

# Serum Leptin Levels in Down's Syndrome Versus Normal Children

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## Abstract

**Introduction:** Leptin produced by the "ob" gene is a proteohormone, produced by adipose tissues. The amount of body fat is the main determinant of circulating levels of this hormone. Leptin is elevated in the blood in obese adults and also in obese children. Since the children with Down's syndrome (DS) are predisposed to obesity, this study aims to detect the role of leptin in children with DS.

**Materials and Methods:** The study was a prospective clinical study of 25 children with DS and 25 normal children. Blood sampling was done on all the 50 children, and simultaneously, anthropometric measures were estimated in all the children. Serum leptin was estimated using the "leptin sandwich enzyme-linked immunosorbent assay" method.

**Results:** Of the 25 children with DS, one child was obese and three were found to be overweight after assignment of body mass index using the formula weight in kg/height in m<sup>2</sup>. The mean value of serum leptin in children with DS was found to be 18.664 ± 14.3151. The mean value of serum leptin in normal children included in our study was 5.060 ± 9.6566.

**Conclusion:** This study shows that the children with DS had increased serum leptin levels for the percent of body fat when compared to normal children in whom the serum leptin levels do not show similar increase. Serum leptin was also increased more in girls than in boys, in children with DS.

**Key words:** Down syndrome, Leptin, Obese

## INTRODUCTION

Obesity is an existing and increasing problem in our country as well as worldwide. In the course of a person's life, some phases have been identified as risk periods which are associated with obesity later in life. One such is the gestational period where there is a direct association of high birth weight with subsequent obesity. Thereafter, in the 1<sup>st</sup> year of life, children undergo changes in nutritional behavior which may influence obesity in later life. The

next crucial phase is the ages of 5-8 years where there is an adiposity rebound. An early adiposity rebound may serve as an index of further obesity. The final risk period for the development of persistent obesity is adolescence.<sup>1</sup> Obesity has an impact on physical well-being and also on psychological health. Children who are obese in childhood go on to develop obesity in adulthood also. According to the report of the International Obesity Task Force (IOTF) in 2000, about 10% (a total of 155 million) of young people aged 5-17 years globally were overweight. Among them, 2-3% (30-45 million) were obese; a further 22 million younger children were also affected according to the previous IOTF global estimates based on the WHO data for the under-fives.<sup>2,3</sup> Eighty percent of overweight 10-14 years old adolescence are at risk of becoming overweight adults compared to 25% of overweight preschool children (<5 years old) and 50% of 6-9 years old overweight children.<sup>4</sup> Obese children are predisposed

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to develop diabetes mellitus, coronary artery disease, and musculoskeletal problems. Obesity is a multifactorial disease and its development is the result of multiple interactions between the genes and environment. Children with Down's syndrome (DS) are known to be predisposed to obesity. The role of the proteohormone leptin in obesity was first studied by Zhang *et al.* in 1994.<sup>5</sup> Leptin was derived from the Greek word "leptos" meaning "thin" and was named by Friedman.<sup>6</sup> Leptin was the first fat-derived hormone (adipokine) to be discovered. Leptin is mainly produced in adipocytes of white adipose tissue and circulates at a level of 5-15 ng/ml in lean subjects.<sup>7</sup> The sources of leptin production are many and are also produced by brown adipose tissue, placenta (syncytiotrophoblast), ovaries skeletal muscles, stomach (the lower part of the fundic glands), mammary epithelial cells, bone marrow, and gastric chief cells. The ob (Lep) gene is located on chromosome 7. Human leptin is a 16 KDa protein with 167 amino acids.<sup>5</sup> Leptin circulates in the blood in the free form and bound form. Leptin is produced in many sites in addition to white adipose tissue, but the amount of body fat is the main determinant of the circulating levels of this hormone. After it is produced, leptin is secreted into the bloodstream, where it circulates attached to proteins, and is transported to the brain, where it stimulates or inhibits release of several neurotransmitters.<sup>14</sup> It downregulates some orexigenic neuropeptides, such as neuropeptides-y, melanin-concentrating hormone orexin, and agouti-related peptide. Leptin upregulates anorexigenic neuropeptides such as melanocytes stimulating hormone, which acts on melanocortin-4 receptor, cocaine- and amphetamine-regulated transcripts, and corticotropin-releasing hormones.<sup>8</sup> Obese individual generally exhibit a higher concentration of circulating leptin than normal weight individuals due to their higher percentage body fat. Although leptin reduces appetite in obese individuals, there is a resistance to leptin, with elevated levels failing to suppress the appetite and modulate weight. Leptin resistance in obese individual could be due to changes in leptin receptor signaling. It could also be due to decreased leptin cerebrospinal fluid levels when compared to that in blood in obese individuals. The reason for the above is that the increased levels of triglycerides in obesity affect the transport of leptin across the blood-brain barrier or due to leptin receptor becoming saturated. Since DS is a chromosome disorder, children with DS may have a genetic predisposition to more severe leptin resistance. Hyperleptinemia is associated with obesity-related hypertension and chronic congestive cardiac failure in humans and vascular endothelial and myocardial dysfunction in animal models.<sup>9,10</sup>

### Aims and Objectives

The aim of this study is to detect the role of leptin in children with DS.

## MATERIALS AND METHODS

Prospective clinical study was done at Genetic Clinic, Kilpauk Medical College Hospital, Chennai, over a period of 1 year in children with DS compared with normal children from 4 to 10 years of age. Ethical Committee approval and consent from the children's parents were obtained. Anthropometric measures were estimated for all children included in the study, and serum leptin level was measured using leptin sandwich enzyme-linked immunosorbent assay method.

## RESULTS

About 25 children with DS were recruited for the study, 25 normal children in 4-10 years age.

It is evident from the study of different age groups that DS has been detected early.

Based on the body mass index (BMI), three children with DS were found to be overweight and one child was obese, i.e., 12% of the children with DS were overweight and 4% were found to be obese.

The waist-hip ratio (WHR) was found to be increased in seven children (28%) with DS, and WHR more than 0.9 was considered obese and <0.9 is normal (Table 4).

The age distribution (Table 1 and Figure 1), sex distribution (Table 2), and BMI status (Table 3) were analyzed with both DS and normal children. No statistical significance exists between both groups in the above-said parameters. There exists a statistical significance for WHR with both DS and normal children. The mean value of DS is 18.664 and normal is 5.060, which clearly

**Table 1: Cross-tabulation of age distribution in DS children and normal children**

Age distribution (years)	Normal	DS	P value**
4-5	4	9	0.244
6-7	9	6	
8-9	9	5	
>9	3	5	
Total	25	25	

\*\*Chi-square test. DS: Down's syndrome

**Table 2: Cross-tabulation of gender in DS children and normal children**

Gender	Normal	DS	P value**
Male	18	14	0.239
Female	7	11	

\*\*Chi-square test. DS: Down's syndrome

**Table 3: Cross-tabulation of BMI in DS children and normal children**

BMI	Normal	DS	P value**
Normal	24	21	0.333
Overweight	1	3	
Obese	0	1	

\*\*Chi-square test. DS: Down's syndrome, BMI: Body mass index

**Table 4: Cross-tabulation of WHR in DS children and normal children**

WHR	Normal	DS	P value**
Normal	25	18	0.004
Increased	0	7	

\*\*Chi-square test. DS: Down's syndrome, WHR: Waist-hip ratio

**Table 5: Serum leptin level in DS children and normal children**

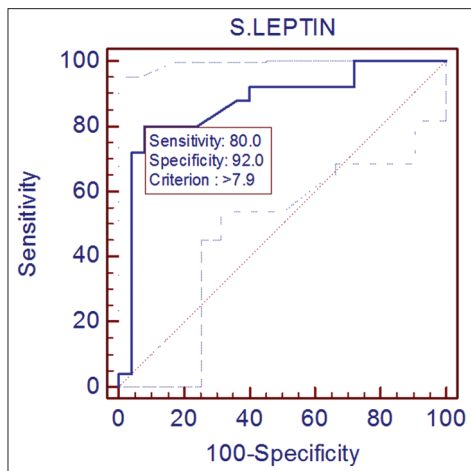
Group	n	Mean	SD	P value**
Normal	25	5.06	9.6566	<0.0001
DS	25	18.664	14.3151	

\*\*Student t-test. SD: Standard deviation, DS: Down's syndrome

**Table 6: Area under the ROC curve (AUC)**

Area under the ROC curve (AUC)	0.868800
Standard error <sup>a</sup>	0.0552
95% confidence interval <sup>b</sup>	0.743219-0.947553
z-statistic	6.685
Significance level P (area=0.5)	<0.0001

<sup>a</sup>Hanley and McNeil, 1928, <sup>b</sup>Binomial exact. AUC: Area under curve, ROC: Receiver operating characteristic



**Figure 1: Receiver operating characteristic curve**

indicates that there is significant elevation of serum leptin level among children with DS (Table 5). Using receiving operative characteristic curve, we found that serum leptin level optimum cutoff value is >7.9, which

has sensitivity 80 and specificity 92. The area under curve is 0.868800 (Table 6).

## DISCUSSION

It has been noticed that the children with DS in the age group 4-10 years initially have lean phenotypes, but later in adolescence, they become obese. Hence, estimation of serum leptin in our study can help us in predicting obesity in adolescence. Of the 25 children with DS, 14 had congenital heart disease (56%). Our results are concurrent with earlier study reported by Singapore Med J. 2007. Karyotyping had been done already in 20 of 25 children included in the study. Of these, 18 had meiotic non-disjunction and two of these children were mosaics. When the BMI was calculated for all the 50 children, it was found that 12% of the children with DS were overweight and 4% were obese. Our study showed that serum leptin was raised more in girls than in boys in children with DS. However, a larger population needs to be studied. The mean value of serum leptin in children with DS was found to be  $18.664 \pm 14.3151$ . The mean value of serum leptin in normal children included in our study was  $5.060 \pm 9.6566$ . This is consistent with a study by Dubey *et al.*<sup>11</sup> In their study, serum leptin levels were higher in obese children  $19.4 \pm 6.4$  ng/ml against  $5.4 \pm 1.7$  ng/ml. Leptin levels correlated with BMI, waist circumference, and WHR in their study. Another similar study was done by Magge *et al.*<sup>12</sup> Leptin levels among prepubertal children with DS compared with their siblings. It was a study of 35 children with DS and 33 infected siblings in tea e group of 4-10 years, and it was concluded that the group of children with DS as increase of leptin levels for percent of body fat that their unaffected siblings and this difference would contribute to the increase of risk of obesity in children with DS.

## CONCLUSION

This study has reinforced the fact that serum leptin levels are responsible/associated with obesity and DS children are also obese because of increased serum leptin levels. Early onset of obesity is associated with diabetes, hypertension, coronary, artery disease, and musculoskeletal problems. Hence, lifestyle modification and dietary modification are mandatory. This study gives the clear view of serum leptin levels and its association with existing obesity and can also be used as a predictor for obesity in adolescence in children with DS. This will help pediatricians in early recognition and timely management by way of weight maintenance, management of comorbidities, and weight loss program. Simply put, an integrated multi-sectorial approach is required.

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