Original article

Characteristics of Thyroid Disease in Pediatric Population

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Abstract

Aim: In the last decade, an increase in the incidence of autoimmune thyroid disease in children has been observed. The aim of the study was to determine the incidence of thyroid disease in the pediatric population treated at the Pediatric Clinic in Osijek; to determine if there was a rise in thyroid disease incidence in pediatric population in the observed period; and to determine whether there was any association of certain factors with an increased incidence of thyroid disease.

Methods: This study was a two-year retrospective study in two separately observed one-year periods (2010 and 2017). All patients with thyroid endocrinological disorders treated at the Pediatric Clinic of the University Hospital Centre Osijek were included in the study. Their medical records were used to obtain data. Differences between variables were tested by the $\chi 2$ test, Fisher's exact test and Mann-Whitney U test. The level of statistical significance was accepted for $p < 0.05$.

Results: There was a 2.4-fold increase in the approximate incidence of thyroid disease, 9.7-fold higher approximate incidence of autoimmune thyroiditis, 9.75-fold higher approximate incidence of unspecified hypothyroidism and a triple increase in the approximate incidence of non-toxic goiter. Other unspecified thyroid diseases are also statistically significantly on the rise. An analysis of factors such as anamnestic features, age, gender, comorbidities and other relevant data could not explain the increased incidence of thyroid disease.

Conclusion: The incidence of thyroid disease has increased considerably in the observed years, following world trends. Efforts should be taken to clarify the mechanisms and factors involved in causing thyroid diseases in the pediatric population.

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Introduction

The normal thyroid secretes thyroid hormones - triiodothyronine (T3) and thyroxine (T4), which are crucial for normal growth and development, body temperature and regulation of energy levels. The basic functions of the thyroid hormones are regulation of oxidation in cells, stimulation of oxidative processes in which heat is generated, stimulation of protein synthesis, stimulation of growth and differentiation and acceleration of the metabolism of carbohydrates, fats and vitamins (1).

Proper thyroid function is essential for early neurocognitive development, growth and development during childhood and adolescence (2). Optimal concentration of thyroid hormones is crucial, since a prolonged hypothyroid condition can result in a variety of disorders. Hypofunction of the thyroid gland occurring before the age of 2 usually leads to delayed maturation of the skeleton and the development of intellectual disability (1). On the other hand, hypothyroidism occurring after a period crucial for neurocognitive development can lead to a slowdown in linear growth and maturation of the skeleton, with no effect on cognitive development and obesity development (3, 4). Furthermore, hypothyroidism diagnosed in the late prepubertal years, which usually happens due to Hashimoto's thyroiditis, can delay the onset of puberty or lead to premature isosexual pseudo-puberty (development of breasts and internal reproductive organs in girls and increased testicular volume without adrenarche in boys). Later in adolescence and young adulthood, hypothyroidism can lead to menstrual disorders, infertility and miscarriages (5, 6). Several dozens of diseases have an autoimmune origin and such diseases affect 5-7% of the world's population (7). Thyroid disorders are one of the most common endocrinological problems in children and adolescents. Autoimmune thyroid disease is estimated to be the most common organospecific autoimmune disease, affecting up to 5% of the general population and 0.3 to 9.6% of the pediatric and adolescent population (8-10).

Epidemiological studies have suggested an increase in the incidence of autoimmune diseases in Western societies over the last few decades (11). The rise in the incidence of autoimmune diseases raises the question of the factors that perpetuate it. Given a decreasing frequency of infections in Western countries, with an increase in the incidence of allergic disorders and neoplasms, which is accompanied by an increase in the incidence of autoimmune diseases, a hygiene hypothesis has been put forward (12). Concordance of autoimmune disease in identical twins is 12-67%, which also highlights the potential role of epigenetics in disease development (13). Over the last few decades, there have been significant changes in nutrition, the environment and exposure to pollution, environmental infections and stress management. Another study highlights the significance of tobacco smoking, psychological distress, iodine intake, intrauterine development, bacterial and viral infections and medications such as interferon (14). Therefore, with the previously established contribution of genetics, increasing attention is shifted on environmental factors and the lifestyle in Western countries (15). The link between the causative factors of autoimmune disease – genetics and the environment – has not yet been fully elucidated. Although much progress has been made in understanding the pathogenesis of autoimmune diseases, many questions remain unanswered.

Numerous studies conducted both in clinical settings and in experimental models have shown that changes in posttranslational histone modifications and DNA methylation – two major epigenetic mechanisms – could potentially cause immune tolerance breakdown and the development of autoimmune diseases (16, 17). Therefore, autoimmune diseases actually reflect the complex interactions between gene variation and the environment (18). In most cases, the origin of the stimuli leading to epigenetic changes in patients with autoimmune diseases remains undefined, but may include different external (e.g. diet, sun exposure, chemicals, environment, medicines) and internal (e.g. aging, stress, sex hormones) stimuli. X-linked genes are typically unmethylated (active)

in males, while females have one methylated and one unmethylated gene. Several molecules encoded on the X chromosome have also been found to play a significant role in the development of autoimmune diseases (7). An epigenetic link between diet and autoimmune diseases has also been observed, since certain foods provide donors of methyl groups (methionine, choline) and cofactors (folic acid, vitamin B12 and pyrodoxal phosphate), which are essential for DNA and histone methylation (19). In addition to nutrition, ultraviolet radiation has been shown to stimulate epigenetic changes involving the hypermethylation of numerous promoter genes, some of which have an immunosuppressive effect (20). Furthermore, studies conducted on twins have shown that, although identical twins are epigenetically minimally different at a young age, they happen to show numerous differences in DNA methylation and histone acetylation later in life (21, 22). Taken together, epigenetics has become increasingly important in the study of the etiopathogenesis of the entire spectrum of diseases, especially autoimmune disorders, and any new insights will be of great importance for a better understanding of this growing health problem.

The objectives of present study were to determine the incidence of thyroid disease in the pediatric population treated at the Pediatric Clinic in Osijek; to determine if there was a rise of thyroid disease incidence in pediatric population in 2010 and 2017; and to determine whether there was any association of certain factors, such as anamnestic features, gender, comorbidities and other relevant factors, with an increased incidence of thyroid disease in childhood for a given period.

Patients and Methods

All pediatric patients treated at the Pediatric Clinic of the University Hospital Centre Osijek within the periods from January 1st 2010 to December 31st 2010 and from January 1st 2017 to December 31st 2017 who were monitored for thyroid disorders were included in the study. Their medical records were used to obtain data. The data collected from medical records included age, sex, diagnoses of thyroid disease, status of thyroid hormones, presence/absence of thyroid gland specific anti-bodies, comorbidities, components of physical status and family history data. During a follow-up period, the same pediatric specialist and pediatric endocrinology subspecialist monitored and guided the patients. The criteria for inclusion of the subjects in the research were as follows: - Patient under the age of 18 treated at the Pediatric Endocrinology Outpatient Clinic in the periods from January 1st 2010 to December 31st 2010 and from January 1st 2017 to December 31st 2017; Patient has one of the following diagnoses of thyroid disease (Revision 10 of the International Classification of Diseases and Related Health Problems): congenital hypothyroidism E03.0 / E03.1, other unspecified hypothyroidism E03.9, non-toxic goiter E04, hyperthyroidism / thyrotoxicosis E05, autoimmune thyroiditis E06.3, unspecified thyroid disorder E07.9, postprocedural hypothyroidism E89.0, malignant thyroid neoplasm C73, and observation Z03. Based on the data of the total population in the Republic of Croatia, the incidence of new pediatric thyroid disease cases was estimated. Since there were no subjects over 14 years of age (specifically, in both years, the oldest ones were 12 years old), the data from the population register for ages 0-14 were used (24). Due to the dynamics of population change and the inability to present current population values, the approximation of the population incidence was expressed at 95% confidence intervals.

The study was approved by the Ethics Committee of the Faculty of Medicine Osijek.

Statistical analysis

Categorical data are represented by absolute and relative frequencies. Numerical data are described by the median and the limits of the interquartile range. Category variables differences were tested by the Hi-square test and, if necessary, by the Fisher's exact test.

The normality of the distribution of numerical variables was tested by the Shapiro-Wilk test. Differences of the numerical variables between the two independent groups were tested with the Mann-Whitney U test. All P-values are two-sided. The significance level was set to Alpha = 0.05. MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018) and SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows) were used for statistical analysis (Version 21.0. Armonk, NY: IBM Corp.).

Results

Categorical data are represented by absolute and relative frequencies. Numerical data are described by the median and the limits of the interquartile range. Category variables differences were tested by the Hi-square test and, if necessary, by the Fisher's exact test.

The normality of the distribution of numerical variables was tested by the Shapiro-Wilk test. Differences of the numerical variables between the two independent groups were tested with the Mann-Whitney U test. All P-values are two-sided. The significance level was set to Alpha = 0.05. MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018) and SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows) were used for statistical analysis (Version 21.0. Armonk, NY: IBM Corp.).

Table 1. Incidence of thyroid diseases by diagnosis during 2010 and 2017

	2010 Newly diagnosed	Incidence	95% C.I	2017 Newly diagnosed	Incidence	95% C.I	P
Autoimmune thyroiditis	9	11.65	5-33	88	113.91	91-26	<0.001
Congenital hypothyroidism	1	1.29	0-3	2	2.59	0-31	>0.999
Unspecified hypothyroidism	4	5.18	1-41	39	50.48	35-88	<0.001
Hyperthyroidism	1	1.29	0-3	1	1.29	1-41	>0.999
Non-toxic goiter	15	19.42	10-87	45	58.25	42-46	<0.001
Other thyroid diseases	0	0.00	0-0	18	23.30	13-81	<0.001

*Incidence per 100,000 inhabitants, C.I. – confidence interval

Table 1 presents the incidence of thyroid diseases by diagnosis during 2010 and 2017 The number of newly diagnosed cases of autoimmune thyroiditis in 2010 was 9, accounting for the incidence of 11.65 per 100,000 inhabitants aged 0-14, and in 2017, the number of newly diagnosed cases was 88, accounting for the incidence of 113 newly diagnosed children per 100,000 inhabitants. Such a 9.7-fold increase in incidence was found to be statistically significant (p <0.001). Also, there was a 9.75-fold increase in the incidence of unspecified hypothyroidism during the years mentioned. In 2010, the incidence of unspecified hypothyroidism was 5.18, and in 2017, 50.48 per 100,000 inhabitants (p <0.001). A threefold increase in the incidence of non-toxic goiter was detected, with an incidence of 19.42 newly diagnosed children in 2010, compared to 58.25 newly diagnosed children per 100,000 inhabitants aged 0-14 (p <0.001). Other unspecified thyroid diseases are also on a statistically significant rise – no cases were reported in 2010, and in 2017, the incidence was 23.3 new cases per 100,000 inhabitants aged 0-14.

Table 2 presents distribution of patients in regard of nutritional status. There were no significant differences in relation to malnutrition, or normal nutrition and overweight/obesity among subjects examined in 2010 and 2017.

Table 2. Distribution of subjects in relation to nutrition status

Nutrition	Number (%) of subjects 2010	2017	Overall	P*
Malnourished	3 (5)	4 (2)	7 (3)	
Normal weight	36 (60)	117 (56)	153 (57)	
Overweight	12 (20)	33 (16)	45 (17)	0.20
Obese	9 (15)	54 (26)	63 (24)	
Overall	60 (100)	208 (100)	268 (100)	

*Hi-square test

Also, no significant differences were observed between two populations studied in terms of specific aspects of physical examination (i.e. characteristics of the skin, eyes, presence of palpitations, appetite, body mass and stool and urination, Table 3).

Table 3. Subjects according to specific aspects of physical examination

	Number (%) children 2010	2017	Total	P*
Skin				
Regular moisture and warmth, without trembling	67 (93)	186 (94)	253 (94)	0.77
Thyroid symptomatology	5 (7)	11 (6)	16 (6)	
Total	72 (100)	197 (100)	269 (100)	
Eyes				
Normal	69 (99)	196 (100)	265 (99.6)	0.26
Pathology	1 (1)	0	1 (0.4)	
Total	70 (100)	196 (100)	266 (100)	
Palpation				
Regular	46 (68)	132 (61)	178 (63)	0.39
Enlarged	22 (32)	83 (39)	105 (37)	
Total	68 (100)	215 (100)	283 (100)	
Appetite				
Regular	68 (94)	151 (92)	219 (92)	0.39
Changed	4 (6)	14 (8)	18 (8)	
Total	72 (100)	165 (100)	237 (100)	
Body mass				
Constant	71 (99)	161 (98)	232 (98)	>0.99
Fluctuating	1 (1)	4 (2)	5 (2)	
Total	72 (100)	165 (100)	237 (100)	
Stool				
Regular	59 (89.4)	159 (94.6)	217 (93.1)	>0.99
Irregular	7 (10.6)	9 (5.4)	11 (4.7)	
Total	66 (100)	167 (100)	233 (100)	
Urination - regular	72 (100)	165 (100)	237 (100)	-

Fisher's exact test

Presence of family history of thyroid diseases was significantly more frequent in data collected in 2017; however, no difference was observed in terms of appearance in paternal, maternal or kin side (Table 4). Also, comorbidities were equally distributed between two studied groups of patients (Table 5).

Table 4. Subjects by family history and years observed

	Number (%) children			P*
	2010	2017	Total	
Family history				
Positive	23 (44)	107 (67)	130 (61)	**0.004**†
Negative	29 (56)	53 (33)	82 (39)	
Total	52 (100)	160 (100)	212 (100)	
Positive family history				
Maternal side	16 (73)	64 (65)	80 (61)	
Paternal side	2 (9)	19 (19)	21 (16)	0.06
Combined (brother/sister/maternal/paternal)	4 (18)	15 (16)	19 (23)	
Total	23 (100)	107 (100)	130 (100)	

*Fisher's exact test; † χ 2 test

Table 5. Distribution according to comorbidities regarding the years observed

	Number (%) of subjects			P*
	2010	2017	Total	
Obesity	1 (3.6)	22 (12.5)	23 (11.27)	0.213
Polycystic ovary syndrome/ dysmenorrhea	0 (0)	4 (2.3)	4 (1.96)	>0.999
Haematological irregularities (↓Trc, anaemia)	0 (0)	4 (2.3)	4 (1.96)	>0.999
Skin disorders (acne, psoriasis, vitiligo, atopy)	0 (0)	7 (4)	7 (3.43)	0.597
Respiratory diseases of allergic etiology (Allerg.rhinitis/bronchitis/asthma)	1 (3.6)	4 (2.3)	5 (2.45)	0.526
JRA, polyarthralgia, Sy Raynaud	1 (3.6)	6 (3.4)	7 (3.43)	>0.999
Benign nodus	0 (0)	6 (3.4)	6 (2.94)	>0.999
Hypertension, heartbeat irregularities/palpitations	0 (0)	8 (4.5)	8 (3.92)	0.602
Celiac disease	0 (0)	5 (2.8)	5 (2.45)	>0.999
Gastritis, GERB	0 (0)	2 (1.1)	2 (0.98)	>0.999
Trembling, vertigo, headache	1 (3.6)	11 (6.3)	12 (5.88)	>0.999
Epilepsy and epileptic convulsions	1 (3.6)	1 (0.6)	2 (0.98)	0.256
Chromosomopathies (Sy Down, Sy Turner, Sy DiGeorge)	0 (0)	5 (2.8)	5 (2.45)	>0.999
Hypotrophy, retarded growth	0 (0)	6 (3.4)	6 (2.94)	>0.999
Accelerated growth, pubertas praecox	2 (7.1)	4 (2.3)	6 (2.94)	0.192
Hyperlipidaemia	1 (3.6)	5 (2.8)	6 (2.94)	0.593

*Fisher's exact test

Discussion

Based on the data of the total population in the Republic of Croatia, the incidence of newly diagnosed children with thyroid disease was estimated. Since no newly diagnosed subjects were over 14 years of age (specifically, in both years, the oldest newly diagnosed subject was 12 years old), the data from the population register for ages 0-14 were used (24). Due to the peculiarity of the pediatric population of eastern Croatia, patients from Osijek-Baranja and Vukovar-Srijem counties gravitate mostly to the University Hospital Centre Osijek. For this reason, the 2010 census data for Osijek-Baranja County and Vukovar-Srijem County were used to approximate the incidence of newly diagnosed subjects, which totalled to 77,257 children aged 0-14 (Osijek-Baranja: 46,806 children, Vukovar-Srijem: 30,451 children). Due to the dynamics of population change and the inability to present current population values, the approximation of the population incidence was expressed at 95% confidence intervals. Our results suggest that the total number of newly diagnosed cases of thyroid disease has increased significantly. A similar trend in the incidence of thyroid disease has been reported in other studies (25). Looking at the incidence of thyroid disease by years, there is a statistically significant increase in the incidence of autoimmune thyroiditis, unspecified hypothyroidism, non-toxic goiter, and other unspecified thyroid diseases. The increase in the incidence of thyroid disease, especially autoimmune thyroid disease, is a global trend, present especially in Western countries, where the decrease of infectious diseases incidence is also being observed (11, 26). This research confirms that a similar trend can be observed in subjects. Furthermore, probably mostly due to the existence of screening for congenital hypothyroidism during the early neonatal period, figures regarding this diagnosis have not changed significantly over the years, and fortunately remained low.

So far, numerous studies on gender and autoimmunity have concluded that thyroid diseases, such as autoimmune thyroiditis and goiter, are more common in women, as confirmed by this research. This pattern has been partially elucidated by the influence of female sex hormones and by X inactivation, but remains to be fully explained (27). In present study, subjects were analyzed regarding the nutrition status expressed by body mass index. Patients with chromosomopathies (Down Syndrome, DiGeorge Syndrome, Turner Syndrome) were excluded, since their growth and development do not follow the usual patterns. Subjects were classified into 4 groups depending on the centile - malnourished, normal weight, overweight and obese subjects. The study showed that the majority of subjects in both observed years had normal body weight (57%), 3% were malnourished, while 41% of subjects were overweight and obese. In both observed years, a large proportion of childre n were overweight and obese. In a 2010 study conducted on healthy Croatian school-age children, it was found that 69.9% of children were normal weight and 30.1% were overweight and obese (28). Taking into account the results of our study on the population of children suffering from thyroid disease, it is obvious that there is a slightly higher proportion of overweight and obese children (by 10.9%) among children with thyroid disorders than the population of healthy children, while the share of children with normal body weight was slightly lower (12.9%). Although statistically insignificant, it could suggest a higher incidence of thyroid disease among children of a higher body mass index, as explained by the interaction of metabolically active adipose tissue and leptin and the thyroid-stimulating hormone (29). Specifically, adipose tissue plays a role in the pathophysiology of thyroid disorders. Fat cells produce leptin, which is why they are considered to be an active endocrine organ. Leptin is a potential link between the TSH and body mass index; it acts as a neuroendocrine regulator of the hypothalamus-pituitary-thyroid axis by regulating TSH gene expression in certain brain regions. Vice versa, the TSH stimulates leptin secretion in adipose tissue. Leptin also promotes the conversion of T4 to T3 (30). In obese children, elevated TSH and T4 levels have become a common finding. Since these values appear to

result from an elevated body mass index, it might be possible to normalize thyroid hormone levels by correcting or losing extra body weight. However, the incidence of thyroid antibodies is low in these patients, suggesting that adiposity via the previously explained association with leptin affects TSH levels, but not the thyroid antibody levels (31, 32). Obesity has become a growing public health problem. At the same time, it also appears to be a perpetuating factor in the increased incidence of thyroid disease.

Other physical status data were also taken from the subjects' medical records to determine if there were significant changes between these variables in 2010 and 2017. By processing the data collected, it was concluded that there was no statistically significant difference between the variables observed in the years compared by which we could explain the increased incidence of thyroid disease.

In addition to all other information, one of the characteristics of thyroid disease is certainly family clustering and a positive family history. A positive family history of thyroid disease in 2010 was present in 44% of the subjects, while in 2017, this number increased statistically significantly to 67%. Given the invariability of the genetic component of the disease, the increase in the number of subjects with a positive family history could be explained by the greater awareness of patients with thyroid disease and cognition of similar diseases within their own families, but also by the indirectly increased incidence of thyroid disease in both the adult and pediatric populations (26).

The most common comorbidities include obesity, diabetes mellitus type 1, cystic ovarian syndrome and dysmenorrhea, skin changes, respiratory diseases of allergic etiology, hypertension, palpitations, celiac disease, gastritis and GERD, chromosomopathies, praecox puberty and accelerated growth, which, according to available literature, have been previously linked to thyroid disease and thyroid hormone imbalance (33-42). However, the difference in the incidence of these comorbidities in the observed years was not found to be statistically significant. Such persistent co-occurence might suggest that there is a pathophysiological link between some of these diseases and autoimmune thyroid disease.

Based on the research conducted and the analysis of the data obtained, several conclusions can be drawn. The incidence of thyroid disease in general, autoimmune thyroiditis, unspecified hypothyroidism and non-toxic goiter increased multiple times in the observed period. Other unspecified thyroid diseases are also on the statistically significant rise. During the observed period, there was a statistically significant increase in the number of diseased female children compared to the male children in each year separately, but the ratio of the diseased did not change significantly during the observed years. Also, there were no significant differences in comorbidities in the subjects compared to the years observed, which could explain the increased incidence. The consistency of a positive family history in the direction of thyroid disease was confirmed, with the prevalence of a positive family history along the maternal line.

Conclusion

In conclusion, it is evident that autoimmune diseases in general are a local and global issue that will appear even more frequently in the future. With the aim of successful treatment and potential prevention, additional efforts are needed to determine the exact incidence and to identify potential risk factors for the development of these diseases.

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Competing interests. None to declare.

References

1. Mardešić D. et al. Pedijatrija. 8. izd. Zagreb: Školska knjiga. 2008.

2. Hanley P, Lord K, Bauer AJ. Thyroid Disorders in Children and Adolescents: A Review. JMA Pediatr. 2016; 170(10):1008-1019.

3. Rivkees SA, Bode HH, Crawford JD. Long-term growth in juvenile acquired hypothyroidism: the failure to achieve normal adult stature. N Engl J Med. 1988; 318:599-602.

4. Kiess W, Galler A, Reich A, Müller G, KapellenT, Deutscher J, Raile K, Kratzsch J. Clinical aspects of obesity in childhood and adolescence. Obes Rev. 2001; 2(1):29-36.

5. Weber G, Vigone MC, Stroppa L, Chiumello G. Thyroid function and puberty. J Pediatr Endocrinol Metab. 2003; 2:253-7.

6. Ryan GL, Feng X, Brasil d'Alva C, Zhang M, Van Voorhis BJ, Modolo Pinto E, Kubias AEF, Antonini SR, Latronico AC, Segaloffet DL. Evaluating the roles of follicle-stimulating hormone receptor polymorphisms in gonadal hyperstimulation associated with severe juvenile primary hypothyroidism. J Clin Endocrinol Metab. 2007; 92:2312–17.

7. Pušeljić S, Tomac V, Milas K, Pušeljić I, Švitek L. Utjecaj čimbenika okoliša na promjenu genske ekspresije. Med Vjesn. 2015; 47:00-00.

8. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F. The incidence of thyroid disorders in the community: a twenty years follow-up of the Wickham survey. Clin Endocrinol (Oxf). 1995; 43(1):55-68. doi: 10.1111/j.1365-2265.1995.tb01894.x.

9. Zois C, Stavrou I, Kalogera C, Svarna E. High prevalence of autoimmune thyroiditis in school children after elimination of iodine deficiency in northwestern Greece. Thyroid. 2003; 13:485–495.

10. Inoue M, Taketani N, Sato T, Nakajima H. High incidence of chronic lymphocytic thyroiditis in apparently healthy school children: epidemiological and clinical study. Endocrinol Jpn. 1975; 22:483–488.

11. Lohi S, Mustalahti K, Kaukinen K, Laurila K, Collin P, Rissanen H, Lohi O, Bravi E, Gasparin M, Reunanen A, Mäki M. Increasing prevalence of coeliac disease over time. Aliment Pharmacol Ther. 2007; 26:1217-1225.

12. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med. 2002; 347:911-920.

13. Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. J Intern Med. 2015; 278:369-395.

14. Prummel MF, Strieder T, Wiersinga WM. The environment and autoimmune thyroid diseases. Eur J Endocrinol. 2004; 150:605–618.

15. Lerner A, Matthias T. Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease. Autoimmun Rev. 2015; 14:479-489

16. Ballestar E, Javierre BM, de la Rica L, Gómez-Cabrero D, Tegnér J, Gomez-Vaquero C, Narvaez J, Hernando H, Rodriguez VC, Vento R, Ciudad L, Rodriguez-Ubreva J. Epigenetics alterations in autoimmune diseases. J Transl Med. 2011; 9(Supp 2):13.

17. Meda F, Folci M, Baccarelli A, Selmi C. The epigenetics of autoimmunity. Cell Mol Immunol. 2011; 8:226–35.

18. Farh KKH, Marson A, Zhu J, Kleinewietfeld M, Housley WJ, Beik S, Shoresh N, Whitton H , Ryan RJH, Shishkin AA, Hatan M, Carrasco-Alfonso MJ, Mayer D , Luckey CJ, Patsopoulos NA, De Jager PL, Kuchroo VK, Epstein CB, Daly MJ, Hafler DA, Bernstein BE. Genetic and epigenetic fine mapping of causal autoimmune disease variants. Nature. 2015 i (7539):337–4

19. Poirier LA. The effects of diet, genetics and chemicals on toxicity and aberrant DNA methylation: an introduction. J Nutr. 2002; 8:2336S–9S., 132 Suppl.

20. Dong Z, Bode AM. The role of histone H3 phosphorylation (Ser10 and Ser28) in cell growth and cell transformation. Mol Carcinog. 2006; 45(6):416-21.

21. Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suñer D, Cigudosa JC, Urioste M, Benitez J, Boix-Chornet M, Sanchez-Aguilera A, Ling C, Carlsson E, Poulsen P, Vaag A, Stephan Z, Spector TD, Wu J-Z, Plass C, Esteller M. Epigenetic differences arise during the li- fetime of monozygotic twins. Proc Natl Acad Sci U S A. 2005; 102(30):10604–9.

22. Bell JT, Tsai PC, Yang TP, Pidsley R, Nisbet J, Glass D, Mangino M, Zhai G, Zhang F, Valdes A, Shin S-Y, Dempster EL, Murray RM, Grundberg E, Hedman AK, Nica A, Small KS, MuTHER Consortium; Dermitzakis ET, McCarthy MI, Mill J, Spector TD, Deloukas P. Epigenome-wide scans identify differentially methylated regions for age and age-related phenotypes in a healthy ageing population. PLoS Genet. 2012; 8:e1002629.

23. Marušić M. et al. Uvod u znanstveni rad u medicini. 4. izdanje. Zagreb

24. Stanovništvo Republike Hrvatske prema starosti i spolu po naseljima; Popis stanovništva RH 2011. Accessed 11.05.2018 Available at: https://www.dzs.hr/hrv/censuses/census2011/results/htm/H01_01_01/H01_01_01.html.

25. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark FJ. Evans G,

Hasan DM, Rodgers H, Tunbridge F, Young ET. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995; 3:55-68.

26. Lerner A, Jeremias P, Matthias T. The World Incidence and Prevalence of Autoimmune Diseases is Increasing. Int J Celiac Dis. 2015; 3:151-155.

27. Li H, Li J. Thyroid disorders in women. Minerva Med. 2015; 106:109-14.

28. Petricevic N, Puharic Z, Posavec M, Pavic Simetin I, Pejnovic Franelic I. Family history and parental recognition of overweight in Croatian children. Eur J Pediatr. 2012; 171:1209-14

29. Jin HY. Prevalence of subclinical hypothyroidism in obese children or adolescents and association between thyroid hormone and the components of metabolic syndrome. J Paediatr Child Health. 2018; 54:975-980.

30. Biondi B. Thyroid and Obesity: An Intriguing Relationship. J Clin Endocrinol Metab. 2010; 95:3614-7.

31. Ghergherehchi R, Hazhir N. Thyroid hormonal status among children with obesity. Ther Adv Endocrinol Metab. 2015; 6:51-5.

32. Canaris G, Tape T, Wigton R. Thyroid disease awareness is associated with high rates of identifying subjects with previously undiagnosed thyroid. BMC Public Health. 2013; 13:351.

33. Ardestani SK, Keshteli AH, Khalili N, Hashemipour M, Barekatain R. Thyroid Disorders in Children and Adolescents with Type 1 Diabetes Mellitus in Isfahan, Iran. J Pediatr. 2011; 21:502–508.

34. Hunter I, Greene SA, MacDonald TM, Morris AD. Prevalence and aetiology of hypothyroidism in the young Arch Dis Child 2000; 83:207–210.

35. Chen CY, Lee KT, Lee CT, Lai WT, Huang YB. Epidemiology and Clinical Characteristics of Congenital Hypothyroidism in an Asian Populat. J Epidemiol. 2013; 23(2):85-94.

36. Zdraveska N, Kocova M. Hashimoto Thyroiditis in Childhood – Review of the Epidemiology, Genetic Susceptibility and Clinical Aspects of the Disease. Maced J Med Sci. 2012; 5:336-345.

37. Ardestani SK, Keshteli AH, Khalili N, Hashemipour M, Barekatain R. Thyroid Disorders in Children and Adolescents with Type 1 Diabetes Mellitus in Isfahan, Iran. J Pediatr. 2011; 21:502–508.

38. Rigon F, Sanctis V, Bernasconi S, Bianchin L, Bona G, Bozzola M. Menstrual pattern and menstrual disorders among adolescents: an update of the Italian data. Ital J Pediatr. 2012; 38:38.

39. Ghaffari J, Rokni GR, Kazeminejad A, Abedi H. Association among Thyroid Dysfunction, Asthma, Allergic Rhinitis and Eczema in Children with Alopecia. Maced J Med Sci. 2017; 5:305-309.

40. Barjaktarovic M, Korevaar TIM, Gaillard R, de Rijke YB, Visser TJ, Jaddoe VWV, Peeters R. Childhood thyroid function, body composition and cardiovascular function. Eur J Endocrinol. 2017; 177:319-327.

41. Cappa M, Bizzarri C, Crea F. Autoimmune Thyroid Diseases in Children. J Thyroid Res. 2011;1-13.

42. Larizza D, Calcaterra V, De Giacomo C, De Silvestri A, Asti M, Badulli C, Autelli M, Coslovich E, Martinettiet M. Celiac disease in children with autoimmune thyroid disease. Nov, J Pediatr. 2001; 139:738-740.

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