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Original Article

Assessing growth parameters of children with congenital hypothyroidism subject to levothyroxine treatment compared to normal growth parameters in healthy newborns

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Abstract

Background and aims: Congenital hypothyroidism (CH) is one of the most common treatable physical growth disorders leading to mental retardation. Most cases of this disease can be detected through the neonatal screening program. Given the high prevalence of this disease and the implementation of screening programs in recent years in Iran, this study aimed to assess the growth indices of newborns with CH.

Methods: In this retrospective cohort study, 66 newborns with CH detected in the screening program in Shahrekord were selected by a census sampling method. Overall, 125 healthy newborns were also selected as controls by the convenience sampling technique according to the inclusion and exclusion criteria. The height, weight, head circumference, and body mass index (BMI) of the samples were measured and then the mean, median, standard deviation, as well as the 3rd, 15th, 25th, 50th, 75th, 85th, and 97th percentiles in the two groups were determined and compared based on gender and age group.

Results: The height, weight, head circumference, and BMI of the boys, in addition to the head circumference and BMI of the girls, were not significantly different from those of the controls ($P>0.05$). However, the height and weight of the girls were significantly lower compared to those in the control group, although the difference in the weight was corrected at the age of 9 months.

Conclusion: In general, the growth indices of newborns with CH were lower than those of the controls. This difference was significant only for the weight and height of girls with CH.

Keywords: Congenital hypothyroidism, Growth indices, Newborn screening

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Introduction

The growth of fetuses and children depends on the function of certain hormones, the most important of which are thyroid and growth hormones (1). Hypothyroidism in newborns is caused by the deficiency of thyroid hormone in fetuses, neonates, and infants and refers to the underactive thyroid gland, which exists before or at birth (2). Congenital hypothyroidism (CH) is considered as one of the most common diseases involving endocrine glands in children and one of the preventable causes of mental retardation (3). This disease is twice as prevalent in girls as in boys (4). In the United States, the prevalence of hypothyroidism increases 3% per year and the deficiency of iodine is still the main cause of the prevalence of this disease worldwide (5). Most newborns with CH do not present with the symptoms of the disease at birth. However, some studies indicate that delayed diagnosis and disease treatment lead to irreversible mental retardation, misaligned eyes, learning difficulties, neurological complications, severe physical growth problems, short stature, and the like (5-7). Oral levothyroxine is the treatment of choice for the disease (4). In Asian countries, especially Iran, the prevalence of CH is higher than the worldwide standard due to consanguineous marriage, iodine deficiency, and genetics (8). The incidence rate of this disease in Iran is 1/400 to 1/900 live births (9). The worldwide incidence

of this disease is 1/2000 to 1/4000 live births. Therefore, the screening program of hypothyroidism in newborns started in 1970. Nowadays, it is implemented in most industrialized and developing countries (10,11). Azizi et al. first implemented the screening program of CH in some provinces of Iran in 1987 (12). The implementation of the screening program, along with the early diagnosis and immediate treatment of the affected newborns, leads to the normalization of their growth and cognitive and intellectual functionality (13).

Screening is conducted to detect, control, and manage the treatment of the affected newborns at birth, as well as to detect the transient cases of the disease (3). Screening, along with early diagnosis and treatment, leads to normal body and brain growth in addition to the normal intellectual and cognitive functionality of newborns with CH (5). Hypothyroidism is caused by a deficiency of the thyroid hormone production or the thyroid gland, or thyroid-stimulating hormone (TSH) deficiency. The biochemical diagnosis must be made immediately after birth (4). The conventional newborn screening was carried out in all the states of the United States to measure the amount of TSH in samples collected from the umbilical cord or the heel stick. To this end, a serum sample was immediately collected from each newborn with a positive screening test in order to confirm low T_4 and high TSH (14). According to national guidelines, the newborn was followed up 2 and 4 weeks after treatment, every 2 months during the first 6 months, every 3 months within the ages of 6-36 months, and if the child develops permanent CH, every 6 months after the age of 36 months (12).

Body mass index (BMI) is a recommended screening tool for children and adolescents (14). One study showed that head circumference was higher in children with CH than the normal range (15). Various studies have investigated the developmental pattern of CH children worldwide and the results showed some differences between the growth indices of these children and healthy individuals. Some of these studies suggested that these children have growth retardation compared to others or their growth is less than that of the other normal children (16-25).

The implementation of the screening program for CH in accordance with national guidelines was successfully implemented in Chaharmahal va Bakhtiari province so that 80% of healthcare centers conducted the program satisfactorily (26).

However, no study has so far focused on this health issue in this province and no comprehensive assessment has yet been carried out on the linear growth and the BMI of children with CH. Therefore, this study aimed to analyze the growth process of children with CH in order to assess the effectiveness of early treatment initiation. For this purpose, the growth indices such as weight, height, head circumference, and the BMI of children with CH taking levothyroxine and those without CH were compared to determine the effectiveness of the CH screening program.

Materials and Methods

In this retrospective cohort study that was conducted in 2014, children diagnosed with CH during the newborn screening program in Shahrekord during 2006-2013 comprised the study population. To select the samples for the treatment group, sampling was conducted by census, while the controls were selected by the convenience sampling method from among the relatives or neighbors of the samples in the treatment group who were matched for residence place, age, and gender with the treatment group. During the newborn screening program implemented in Shahrekord between 2006 and 2013, 102 children were diagnosed with the disease. According to the inclusion and exclusion criteria, 66 children diagnosed with the disease and 125 healthy children were assigned to the treatment and control groups, respectively. The exclusion criteria were the presence of a simultaneous disease, malnutrition, prematurity (giving birth before the 37^{th} week of gestation), intrauterine growth restriction and small for the gestational age, and children with genetic problems like Down syndrome or severe anomalies. After obtaining the parents' consent forms and assuring the confidentiality and lack of imposing costs, the necessary approvals of the Provincial Health Center and the information about the growth indices of children from birth to 5 years of age were collected from the health care centers.

The collected information included height (cm), weight (g), head circumference (cm, in children under 2 years of age), and BMI (kg/m^2, in children aged 2 years and over). The mean, median, standard deviation, and the 3^{rd}, 15^{th}, 25^{th}, 50^{th}, 75^{th}, 85^{th}, and 97^{th} percentiles were calculated based on age and gender in both the treatment and control groups and compared in order to describe the data. Finally, descriptive and inferential statistics (*t* test) in the SPSS were used for data analysis.

Results

Out of the 66 children with CH in the treatment group, 41 (62.1%) cases were boys and 25 (37.9%) of them were girls. From among 125 children in the control group, 65 (52%) and 60 (48%) of them were boys and girls, respectively. No significant difference was observed in the mean height and weight between boys with CH and healthy boys in all age groups ($P > 0.05$). Although height and weight were lower in boys with CH in almost all age groups compared to healthy boys, the height of the girls with CH was significantly lower than that of healthy girls in all age groups except for birth height at 1 and 3 years of age. The weight of the girls with CH was significantly lower than that of healthy girls at 2, 3, 4, and 6 months of age ($P < 0.05$), the details of which are provided in Table 1.

Although the head circumference and BMI of healthy

Table 1. The comparison of height and weight in girls and boys with and without congenital hypothyroidism

Age	Sex	Height (cm)			Weight (g)		
		Healthy	With CH	*P* value	Healthy	With CH	*P* value
0	Girls	49.45±2.03	49.15±2.13	0.55	3057.83±440.70	3010±548.80	0.67
	Boys	49.46±2.03	49.04±3.07	0.39	3460.30±3197.44	3134.87±532.82	0.52
2 months	Girls	57.46±2.56	56.12±3.41	0.05*	5075.47±534.98	4522±605.54	0.000*
	Boys	57.54±2.56	57.10±3.14	0.44	5312.90±743.38	5224.39±977.76	0.60
3 months	Girls	60.09±2.57	58.60±3.19	0.03*	5765.38±41667	5375±660.36	0.02*
	Boys	60.81±2.54	63.27±3.02	0.33	6056.66±687.26	5943.75±903.63	0.46
4 months	Girls	62.82±2.57	61.16±2.70	0.01*	6424.54±777.57	5892±693.97	0.004*
	Boys	63.62±2.67	63.46±2.90	0.76	6867.74±806.68	6670.73±977.49	0.26
6 months	Girls	66.47±2.50	64.45±2.46	0.002*	7425±992.06	6881.81±805.71	0.02*
	Boys	68.04±4.47	67.11±2.99	0.25	7693.43±862.59	7656.41±1014.25	0.84
9 months	Girls	70.92±2.60	69.44±3.33	0.05*	8403.63±1123.76	7865.78±904.62	0.06
	Boys	72.32±3.17	71.25±3.21	0.11	8698.36±1022.29	8562.50±1132.40	0.54
1 year	Girls	75.23±3.81	73.82±3.43	0.07	9211.11±1174.27	8180±2016.66	0.08
	Boys	76.12±3.67	75±3.07	0.13	9643.44±1218.45	9276.47±1140.65	0.29
1.5 years	Girls	81.26±3.16	79.23±3.63	0.03*	10445.92±1296.94	9876.47±1205.99	0.11
	Boys	82.57±3.88	81.12±3.36	0.07	10841.53±1434.46	10489.39±1280.97	0.24
2 years	Girls	86.63±3.67	83.75±3.82	0.01*	11566.30±1445.03	10935.71±1334.51	0.15
	Boys	86.99±4.02	86.13±4.19	0.36	12286.79±2276.47	11541.67±1417.14	0.10
3 years	Girls	95.05±5.65	92.69±5.52	0.20	13523.53±1701.16	12866.67±1613.20	0.25
	Boys	95.04±4.51	93.63±5.08	0.37	13708.54±1634.62	13396±184062	0.47
4 years	Girls	104.63±5.05	100.42±2.22	0.04*	15743.48±2447.04	14728.57±1717.27	0.31
	Boys	101.24±4.23	99.85±6.36	0.36	15835.48±2190.66	1540±2961.24	0,59
5 years	Girls	113.32±4.70	106.50±1.73	0.01*	18617.65±2788.19	16250±2061.55	0.12
	Boys	110.10±4.37	107.26±8.17	0.20	17711.11±2743.52	18073.33±4673.09	0.78

Note. *Significant difference at the level of $P<0.05$; CH: Congenital hypothyroidism.

boys were higher than those of boys with CH, no significant difference was observed in any of the age groups. Further, no significant difference was found in head circumference and BMI between healthy girls and girls with CH in almost all age groups ($P>0.05$), data of which are presented in Table 2.

The mean TSH of newborns with CH at birth and 3 years of age was greater than 5, while it was lower than 5 in other age groups. In children with CH, the T_4 levels were almost normal in all age groups except for children at birth (Table 3).

The comparison of height percentiles in boys revealed that the height was almost higher in healthy boys at the percentiles of 3, 15, and 25 compared to boys with CH in different age groups. At the percentile of 50, height was almost higher in healthy children compared to children with CH except for 4 months old and at the percentile of 75 except for 3 months old.

At the percentile of 85, in newborns at birth and 2, 3, and 6 months and 4 years of age, the height was almost higher in children with CH compared to healthy children.

At the percentile of 97, at 2 and 4 months, as well as 2, 4, and 5 years of age, the height was almost higher in children with CH compared to healthy children. In general, a small difference in height was observed between the two groups at higher percentiles.

Furthermore, the height was higher in healthy girls at the percentile of 3 compared to girls with CH in all age groups except for 3, 4, and 5 years of age. At other percentiles, the height was higher in healthy girls when compared with those girls with CH in all age groups (Figure 1).

At the percentile of 3, the weight at the age of 2 months was higher in newborns with CH as compared to healthy newborns. However, the weight became higher in healthy children after 2 months of age. At percentiles of 15 and 25, the weight of healthy children was higher than that of children with CH in all age groups.

Moreover, the weight was higher in children with CH at the percentile of 50 at birth in addition to 4, 6, 9, and 12 months of age when compared to healthy children, while it was lower in children with CH in the other age groups. Additionally, the results revealed that the weight was higher in children with CH at the percentile of 75 at birth, 2 months, as well as 1.5, 3, 4, and 5 years of age

Table 2. The comparison of BMI and head circumference for age in both girls and boys with and without congenital hypothyroidism

Variable	Age	Sex	Healthy	With CH	*P* value
Head circumference (cm)	0	Girls	34.49±1.30	34.18±2.00	0.41
		Boys	34.91±1.33	34.68±1.42	0.39
	2 months	Girls	38.62±1.18	37.37±2.83	0.008*
		Boys	39.19±1.17	38.51±1.61	0.053
	3 months	Girls	39.70±1.15	39.10±1.86	0.09
		Boys	40.50±1.19	40.02±1.57	0.08
	4 months	Girls	40.78±1.05	40.20±1.56	0.05*
		Boys	41.77±1.35	41.32±1.35	0.09
	6 months	Girls	42.51±1.19	42.09±1.45	0.18
		Boys	43.65±1.30	43.09±1.50	0.052
	9 months	Girls	44.34±1.31	43.91±1.27	0.21
		Boys	45.32±1.27	44.81±1.76	0.10
	1 year	Girls	45.61±1.24	45.11±0.95	0.11
		Boys	46.41±1.15	46.14±1.64	0.36
	1.5 years	Girls	47.04±1.45	46.58±1.17	0.25
		Boys	47.29±1.25	47.79±1.92	0.53
BMI	2 years	Girls	15.40±1.65	15.63±0.99	0.62
		Boys	16.27±2.29	15.53±1.04	0.10
	3 years	Girls	14.82±1.21	15.36±1.54	0.22
		Boys	15.30±1.34	15.24±1.12	0.83
	4 years	Girls	14.42±1.74	14.60±1.56	0.81
		Boys	15.26±1.44	15.29±1.66	0.77
	5 years	Girls	14.58±1.55	14.35±1.53	0.79
		Boys	14.53±1.61	15.48±2.19	0.16

Note. *Significant difference at the level of $P<0.05$; BMI: Body mass index; CH: Congenital hypothyroidism.

Table 3. Thyroid-stimulating hormone and T_4 in girls and boys with congenital hypothyroidism

Age	T4		TSH	
	Girls	Boys	Girls	Boys
0	79.47±38.03	86.04±18.31	42.16±33.40	20.39±13.44
2 months	161.98±49.03	137.39±45.76	3.84±5.30	3.534.58
3 months	120.51±39.68	122.47±20.34	7.47±11.98	2.68±2.76
4 months	145.01±54.13	130.20±28.53	0.66±1.21	1.20±2.16
6 months	109.53±13.42	125.61±25.22	2.97±5.38	2.70±3.10
9 months	121.24±38.72	110.23±14.44	1.30±1.32	1.91±1.64
1 year	101.21±15.21	105.39±10.23	3.22±3.22	2.26±1.37
1.5 years	110.55±21.36	121.37±23.81	2.06±1.68	3.07±1.65
2 years	112.1±16.2	106.28±13.45	2.38±1.079	2.73±2.41
3 years	131.28±34.40	112.47±34.79	1.09±1.06	2.80±1.68
4 years	107±19.7	131.1±28.13	1.20±1.8	2.81±0.83
5 years	114.3±20.2	127.38±26.23	3±1.9	4.91±3.21

Note. TSH: Thyroid stimulating hormone.

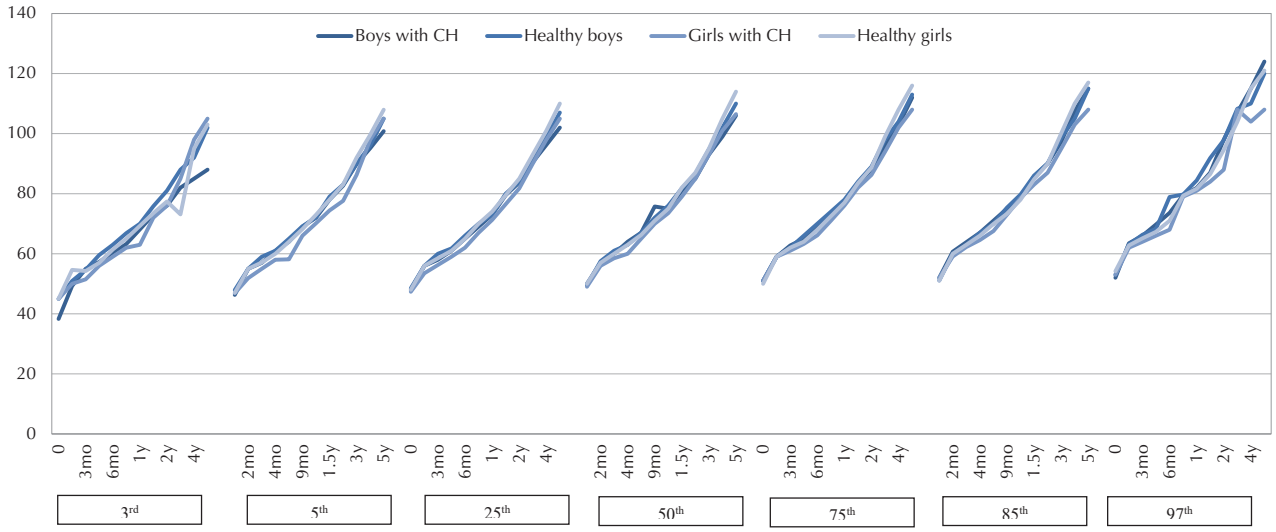

Figure 1. Height for age percentiles for both genders with and without congenital hypothyroidism.

compared to healthy children. Based on the results, the weight was higher in children with CH at the percentile of 85 at birth and 4 years of age in comparison with healthy children, while it was lower in the other age groups. Finally, the weight was higher in children with CH at the percentile of 97 at 2, 3, 4, 6, and 9 months, along with 4 and 5 years of age when compared to healthy children. In general, the weight was higher in boys with CH at high percentiles as compared to healthy children (Figure 2).

The head circumference at all percentiles and age groups was higher in healthy boys compared to boys with CH and the difference between the two groups was smaller at higher percentiles (Figure 3).

In addition, the head circumference was higher in healthy girls when compared to girls with CH. There were some exceptions regarding the head circumference at the percentile of 3 at 1 year and 1.5 years of age, at the percentile of 25 at 6 months of age, at the percentile of 50 at birth, at the percentile of 85 at birth and 6 months of age, and at the percentile of 97 at 3 months of age, which were higher in children with CH in comparison with healthy children.

The results further demonstrated that the BMI was higher in healthy boys at the percentile of 3 as compared to boys with CH in all age groups. At this percentile, the BMI was higher in girls with CH compared to their healthy counterparts in all age groups. At other percentiles, there was no specific order between the BMI of healthy children and those with CH in different age groups (Figure 4).

Discussion

This study comparatively assessed the growth indices of children with CH, who were diagnosed in the screening program and underwent levothyroxine treatment, and healthy children by the age of 5. According to the findings of this study, the height, weight, head circumference, and BMI of healthy children and children with CH were comparable and no significant difference was observed between these two groups. The head circumference and BMI of girls with CH and healthy girls were not significantly different, while the height and weight of girls with CH and healthy girls represented a significant difference. Regarding the weight of girls with CH, the difference was adjusted over time at the age of 9 months. Overall, the number of children with normal height, weight, BMI, and near normal head circumference can be increased through the timely diagnosis and treatment of children with CH in the studied area.

Various studies have shown that the growth pattern of children becomes normal through early treatment (17). The findings of the study by Grant on 472 children with CH in a period of 2 years demonstrated that the growth pattern became normal through early treatment (22). In the newborn screening program in Barcelona, no difference was reported in height, weight, and BMI between children with CH and the general population (23).

In another study, Sato et al evaluated the height, weight, and head circumference of 2341 children with CH and found that these children have similar growth to that of normal children (25). In one study in China, the height, weight, and BMI of children with CH from birth to 12 years of age were assessed and compared to those of the healthy children and the findings revealed that the height growth of the two groups was similar (27).

The findings of this study and the previous studies indicated that growth in children with CH becomes similar to that of healthy children through early treatment. In this study, the observed difference between girls with CH and healthy girls regarding height and weight may be due to the difference in levothyroxine dosage between girls and boys or unsatisfactory adherence, treatment measures, and follow-

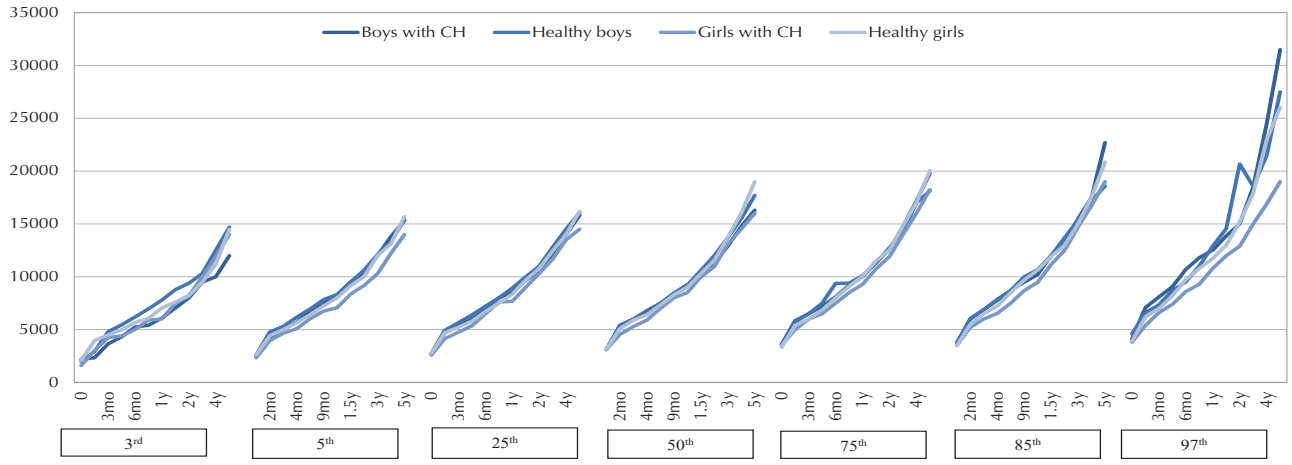

Figure 2. Weight for age percentiles for both genders with and without congenital hypothyroidism.

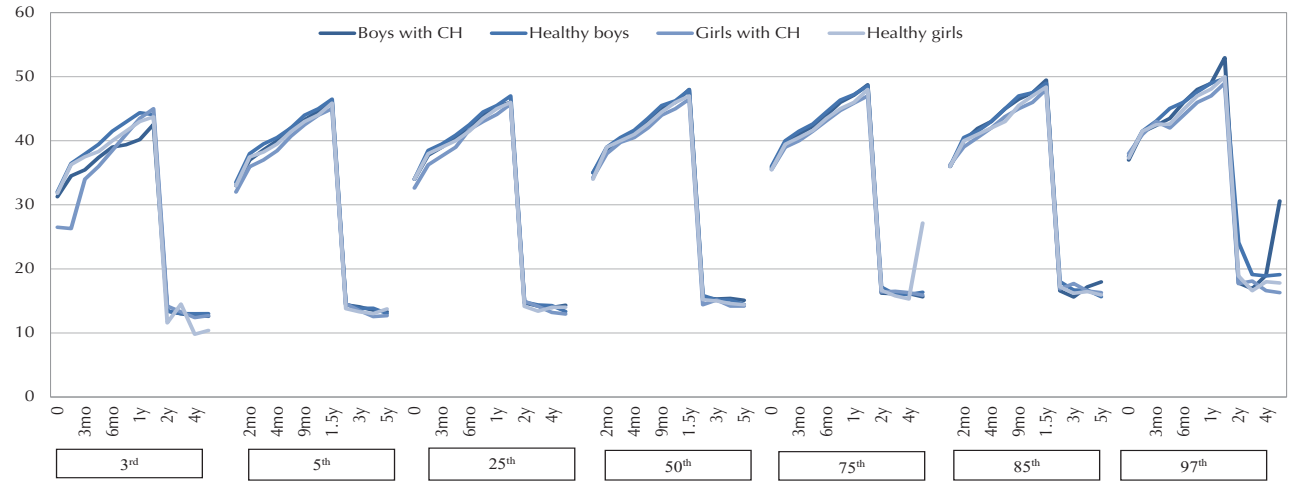

Figure 3. Head circumference for age percentiles for both genders with and without congenital hypothyroidism

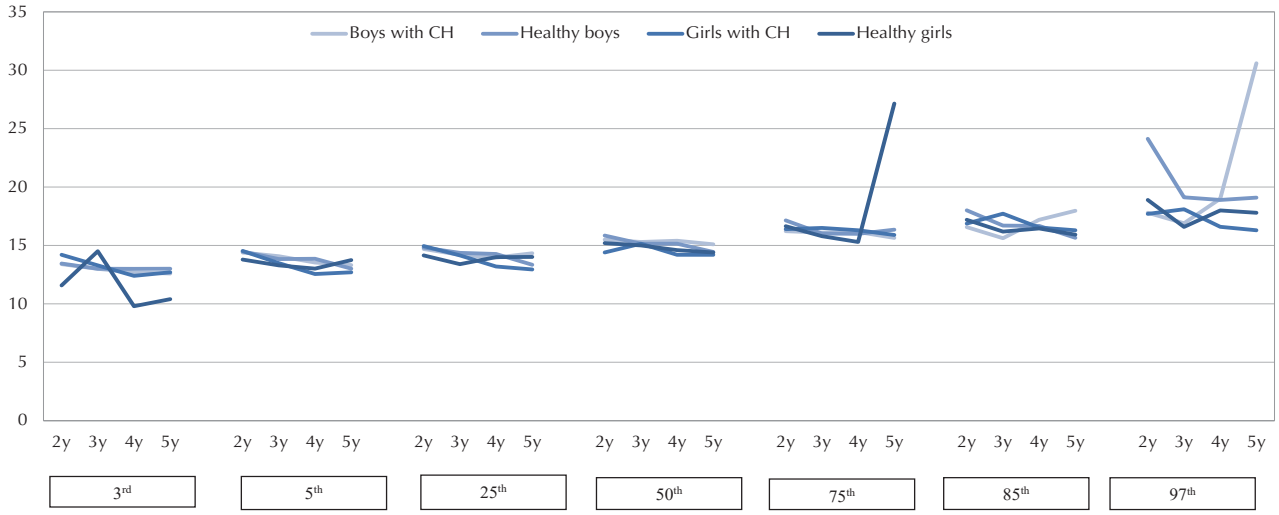

Figure 4. Body mass index for age percentiles for both genders with and without congenital hypothyroidism.

ups in girls. Aronson et al observed growth restriction in children with CH during the first year of life (20), which is inconsistent with the results of the above-cited studies. The findings of several studies have highlighted growth restriction in children with CH (21,28,29). In the study of Feizi et al, the specific growth indices in children with CH detected in the newborn screening program were assessed, indicating that the growth indices of children with CH were different from those of the healthy children (7). However, these differences were less pronounced at higher percentiles and the height, weight, head circumference, and BMI of children with CH became closer to those of the healthy children and therefore the difference became less pronounced by increasing age. This phenomenon occurs sooner for weight and later for head circumference (7). Regarding height, no significant difference was observed between boys with CH and healthy boys, although the height of females with CH was significantly lower than that of the healthy girls. Although in some studies no difference was reported in height growth in children with CH (15,25,27,29), the height at the age of 5 years became normal in the study of Feizi et al. Based on the findings of Moschini et al, the normal height growth of children occurred at 6 years of age and their mean age was 33 days at the beginning of treatment (21). In our study, the height of girls would become close to the normal value in subsequent follow-up sessions if any. In another study conducted in Liverpool, the height and head circumference of children with CH were assessed at 3 years of age and the findings revealed that the height in all children with CH was within a normal range and no growth disorder was observed regardless of the type and causes of the disease (15). The findings of a similar study conducted in Italy on the height growth, puberty, and final height of children with CH represented that the final height in all subjects with different etiologies of the disease was within a normal range (29). As regards weight, no significant difference was found between boys with CH and healthy ones. However, a difference in the weight of girls with CH was reported by the age of 9 months that was adjusted at higher ages. Feizi et al reported that weight in children did not reach the expected values by the age of 5 years but tended to indicate an increase (7). Sato et al indicated that children with CH had normal weight (25). Another research reported weight gain (29). The main cause of the observed weight gain in previous studies seems to be the inappropriate treatment or inadequate cooperation of parents during the treatment. As already argued, this observation could be unrelated to the linear growth of children afflicted with the disease (30). The head circumference up to the age of 1.5 years was lower in children with CH than in healthy children, although the difference was not statistically significant. In the study of Feizi et al, the head circumference of children with CH was lower than the normal value, while it became normal at the age of 3 years (7). However, this index was higher than normal in another study (15). This inconsistency may be due to the etiological differences of the disease in different countries (31). In Iran, the prevalence of the disease is higher than the worldwide standard. In our studied region, ethnic and racial differences exist and consanguineous marriage is common. Unlike the other regions, dyshormonogenesis is considered as the main cause of the disease in this region (32). In dyshormonogenesis, the hormones may first seem normal but then change to a hormone disorder. In a study in Qatar, 45 children with permanent CH were compared to the healthy children of the same age and no significant difference was reported in head circumference at birth and mean weight. In addition, the mean height of children with CH at the age of 5 years was significantly low compared to that of the children of the same age. The screening program accompanied with treatment led to the normal linear growth and appropriate mental development of the affected children (28).

Similarly, Lotfi et al found that the abnormal growth of height, weight, and head circumference was downward and no significant difference was reported in the growth disorders of the height, weight, and head circumference of children with CH and healthy children at the completion of 5 years according to the World Health Organization (WHO) standards (18).

Some studies investigated the growth indices of children with CH undergoing the treatment in accordance with the WHO standards (7,18). The present study comparatively investigated the height, weight, head circumference, and BMI of children with CH and healthy children from the same region. The data related to the comparison of the growth indices of children with CH and healthy children from the same region were compared and more reliable results were obtained accordingly. The findings of this study are consistent with those of studies conducted in Barcelona, Spain (23), and China (27), in which children with CH were compared with healthy controls from the same region. In a study conducted in the northwest of Iran, no significant difference was observed between the mean weight of children with CH and that of the healthy children at the age of beginning primary education, but the mean height of children with CH was significantly lower than that of the healthy children. On the other hand, the mean head circumference of children with CH at birth was slightly higher than that of the healthy children, although the difference was not statistically significant (33).

In this study, the BMI was assessed in children from the age of 2 years and no significant difference was observed between children with CH and healthy children among both girls and boys. In the study of Feizi et al, the BMI of the treatment group was lower than the expected values, which may be due to the impact of weight (7). In one study conducted in Greece, it was found that the BMI of children with CH in early childhood tends to become normal at the beginning of adolescence and the expected variations

of BMI during the first year of life in these children are not noticeable (24).

In this study, the reason for the high percentage of transient hypothyroidism in screening tests can be explained by low birth weight newborns and the mothers' use of certain treatments like those for asthma and disinfectants containing iodine before giving birth and undergoing caesarean section. However, this issue deserves further investigation.

Nonetheless, having knowledge about transient CH, either iatrogenic or non-iatrogenic, is effective in identifying the actual prevalence of permanent hypothyroidism, avoiding the excessive drug consumption, and seeking the family acceptance of permanent treatment.

Abnormal growth may be considered as a symptom of a chronic disease, malnutrition, or developmental and mental problems. Children suffering from severe and chronic communicable and non-communicable diseases are more predisposed to growth disorders compared to other children (34). Further, newborns with CH have normal appearance and develop few and nonspecific symptoms at birth. Therefore, to prevent the effects of hypothyroidism, it is recommended not to wait for its symptoms (35). The complications of CH may be prevented to a great extent through conducting the screening program and early diagnosis and treatment. The limitations of our study include the migration of some participants and the lack of access to some of their information, along with the lack of timely referral of some clients to health care centers based on the predetermined scheme regarding the assessment of their growth indices.

Conclusion

In this study, the height, weight, head circumference, and BMI of boys, as well as the head circumference and BMI of girls, were not significantly different from those of healthy controls, while the height and weight of girls were significantly different from those of healthy controls. However, the difference in weight was adjusted at the age of 9 months. In general, it can be argued that early diagnosis and treatment of newborns with CH will lead to the corrections of their growth indices. It is obvious that the age at the beginning of the treatment, the severity of the disease, and the dosage of the drug can contribute to differences between healthy and affected children.

Accordingly, future studies are recommended to assess the effects of age at the beginning of the treatment, as to by considering first medicine dosage and then the severity of the disease on the growth process of children, and subsequently compare the effective dosage of levothyroxine in boys and girls.

Conflict of Interests

None.

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Ethical Statement

The study protocol was approved by the Ethics Committee of Shahrekord University of Medical Sciences (code: IR.SKUMS. 92-11-20).

Authors Contribution

GP and AK and FG : designed the study, carried out data collection.
FG: participation in analysis and carried out data collection.
MA-M and MRMA: contributed to collected all of samples.
G P:contributed to study design and manuscript drafting.
All authors approved the final version manuscript.

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