especially those living in areas with iodine deficiency, through the research undertaken and its expansion.

A first step towards achieving the objectives is represented by: making brochures to raise awareness among the population and medical staff about the problems that may arise related to iodine deficiency; elaboration of algorithms to investigate the growth disorders in children and their causes, intended for family doctors and specialists; development of an online application with which to check whether, according to national and international standards, the child falls within the normal parameters of growth and development.

II.5.2. Brochure

The brochure is used to provide brief, relevant and necessary information for the population about iodine deficiency and disorders that may occur in the newborn, child or adult related to iodine deficiency, as well as actions that can be taken to prevent all these changes.

II.5.3 Diagnostic algorithm

Numerous algorithms for detecting and treating problems related to growth disorders in children have been developed and are found in the literature and in guidelines on the treatment of these pathologies. We aim to develop an algorithm that includes the main causes that can cause stature retardation in children, adapted from the literature, to simplify and provide assistance to physicians to guide a possible pathological cause underlying the small stature of children, as well as the main investigations that can be performed to confirm or disprove the suspected diagnosis.

II.5.4 Computer application

Currently, the assessment of the somatic development of children, by the doctor or parent, is done by using the growth nomograms provided by various national or international institutions, research centers or companies operating in the health field. The calculated standard values are the result of clinical trials conducted by WHO, national or regional institutes or research bodies.

A computer application through which to assess the somatic development of the child, can be a useful tool, fast, available to any user of an electronic device related to the Internet; parent or doctor. In addition, the application can evaluate the somatic development of the child compared to the values of the standards calculated at regional, national and international level. The application is also a database in which administrators can enter the reference values of the various evaluation indices, available at all levels. The application database can be developed by entering the measurements performed by the doctors who use it, with the patient's consent, in accordance with the legal conditions in force regarding the protection of personal data.

The application can be accessed from any type of electronic device: computer, tablet or mobile phone, regardless of the operating system. The application can be accessed using any internet browser.

The application can be improved and optimized by using programs designed to design computer applications that offer extensive programming capabilities.

This application can be used by anyone, depending on the type of user they fall into.

GENERAL CONCLUSIONS

1. Periodic assessment of the growth and development of children, by determining anthropometric indices, is an essential component in detecting as early as possible the growth disorders that may occur during childhood, as well as their proper treatment.
2. The etiology of growth disorders, and in particular short stature, is multifactorial, resulting from the involvement of genetic, endocrine, non-endocrine or idiopathic factors.
3. Iodine deficiency in children can cause, by affecting the morphology and function of the thyroid gland, the appearance of endemic goiter in the affected geographical areas, following the association of problems related to mental and somatic growth and development in newborns and children manifested by mental retardation and/or short stature.
4. Although many efforts have been made worldwide to combat iodine deficiency, it still remains a public health problem present in some geographical regions, as well as in the mountainous and sub-mountainous areas of our country.
5. The target population of our research was represented by 1946 children, schoolchildren aged 6 to 14, from different localities of Sibiu County located in different geographical areas: mountainous, submontane and hilly; from urban or rural areas.
6. In the period October 2013-December 2013 we performed anthropometric determinations by determining the height and weight of the group of children, of which 52.16% (N = 1,015) were female and 47.84% (N = 931) sex male.
7. 79.29% (N = 1,543) of children came from rural areas, and 20.71% (N = 403) from urban areas, 53.19% being residents of localities in the submontane area and 46.81% of inhabitants of localities in the hilly area.
8. The measured children showed on average higher heights than Prader's references from 1989, as well as those published by the WHO in 2007, and lower heights than those published in 2016 for Romania, both for females and the male.
9. The measured children had on average a body mass and a BMI higher than the WHO standards, but lower than the standards for our country, for both sexes.
10. Of the 1946 children evaluated, we found a number of 125 (6.42%) children with stature retardation, 84.80% being male and 15.20% female.
11. We found a higher percentage of children of short stature who come from the submontane area, compared to the hilly area, both for boys, 58.49%; as well as for girls, 63.16%.

12. 88.75% of the total children evaluated were normal weight, 2.92% of the children were underweight, 8.33% were overweight and obese (5.45% and 2.88%, respectively), with a ratio of girls / 1: 1 boys.
13. Our results on the prevalence of childhood obesity are below the values obtained both in our country and in Europe.
14. There is a higher incidence of overweight and obesity in children in the hilly area than in the sub-mountain area, both in females (10.37% in the hilly area compared to 7.24% in the sub-mountain area) and in male (10.69% in the hilly area compared to 5.57% in the submontane area).
15. We determined the concentration of urinary iodine in 112 children detected with short stature, with an average age of 9 years, 46 (41.07%) of them residents of the hilly area and 66 (58.93%) of them belonging to the localities included in submontane area.
16. The average value of urinary iodine was significantly higher ($p<0.001$) in children in the hilly area (112.74 µg/l) compared to that obtained in children in the submontane area (77.34 µg/l).
17. Our results show that, at the localities located in the submontane area, there is still a slight iodine deficiency among the school population in that area.
18. We investigated from a clinical, paraclinical and imaging point of view a number of 56 children, 42 boys and 14 girls, of those previously detected with small stature, with an average age of 9 years, 24 of them coming from localities from the hilly area and 32 being residents of the submontane area.
19. Following the laboratory investigations performed (urinary iodine, TSH, FT4, GH, IGF-1), statistically significant differences are observed between the average values obtained for urinary iodine, TSH and FT4 ($p<0.05$).
20. At the clinical examination of the thyroid gland we found the presence of grade I goiter in 33.33% of the children living in the hilly area, statistically significant ($p = 0.045<0.05$) lower than that obtained in children in the submontane area of 59.38% for the presence of grade I goiter, while 6.24% of children in the submountain area had grade II goiter.
21. Regarding the thyroid volume calculated following the thyroid ultrasound, there were statistically significant differences ($p<0.05$) between the values obtained in children in the hilly area compared to those in the submontane area, for the age groups 6-9 years .
22. The values of thyroid volume are positively correlated ($r = 0.690$; $r = 0.625$) with the height and body mass of the evaluated children.

23. Of the 1946 children evaluated, and subsequently of the 56 children whose endocrine paraclinical determinations were performed, two children were diagnosed with primary hypothyroidism based on the results of hormonal dosing, and two children were diagnosed with GH deficiency.
24. The periodic assessment from the auxological point of view of children, regardless of their age, is extremely important for detecting possible growth and development problems, the iodine deficiency present in certain geographical areas contributing to the appearance of mental and stature retardation.
25. It is imperative that family doctors, as well as those in school offices, know the basis of the algorithm for detecting growth disorders in children, in order to guide parents to the specialist, in order to fully investigate the small stature of the child.
26. I have proposed, as an auxiliary means for the auxological assessment of children, as well as for the detection of growth disorders that may occur in them; a brochure for doctors and the general public to provide information on iodine deficiency and its health consequences; a diagnostic algorithm regarding the main causes that can determine the appearance of short stature; as well as a computer application that can assess the somatic development of children.

RESEARCH DEVELOPMENT PERSPECTIVES

It is well known that children's health is the main vector of social and economic development of a society and the main requirement for supporting sustainable development. Thus, the main concern of parents in particular, but also of specialized medical staff who is directly or indirectly involved in the prevention and treatment of pediatric pathologies, must be the periodic assessment from the auxological point of view of children, in order to detect problems related to their psychic and somatic development, in order to be able to intervene as soon as possible for their treatment.

For the development of our research, we propose the main future research directions focused on:

- anthropometric evaluation of as many children as possible from as many localities in urban and rural areas;

- detecting children with problems related to growth and development, especially those with stature retardation;

- guiding parents to specialized centers to investigate the possible pathological causes of the short stature of their children;

- obtaining cooperation with the competent institutions to facilitate the organization of these actions, as well as providing assistance to the extent necessary;

- extending these steps to other counties in the country by collaborating with our fellow endocrinologists, pediatricians, family doctors;

- further implementation of the proposed online application, which we want, by investigating as many children as possible and adding them to the database, to obtain an overview of the anthropometric indices of children in our country, the possibility of statistical analysis of data entered with the generation of the most up-to-date references at national and local level, but also to obtain a general situation related to the pathologies that underlie the appearance of growth disorders among children.

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