IMPROVING BODY COMPOSITION AND PHYSICAL ACTIVITY IN PRADER-WILLI SYNDROME

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Objective To determine if muscle training in Prader-Willi Syndrome (PWS) can improve local body composition, physical capacity, and activity.

Study design Seventeen children and adolescents with PWS and 18 control children were enrolled in a daily short calf muscle training program for 3 months. Before (t_0) and after 3 months of training (t_{3m}), spontaneous physical activity and exercise capacity were assessed by pedometer registrations and activity protocols. Local body composition was determined by calf circumference and skinfold measurements at t_0, t_{3m}, and 3 months after t_{3m} (t_{6m}).

Results During training, calf skinfold decreased from 1.1 to 0.8 SD ($P < .01$) and calf circumference in PWS increased from 1.4 to 1.9 SD ($P < .05$), reflecting improved muscle mass. At t_{3m}, a significant increase in spontaneous physical activity (from 45% to 71%, compared with baseline data of control children, $P < .05$) and physical capacity (from 31%-78%, $P < .01$) was found.

Conclusions In persons with PWS, a well-defined and easy-to-accomplish training program improves local body composition and has generalized effects on physical activity and capacity, opening up a new therapeutic option to improve metabolic conditions. *(J Pediatr 2003;142:73-8)*

Prader-Willi syndrome (PWS) is the most common syndromal cause of marked obesity. Hypothalamic dysfunction, as already originally presumed by Prader et al,[1] appears to underlie many of the features of PWS,[2-4] including hypogonadism[5-7] and insufficient growth hormone (GH) secretion.[8] In contrast to nonsyndromal obesity, increased fat mass in PWS is accompanied by a decrease in lean body mass,[9-12] resulting in low energy expenditure.[13-15] The relation between diminished muscle mass and reduced activity in PWS is not clear. It has been shown that the presence of a hypothalamic GH deficiency contributes to a reduced lean body mass[11] and that GH treatment improves muscle mass,[15] physical strength, and agility.[16] However, even long-term treatment with GH normalizes growth but only partially compensates for the initial deficit of lean mass.[10] A peripheral muscle disorder[17] or a defect of feedback signaling between the central nervous system and muscle may also be present. The finding of alterations in muscle fibers in PWS raised the question of whether muscles are able to grow adequately in response to training activity. It has not been documented whether it is possible to increase muscle mass and to improve hypotonia by physical exercise in PWS. One of the reasons for the lack of such data might be that it was thought to be too difficult to motivate persons with PWS to adhere to a training program.

We aimed to quantify the level of spontaneous activity in children and adolescents with PWS and in control children by pedometer registrations and daily activity protocols. Second, we investigated whether a specific physical training program adapted for children with PWS can improve their local body composition to an extent similar to that in healthy children. Third, we studied the effects of a muscle training program on spontaneous physical activity and physical capacity. The achievement of an increase in physical activity would open up a new approach in the treatment of PWS to improve metabolic conditions and perhaps to prevent the development of severe obesity.

GH	Growth hormone
PWS	Prader-Willi syndrome
SDS	Standard deviation score

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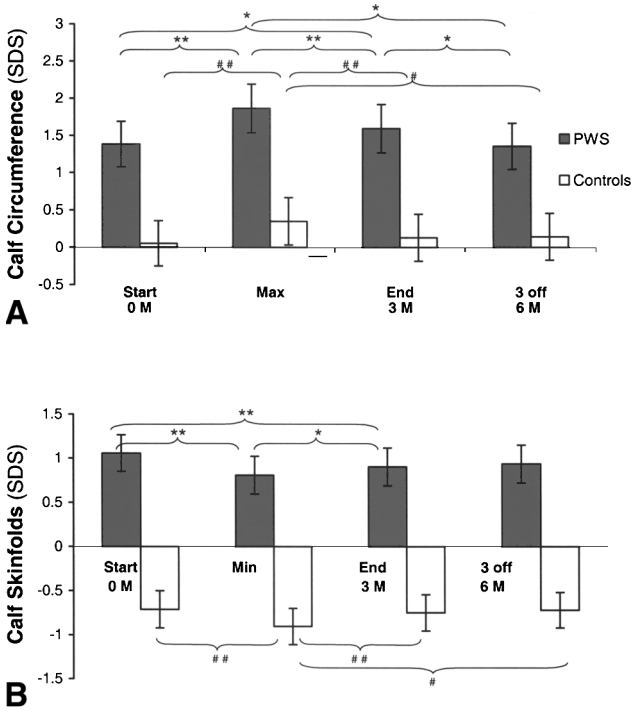

Fig 1. Calf circumference **(A)** and skinfold **(B)** of children with PWS (n = 17) and control children (n = 18) at start of training program (0 months), at maximum (calf circumference) and minimum (calf skinfold) effects, and at the end of the training program (3 months) and 3 months after end of training program. Results are expressed as mean ± SEM. Significant differences within PWS group and control group, tested by Wilcoxon test, are indicated as $^{*}P < .05$ and $^{**}P < .01$ and $^{\#}P < .05$ and $^{\#\#}P < .01$, respectively.

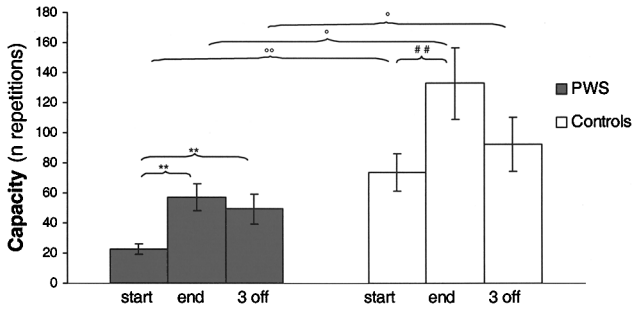

Fig 2. Physical capacity before start, at end, and 3 months after end of training program of children with PWS (n = 17) and control children (n = 18). Results are expressed as mean ± SEM. Significant differences within PWS group and control group, tested by Wilcoxon test, are indicated as $^{**}P < .01$ and $^{\#\#}P < .01$, respectively. Significant differences between PWS and control group, tested by Mann-Whitney *U* test, are indicated as $^{\circ}P < .05$ and $^{\circ\circ}P < .01$, respectively.

METHODS

Of a total of 32 persons with PWS participating in a long-term open treatment trial,[15] 17 children and adolescents were enrolled in the study program. All had caught up in growth and muscle mass under GH treatment for an extended period of time (mean, 5.3 years; range, 3.4-7.2). For comparison, a control group of 18 age-matched healthy persons (8 girls, 10 boys; 4 boys and 2 girls had entered puberty) was included. The PWS group consisted of 8 girls and 9 boys; 3 boys and 3 girls had entered puberty according to clinical criteria: breast stages 2 or 3 according to Tanner, or testicular volume >3 mL. Informed consent was obtained from the parents. In all persons with PWS, the diagnosis had been confirmed genetically, documented by deletion or uniparental disomy of chromosomes.[15] According to the previously published study design,[18] the parents were instructed to ensure that their child's energy intake remained stable throughout the study. One girl and 3 boys from the PWS group received substitution therapy with sex steroids in addition to GH. For the control group, 16 persons were recruited from 11 families of the PWS children, each contributing 1 to 3 brothers and sisters, and 2 control girls were friends of a PWS family. This design was chosen to strengthen the motivation of the children with PWS and their compliance with the training program as well as to facilitate the comparison of the obtained results within the same social environment. None of the control children received any medication.

All outcome measures indicated below were determined before the start of the 3-month training program (t_0) and after its end (t_{3m}). To assess long-term changes, physical capacity and calf circumference and skinfold were measured again 3 months after the end of the training program (t_{6m}).

Anthropometric Measurements

Height was measured on a Harpenden stadiometer and weight on an electronic balance (SECA 708, Hamburg Germany, d = 0.1 kg; coefficient of variation, 0.055%), whereby the values at t_0 and t_{3m} were determined. During the 3 months of the training program, the same investigator visited families at 1- to 2-week intervals in their homes, measured calf circumference and calf skinfold, and supervised the training compliance protocol. Three months after the end of the training (t_{6m}), calf circumference and skinfold were measured again. Calf circumference was measured according to the technique used in the First Zurich Longitudinal Study.[16] Calf skinfold was measured by a high-quality metal caliper (Holtain LTD, Crymych, UK) according to the Anthropometric Standardization Reference Manual.[17] During the course of the study, sex and age-related growth changes occurred; therefore, all anthropometric data are provided in standard deviation scores (SDS, difference between patient's data and the age- and sex-related mean of the normal reference group divided by the age- and sex-related standard deviation of the reference group), with the First Zurich Longitudinal Study[16] used as reference. Only calf skinfold had to be compared with German reference data from the Institute of Human Genetics and Anthropology, University of Jena, because they are not reported in the Zurich Longitudinal Study.

Reference Values for Calf Skinfold

The reference values for calf skinfold (see the Appendix in *The Journal of Pediatrics Online* at

Table. Anthropometric data at baseline and after 3 months of training

Group	Age (y) Mean (range)	Height SDS ± SD	WfH SDS ± SD
PWS (n = 17)	10.5 (4.4–18.8)	–0.3 ± 1.2	2.3 ± 1.9*
Baseline (t_0)		–0.4 ± 1.2	2.5 ± 2.0*
End of training (t_{3m})		–0.35 ± 1.3	2.3 ± 2.0
3 mo after end of training (t_{6m})			
Control (n = 18)			
Baseline (t_0)	11.1 (5.0–19.8)	–0.6 ± 1.0	0.4 ± 1.5
End of training (t_{3m})		–0.6 ± 1.0	0.3 ± 1.5
3 mo after end of training (t_{6m})		nd	nd

WfH, Weight-for-height; *nd*, not done.
Significant differences between PWS group and control group, tested by Mann-Whitney *U* test, are indicated as *$P < .01$.

www.mosby.com/jpeds) are based on data of Jena schoolchildren between 4 and 16 years examined in 1995 (boys: n = 1526; girls: n = 1400).[18,19] The skinfolds were measured according to the Anthropometric Standardization Reference Manual[17] with the use of a GPM skinfold caliper. By using the LMS method of Cole,[20] which includes median (M), coefficient of variation (S), and a measure of skewness based on the Box-Cox power (L), conversions of individual skinfold values to SDS scores can be calculated with the same fomulas as published before for body mass index scores.[21]

Assessment of Physical Activity

During 3 days before the start (t_0) and 3 days after the end (t_{3m}) of the training program, daily movements and activity were measured with a pedometer (Mechanical Pedometer, Eschenbach, Germany; kindly provided by Dr Karsegard, Department of Nutrition, University Hospital Geneva)[22] and activity report protocols.[23] This allowed for an unbiased assessment of the physical activity, irrespective of the training activity as such.

The pedometer provides a means of converting impulses of movement into distance. The results are read in kilometers. All pedometers were validated for proper functioning and individually adjusted for stride length before the start of the study. Parents and children received instructions for use on an individual basis. Patients and control children had to wear the pedometer for 3 consecutive days, except when sleeping, bathing, showering, swimming, or engaging in sports activities in which the pedometer could have been damaged. Such sports activities had to be reported on the activity protocols. Activity protocols had to be completed during the same 3 days by the parents or, if old enough, by the children, supervised by the parents. For each half-hour of the day, the child's activity had to be rated from 1 to 4. For each of the 4 numbers, several examples were quoted: 1 *(lying)*; 2 *(sitting)*; 3 *(walking)*; and 4 *(running)*. All figures were added up, and an activity score over the period of 3 days was calculated, with a detectable minimum of 144 points and a maximum of 574 points.

Training Program

The following training pattern was used for the children of the PWS and the control group: persons were standing on tiptoes on a step of a stair, holding the banister with one hand; then, they lowered their heels as far as possible. This exercise was performed 12 times, repeated in 3 blocks, with a 1-minute break between the blocks, leading to a total of 36 repetitions, if fully completed. Total training time was ~3 to 4 minutes. The training had to be conducted once per day over a period of 3 months, always at approximately the same time of the day. A training protocol had to be filled out by the parents, indicating for each day whether their children had done the training and how many repetitions in total they had reached if they had not been able to complete the full program.

Assessment of Physical Capacity

Physical capacity was assessed at the start (t_0), at the end (t_{3m}), and 3 months after the end (t_{6m}) of the training program by means of a simple test: The above-described exercise had to be conducted as many times as possible without a break. The absolute number of repetitions was counted.

Statistical Methods

All data were processed by GAS 4.1 of the Institute for Medical Informatics (IMI, Zurich, Switzerland). Data are shown as mean ± SEM. Changes within one group before and after training were tested for significance by the nonparametric Wilcoxon signed-rank test for paired samples because there was no normal distribution of data. The Mann-Whitney *U* test was used to identify significant differences between the two groups. Bivariate linear regressions between physical capacity, spontaneous activity by protocol, or by pedometer and anthropometric data were presented as Spearman correlation coefficients. In all tests, values of $P < .05$ were considered significant.

RESULTS

The following results were also observed when children who had entered puberty were excluded from statistical analysis.

Anthropometric Measurements

As expected, there was a significant difference ($P < .01$) between the PWS group and the control children in weight-for height SDS at t_0 and t_{3m} (Table). No significant difference was found in height SDS because in persons with PWS, height SDS was already normalized by GH treatment. Both calf circumference and calf skinfold were significantly ($P < .01$) increased in the PWS group compared with the control group at t_0, t_{3m}, and t_{6m}.

Because in children with PWS and in control children calf circumference was correlated with age at all time points ($r = 0.86$ and $r = 0.9$, respectively, both $P < .0001$), data are also provided in SDS (Fig 1). During training, calf circumference significantly increased in children with PWS from 31.1 cm at t_0 to a maximum of 32.2 cm, reached on average after 52.8 days of training. At t_{3m}, calf circumference was still increased to 31.8 cm compared with the baseline value and then further decreased to 31.6 cm at t_{6m}. The control group increased calf circumference from 29 cm at t_0 to a maximum of 29.8 cm, on average, after 46.3 days of training. At t_{3m}, calf circumference was 29.4 cm and at t_{6m} it was 29.9 cm. At t_{3m}, the increases of calf circumferences in SDS were similar in the PWS and in the control groups, but there was a trend to an even higher increase in the PWS group if the maximal difference of calf circumference was compared with the control data (median calf $circ_{max}$=0.6 SD and 0.2 SD, respectively, $P = .08$).

Calf skinfold in the PWS group was correlated with age ($r = 0.549$, $P < .05$), but to a lesser extent than in the control group ($r = 0.855$, $P < .001$); therefore, data are provided in SDS in Fig 1. In children with PWS they dropped significantly, after a mean of 50.4 days, from 17.9 mm at t_0 to a minimum of 16.6 mm, and remained significantly below the initial value at t_{3m} (17.1 mm). However, at t_{6m}, a significant increase to 17.4 mm was seen. In the control group, calf skinfold dropped significantly from 10.5 mm at t_0 to a minimum of 9.8 mm after a mean of 35.8 days. At t_{3m}, a mean of 10.3 mm was measured, a value that remained nearly stable at t_{6m} (10.4 mm). At all times, there was a significant difference in these anthropometric measurements between the PWS and the control group, but the decrease in SDS did not differ significantly between both groups.

Assessment of Physical Activity

In the PWS group, pedometer measurements at t_0 revealed a mean walking distance of 11.1 km over the period of 3 days, whereas the control group walked 24.6 km ($P < .05$). In the activity protocol scores at t_0, the PWS group reached 256 points and the control group reached 274 points ($P < .01$). At t_{3m}, the mean walking distance over the period of 3 days was significantly augmented in the PWS group ($P < .05$) to 17.4 km, whereas the level of the control group remained nearly the same (25.6 km). The activity protocol scores remained unchanged in both groups (PWS group, 255 points; control group, 273 points).

Assessment of Physical Capacity

Before the start of the exercise program, physical capacity was correlated with age in healthy children ($r = 0.488$, $P < .05$) but not in the PWS group (Fig 2). Physical capacity significantly improved in both groups during training ($P < .01$): At t_0, children with PWS reached a mean score of 22.7 repetitions (31% compared with baseline data of the control group), and at t_{3m}, the capacity improved to a mean of 57.3 repetitions (78%). At t_{6m}, physical capacity decreased to 49.4 repetitions (67%) but remained significantly above the values than before the beginning of the study. The control group augmented its mean score from 73.6 repetitions (100%) at t_0 to 132.8 repetitions (180%) at t_{3m}. At t_{6m}, there was also a significant decrease to 92.3 repetitions (125%). At all times, capacity was significantly ($P < .05$) higher than in the PWS group.

Correlations

To assess the interrelation between changes in local body composition, physical activity, or physical capacity, the corresponding parameters investigated were correlated. Significant correlations were found only between pedometer distance and activity protocol scores in children with PWS at t_0 ($r = 0.752$, $P < .001$) and in both the PWS and control groups at t_{3m} ($r = 0.752$, $P < .001$, and $r = 0.720$, $P < .01$). In the PWS group, calf skinfold in centimeters at t_{3m} was negatively correlated with the increase of capacity between 0 and 3 months ($r = -0.6$, $P < .05$), and there was a weak negative correlation between skinfold SDS and physical capacity at t_{3m} ($r = -0.47$, $P = .77$).

DISCUSSION

Overeating in PWS is well studied,[4] and dietary restriction is accepted as the main approach in the care of affected persons.[27] In an effort to prevent obesity in PWS, surprisingly little attention has been attributed to the lack of activity.[13,14] However, intervention strategies to enhance physical activity seem to be promising because an inverse relation between adiposity and physical activity in children with PWS has been demonstrated.[11] In the current study, we included only persons with PWS who had received GH therapy for an extended period of time (>3 years) and who had already caught up in growth and muscle mass.[10]

Before the start of the training program, spontaneous physical activity was assessed by means of activity protocols and pedometer registrations. Activity protocols are frequently used to assess physical activity[28] and their validity is widely accepted,[29-31] but they rely on subjective judgment. Pedometer measurements represent a more objective technique. In the past, there were some concerns about their reliability,[28] but they currently offer the best solution for a low-cost, objective monitoring of physical activity.[30-32] Pedometer registrations of persons with PWS were not only 50% below the values of normal control children, but children and adolescents with PWS also had significantly diminished scores in the activity protocols. This means that there is a considerable spontaneous hypoactivity in PWS despite long-term growth hormone treatment and in the absence of severe obesity. Moreover, in both groups, reliability of the methods used was confirmed, since we found excellent correlations between activity measured by pedometer and by protocol, with the exception of the

first assessment in the control group. Activity protocols may not be sensitive enough to quantify the intensity of routine and sports activity in normal children because they were designed to assess the levels of activity in hypoactive children.[33]

Motivated exercise adherence is the single most important component of exercise intervention.[34] Our training for the calf muscle proved to be a suitable exercise method, even for children with PWS. From the fact that during training, calf circumference increased and in the meantime calf skinfold decreased significantly in both groups, both in centimeters and in SDS, it may be deduced[35] that muscle mass of the calf increased to a similar extent in both groups. Muscle mass in PWS therefore adequately responds to enhanced physical activity, pointing to diminished spontaneous physical activity as the cause for decreased muscle mass in persons with PWS, even after growth hormone treatment. These data are evidence that the primary cause of the decreased lean mass in PWS is not a disturbance of muscle function or caused by a feedback defect of signaling between muscle and the central nervous system. The decrease in calf skinfold, reflecting local fat mass, could be due to geometric factors secondary to hypertrophy of the calf muscle[36] or could point to a local short-loop regulation system for muscle and fat tissue.

In both groups, the nadir of training effect concerning local body composition was seen at approximately 7 weeks of training (PWS: mean, 52 days; control: mean, 46 days), which is most probably due to a reduction of training adherence thereafter, as observed in the training compliance protocols. However, it was surprising that the PWS group, in contrast to the control group, still showed a significant improvement at the end of the training. This could either indicate better motivation as the result of direct concern or a greater effect of training and a larger discrepancy between basal state and training state in the PWS group.

In persons with PWS, a significant increase in spontaneous physical activity was observed at the end of the training program. Daily walking distance, measured by pedometer, increased from 45.1% to 70.7% compared with the baseline data of the control group. This means that it is possible to improve the sedentary behavior pattern in patients with PWS by means of an easy daily 3-minute physical training program. Finally, the training program led to a significant increase in physical capacity in both groups. Persons with PWS had nearly increased their performance 3-fold, whereas the control children had at least doubled theirs at the end of the training program.

To exclude a natural course of the described parameters and to verify the real impact of our intervention, we investigated changes in calf circumference, in skinfold, and in physical capacity 3 months after the end of the training program. It was demonstrated that without special training, calf circumference decreased and calf skinfold increased significantly in both groups, reflecting a decrease in muscle mass close to the level before the start of the training. Physical capacity also decreased significantly in both groups but nevertheless remained higher than at the beginning of the study, indicating a possible long-term training effect.

This study demonstrates that persons with PWS not only are able to adhere and respond to a training program but that it is also possible by means of a simple intervention to increase spontaneous physical activity and to improve physical capacity. Self-motivation of persons with PWS, as described by others,[34] was also remarkable in this study.

We suggest a personal and regular physical training program for persons with PWS, including a workout of a variety of different muscle groups to avoid boredom. This new approach in the treatment of PWS opens up a complementary therapeutic option to the restrictive control of diet.

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REFERENCES

1. Prader A, Labhart A, Willi H. Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myotonieartigem Zustand im Neugeborenenalter. Schweiz Med Wochenschr 1956;86:1260-1.

2. Schwartz M, Woods S, Porte D Jr, Seeley R, Baskin D. Central nervous system control of food intake. Nature 2000;404:661-71.

3. Holm V, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitmann BYGF. Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics 1993;91:398-402.

4. Lindgren AC, Barkeling B, Hagg A, Ritzen EM, Marcus C, Rossner S. Eating behavior in Prader-Willi syndrome, normal weight, and obese control groups. J Pediatr 2000;137:50-5.

5. Hamilton CR, Scully R, Kliman B. Hypogonadotropism in Prader-Willi syndrome: induction of puberty and spermatogenesis by clomiphene citrate. Am J Med 1972;52:322-9.

6. Jeffcoate WJ, Laurance BM, Edwards CRW, Besser GM. Endocrine function in the Prader Willi syndrome. Clin Endocrinol (Oxf) 1980;12:81-9.

7. Cassidy SB, Rubin KG, Mukaida CS. Genital abnormalities and hypogonadism in 105 patients with Prader-Willi syndrome. Am J Med Genet 1987;28:922-3.

8. Eiholzer U, Bachmann S, l'Allemand D. Is there a growth hormone deficiency in PWS? Six arguments to support the presence of a hypothalamic GHD in PWS. Horm Res 2000;53(Suppl 3):44-52.

9. Schoeller D, Levitsky L, Bandini L, Dietz W, Walczak A. Energy expenditure and body composition in Prader-Willi syndrome. Metabolism 1988;37:115-20.

10. Eiholzer U, l'Allemand D, van der Sluis I, Steinert H, Ellis K. Body composition abnormalities in children with Prader-Willi syndrome and long-term effects of growth hormone therapy. Horm Res 2000;53:200-6.

11. van Mil E, Westerterp K, Gerver W, Marken Lichtenbelt W, Kester A, Saris W. Body composition in Prader-Willi syndrome compared with non-syndromal obesity: relationship to physical activity and growth hormone function. J Pediatr 2001;139:708-14.

12. Brambilla P, Bosio L, Manzoni P, Pietrobelli A, Beccaria L, Chiumello G. Peculiar body composition in patients with Prader-Labhart-Willi syndrome. Am J Clin Nutr 1997;65:1369-74.

13. van Mil E, Westerterp K, Kester A, Curfs L, Gerver W, Schrander-Stumpel C, et al. Activity related energy expenditure in children and adolescents with Prader-Willi syndrome. Int J Obes Relat Metab Disord 2000;24:429-34.

14. Davies PS, Joughin C. Using stable isotopes to assess reduced physical activity of individuals with Prader-Willi syndrome. Am J Ment Retard 1993;98:349-53.

15. Eiholzer U, Gisin R, Weinmann C, Kriemler S, Steinert H, Torresani T, et al. Treatment with human growth hormone in patients with Prader-Labhart-Willi syndrome reduces body fat and increases muscle mass and physical performance. Eur J Pediatr 1998;157:368-77.
16. Carrel A, Myers S, Whitman B, Allen D. Growth hormone improves body composition, fat utilization, physical strength and agility in Prader-Willi syndrome: a controlled study. J Pediatr 1999;134:215-21.
17. Sone S. Muscle histochemistry in the Prader-Willi syndrome. Brain Dev 1994;16:183-8.
18. Eiholzer U, l'Allemand D. Growth hormone normalises height, prediction of final height and hand length in children with Prader-Willi syndrome after four years of therapy. Horm Res 2000;53:185-92.
19. Prader A, Largo R, Molinari L, Issler C. Physical growth of Swiss children form birth to 20 years of age. Helv Paediatr Acta 1989; 43 (Suppl 52):1-125.
20. Lohmann TG, Roche AF, Martorell R. Anthropometric Standardization Reference Manual. Champaign, Ill: Human Kinetics; 1988.
21. Zellner K, Kromeyer K, Jaeger U. Growth Studies in Jena, Germany: historical background and secular changes in stature and weight in children 7–14 years. Am J Hum Biol 1996;8:371-82.
22. Kromeyer-Hauschild K, Jaeger U. Growth studies in Jena, Germany: changes in body size and subcutaneous fat distribution between 1975 and 1995. Am J Hum Biol 1998;10:579-87.
23. Cole T. The LMS method for constructing normalized growth standards. Eur J Clin Nutr 1990;44:45-60.
24. Kromeyer-Hauschild K, Wabitsch M, Kunze F, Geller H, Geiss HC. Percentiles of body mass index in children and adolescents evaluated from different regional German studies. Monatsschr Kinderheilkd 2001;149: 807-18.
25. Sequeira M, Rickenbach M, Wietlisbach V, Tullen B, Schutz Y. Physical activity assessment using a pedometer and its comparison with a questionnaire in a large population survey. Am J Epidemiol 1995;142:989-99.
26. Bachmann S. Wachstumshormon-Behandlung von jungen noch nicht adipösen Kindern mit Prader-Willi Syndrom: Gewichtsverlauf und Einflussfaktoren. Dissertation, University of Zurich, 2000. p. 10–20.
27. Stadler DD. Nutritional Management. In: Greenswag LR, Alexander R, editors. Management of Prader-Willi Syndrome. New York, NY: Springer-Verlag New York, Inc; 1995. p. 88-114.
28. Haskell W, Leon A, Caspersen C, Froelicher V, Hagberg J, Harlan W, et al. Cardiovascular benefits and assessment of physical activity and physical fitness in adults. Med Sci Sports Exerc 1992;24:S201-20.
29. Sallis J, Buono M, Roby J, Micale F, Nelson J. Seven-day recall and other physical activity self-reports in children and adolescents. Med Sci Sports Exerc 1993;25:99-108.
30. Puhl J, Greaves K, Hoyt M, Baranowski T. Children's Activity Rating Scale (CARS): description and calibration. Res Q Exerc Sport 1990;61:26-36.
31. Albanes D, Conway J, Taylor P, Moe P, Judd J. Validation and comparison of eight physical activity questionnaires. Epidemiology 1990;1:65-71.
32. Tudor-Locke C, Myers A. Methodological considerations for researchers and practitioners using pedometers to measure physical (ambulatory) activity. Res Q Exerc Sport 2001;72:1-12.
33. Bachmann S, l'Allemand D, Gasser T, Eiholzer U. Einfluss von Ernaehrung und Erziehung auf das Gewicht bei Kindern mit PWS im Vergleich zu normalgewichtigen Kindern. Aktuel Ernaehr Med 2000;25:260.
34. Epstein L, Coleman K, Myers M. Exercise in treating obesity in children and adolescents. Med Sci Sports Exerc 1996;28:428-35.
35. Gasser T, Ziegler P, Largo R, Molinari L, Prader A. A longitudinal study of lean and fat areas at the arm. Ann Hum Biol 1994;21:303-14.
36. Krotkiewski M, Aniansson A, Grimby G, Bjorntorp P, Sjostrom L. The effect of unilateral isokinetic strength training on local adipose and muscle tissue morphology, thickness, and enzymes. Eur J Appl Physiol Occup Physiol 1979;42:271-81.
37. Nardella M, Sulzbacher S, Worthington-Roberts B. Activity levels of persons with Prader-Willi syndrome. Am J Ment Defic 1983;87:498-505.