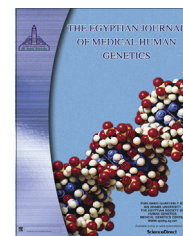




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ORIGINAL ARTICLE

# Leptin, insulin like growth factor-1 and thyroid profile in a studied sample of Egyptian children with Down syndrome

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## KEYWORDS

Leptin;  
IGF-I;  
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FT4;  
Obesity;  
Down syndrome

**Abstract** *Background:* Several mechanisms have been suggested for obesity in Down syndrome.

*Aim of the study:* Assessment of serum levels of leptin, insulin like growth factor-I (IGF-I), thyroid stimulating hormone (TSH) and free thyroxin (FT4) in a prepubertal Egyptian sample of children with DS compared to their age and sex matched healthy controls and sibs of some of them.

*Subjects and methods:* A prospective case control study was conducted on 80 children, classified as follows: Groups I & II: enrolled 20 cases with DS for each, sibs were studied only for group I, Group III: 20 healthy siblings of group I, and Group IV: 20 healthy controls. Anthropometric measurements, serum leptin, IGF-1, TSH, and FT4 assessment using enzyme linked immuno-sorbent assay (ELISA) were carried out for all studied children.

*Results:* DS children whether with studied sibs or without studied sibs had significantly higher mean values of leptin levels compared to sibs of group I & IV ( $P = 0.0001$  for all). Meanwhile, mean values of IGF-I showed statistically insignificant differences between all studied groups ( $p > 0.05$  for all). Studied DS children whether with studied sibs or without studied sibs had significantly higher mean values of TSH levels compared to sibs of group I and controls ( $P = 0.0001$  for all). Mean values of FT4 were significantly higher in enrolled DS without their studied sibs compared to sibs of group I ( $p = 0.01$ ), while mean values of FT4 were significantly lower in sibs of group I compared to controls ( $p = 0.001$ ).

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**Conclusion:** Serum leptin levels were significantly higher in studied DS children compared to both studied sibs and healthy controls and they were also positively correlated with BMI in studied DS children and their sibs highlighting a possible role of body fat% and leptin values in the pathogenesis of obesity in DS children.

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## 1. Introduction

Down syndrome (DS) is the most common chromosomal anomaly among live-born infants, occurring at a frequency of one in 700 live births [1]. Individuals with DS are at increased risk for several endocrinological conditions, including hypothyroidism, growth retardation, diabetes mellitus, and obesity [2,3]. The reason for the increased risk of obesity in DS individuals is unclear, but several mechanisms have been suggested, including a decreased resting metabolic rate [4,5], and differences in physical activity patterns [6]. With the increase in the life expectancy of people with DS, obesity and related morbidity and mortality are emerging as important long term consequences [3]. Adipokines such as leptin have been implicated in the pathophysiology of obesity. Leptin is a hormone secreted by adipocytes, acting in the hypothalamus to suppress appetite and regulate body weight [7]. It is positively correlated with percentage of body fat; thus, it is postulated that obese individuals have some degree of leptin resistance [8]. It is unclear whether this mechanism is also at work in children with DS.

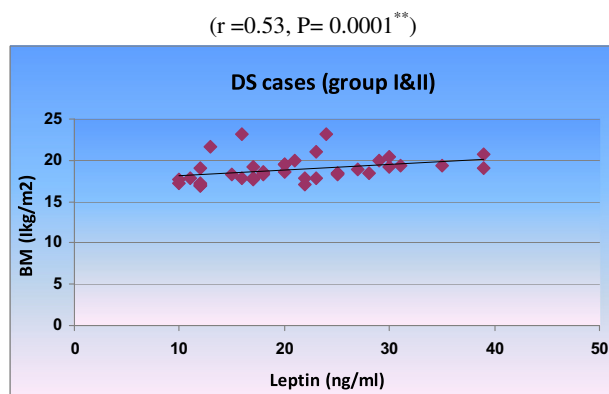
The current study was carried out in accordance to the code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. This study was also done after taking consent of legal caregivers of enrolled patients and controls as well as the acceptance of the Ethics Committee of our University. It aimed at the assessment of serum levels of leptin, IGF-I (insulin like growth factor-I), and thyroid profile (TSH&FT4) in a sample of prepubertal Egyptian children with Down syndrome compared to their age and sex matched healthy controls and the sibs of some of them in order to investigate the hormonal mechanisms of obesity in DS children.

## 2. Subjects and methods

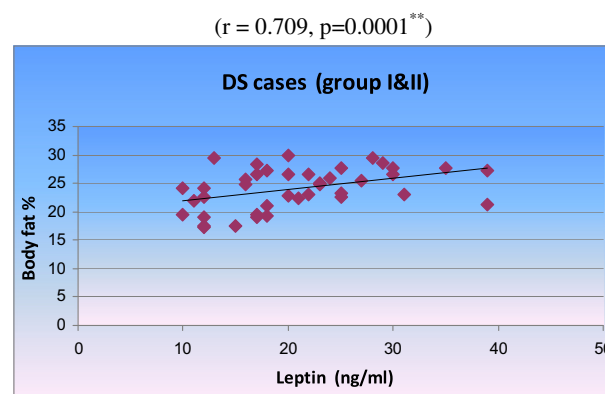
The present study was designed to be a prospective case control study that was conducted on 80 children. They were classified into four groups: *Group I*: included 20 cases with DS whose siblings were studied as well; 9 males (45%) and 11 females (55%). Their ages ranged from 3 to 10 years with a mean value of  $6.4 \pm 2.3$  years. *Group II*: included 20 cases with DS without studied siblings; 10 males (50%) and 10 females (50%). Their ages ranged from 3 to 11 years with a mean value of  $7.1 \pm 2.6$  years. Children of both groups were recruited from the Special Needs Clinic, Ahmed Maher Teaching Hospital and Special Needs Unit, Institute of Postgraduate of Childhood Studies, Ain Shams University during the period of clinical part of the study from January 2011 to May 2011. *Group III*: included 20 healthy siblings of group I; 6 males (30%) and 14 females (70%). Their ages ranged from 5 to 11 years with a mean value of  $9.06 \pm 1.7$  years. *Group IV*: included 20 healthy control children; 10 males (50%) and 10 females (50%). Their ages ranged from 3.75 to 10.5 years with a mean value of  $6.6 \pm 1.9$  years. They were sibs of outpatients attending the Pediatrics Clinic, Ahmed Maher Teaching Hospital during the clinical period of study from January 2011 to May 2011.

Inclusion criterion for all studied children was a BMI between 5th to 95th percentile for age and sex. Exclusion criteria for DS cases (group I & II): Down syndrome associated with (1) cancer including leukemia, (2) congenital heart disease necessitating open heart surgery, (3) children with history of intestinal resection or (4) other chronic conditions affecting the growth or energy balance.

All children enrolled in the current study were subjected to the following: (I) full history taking: laying stress on age, sex, consanguinity, dietetic history, history of perinatal hazards,



**Figure 1** Statistically significant positive correlation recorded between serum leptin (ng/l) levels and BMI ( $\text{kg/m}^2$ ) of all studied DS cases (group I & II). ( $r = 0.53, P = 0.0001^{**}$ ).



**Figure 2** Statistically significant positive correlation recorded between serum leptin (ng/l) levels and body fat% of all DS cases (group I & II). ( $r = 0.709, p = 0.0001^{**}$ ).

past history of any important illness or event and family history of similar conditions, (II) thorough clinical examination with special emphasis on: general and all body systems' examination: including chest, heart, abdomen and neurological evaluation, (III) auxological assessment including measurements of weight (in kilograms), height (in meter), BMI and skin fold thickness. Weight was recorded while subjects of the study were wearing light clothes as possible with no shoes [9]. Height: each subject was measured with his head in the frankfort plane (look straight ahead), heels, knees, buttocks and head touching the vertical plane with the feet close together without shoes. Hats and head ornaments were removed. Three recordings were done and the average was calculated [9]. BMI was calculated as weight in kilogram divided by height in meter squared [10]. Skin fold thickness is useful in determining not only the amount of subcutaneous fat but also of total body fat [11]. There were certain sites in the body that were chosen for measurement but the technique was the same for all. Skin fold thickness was measured by using skinfold calipers. The skinfold was firmly grasped and slightly lifted up between the index finger and thumb of the left hand, care being taken not to include the underlying muscles. The skinfold caliper was applied about 1 cm below operator's fingers at a depth equal to the skinfold. The dial was read approximately 4 s after the pressure from operator's hands released on the lever arm of the caliper [12]. The caliper exerted a constant pressure (10 gm/mm<sup>2</sup>) through the whole range of skinfold thickness at all distances of separation of jaws. Three readings were taken for the same area and the average was calculated [13]. Triceps, biceps, subscapular, and supra iliac skinfolds were measured. In this study the used caliper was slim guide caliper. (IV) Blood samples were withdrawn after 12 h overnight fast from all children, centrifuged and sera were separated and stored in -20 °C for subsequent use. Measurement of serum levels of leptin, IGF-I, TSH and FT4 using kits for ELISA (Enzyme Linked Immuno-sorbent Assay) was carried out for all studied children.

All statistical analyses were performed using the *Statistical package for social science (SPSS) program version 16 (2007)* [14]. Chi-Square test X<sup>2</sup> was used to compare categorical or qualitative variables between different studied groups. Student's t-test was used to compare quantitative parametric vari-

ables between different studied groups. The correlation coefficient (r) was calculated and used to correlate different studied parametric variables. Probability (p) value: p values were considered statistically insignificant when p values > 0.05, significant at p values < 0.05, and highly significant at P values < 0.01.

### 3. Results

There were statistically non significant differences between DS cases with studied sibs, DS cases without studied sibs and healthy controls as regards age distribution ( $P > 0.05$ ). On the other hand, mean values of age were significantly lower in DS cases with studied sibs, DS cases without studied sib, and healthy controls compared to sibs of group I ( $P = 0.0001, 0.01, \text{ and } 0.0001$ , respectively). The statistical analysis of the obtained data showed also non significant differences between studied groups as regards sex distribution ( $p > 0.05$ ). Consanguinity rate was 15% in DS cases with studied sibs compared to 20% in DS cases without studied sibs and 10% in healthy controls ( $p > 0.05$  for all). Family history of obesity was encountered in 7 DS cases with studied sibs (35%) compared to 4 cases (20%) of DS cases without studied sibs and 6 cases (30%) of healthy controls ( $p > 0.05$  for all).

Mean values of BMI were significantly higher in DS cases with studied sibs compared to their sibs and healthy controls;  $P = 0.0001, 0.0001$  respectively. Also, mean values of BMI were significantly higher in DS cases without studied sibs compared to DS cases with studied sibs, sibs of group I and healthy controls;  $P = 0.02, 0.0001, 0.0001$  respectively. Also, mean values of BMI were significantly higher in sibs of group I compared to healthy controls;  $P = 0.003$ ; [Table 1](#)

There were statistically non significant differences between DS cases with studied sibs and DS cases without studied sibs as regards body fat% ( $P = 0.4$ ). On the other hand, mean values of body fat% in DS cases with studied sibs were significantly higher compared to their sibs and healthy controls ( $P = 0.0001, 0.0001$ ). Also, mean values of body fat% were significantly higher in DS cases without studied sibs compared to sibs of group I and healthy controls ( $p = 0.0001, 0.001$  respectively). Also, mean values of body fat% were signifi-

**Table 1** Statistical comparison between mean values of BMI (kg/m<sup>2</sup>) of different studied groups.

Variable	Group										
	Group I DS with studied sibs No = 20		Group II DS-without studied sibs No = 20		Group III Sibs of group I No = 20		Group IV Healthy controls No = 20				
	Range	M ± SD	Range	M ± SD	Range	M ± SD	Range	M ± SD			
BMI (kg/m <sup>2</sup> )	16.9–21.1	18.3 ± 0.9	17–23.2	19.4 ± 1.7	15.6–18.1	16.8 ± 0.8	14.8–18.1		15.9 ± 0.9		
Group I VS II	Group I VS III		Group I VS IV		Group II VS III		Group II VS IV		Group III VS IV		
<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>
2.387	0.02*	5.19	0.0001**	7.759	.0001**	5.937	0.0001**	7.77	0.0001**	3.171	0.003*

N.B. Student "t" test was used for statistical comparison.

P value > 0.05 = statistically non significant. P value < 0.05\* = statistically significant.

P value < 0.01\*\* = statistically highly significant. M: mean; SD: standard deviation.

BMI: body mass index.

**Table 2** Statistical comparison between mean values of body fat% of different studied groups.

Variable	Group											
	Group I DS with studied sibs No = 20		Group II DS-without studied sibs No = 20		Group III Sibs of group I No = 20		Group IV Healthy controls No = 20					
	Range	M ± SD	Range	M ± SD	Range	M ± SD	Range	M ± SD				
Body fat%	17.6–29.8	24.5 ± 3.6	17.3–29.5	23.5 ± 3.5	15.4–22.8	20.2 ± 2.5	13.3–23	17.5 ± 3.0				
Group I VS II	Group I VS III		Group I VS IV		Group II VS III		Group II VS IV		Group III VS IV			
	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>		
	0.81	0.4	4.314	0.0001**	6.54	0.0001**	3.451	0.001**	5.769	.0001**	2.96	0.005**

N.B. Student “*t*” test was used for statistical comparison.

*P* value > 0.05 = statistically non significant. *P* value < 0.05 = statistically significant.

*P* value < 0.01\*\* = statistically highly significant.

**Table 3** Statistical comparison between mean values of serum leptin level of different studied groups.

Variable	Group											
	Group I DS with studied sibs No = 20		Group II DS-without studied sibs No = 20		Group III Sibs of group I No = 20		Group IV Healthy controls No = 20					
	Range	M ± SD	Range	M ± SD	Range	M ± SD	Range	M ± SD				
Leptin (ng/ml)	10–39	21.2 ± 7.2	10–39	20.3 ± 8.1	2.4–8	5.2 ± 1.6	2.5–10	5.2 ± 2.05				
Group I V II	Group I VS III		Group I VS IV		Group II VS III		Group II VS IV		Group III VS IV			
	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>		
	0.354	0.7	9.64	0.0001**	9.5	0.0001**	8.103	0.0001**	8.011	0.0001**	0.025	0.9

N.B. Student “*t*” test was used for statistical comparison.

*P* value > 0.05 = statistically non significant. *P* value < 0.01\*\* = statistically highly significant.

M: mean; SD: standard deviation.

cantly higher in sibs of group I compared to healthy controls ( $p = 0.005$ ); [Table 2](#)

Mean values of serum leptin levels in DS cases with studied sibs were significantly higher compared to their sibs and healthy controls ( $p = 0.0001, 0.0001$  respectively). Also, serum leptin levels were significantly higher in DS cases without studied sibs compared to sibs of group I and healthy

controls ( $P = 0.0001, 0.0001$ ). On the other hand, there were statistically non significant differences between DS cases with studied sibs and DS cases without studied sibs as regards serum leptin levels ( $P = 0.7$ ). Also, there were statistically non significant differences between sibs of group I and healthy controls as regards serum leptin levels ( $P = 0.9$ );

[Table 3](#)

**Table 4** Statistical comparison between mean values of IGF-I level (ng/l) of different studied groups.

Variable	Group											
	Group I DS with studied sibs No = 20		Group II DS-without studied sibs No = 20		Group III Sibs of group I No = 20		Group IV Healthy controls No = 20					
	Range	M ± SD	Range	M ± SD	Range	M ± SD	Range	M ± SD				
IGF-I (ng/l)	77.5–170	125.1 ± 29	57.5–220	127.4 ± 35.7	75.5–155	123.9 ± 22.8	47.5–172	126.7 ± 29.5				
Group I VS II	Group I VS III		Group I VS IV		Group II VS III		Group II VS IV		Group III VS IV			
	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>		
	0.22	0.82	0.145	0.88	0.170	0.86	0.366	0.7	0.067	0.9	0.332	0.7

N.B. Student “*t*” test was used for statistical comparison.

*P* value > 0.05 = statistically insignificant. M: mean; SD: standard deviation.

IGF-I: insulin like growth factor-I.

**Table 5** Statistical comparison between mean values of serum TSH levels of different studied groups.

Variable	Group											
	Group I DS with studied sibs No = 20		Group II DS-without studied sibs No = 20		Group III Sibs of group I No = 20		Group IV Healthy controls No = 20					
	Range	M ± SD	Range	M ± SD	Range	M ± SD	Range	M ± SD				
TSH (uIU/ml)	2.9–5	4.2 ± 0.7	2.1–5	4.1 ± 0.85	1.3–3.6	2.3 ± 0.77	1.3–3.9		2.8 ± 0.76			
Group I VS II	Group I VS III		Group I VS IV		Group II VS III		Group II VS IV		Group III VS IV			
	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>		
	0.34	0.7	8.23	0.0001**	6.26	0.0001**	7.164	0.0001**	5.36	0.0001**	1.92	0.06

N.B. Student “*t*” test was used for statistical comparison.  
*P* value > 0.05 = statistically non significant. *P* value < 0.01\*\* = statistically highly significant.  
 M: mean; SD: standard deviation.  
 TSH: thyroid stimulating hormone.

Mean values of serum leptin levels were significantly higher in females compared to males of different studied groups (*P* < 0.01).

There were statistically non significant differences between different studied groups regarding their serum IGF-I concentrations (*p* > 0.05 for all); [Table 4](#)

Mean values of serum TSH levels were significantly higher in DS cases with studied sibs compared to their sibs and healthy controls (*p* = 0.0001, 0.0001, respectively). Also, mean values of serum TSH levels were significantly higher in DS cases without studied sibs compared to sibs of group I and healthy controls (*P* = 0.0001,0.0001). On the other hand, there were statistically non significant differences between DS cases with studied sibs and DS cases without studied sibs as regards serum TSH levels (*P* = 0.7). Also, there were statistically non significant differences between sibs of group I and healthy controls as regards serum TSH levels (*P* = 0.06); [Table 5](#)

Mean values of serum free thyroxin levels showed statistically non significant differences in DS cases with studied sibs compared to DS cases without studied sibs, their sibs and healthy controls (*P* = 0.2, 0.132, and 0.134 respectively). Also, there were statistically non significant differences between DS cases without studied sibs and healthy controls as regards serum FT4 levels (*P* = 0.9). On the other hand, mean values of

serum FT4 levels were significantly higher in DS cases without studied sibs compared to sibs of group I; *P* = 0.01. Also, mean values of serum FT4 were significantly higher in healthy controls compared to sibs of group I (*p* = 0.001); [Table 6](#). Statistically significant positive correlations were recorded between serum leptin and both BMI and body fat % in studied DS cases with and without studied sibs; [Figs. 1 and 2](#)

**4. Discussion**

Obesity, a state of excess body fat, is commonly assessed using the body mass index (BMI); a ratio of weight (kg) to height (m<sup>2</sup>) [15]. In the current study, BMI (kg/m<sup>2</sup>) was found to be significantly higher in DS children with studied sibs compared to their siblings. These findings were in agreement with Magge et al. [16] who found that prepubertal children with DS aged 4–10 years had higher BMI compared to their siblings, although most subjects were not obese. Also, Samarkandy et al. [17] observed that prepubertal children with DS aged 5–12 years had higher BMI compared to their siblings. They were shorter than their siblings, but had comparable weights. In contrast, Sharav and Bowman [18] found that there were no significant differences between the DS children aged 2–11 years and their siblings aged 2–14 years in terms of body mass index and

**Table 6** Statistical comparison between mean values of serum FT4 (pmol/l) level of different studied groups.

Variable	Group											
	Group I DS with studied sibs No = 20		Group II DS-without studied sibs No = 20		Group III Sibs of group I No = 20		Group IV Healthy controls No = 20					
	Range	M ± SD	Range	M ± SD	Range	M ± SD	Range	M ± SD				
FT4 (pmol/l)	10.5–17.7	13.3 ± 1.9	9.8–19.3	14.29 ± 2.5	10.5–16.2	12.5 ± 1.5	12.1–17.6		14.21 ± 1.5			
Group I VS II	Group I VS III		Group I VS IV		Group II VS III		Group II VS IV		Group III VS IV			
	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>		
	1.29	0.2	1.537	0.132	1.53	0.134	2.688	0.01*	0.122	0.9	3.514	0.001**

N.B. Student “*t*” test was used for statistical comparison.  
*P* value > 0.05 = statistically non significant. *P* value < 0.05\* = statistically significant.  
*P* value < 0.01\*\* = statistically highly significant. M: mean; SD: standard deviation.  
 FT4: free thyroxin.



weekly caloric intake. They postulated that weight gain in children with DS was influenced by both genetic and environmental factors, such as dietary control and involvement in physical activity. Also, BMI ( $\text{kg}/\text{m}^2$ ) was found to be significantly higher in DS children with studied sibs compared to healthy controls ( $P = 0.0001$ ). Similarly, BMI was found to be significantly higher in DS children without studied sibs compared to sibs of group I and healthy controls ( $P = 0.0001, 0.0001$ , respectively). These findings were in agreement with a study on Saudi DS children younger than 5 years conducted by Al Husain [19] who found that there was a trend of a steady increase in the mean BMI curve for children with DS at each age group compared with a downward trend of the mean BMI curve for control children. The mean BMIs for both children with DS and controls were below the international cut-off points for BMI for overweight and obesity, at all age.

Enrolled DS children with studied sibs had significantly higher body fat% than their sibs. In agreement with Magge et al. [16] who observed that prepubertal children with DS aged 4–10 years had higher body fat percentage compared to their siblings. Body fat% were found to be significantly higher in DS children with studied sibs compared to healthy controls ( $P = 0.0001$ ). Also, body fat% were found to be significantly higher in DS children without studied sibs compared to sibs of group I and healthy controls ( $P = 0.001, 0.0001$ , respectively). Similarly, Soler Marín and Xandri Graupera [20] reported that young adults with Down syndrome have higher body fat percentage than age and sex matched persons without DS.

Adipocytes secrete leptin hormone which rises in direct proportion to adipose mass [21]. Interestingly, in obese individuals, a persistent eating behavior (overeating) remains, although blood leptin levels are elevated [22]. Serum leptin concentrations correlated with percentage of body fat, suggesting that most obese persons are insensitive to endogenous leptin production. So, it is postulated that obese individuals, with hyperleptinemia, have some degree of leptin resistance [8]. In the present study, serum leptin levels were significantly higher in DS children with studied sibs compared to their siblings. This finding could be explained by the observation that enrolled DS children had higher percentage of body fat compared to their siblings. These findings were in agreement with Magge et al. [16] who found that leptin levels were higher in prepubertal children with DS compared to their siblings. Also, they found that leptin and percent body fat were positively associated in both groups, but with a significantly greater association among the children with DS. They concluded that the difference in the magnitude of the association between leptin and adiposity in DS children compared to controls may represent increased leptin resistance in DS children.

Serum leptin levels were significantly higher in DS children with studied sibs compared to healthy controls. Similarly, serum leptin levels were significantly higher in DS children without studied sibs compared to sibs of group I and healthy controls. Also, this finding could be explained by the observation that enrolled DS children without studied sibs had higher percentage of body fat compared to sibs of group I and healthy controls. These findings disagree with Radunovic et al. [23] who demonstrated that fetuses with DS had significantly lower plasma leptin levels than control euploid fetuses matched for gestational age, leading to the hypothesis that damage beginning from this stage may compromise the synthesis and secretion of leptin. Also, Proto et al. [24] have found that total and free leptin levels in obese women with DS were in the range of

normal weight controls and significantly lower than those found in obese controls, but no significant differences were found in soluble receptors levels and this gave evidence against a deficit in receptor synthesis in DS. They also suggested that low leptin levels in obese DS individuals could depend on an impaired secretory activity of adipocytes, as leptin is released by fat mass, and DS patients could have a lower percentage of fat compared to controls subjects. Yahia et al. [25] found that there were non significant differences in serum leptin levels among non obese prepubertal DS children aged from 2–10 years and healthy control children.

A significant gender influence on serum leptin levels in prepubertal DS children with studied sibs, DS children without studied sibs, sibs of group I and healthy children was found. Girls had higher leptin levels compared to boys. In agreement with several studies in normal prepubertal children conducted by Werner et al. [26] showed a significant gender difference especially in late puberty and adolescence. Also, Fors et al. [27] found that gender differences in leptin levels in prepubertal children, girls had higher leptin levels than boys, may at least in part be explained by differences in body composition. Similarly, Dencker et al. [28] found that in case of true gender difference in leptin levels in young children, girls had higher mean values than boys for leptin. They explained this difference in leptin concentration by a larger amount of body fat content in girls than in boys. In contrast to these findings, Garcia-Mayor et al. [29] demonstrated that before puberty, leptin levels in normal boys increased in parallel with body weight, in a similar pattern to girls. Also, Magni et al. [30] found that leptin values did not differ according to gender in prepubertal children with DS.

In the present study, serum leptin concentrations showed a significant positive correlation with BMI in all DS children. Findings concerning the correlation between leptin and BMI in DS persons were similar in many studies e.g. Cento et al. [31] reported that leptin concentrations correlate with BMI in adult obese women with DS. Similarly Magni et al. [30] observed positive correlation between leptin concentrations and BMI in prepubertal DS children. Also, serum leptin concentrations showed a significant positive correlation with BMI in sibs of group I and healthy children. In agreement with Werner et al. [26], Fors et al. [27] and Plonka et al. [32] reported that there was a significant positive correlation between leptin concentrations and BMI in healthy children. Similarly, Ostadrahimi et al. [33] found that serum leptin concentration correlated positively with BMI in healthy normal, over weight and obese Iranian reproductive age women.

There was a significant positive correlation between leptin levels and percent body fat in all DS children (group I & II), the greater the percent of body fat the higher the leptin levels. In agreement with a study conducted in prepubertal DS children by Magge et al. [16]. Also, there were significant positive correlations between leptin levels and percent body fat in sibs of group I and healthy controls. In agreement with foregoing findings, studies conducted in healthy children by Werner et al. [26], Fors et al. [27] and Bandini et al. [34].

In the present study, there were no significant differences between DS children and their siblings regarding their serum IGF-I concentrations. These findings were in accordance with the results of Magge et al. [16] who did not observe any significant differences between serum levels of IGF-I in healthy DS children and their siblings. Similarly, there were no significant differences between DS children with studied sibs and healthy

controls regarding their serum IGF-I concentrations. Also, insulin like growth factor-I levels in DS children without studied sibs was not significantly different from sibs of group I and healthy controls, IGF-I levels were within normal range. These results were in agreement with Hestnes et al. [35] who compared 29 adults with chromosomally verified DS aged 21–72 years with 29 mentally retarded controls from the same institutions. They concluded that IGF-I level in adults with DS was found to be in the normal general population range and there was no significant difference observed in IGF-I between adult with DS and other mentally retarded adult. Also, Ragusa et al. [36] investigated IGF-I levels in prepubertal, pubertal children with DS, normal children and adolescents and demonstrated that IGF-I levels in DS patients were generally within the normal range. In contrast to these results, Sara et al. [37] and Anneren et al. [38] reported low levels of IGF-I in patient with DS during childhood and adolescence. Similarly, Anneren et al. [39] reported that there were low concentrations of serum IGF-I in DS children aged 6 to 9 months and its levels became normal during growth hormone treatment.

TSH levels in DS children with studied sibs were not significantly different from DS children without studied sibs and TSH concentrations were within the normal levels. Serum TSH levels were significantly higher in DS children with studied sibs compared to their sibs, although TSH concentrations were within the normal levels. In agreement with Magge et al. [16] who found that although children requiring treatment for hypothyroidism were excluded from the study, TSH values were higher among children with DS than among their siblings, although TSH values were within the normal range. Serum TSH levels were significantly higher in DS children with studied sibs compared to healthy control children. Also, TSH concentrations were within the normal limits. Serum TSH levels were significantly higher in DS children without studied sibs compared to sibs of group I and healthy controls, TSH concentrations were within the normal levels. These results were in agreement with Meyerovitch et al. [40] who observed higher TSH levels in DS patients who were not diagnosed with thyroid disease or did not receive thyroid modulating medication than the control group of healthy age and sex matched subjects. They suggested that the upward shift in the distribution of TSH was inherent to DS and not an indication of subclinical hypothyroidism in a large subset of patients with DS. Similarly, Yahia et al. [25] showed a significantly higher TSH levels in DS children than healthy children, but still within reference range median values. In contrast to these findings, many studies showed abnormal TSH levels in DS, Magni et al. [30] found that about 33% of studied prepubertal children with DS, who were clinically euthyroid, had elevated TSH concentration above the higher limits. Also, Hasanhodzic et al. [41] reported higher frequency of thyroid dysfunction in DS patients as they found significantly higher values of TSH in 60% of the examined DS patients compared to the control group. Also, Chen et al. [42] reported that there was a significantly higher prevalence (18%) of thyroid dysfunction in DS patients, regarding the elevation of TSH levels as major thyroid dysfunction.

There were no significant differences between DS children with studied sibs and DS children without studied sibs regarding their serum FT4 levels, free thyroxin concentrations were within the normal levels. In agreement with Magni et al. [30] who found normal free thyroxin concentrations in prepubertal children with Down syndrome. Serum FT4 concentrations

were not significantly different in DS children with studied sibs compared to their sibs, FT4 levels were within the normal limits. Similarly, serum FT4 concentrations were not significantly different in DS children with studied sibs compared to healthy control children, FT4 levels were within the normal limits. Serum free thyroxin levels were not significantly different in DS children without studied sibs compared to healthy control children, FT4 levels were within the normal limits. These results were in agreement with Chen et al. [42] who found that serum FT4 levels were within normal limits or close to the lower limit of normal range in DS patients aged 12.9 to 52.5 year. Also, in a retrospective study in DS children their mean age 4.5 years and followed up for 6.8 years, Faria et al. [43] observed that values of free T4 remained normal in DS children. In contrast, Pueschel et al. [44] found that FT4 levels were significantly lower in Down syndrome children compared to control children, about 16% showed the evidence of hypothyroidism. FT4 levels were significantly higher in DS children without studied sibs compared to sibs of group I, although FT4 levels were within the normal limits. Similarly, Yahia et al. [25] observed that serum thyroxin levels were significantly higher in Egyptian DS children aged 2–10 years compared to healthy children but still within the normal reference range. Serum free thyroxine concentrations were significantly higher in healthy control children compared to healthy sibs of group I although, FT4 levels were within the normal limits.

## 5. Conclusion

Serum leptin levels were significantly higher in studied DS children with or without their sibs compared to both studied sibs and healthy controls. Serum leptin values were found to be positively correlated with BMI in studied DS children as well as their sibs highlighting a possible role of body fat% and leptin values in the pathogenesis of obesity in DS children.

## Conflict of interest

The authors declare no conflict of interest, no financial and or personal relationships with other people or organizations that could inappropriately influence our study or theirs.

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