Body fat determined by skinfold measurements is elevated despite underweight in infants with Prader-Labhart-Willi syndrome

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Body composition and leptin were studied in 13 young, still underweight and 10 older overweight children with Prader-Labhart-Willi syndrome. Not only the older overweight children but also the young underweight children had elevated skinfold standard deviation scores for body mass index and elevated body mass index–adjusted leptin levels, suggesting relatively increased body fat despite underweight. Our data indicate that body composition in Prader-Labhart-Willi syndrome is disturbed already in infancy, long before the onset of obesity. Leptin production appears to be intact. (J Pediatr 1999;134:222-5)

Prader-Labhart-Willi syndrome, the most common syndromal cause of marked obesity, was first described in 1956 and affects 1 in 16,000 live births. It is caused by a lack of a specific part of the paternal homolog of the long arm of chromosome 15, which is due to a deletion or a maternal uniparental disomy. The characteristic features during early infancy are general muscle hypotonia, feeding difficulties, and underweight. The development of body weight is clearly biphasic, with the children becoming very obese between the third and fifth years of life. There is evidence that various hypothalamic centers are involved. Apart from short stature, which is most probably related to deficiency of growth hormone,[1,2] other typical features are hypogenitalism, cryptorchidism, and delayed or incomplete puberty caused by gonadotropin deficiency, as well as mental retardation and behavioral problems. Unlike in nonsyndromal obesity, it has been demonstrated that overweight children with PWS have reduced lean body mass,[3] as well as low insulin levels[4] for their age.

See related articles, p. 215 and p. 226.

BMI	Body mass index
PWS	Prader-Labhart-Willi syndrome
SDS	Standard deviation score
WfH	Weight for height

Leptin, the product of the *ob* gene, is a protein hormone with a molecular weight of 16 kd, thought to play a key role in the regulation of body weight and produced by differentiated adipocytes. It acts on the hypothalamus, suppressing food intake and stimulating energy expenditure. Multiple relationships with other endocrine axes have been described, the most important variable determining circulating leptin levels being body fat.[5] In prepubertal overweight children and adults with PWS, it was shown that as in simple obesity, leptin levels are normal for body fat mass.[6,7]

For a better understanding of the sudden switch from underweight to compulsive eating and overweight, and in order to gain more insight into the etiology of obesity in PWS, we investigated body composition and plasma leptin levels in very young and still underweight children with PWS and

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Table I. Anthropometric and laboratory data

	Young underweight (n = 13)		Older overweight (n = 10)		
	Mean ± SD	Range	Mean ± SD	Range	*P* value*
Age (y)	1.4 ± 1.1	0.3 - 4.1	5.9 ± 2.2	1.5† - 9.5	—
WfH SDS	–1.6 ± 0.7	–2.8 - –0.6	3.3 ± 1.7	0.4† - 6.1	—
BMI SDS	–1.6 ± 0.8	–3.2 - –0.3	3.0 ± 1.6	0.5 - 5.4	<.001
Height SDS	–2.1 ± 1.2	–4.8 - –0.7	–1.7 ± 0.6	–2.5 - –0.7	NS
Weight SDS	–2.3 ± 0.9	–4.4 - –1.2	0.7 ± 1.1	–1.1 - 1.9	<.001
Skinfold subscapular SDS	0.3 ± 1.5	–1.2 - 4.4	9.1 ± 5.1	2.0 - 16.2	<.001
Skinfold triceps SDS	0.2 ± 0.8	–1.1 - 1.2	3.1 ± 1.7	0.7 - 5.2	<.001
Arm circumference SDS	–1.2 ± 1.0	–2.9 - 1.0	1.5 ± 0.8	0.0 - 2.8	<.001
DEXA fat mass (%)			43.6 ± 6.5‡	30.6 - 54.2	
Leptin SDS§	2.1 ± 1.0	0.7 - 3.8	1.7 ± 1.2	0.2 - 3.5	NS

NS, Not significant; *DEXA,* dual-energy x-ray absorptiometry.
*Significance between underweight group and overweight group.
†See text (Patients and Methods section).
‡n = 8.
§SDS adjusted for gender and BMI.[9]

compared them with older overweight children with PWS.

PATIENTS AND METHODS

Children with PWS (n = 23) with documented deletion or uniparental disomy of chromosome 15 were included in this study. All were prepubertal. All anthropometric measurements were performed by the same investigator, according to standard techniques.[8] Body mass index was calculated as weight (in kilograms) divided by the square of height (in meters). For calculation of age-related standard deviation scores, the First Zurich Longitudinal Study was used as a reference.[8] Because of the biphasic weight pattern, the children were subdivided into 2 groups. The young underweight group consisted of 13 children with weight for height below the mean; the older overweight group consisted of 10 children with a WfH above the mean (Table I). WfH, and not age, was chosen as the grouping factor, because the beginning of compulsive eating behavior and obesity is variable between individuals and usually begins between the third and fifth years of life. This is a clear and reproducible criterion by which, in our data, we obtain the same groups as on the basis of the clinical situation, with the exception of one patient (age, 1.5 years; WfH, +0.4 SDS), who had to be allocated to the older overweight group, despite being young and presenting with the typical picture of the young, underweight group.

Blood samples were taken between 8:00 and 9:00 AM, after a 12-hour overnight fast. Plasma levels of leptin were measured by radioimmunoassay.[9] In one of the youngest children (young underweight group), we could not obtain enough serum to measure leptin.

To clarify the crucial question of whether BMI underestimates body fat in children with PWS, a regression of skinfold SDS (for triceps and subscapular) on BMI SDS was calculated by including the children of the First Zurich Longitudinal Study as control subjects. By definition, these normal healthy children have, on average, a skinfold SDS of zero relative to BMI SDS. With the same equation, expected skinfold SDSs relative to BMI SDSs were calculated for the children with PWS.

Fat mass was measured and expressed as percentage of total body weight in 8 children in the older overweight group by dual-energy x-ray absorptiometry (Hologic QDR 2000, Software Version 7.10B, Waltham, Mass). This examination could not be conducted in the younger children because of the need for sedation.

All data were processed by GAS 3.0 of Institute for Medical Informatics (IMI, Zurich, Switzerland). For testing significance the one-sample and the two-sample Wilcoxon tests were used, with *P* values less than .05 considered significant.

RESULTS

Anthropometric Data

In both subgroups WfH was comparable to BMI (Table I).

In spite of underweight, skinfold thickness in the underweight group was normal, even in the presence of a reduced arm circumference. In the overweight group skinfold thickness was massively increased, more in the subscapular region than over the triceps in the presence of an above-average arm circumference.

Leptin levels in the overweight group (10.9 ± 5.8 μg/L) were high compared with those of healthy chil-

Table II. Skinfold thickness and arm circumference SDS related to BMI SDS

	Young underweight (n = 13)			Older overweight (n = 10)	
	Mean ± SD	*P* value*	*P* value†	Mean ± SD	*P* value*
Subscapular skinfold measurements	1.2 ± 1.3	.001	<.001	7.2 ± 4.8	.002
Triceps skinfold measurements	0.9 ± 0.7	.002	.4	1.3 ± 1.8	.04
Arm circumference	0.06 ± 0.9	NS	.01	–1.0 ± 0.9	.006

NS, Not significant.
*Significance with respect to the null hypothesis (mean = 0), as by definition in the First Zurich Longitudinal Study (reference group), see text (Patients and Methods).
†Significance between overweight and underweight group.

dren both in absolute values and SDS adjusted for BMI and gender.[9]

In the underweight group the mean leptin level was 3.2 ± 1.4 μg/L. According to the same equations as used for the overweight group,[9] leptin related to BMI was also high but did not differ from that of the overweight group.

Skinfold SDSs relative to BMI SDSs are significantly increased in the overweight group (Table II), indicating that these children have thicker skinfolds for their BMI than the children of the First Zurich Longitudinal Study.

The same was true for the underweight group, both for relative subscapular skinfold SDS and for triceps skinfold SDS. In spite of elevated skinfold SDS, arm circumference SDS was negative (overweight group) or average (underweight group).

Correlations

Correlations were calculated between leptin levels and body fat parameters, expressed in SDS to exclude the age dependence of body fat. The correlations with WfH, subscapular and triceps skinfold measurements, and BMI were all highly significant with *r* values between 0.8 and 0.85.

DISCUSSION

In these patients with PWS we found high leptin levels and a high correlation between leptin and measures of body fat, as reported for obese children and adults with[10] or without PWS.[5] BMI-adjusted leptin levels[9] were markedly increased, apparently as an artefactual underestimation of body fat by BMI. This was demonstrated by calculating a regression of skinfold SDS on BMI SDS for the healthy children of the First Zurich Longitudinal Study as a reference group. According to the same regression equations, skinfold SDSs relative to BMI SDSs were significantly increased for the children with PWS, indicating that they have thicker skinfolds for their BMI than healthy children. This, together with the diminished arm circumference SDS, indicates that an abnormally high proportion of the body consists of adipose tissue at the expense of lean body mass, in agreement with measurements obtained by other methods.[11] The decrease in fat-free mass is considered to be a consequence of a growth hormone deficiency in these patients.

Most important was the finding that not only the older overweight group but also the children in the young, still underweight group had elevated skinfold SDS related to BMI SDS compared with the healthy children of the First Zurich Longitudinal Study, suggesting that these children have elevated body fat in spite of underweight. Therefore it is not surprising that leptin levels, expressed in SDS related to BMI, were also elevated. Furthermore, from the presence of increased body fat despite underweight, it may be deduced that fat-free mass must be reduced compared with that of healthy children.

Our data indicate a disturbed body composition in PWS already in early infancy, long before development of obesity. It may be hypothesized that muscle hypotonia and lack of autonomy prevent compulsive eating and obesity in the early years. Only at a later stage, when muscle hypotonia is attenuated and autonomy increases, does overeating become a characteristic feature.

Leptin production per se is intact and seems neither causally involved in the accumulation of body fat mass, nor in the etiology of insatiable appetite. Underweight for height in the presence of augmented body fat in the young children with PWS raises the question of whether body fat is properly perceived by the hypothalamic "adipostat." Indeed, main features of PWS such as decreased muscle mass,[12] decreased insulin secretion,[4] and gonadotropin deficiency[13,14] are not seen in simple obesity but are typical of starvation. Symptoms of starvation and augmented body fat mass seem paradoxical and raise the hypothesis that in PWS, leptin resistance leads to metabolic symptoms compatible with starvation, despite augmented body fat.

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