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,\(^2\) including hypogonadism\(^3\)–\(^7\) 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.

**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)
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 (t0) and after its end (t3m). To assess long-term changes, physical capacity and calf circumference and skinfold were measured again 3 months after the end of the training program (t6m).

**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 t0 and t3m 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 (t6m), 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 Study16 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...
www.mosby.com/jpeds) are based on data of Jena school-children 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 Manual17 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 formulas as published before for body mass index scores.21

Assessment of Physical Activity

During 3 days before the start (t0) and 3 days after the end (t3m) 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 (t0), at the end (t3m), and 3 months after the end (t6m) 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 t0 and t3m (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 t0, t3m and t6m.

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 t0 to a maximum of 32.2 cm, reached on average after 52.8 days of training. At t3m, calf circumference was still increased to 31.8 cm compared with the baseline value and then further decreased to 31.6 cm at t6m. The control group increased calf circumference from 29 cm at t0 to a maximum of 29.8 cm, on average, after 46.3 days of training. At t3m, calf circumference was 29.4 cm and at t6m it was 29.9 cm. At t7m, 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 t0 to a minimum of 16.6 mm, and remained significantly below the initial value at t3m (17.1 mm). However, at t6m, a significant increase to 17.4 mm was seen. In the control group, calf skinfold dropped significantly from 10.5 mm at t0 to a minimum of 9.8 mm after a mean of 35.8 days. At t3m, a mean of 10.3 mm was measured, a value that remained nearly stable at t6m (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 t0 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 t0, the PWS group reached 256 points and the control group reached 274 points (P < .01). At t3m, 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 t0, children with PWS reached a mean score of 22.7 repetitions (31% compared with baseline data of the control group), and at t3m, the capacity improved to a mean of 57.3 repetitions (78%). At t6m, 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 t0 to 132.8 repetitions (180%) at t3m. At t6m, 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 t0 (r = 0.752, P < .001) and in both the PWS and control groups at t3m (r = 0.752, P < .001, and r = 0.720, P < .01). In the PWS group, calf skinfold in centimeters at t3m 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 t3m (r = -0.47, P = .77).

DISCUSSION

Overeating in PWS is well studied, and dietary restriction is accepted as the main approach in the care of affected persons. In an effort to prevent obesity in PWS, surprisingly little attention has been attributed to the lack of activity. 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. 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.

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 and their validity is widely accepted, but they rely on subjective judgment. Pedometer measurements represent a more objective technique. In the past, there were some concerns about their reliability, but they currently offer the best solution for a low-cost, objective monitoring of physical activity. 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. Motivated exercise adherence is the single most important component of exercise intervention. 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 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 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 in PWS. 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, 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.

We thank Professor Theo Gasser (Department of Biostatistics, Institute of Social and Preventive Medicine, University of Zurich) and Professor Eckhard Schömann (Department of Pediatrics, University Hospital Cologne) for their useful comments. We thank Mrs Karin Stutz for her help in translating and Mrs Claudia Weinmann for research coordination and assistance. Our special thanks go to the PWS Association of Switzerland and the parents and their children for their great commitment and efforts.

REFERENCES


Appendix. Reference values for calf skinfold for boys

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<th>P10</th>
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Number (n), median (M), coefficient of variation (SD), and a measure of skewness based on the Box-Cox power (L) as well as the percentiles (P) are provided. Data are given in mm.