Early Adiposity Rebound and Obesity in Children with Congenital Hypothyroidism

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Key Words
adiposity rebound; congenital hypothyroidism; obesity

Background: Earlier adiposity rebound (AR) is correlated with obesity. Our goal is to examine rates of obesity and AR in congenital hypothyroidism (CHT) and analyze the risk factors of obesity.

Methods: We retrospectively reviewed the cases with abnormal newborn screens of thyroid-stimulating hormone (TSH) from 1990 to 2005 and enrolled permanent CHT patients who continued to receive treatment after the 3rd year of life. We determined subgroups of obesity/being overweight and normal body mass index (BMI) by the latest BMI at 6–7 years of age. BMI at each age and the age of AR were compared with the general population in Taiwan. The statistical correlation of obesity with the age and BMI at both AR and first peak, and thyroid function was calculated.

Results: A total of 90 cases of CHT were enrolled. The prevalence of obesity/being overweight was 32.2%. The age of AR was 4.94 ± 1.81 and 4.58 ± 1.86 years old in boys and girls, respectively. The age of AR in the girls with CHT was earlier than in girls in general, but no statistical significance was found in boys with CHT compared to the general population. Obesity was correlated with earlier age of AR, higher BMI at first peak and AR, and lower T4 after treatment, but not with the age of first peak of BMI, T4/TSH at diagnosis and AR, and TSH after treatment.

Conclusion: Children with CHT have a higher risk of obesity due to earlier age of AR. We recommend that supervision and intervention on weight control should be provided to prevent the occurrence of obesity later.

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1. Introduction

All newborns in Taiwan have received a nationwide screen since 1985, and thyroid function is assessed using a primary thyroid-stimulating hormone (TSH) approach on filter paper. If the TSH level of the initial blood spot is $>40$ mU/mL in the first screen or remains within 10–40 mU/mL in repeated screens, infants are referred to a pediatric endocrinologist for further assessment. Plasma T4, T3, and TSH are measured at the first visit, and the thyroid image examination is performed to confirm the diagnosis. Hypothyroidism is diagnosed if the plasma TSH level is $>10$ mU/mL or TS4 is $<6$ μg/dL. For patients with congenital hypothyroidism (CHT), early treatment with levothyroxine (L-T4) can prevent brain damage and subnormal intelligence quotients. L-T4 supplement can also lead to normal adult height and normal sexual development. Some reports have found that patients with CHT are heavier than the general population during childhood and adolescence. However, the relationship between obesity and CHT is not well established.

Among children in general, body mass index (BMI) increases rapidly in infancy and peaks at around the 1st year of life. After the first BMI peak, BMI decreases gradually and reaches a nadir on average at around 5 years of age. The point of BMI nadir is defined as the adiposity rebound (AR). Earlier AR is associated with higher BMI in later life. One previous report found that children with CHT had an earlier AR than the general population. However, no studies have focused on the prevalence of obesity, timing of AR, and the relationship of obesity with thyroid function after treatment of CHT. The purposes of this study were, therefore, to determine the rate of obesity and AR in children with CHT, and to analyze the risk factors related to obesity.

2. Methods

2.1. Patients

We collected all cases of patients with abnormal newborn screens of TSH that were referred to the National Cheng Kung University Hospital in Taiwan from 1990 to 2005. The medical records and growth curves were retrospectively reviewed to analyze BMI from infancy to late childhood. Patients with other congenital anomalies or associated disorders were excluded due to possible confounding factors on their growth. There were a total of 299 referral cases of patients with abnormal newborn screens of TSH. Of these, the 132 cases who showed normalization of thyroid function in confirmed tests after birth, and the 77 cases who did not require L-T4 supplement after the 3rd year of life were classified as transient hypothyroidism. We finally enrolled 90 patients with permanent CHT who met the criteria for this study (Figure 1). Our study was approved by the institutional review board of the National Cheng Kung University Hospital.

2.2. Determination of obesity and timing of AR

Growth and thyroid function were assessed at each outpatient visit every 2–4 months in the first 3 years of life, and bi-annually after 3 years of age. We measured supine length up to about 2 years of age, after which we shifted to standing height. BMI was calculated for each measurement based on weight/height² (kg/m²). The patients with CHT were divided into subgroups of those with obesity/who were overweight (with a BMI above the 85th percentile of the general population) and those with a normal BMI (with a BMI below the 85th percentile), according to the latest BMI at 6–7 years of age by Taiwanese standards. AR was

![Figure 1](image_url)  
**Figure 1**  Patient enrolment and the prevalence of obesity/being overweight in children with congenital hypothyroidism. *Transient hypothyroidism was defined as patients who did not require a levo-thyroxine supplement after the 3rd year of life. †Obesity/overweight was defined according to the latest BMI at age 6–7 years old in comparison with growth charts for Taiwanese children. Obesity/overweight means a BMI that is $>\text{the 85}^{\text{th}}$ percentile, while normal BMI means a BMI $<\text{the 85}^{\text{th}}$ percentile. In more detail, obesity means a BMI that is $>\text{the 97}^{\text{th}}$ percentile, and overweight means a BMI that is between the 85th and 97th percentile. BMI = body mass index.
determined according to previous literature; an individual plot of BMI against age was constructed for each patient using Microsoft Excel, and the exact point of the nadir of BMI following the initial peak was determined. The BMI after that nadir point must show an increase, and this increase has to be $>0.1 \text{kg/m}^2$, to exclude random fluctuations due to inaccuracies in measurements.

2.3. Statistical analysis

Data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). We compared the age of AR and BMI at each age in children with CHT against the general population in Taiwan by one-sample $t$ test. Variables, including birth weight, mean BMI, age of AR and first peak, and mean thyroid function, were analyzed using the independent-sample $t$ test. As T4, TSH, and BMI were serial data, we studied their correlation with generalized estimating equation analysis. The Spearman correlation coefficient was used to study the relationship between BMI at 5 to 10 years of age and percentage BMI changes from first peak to nadir in boys and girls with CHT. Statistical significance was taken as a $p$ value of $<0.05$.

3. Results

3.1. Characteristics of patients and prevalence of obesity

In total, 33 males and 57 females with CHT were enrolled in this study. The number of obese/overweight patients and those with a normal BMI in the CHT group was 29 and 61, respectively (Figure 1). The prevalence of obesity/being overweight at the age of 6–7 years old was 30.3% in boys with CHT and 33.3% in girls with CHT, with a total prevalence of 32.2%. The anthropometric characteristics are listed in Table 1. No difference in birth body weight and parental BMI was noted between the subgroups of obese/overweight patients and those with a normal BMI.

3.2. Longitudinal BMI at each age and comparison of timing of AR

Mean BMI at each age was studied until the age of 10 years old (Table 2). Among girls with CHT, mean BMI was above the 50th percentile of BMI in the general population from age 2 to 10 years old. This difference was also statistically significant among boys with CHT from age 2 to 4 years old.

Figure 2A and B show the curve produced by fitting the mean BMI to the age of children with CHT and the 50th percentile of BMI in the general population. The absolute and percentage BMI changes from first peak to nadir in boys with CHT were $-3.08 \pm 1.21$ and $-17.21 \pm 5.87\%$, respectively, while in girls with CHT the corresponding values were $-2.75 \pm 1.23$ and $-15.46 \pm 6.63\%$, respectively. The mean age of AR was 4.94 $\pm$ 1.81 years old in boys with CHT and 4.58 $\pm$ 1.86 years old in girls with CHT. The mean age of AR in girls with CHT was earlier than that in the girls of the general population with BMI in the 50th percentile [4.58 $\pm$ 1.86 vs. 5.67 years old; $p < 0.001$ (Figure 2B)]. In the subgroup of obese/overweight girls with CHT, the mean age of AR was also lower than that in the girls of the general population with a BMI in the 97th percentile (3.17 $\pm$ 1.38 vs. 3.92 years old, $p = 0.034$). Similar results were obtained in the subgroup of obese/overweight boys with CHT.

### Table 1: Characteristics of subgroups of obese/overweight and normal weight children with congenital hypothyroidism.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Obese/Overweight*</th>
<th>Normal BMI*</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth body weight (g)</td>
<td>21 3092.90 $\pm$ 418.31</td>
<td>44 3081.93 $\pm$ 457.59</td>
<td>0.926</td>
</tr>
<tr>
<td>BMI of father (kg/m²)</td>
<td>21 25.25 $\pm$ 3.50</td>
<td>46 24.29 $\pm$ 3.26</td>
<td>0.284</td>
</tr>
<tr>
<td>BMI of mother (kg/m²)</td>
<td>20 22.53 $\pm$ 4.68</td>
<td>46 21.92 $\pm$ 3.91</td>
<td>0.586</td>
</tr>
<tr>
<td>Age of AR (years)</td>
<td>28 3.18 $\pm$ 1.26</td>
<td>61 5.42 $\pm$ 1.63</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>BMI at AR (kg/m²)</td>
<td>28 16.07 $\pm$ 1.47</td>
<td>61 14.20 $\pm$ 1.00</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Age of 1st peak (years)</td>
<td>28 1.16 $\pm$ 0.85</td>
<td>61 1.10 $\pm$ 0.72</td>
<td>0.721</td>
</tr>
<tr>
<td>BMI at 1st peak (kg/m²)</td>
<td>28 18.46 $\pm$ 2.05</td>
<td>61 17.30 $\pm$ 1.20</td>
<td>0.001</td>
</tr>
<tr>
<td>TSH (screen) (µU/mL)</td>
<td>22 89.15 $\pm$ 73.96</td>
<td>43 124.96 $\pm$ 105.31</td>
<td>0.160</td>
</tr>
<tr>
<td>Initial TSH (µU/mL)</td>
<td>28 147.87 $\pm$ 99.73</td>
<td>59 169.91 $\pm$ 97.94</td>
<td>0.332</td>
</tr>
<tr>
<td>Initial T4 (µg/dL)</td>
<td>28 4.76 $\pm$ 2.93</td>
<td>60 4.08 $\pm$ 3.22</td>
<td>0.346</td>
</tr>
<tr>
<td>Initial T3 (ng/dL)</td>
<td>23 104.49 $\pm$ 53.48</td>
<td>47 94.47 $\pm$ 44.87</td>
<td>0.413</td>
</tr>
<tr>
<td>TSH at AR (µU/mL)</td>
<td>28 3.11 $\pm$ 3.23</td>
<td>61 4.43 $\pm$ 9.14</td>
<td>0.461</td>
</tr>
<tr>
<td>T4 at AR (µg/dL)</td>
<td>28 10.97 $\pm$ 2.14</td>
<td>61 11.33 $\pm$ 2.63</td>
<td>0.523</td>
</tr>
<tr>
<td>Following TSH before AR (µU/mL)</td>
<td>28 4.97 $\pm$ 3.86</td>
<td>61 8.22 $\pm$ 8.56</td>
<td>0.059</td>
</tr>
<tr>
<td>Following T4 before AR (µU/mL)</td>
<td>28 10.88 $\pm$ 1.23</td>
<td>61 11.38 $\pm$ 1.83</td>
<td>0.187</td>
</tr>
<tr>
<td>Following TSH before 7 years of age (µU/mL)</td>
<td>28 6.99 $\pm$ 6.72</td>
<td>61 7.61 $\pm$ 6.36</td>
<td>0.675</td>
</tr>
<tr>
<td>Following T4 before 7 years of age (µg/dL)</td>
<td>28 10.36 $\pm$ 1.09</td>
<td>61 11.26 $\pm$ 1.72</td>
<td>0.013</td>
</tr>
</tbody>
</table>

AR = adiposity rebound; BMI = body mass index; SD = standard deviation; TSH = thyroid-stimulating hormone.

* Obese/overweight means a BMI that is $>85\%$, while normal BMI means a BMI that is $<85\%$, according to the latest BMI at 6 to 7 years of age by Taiwanese growth charts. 

1 One case was excluded due to incomplete records before 6 years old.

2 Significant difference.
(3.20 ± 1.09 vs. 4.92 years old in boys of the general population with a BMI in the 97th percentile, \( p = 0.001 \)), although no statistical significance was noted in the total boys with CHT (4.94 ± 1.81 compared with 5.08 years old in the boys of the general population with a BMI in the 50th percentile; \( p = 0.659 \)).

### 3.3. Correlation of obesity with AR, first peak of BMI, and initial thyroid function

Table 1 shows a comparison of AR, first peak of BMI, initial thyroid function at diagnosis, T4/TSH at AR, and the following T4/TSH before AR and 7 years of age between children with CHT who were obese/overweight and those who had a normal BMI. The age that AR occurred was 3.18 ± 1.26 years old in the subgroup of obese/overweight children, which was earlier than in the subgroup of children with a normal BMI (5.42 ± 1.63 years old; \( p < 0.001 \)). The BMI value at AR in the subgroup of obese/overweight children was higher than that in the subgroup with normal BMI (16.07 ± 1.47 vs. 14.20 ± 1.00 kg/m²; \( p < 0.001 \)). A comparison of BMI values at the first peak of BMI also yielded similar results (18.46 ± 2.05 vs. 17.30 ± 1.20 kg/m², \( p = 0.001 \)). The following T4 level before 7 years of age in the subgroup of obese/overweight children was 10.36 ± 1.09 μg/dL, which was lower than the value of 11.26 ± 1.72 μg/dL in the subgroup with normal BMI (\( p = 0.013 \)). No difference was noted in the age of first peak of BMI, initial thyroid function, T4/TSH at AR, mean T4/TSH before AR, and following TSH level before 7 years of age.

After generalized estimating equation analysis of the serial data, obesity before 7 years of age was associated with the age of AR (\( p < 0.001 \)), BMI at AR (\( p < 0.001 \)), BMI at first peak of BMI (\( p < 0.001 \)), and the following T4 before 7 years of age (\( p < 0.001 \)). There was no statistical evidence linking TSH level and obesity (\( p = 0.1088 \)).

Figure 3A and B represent the correlation of BMI at the age of 7 years with the age of AR (\( r = -0.723, p < 0.001 \)) and BMI at AR (\( r = 0.751, p < 0.001 \)) in patients with CHT, respectively. This significant correlation can also be noted from the ages of 5 to 10 years (data not shown).

### 4. Discussion

In our study, the prevalence of obesity/being overweight among 6–7-year-old children with CHT was 32.2%. Chu et al. reported the prevalence of obesity/being overweight among 7-year-old children in general in Taiwan to be 21.4% in 2007. The prevalence of obesity/being overweight seemed higher in children with CHT.

Our study also showed that the mean BMI of girls with CHT from the ages of 2 to 10 and boys with CHT from the ages of 2 to 4 was higher than the 50th percentile of the general population. Salerno et al. reported that the BMI values of 55 children with CHT were higher than the 95th percentile of the general population during the first 6 years of life, while they remained between the 50th and 80th percentile of the general population in the postpubertal period until adulthood. Livadas et al. reported that 152 children with CHT were heavier than their peers during the first 4 years of life, but not subsequently. All of these results suggest that children with CHT are heavier than the general population at preschool age, but not after that.

In analysis of AR, our percentage BMI changes were significant, with 17.21 ± 5.87% and 15.46 ± 6.63% in boys and girls with CHT, respectively. Wong et al. analyzed AR in CHT patients, and they also found obvious AR. However, Livadas et al. found that the slope of the BMI curve in children with CHT from first peak to nadir was blunted so that AR was less evident. In their study, the percentage change from peak to nadir was 7.5% and 8.6% in CHT-affected boys and girls, respectively, whereas the change for boys and girls not affected by CHT was 15.9% and 13.8%, respectively. AR is most likely genetically programmed but modifiable by the hormones and environmental factors. The variations of AR in children with CHT may be related to ethnic or environmental differences.

The mean age of AR in the girls with CHT in our study was significantly lower than that of the girls in the general population with a BMI at the 50th percentile. AR also occurred at a lower age in our subgroups of obese/overweight CHT-affected boys and girls than the general population.
population with a BMI in the 97th percentile. No statistical significance was noted in boys with CHT, and this may be related to the limited case numbers. Wong et al. found that, by the age of 49 months, 54.7% of children with CHT had reached AR, compared with 21.4% of children not affected by CHT. These results indicate that the age of AR in children with CHT occurs earlier than in the general population. Since early AR is associated with an increased risk of adult obesity, children with CHT may have the potential of a higher BMI.

There are some concerns about weight in children who experience their AR earlier, which may lead parents to encourage higher amounts of caloric intake during the period when BMI is declining prior to AR. This explanation could not be applied to children with CHT because their BMI was higher than children in general at a young age.

In analysis of the risk factors of obesity in children with CHT, we did not find any significant correlations with the age of first BMI peak, TSH levels at newborn screens, initial confirmatory thyroid function test, T4/TSH at AR, and mean T4/TSH before AR. Obesity was related to lower following T4 in our study. The thyroid function in the children with CHT in our study was kept within a normal range, but relatively lower T4 may influence weight and AR indirectly through positive energy balance from slower body metabolism despite similar amounts of food. We did not find a correlation of obesity with the following TSH. In the study of subclinical hypothyroidism, median TSH was higher in obese/overweight patients than in normal-weight ones. Further prospective studies may be needed to determine...
the effects of following TSH on the obesity of children with CHT.

In our study, there are certain limitations that must be discussed. As the National Cheng Kung University Hospital is a referral center, our patients came from different areas in Taiwan. Therefore, we used the age-matched data of the general population from published references of Taiwanese children to compare with our children with CHT. Furthermore, it was difficult to observe the effects of AR on tendency of obesity if we defined subgroups of obese/overweight children according to BMI at too early an age. We used the latest BMI at 6–7 years of age because we had 84 patients with complete growth charts up to 7 years of age. In analysis of these 84 CHT-affected children, only three out of 60 patients with a normal BMI at 7 years old were overweight at the age of 6 years, but the other children maintained their BMI.

In conclusion, children with CHT have a higher risk of obesity due to AR occurring at an earlier age than the general population. However, the occurrence of obesity may be prevented if early supervision or intervention is provided during regular follow-up in outpatient clinics.

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References