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Longitudinal Growth Dynamics of Children with Congenital Hypothyroidism during Pre-school Years

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ABSTRACT

Background: *Congenital hypothyroidism (CH) defined as deficiency of thyroid hormone present at birth is a preventable cause for mental and growth retardation. Deceleration of growth is usually the first clinical manifestation of hypothyroidism in children, which often goes unrecognized. The complete absence of serial data on the auxological attainments of Indian children with congenital hypothyroidism, has prompted us to study longitudinal growth pattern of male and female children with congenital hypothyroidism(CH).*

Methods: *A total of 301 observations made on 114 children (Boys: 58, Girls:56) diagnosed as cases of CH, aged 1 to 5 years, enrolled from Pediatric Endocrinology Clinic of Advanced Pediatrics Centre, PGIMER, Chandigarh, India comprised sample for this mixed-longitudinal study. Weight, length/height, head circumference, mid-upper arm circumference(MUAC), triceps skinfold thickness (TSFT) and subscapular skinfold thickness (SSFT) measurements were recorded at 6 monthly age intervals using standardized techniques and instruments in Growth Laboratory/Growth Clinic. Mean (SD) for all anthropometric measurements were computed. Unpaired Student's t-test was employed to ascertain gender differences.*

Results: C*hildren with CH demonstrated regular increase in mean weight and length/height from 1 to 5 years. While, growth of BMI, MUAC and skinfold thicknesses showed an inconsistent increase. CH children remained lighter, shorter and had smaller head circumferences when contrasted with their normal MGRS counterparts and became short statured around 3 years of age. However, their BMI and TSFT measured more than their normal MGRS peers.*

Conclusions: C*hildren with CH in general, depicted impaired physical growth during pre-school years when contrasted with their normal peers. However, higher TSFT, BMI and an early age of adiposity rebound recorded for these children indicate a higher tendency to accumulate sub-cutaneous fat and greater risk of developing metabolic syndrome later in life. Further longitudinal studies need to be conducted to see the effect of disease on growth of these children beyond pre-school years.*

Keywords: Congenital Hypothyroidism, Pre-school years, Indian origin, Physical growth

INTRODUCTION

Congenital hypothyroidism (CH) defined as deficiency of thyroid hormone present at birth, affecting around 1 in every 3000 to 4000 newborns, is a preventable cause for mental and growth retardation (Rastogi & Lafranchi, 2010). Its prevalence varies with race/ethnicity and the method of screening (Haddow et al., 1999; Waller et al., 2000) and has been found to be 1 in 2640 in India (Desai, 1997) while, prevalence of subclinical hypothyroidism (SH) in the pediatric population is < 2%.

Deceleration of growth is usually the first clinical manifestation of hypothyroidism in children, which often goes unrecognized. Most babies with this disease have normal length and weight at birth, however, deceleration in linear growth and skeletal maturation can be noticed after 3 years of age. The prognosis of patients with congenital hypothyroidism appropriately treated within 6 weeks of birth is excellent. Failure to detect and treat at early stage may lead to growth retardation (Dalili et al., 2014). Besides, other signs and symptoms, slow growth, delayed osseous maturation, and increased weight are some important features of hypothyroidism (Olivieri et al., 2002). Severe stunting has been reported among 39% of children with hypothyroidism (Seshadri, 2012). However, children with acquired hypothyroidism who receive adequate treatment at least for 5 years before the onset of puberty typically achieve a final adult height consistent with their genetic potential. Hence, periodic growth monitoring becomes an essential tool for assessment of health status of children with CH.

Growth studies conducted by earlier researchers (Cetinkaya et al., 2003; Feizi et al., 2013; Morin et al., 2002; Ng et al., 2006; Aronson et al., 1990; Grant, 1994; Dickerman & DeVries, 1997; Kik & Noczynska., 2001; Soliman et al., 2012; Siragusa et al., 1996) report improvement in growth status of children with hypothyroidism with adequate thyroxine therapy. On the contrary, growth delay despite, therapy has also been reported (Bucher, 1985). A bipolar trend with regard to growth pattern of Norwegian children with congenital hypothyroidism was reported, wherein the authors observed reduction in growth during second half of infancy and increase in growth, thereafter (Heyerdahl et al., 1997). Thus, available evidence remains inconclusive and no clear picture with regard to growth pattern of children with congenital hypothyroidism emerges. In majority of the instances efforts have been made to report pattern of body weight and height growth and hardly any attempt has been made to unfold the auxological dynamics of other important parameters of children with

CH. The complete absence of serial data on the auxological attainments of Indian children with congenital hypothyroidism, has prompted us to study the growth pattern of these children by means of anthropometry.

MATERIAL AND METHODS

A total of 114 children (58 male, 56 female) aged 1 to 5 years, diagnosed as cases of congenital hypothyroidism (Soldin et al., 2009) comprised the sample for this mixed-longitudinal study. These children were enrolled from Pediatric Endocrinology Clinic of the Department where they come periodically to seek treatment. These children were on thyroxine therapy known to be bio-chemically euthyroid at the time of enrolment. Every child was included in the study after taking a written informed consent from his/her parents/care takers. Socioeconomic status of each patient was determined by using scale given by Kuppuswamy (Kumar et al., 2012). The study was approved by the Institutional Ethics Committee and Department Review Board.

Patients receiving other drugs (e.g Steroids, Insulin, Anti-epileptic drugs, Second generation anti-psychotic drugs, Selective Serotonin reuptake inhibitors, Chemotherapeutic drugs, Amiodarone, Acetazolamide, Amphotericin B) known to modify growth pattern were excluded. Patients with other causes for short stature, severe malnutrition (weight for age and height for age less than -2SD), with clinical features of micronutrient deficiency and having any neurological and physical disability also were excluded from this study.

Each child included in the study was measured for body weight (kg), crown-heel length/Height (cm), head circumference (cm), mid upper arm circumference (MUAC) (cm), triceps skinfold thickness (TSFT) (mm) and subscapular skinfold thickness (SSSFT) (mm) from January 2014 to July 2015 using standardized anthropometric techniques and instruments (Weiner & Lourie, 1969). Body Mass Index (kg/m^2), BMI of each child was calculated from body weight (kg) and length/height (cm) measurements. The magnitude of inter/intra rator error was ±50 g for weight, ±1 mm for length/ height and circumferential measurements, ±0.2 mm for skinfold thicknesses.

Every child was measured for these body parameters at the time of enrolment and subsequently at 6 monthly age intervals (tolerance limit ± 1 month) in the Growth Laboratory and Growth Clinic of Department of Pediatrics, PGIMER following mixed longitudinal growth research design (Tanner, 1977). Information with regard to dietary intake of every

child at each visit was recorded using 24 hours Dietary Recall Method. Necessary record of any disease/ailment experienced by the child and treatment given was also kept.

Statistical Considerations

Age and sex specific average distance (gross-size) growth attainments in terms of mean and standard deviation (SD) for each body parameter of male and female patients were computed. Student's unpaired t-test was employed to quantify gender differences. A p value less than 0.05 was considered as statistically significant.

RESULTS

A total of 301 observations obtained on the study subjects i.e. 147 on male (48.84%) and 154 on female (51.16%) children, examined at half-yearly follow-ups using mixed-longitudinal growth research design comprised data for this serial study. The study subjects representing north-western regions of India, were from lower middle (36.8%) and upper lower socioeconomic strata (35.08%) followed by upper middle (14.12%), lower (7.9%) and upper (6.1%) socio-economic classes. Mean (SD) computed for all body parameters of male and female children with CH are shown in Tables 1 & 2. The children with congenital hypothyroidism demonstrated regular increase in mean weight and length/ height from 1 to 5 years. While, the growth of BMI, MUAC and skinfold thicknesses showed an inconsistent increase in mean values. Barring 2.5 and 5.0 years for body weight ($p \leq 0.05$) and at 5.0 years for height ($p \leq 0.05$), gender differences for these two growth parameters remained statistically non-significant. Head circumference of both male and female children with CH, showed a gradual increase however, the rapidity of this increase became slower after around 2.5 years of age. Despite, depicting marginally higher mean values in female patients till 2.5 years the magnitude of gender difference for head circumference remained statistically non-significant (Table-3).

Mid-upper arm circumference in male children measured larger than their female peers except at 2.5 and 3.5 years however, gender differences never became statistically significant (Table-3). Female children with congenital hypothyroidism in general, had greater BMI than the male patients except from 2 to 3 and at 5 years of age. Gender differences remained statistically non-significant (Table-3).

Children with CH, generally, remained lighter, shorter and had smaller head circumferences when contrasted with their normal MGRS counterparts. However, their BMI

and triceps SFT measured more than their normal MGRS peers which points towards more accumulation of sub-cutaneous fat in children with congenital hypothyroidism.

DISCUSSION

The growth curves plotted for body weight (Fig 1) and CHL/height (Fig 2) of both male and female children with CH experienced a regular but inconsistent increase from 1 to 5 years. Male children in general, weighed marginally heavier and taller than females but gender differences did not approach statistically significant levels. These observations are in consonance with those of Soliman et al., 2012 and Adachi et al., 2003 who also noticed absence of gender difference, among CH patients of Qatar and Japanese origin, respectively.

The lighter body weight (Fig 1) and shorter CHL/height attainments (Fig 2) of our CH children than their normal MGRS counterparts confirms a compromised growth status of our study children who became short statured around 3 years of age as their height growth curve ran below the 3rd centile of MGRS standards. Our findings corroborate with those reported among Iranian children by Feizi et al., 2013; these authors attributed it to effect of disease severity, delayed start of therapy and poor compliance to medications. It is worth mentioning that in 53% of our study children treatment was started after 1 year of age (mean age of initiation of therapy being 17.58 months), which may be an important reason for growth impairment noticed in our children with CH. Poor height and weight growth catch up among children in whom therapy was started after 1 year of age (Bucher et al., 1985) also matches with our findings. Lower height and weight in children with hypothyroidism as compared to normal population was attributed to delayed start of treatment by Siragusa et al., 1996 amongst children who were treated on the basis of clinical manifestations of the disease. Above discussion shows that delayed start of therapy appears to be an important factor adversely affecting the physical growth attainment of children with CH. However, few studies conducted outside India (Cetinkaya et al., 2003; Feizi et al., 2013; Morin et al., 2002; Ng et al., 2006; Aronson et al., 1990; Grant, 1994; Dickerman & DeVries, 1997; Kik & Noczynska, 2001; Soliman et al., 2012; Siragusa et al., 1996) documented normalisation of growth amongst children with CH in whom treatment was started immediately after neonatal screening. In a study conducted by Butcher et al., 1985 who divided patients based on age of start of therapy, also confirms normalisation of growth in the group of children in whom treatment was started before 1 year of age.

Smaller head circumference among our male and female children as compared to normal MGRS children showed close resemblance with similar findings reported by Dalili et

al., 2014 and Feizi et al., 2013 among patients of Iranian origin upto first 3 years of life. At present no explanation could be offered to explain impaired head growth noticed in our patients but smaller head circumference noticed among Iranian subjects has been attributed to dyshormonogenesis (Dalili et al., 2014; Feizi et al 2013). This could also be the case in our current study.

Greater BMI recorded for male and female children with CH as compared to normal MGRS and American counterparts shows that our study subjects have tendency to be relatively fatter due to more accumulation of fat (Fig 3). Tendency to accumulate more fat in our children with CH also becomes evident from the acceleratory trend noticed for triceps and sub-scapular skinfold thicknesses beyond 3 years of age. A trend towards early adiposity rebound i.e. at the age of 3 years in female and 4 years in male children was also recorded among our children with CH. Similar findings of higher BMI in CH children have also been reported by Grant, 1994; Salerno et al., 2001; Kik et al., 2011 and Livadas et al., 2007. However, Grant, 1994 attributed it to be due to the ethnic differences between their study and control populations rather than the effect of the disease itself. While, Livadas et al., 2007 placed the effect of abnormal hormonal balance on the adipocytes as a reason for higher BMI and earlier age of adiposity rebound in these children. Though the exact cause for early adiposity rebound remains inconclusive, lack of BMI plasticity in these children due to effect of hypothyroidism may be a probable explanation.

Conclusions

It clearly emerges from aforementioned discussion that male and female children with congenital hypothyroidism in general, depict impaired physical growth during pre-school years when contrasted with their normal peers. However, higher triceps skinfold thickness, BMI and an early age of adiposity rebound recorded for these children with CH indicate a higher tendency to accumulate fat and a greater risk of developing metabolic syndrome later in life. However, further longitudinal studies need to be conducted to see the effect of disease on the growth of these children beyond pre-school years.

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Declaration

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Conflict of interest: None declared.

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Table 1: Mean and SD of Different Anthropometric Parameters in Male Children with Congenital Hypothyroidism.

Age	No. of Observations	Body Weight (kg)		CHL/Height (cm)		Head Circumference (cm)		MUAC (cm)		Triceps SFT (mm)		Sub-scapular SFT (mm)		BMI (kg/m^2)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1.0	15	08.51	1.81	71.35	5.93	44.46	1.82	14.10	1.33	8.26	1.04	5.64	0.80	16.60	2.48
1.5	15	10.19	2.27	75.70	7.65	45.77	1.79	14.85	1.07	9.20	1.00	6.04	1.08	17.67	2.72
2.0	17	11.47	2.57	81.46	8.70	46.69	2.04	14.81	1.12	8.78	1.42	5.64	1.25	17.23	2.63
2.5	11	12.86	1.66	85.24	5.65	47.15	0.78	14.05	1.26	9.25	1.52	5.43	1.28	17.86	3.21
3.0	14	11.97	2.19	86.05	5.79	47.44	1.58	14.14	1.38	8.71	1.74	5.11	1.36	16.09	1.90
3.5	7	12.50	1.76	88.90	4.86	48.66	1.45	13.86	1.02	9.14	2.02	5.71	1.80	15.78	1.28
4.0	17	14.70	2.87	97.60	5.75	49.42	2.07	14.87	1.21	8.95	1.19	5.80	1.16	15.38	1.73
4.5	23	15.64	2.07	100.81	5.10	49.58	1.76	15.27	1.23	8.70	1.72	5.71	1.40	15.36	1.42
5.0	28	17.36	2.35	103.83	6.48	49.77	0.92	15.57	1.27	9.50	1.40	6.37	1.25	16.11	1.68

Table 2: Mean, SD of Different Anthropometric Parameters in Female Children with Congenital Hypothyroidism.

Age	No. of Observations	Body Weight (kg)		CHL/Height (cm)		Head Circumference (cm)		MUAC (cm)		Triceps SFT (mm)		Sub-scapular SFT (mm)		BMI (kg/m^2)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1.0	18	08.76	2.97	71.02	8.89	44.83	1.46	13.79	1.55	8.40	1.74	5.43	1.52	16.94	2.32
1.5	18	10.57	2.79	76.78	7.89	46.06	0.95	14.28	1.49	9.17	1.23	6.12	1.30	17.73	2.30
2.0	20	11.13	2.84	81.08	7.80	46.74	1.37	14.42	1.33	9.03	1.82	5.96	1.48	16.78	2.34
2.5	12	11.24	1.90	83.87	6.17	47.62	1.18	13.62	3.68	9.32	1.39	6.40	1.15	15.90	1.36
3.0	10	11.47	1.90	85.58	9.53	46.92	1.26	13.60	1.13	7.80	1.45	5.16	1.01	15.71	1.54
3.5	9	13.92	3.16	90.44	6.12	47.59	1.91	14.33	1.44	9.07	1.12	5.89	0.61	17.15	4.51
4.0	21	14.70	2.87	94.47	94.47	48.79	1.82	14.86	1.56	8.56	1.30	5.43	1.30	16.50	3.04
4.5	16	15.75	3.20	97.04	7.70	49.38	1.58	15.40	1.25	8.41	1.66	5.88	1.56	16.74	3.16
5.0	30	15.81	2.31	99.41	6.19	49.75	1.58	15.25	0.99	8.46	1.75	5.77	1.12	15.97	1.52

Table 3: Gender Differences for Different Anthropometric Parameters in Male and Female Children with Congenital Hypothyroidism

Age	Body Weight (kg)	CHL/Height (cm)	Head Circumference (cm)	MUAC (cm)	Triceps SFT (mm)	Sub-scapular SFT (mm)	BMI (kg/m^2)
1.0	0.773	0.901	0.524	0.545	0.796	0.630	0.685
1.5	0.674	0.695	0.559	0.230	0.933	0.846	0.939
2.0	0.702	0.888	0.927	0.350	0.644	0.497	0.583
2.5	0.042*	0.583	0.286	0.712	0.919	0.072	0.066
3.0	0.564	0.882	0.402	0.324	0.189	0.929	0.604
3.5	0.307	0.594	0.241	0.472	0.925	0.788	0.452
4.0	1.000	0.175	0.319	0.985	0.344	0.363	0.187
4.5	0894	0.073	0.722	0.748	0.601	0.737	0.073
5.0	0.033*	0.025*	0.968	0.344	0.027*	0.101	0.767

*p≤0.05, **p≤0.01, ***p≤0.0001

Figures

Fig 1: Comparison of Body Weight (kg) of Male and Female Patients with Congenital Hypothyroidism and Normal Children

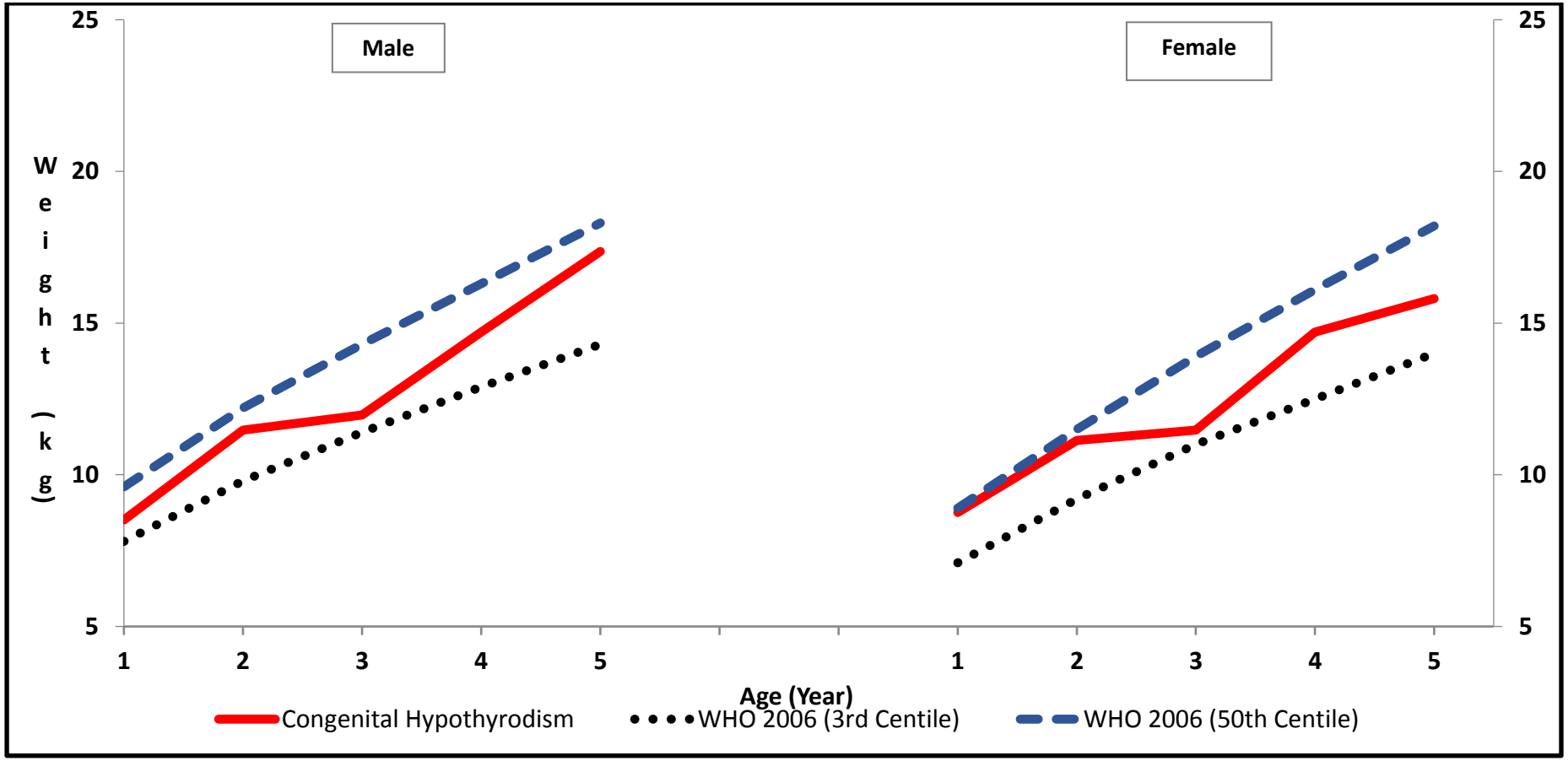

Fig 2: Comparison of Crown-heel Length/Height (cm) of Male and Female Patients with Congenital Hypothyroidism and Normal Children

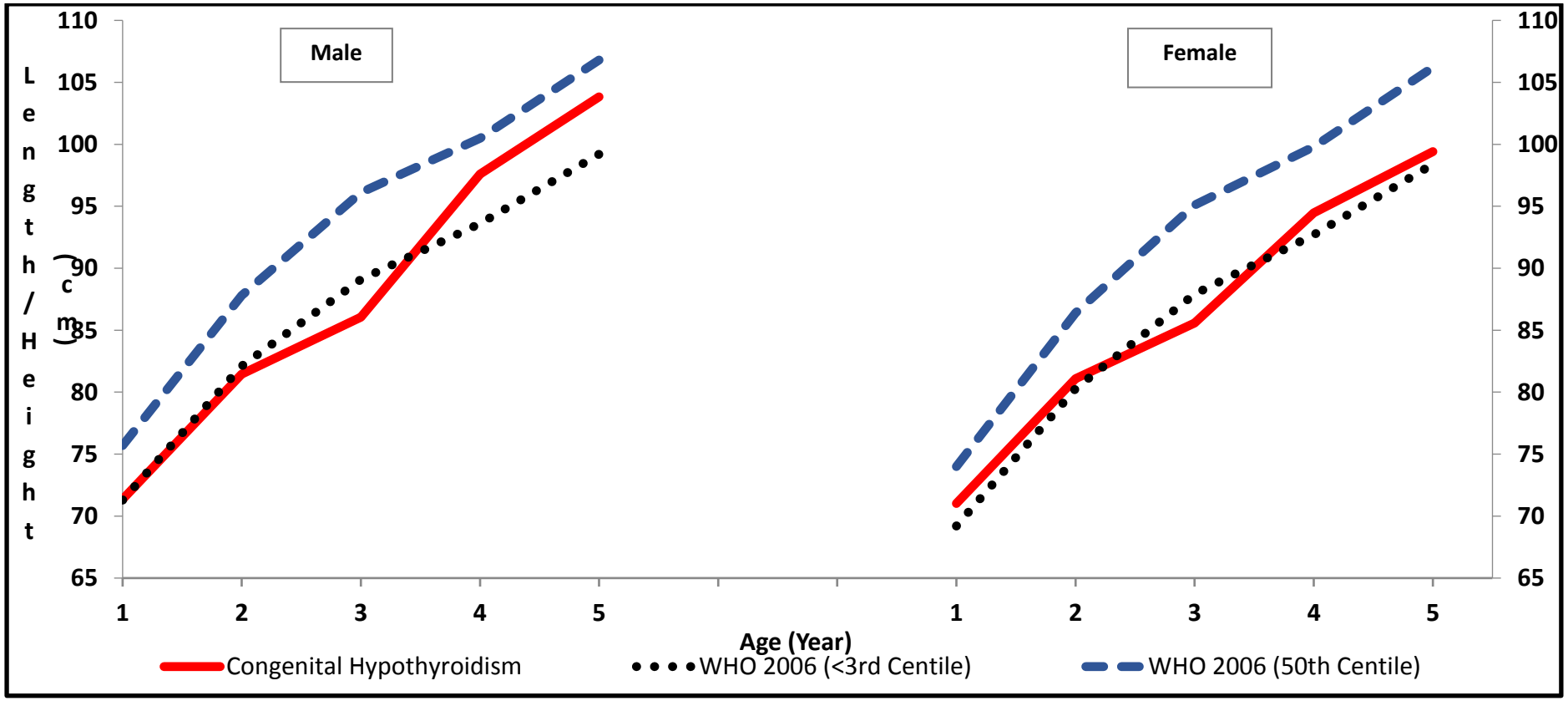

Fig 3: Comparison of Body Mass Index (kg/m^2) of Male and Female Patients with Congenital Hypothyroidism and Normal Children