0163-769X/01/$03.00/0
Printed in U.S.A.

Endocrine Reviews 22(6):787–799

Endocrine Dysfunction in Prader-Willi Syndrome: A Review with Special Reference to GH

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Prader-Willi syndrome is a genetic disorder occurring in 1 in 10,000–16,000 live-born infants. In the general population, approximately 60 people in every 1,000,000 are affected. The condition is characterized by short stature, low lean body mass, muscular hypotonia, mental retardation, behavioral abnormalities, dysmorphic features, and excessive appetite with progressive obesity. Furthermore, morbidity and mortality are high, probably as a result of gross obesity. Most patients have reduced GH secretory capacity and hypogonadotropic hypogonadism, suggesting hypothalamic-pituitary dysfunction. Replacement of GH and/or sex hormones may therefore be beneficial in Prader-Willi syndrome, and several clinical trials have now evaluated GH replacement therapy in affected children. Results of GH treatment have been encouraging: improved growth, increased lean body mass, and reduced fat mass. There was also some evidence of improvements in respiratory function and physical activity. The long-term benefits of GH treatment are, however, still to be established. Similarly, the role of sex hormone replacement therapy needs to be clarified as few data exist on its efficacy and potential benefits. In summary, Prader-Willi syndrome is a disabling condition associated with GH deficiency and hypogonadism. More active treatment of these endocrine disorders is likely to benefit affected individuals. (*Endocrine Reviews* 22: 787–799, 2001)

I. Introduction

SINCE PRADER-WILLI SYNDROME was first described around 45 yr ago (1, 2), there has been interest in the endocrine aspects of the condition. Recent years, however, have seen a growth of interest in this area; therefore, in this review we aim to provide a thorough analysis of endocrine dysfunction in Prader-Willi syndrome and give a full account of the therapeutic options available.

Abbreviations: BMI, Body mass index; DEXA, dual energy x-ray absorptiometry; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; GHD, GH deficiency; LBM, lean body mass.

A. A brief description of the syndrome

Prader-Willi syndrome is a genetic disorder characterized by both mental and physical abnormalities. Occurring in 70–75% of affected individuals, the principal genetic mutation associated with the condition is deletion of a segment of the paternally derived chromosome 15 (15q11-q13). Several other abnormalities have also been linked with the syndrome: 20–25% of patients exhibit maternal disomy of the same region of chromosome 15, 2–5% have imprinting center mutations, and 1% have translocations (3–5). The individual gene or genes from within 15q11-q13 that cause the condition have yet to be identified. More detailed reviews of the genetics associated with Prader-Willi syndrome are given by Cassidy (4) and Nicholls *et al*. (6).

Clinically, Prader-Willi syndrome is characterized by a range of mental and physical symptoms. These include short stature, muscular hypotonia, excessive appetite with progressive obesity, hypogonadism, mental retardation, behavioral abnormalities, sleep disturbances (including sleep apnea), and dysmorphic features (7, 8). The photograph of a boy with Prader-Willi syndrome illustrates the typical physical features of the condition (Fig. 1). Diagnosis of Prader-Willi syndrome is made according to a set of consensus clinical criteria that were published in 1993 (Table 1). On this basis, it is estimated that one child in every 10,000–25,000 live births suffers from the syndrome (9–11). However, as diagnosis relies on subjective identification of characteristic symptoms and signs, it is likely that this figure is not completely accurate. More recent studies of "at-risk" populations, including newborns, suggest that the prevalence is likely to be around 1:15,000, ranging from 1:10,000–1:16,000 (4, 12, 13). Mass screening for distinctive genetic abnormalities in the 15q11-q13 chromosomal region would enable a

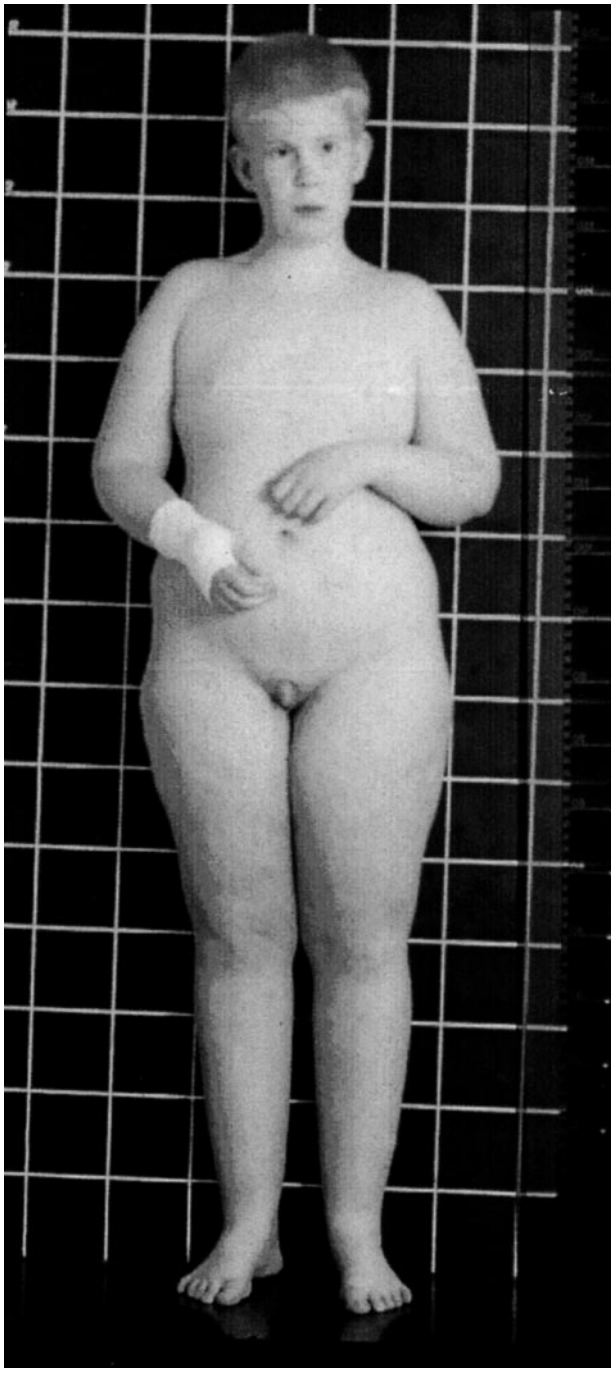

FIG. 1. A typical 11-yr-old boy with Prader-Willi syndrome. He is short for his age, has central obesity, low muscular mass, cryptorchidism, and typical facial feature with narrow bifrontal diameter, almond shaped eyes, small appearing mouth with thin upper lip, and down turned corners of mouth. In addition, his hands and feet are small. [Reproduced with permission.]

"true" prevalence to be calculated, but a study of this nature would not be cost effective. To date, screening of high-risk populations (12) remains the most efficient method of identifying patients with Prader-Willi syndrome.

In the newborn child, Prader-Willi syndrome first manifests as muscular hypotonia. It is often so pronounced that babies are described as "floppy." They frequently have feeding difficulties due to poor suck and thus require tube feeding for several weeks or months (7, 9).

TABLE 1. Clinical diagnostic criteria for Prader-Willi syndrome

Major criteria (1 point each)
Neonatal and infantile hypotonia
Infantile feeding problems or failure to thrive
Excessive or rapid weight gain between the ages of 1 and 6 yr
Characteristic facial features, including narrow face, almond-shaped eyes, small-appearing mouth with thin upper lip, down-turned corners of the mouth (three or more required)
Hypogonadism (impaired function of the gonads) with underdeveloped genitalia and/or impaired pubertal development
Developmental delay, mental retardation, or learning problems
Hyperphagia, food foraging, or obsession with food
Deletion 15q11-q13 on high-resolution cytogenetic analysis or other abnormality of the Prader-Willi chromosome region
Minor criteria (0.5 points each)
Decreased fetal movement or infantile lethargy
Typical behavioral problems: temper tantrums, violent outbursts; obsessive/compulsive behavior, argumentative, rigid, possessive, stubborn manipulative, stealing, lying (five or more required)
Sleep disturbances or sleep apnea
Short stature for family by the age of 15 yr
Fairer eyes, skin, and hair than expected
Smaller hands and feet than expected for height and age
Narrow hands with straight ulnar border
Esotropia or myopia
Viscous saliva
Speech articulation defects
Skin picking
Supportive criteria (0 points, but help to confirm diagnosis)
High pain threshold
Reduced incidence of vomiting
Temperature control problems
Scoliosis or kyphosis
Early adrenarche
Osteoporosis
Unusual skill with jigsaw puzzles
Normal neuromuscular findings

Five points (≥4 points from major criteria) strongly suggest Prader-Willi syndrome in children ≤3 yr old, whereas 8 points (≥5 points from major criteria) are indicative in older individuals. [Adapted with permission from *Pediatrics*, Vol. 91, page(s) 398–402, Table 1, © 1993 (8).]

Children with Prader-Willi syndrome usually become overweight by the age of 4 yr as a consequence of their insatiable appetite and compulsive eating (14). Unfortunately, obesity progresses with age (15–17), and historically we have observed that about one-third of individuals with Prader-Willi syndrome are more than twice their ideal body weight (18, 19). Obesity is a risk factor for many other serious conditions, including cardiovascular disease and diabetes; hence, it is a major cause of increased morbidity and mortality among patients with Prader-Willi syndrome (20, 21).

Restriction of growth is also a frequently observed sequel of Prader-Willi syndrome: approximately 90% of affected individuals are short in stature (9). This problem is illustrated by a study in which the weight and height of 71 Caucasian Americans, aged 4–24 yr, with Prader-Willi syndrome were compared with healthy subjects. The 50th centile for height in the patient group fell below the normal 5th centile by the age of 12–14 yr, whereas the 50th centile for weight in the affected individuals approximated the 95th centile in the healthy pop-

ulation (22). As a result of their feeding difficulties, affected infants often fail to thrive and, during the first year, this may result in growth below the 3rd percentile. Thereafter, linear growth is only slightly compromised, remaining at the 10th percentile or below until the age of 10 yr for females and 12 yr for males. After this time, height velocity often declines relative to the norm at these ages, due to a lack of growth spurt (9, 22). This growth pattern may vary in the individual child, partly as a consequence of evolving obesity or dietary interventions. Thus, it is not uncommon to see temporary growth arrest when caloric restrictions take effect after late diagnosis, or, conversely, an improvement in growth rate may be seen when obesity develops. Cassidy (4) reported that the mean adult heights achieved by men and women with Prader-Willi syndrome were 155 and 148 cm, respectively. Wollmann *et al*. (16), however, found that mean height was slightly higher at 162 and 150 cm for men and women, respectively, while Hauffa and colleagues (23) noticed a near final mean height of 159 cm in boys and 149 cm in girls. Nagai and co-workers (24) constructed growth curves for Japanese children with Prader-Willi syndrome and found that mean final height was approximately 141 cm in girls and 148 cm in boys. These values are considerably below −2 SD scores for healthy Japanese individuals.

During their first 6 yr of life, children with Prader-Willi syndrome often do not achieve normal levels of cognitive, motor, and language development. Indeed, according to one study, these individuals have a below-average IQ of about 70 (25). A review of cognitive ability among 575 affected individuals confirms this, showing that just 5% of patients had a normal IQ (*i.e.*, > 85) (26). Borderline mental retardation was observed in 28% of patients, while 34%, 27%, and 5%, respectively, were mildly, moderately, or severely mentally retarded. In addition to impaired mental development, many sufferers of Prader-Willi syndrome display a range of behavioral problems (4). As mentioned earlier, these include excessive appetite and lack of food selectivity, but there is also a high incidence of stubbornness, verbal perseverance, skin picking, and temper tantrums. Furthermore, affected individuals have a tendency toward depression and a diminished ability to initiate and maintain social contacts. A high pain threshold is also characteristic of the condition, and sleep apnea and excessive daytime sleepiness are particularly common among older children. Given these problems it is not surprising that many children with Prader-Willi syndrome experience learning disabilities and often require special education services (8).

The handicaps associated with Prader-Willi syndrome have significant implications in later life, as many of those affected are incapable of independent living. According to a large survey of adults with the condition (20), the majority lived in group homes or with their family. More than one-third (35%) did not work; of those who did work, the vast majority were employed in a sheltered environment. There was still a high incidence of behavioral problems, and hospital admissions due to physical or psychiatric problems were frequent. The author reported that the identified aberrant behaviors resulted from the physical aspects of the syndrome, *i.e.*, the relentless hunger and the psychosocial pressures of being obese, sexually immature, and cognitively limited.

B. Body composition in patients with Prader-Willi syndrome

Prader-Willi syndrome is associated with high body fat mass and low muscle mass. Accurate determination of body composition is, therefore, an important aspect of monitoring both the progression of the condition and its treatment. Bioelectrical impedance analysis (which separates fat-free mass from fat mass), skinfold thickness (in which sc fat mass at various locations is recorded), and dual energy x-ray absorptiometry (DEXA, which provides a measure of fat tissue, bone, and non-bone lean mass) are the most widely used methods of assessing body composition. Bioelectrical impedance analysis, however, may be inadequate to measure changes in body composition in Prader-Willi syndrome because the ratio of lean to fat mass is decreased, requiring a special adaptation of mathematical estimates (27). For healthy subjects, DEXA is presently regarded as the "gold standard" because it allows different regions of the body to be assessed, and fat, bone, and lean mass are directly visualized and calculated. Further research is required, however, to determine whether it is worthy of the same status in Prader-Willi syndrome. One of the main limitations of DEXA and, indeed, of other methods, is that muscle mass can only be deduced indirectly, as the "lean mass" parameter comprises both water and cellular components. Accurate evaluation of muscle mass requires additional investigations, such as assessment of total potassium and/or extracellular water mass.

Despite their inherent limitations, data from the above methods have been found to correlate with each other. All three techniques and the "weight for height" method have also consistently confirmed distinct differences in the body composition of patients with Prader-Willi syndrome when compared with healthy controls. For example, in three studies involving young individuals affected with the condition, the mean percent body fat was 42% [n = 14 (28)], 51% [n = 5 (29)], and 47% [n = 27 (15)]. In contrast, in a population of 403 healthy Dutch individuals aged 4–20 yr, mean percent body fat was only 11% in males, 15.5% in girls less than 15 yr old, and 24% in females older than 15 yr (30). Similar results have been reported in an Australian study involving 265 healthy individuals aged 4–26 yr, with percent body fat ranging from 4.8% to 34.1% (median, 14.4%) in males and from 10.4% to 47.7% (median, 22.8%) in females (31).

Recently, Brambilla and co-workers (15) used DEXA to show that patients with Prader-Willi syndrome had a low lean body mass (LBM) as well as a higher ratio of fat mass to LBM compared with both healthy individuals of normal weight and, importantly, those with simple obesity (Fig. 2). The study also suggested that LBM declines further with age. Young children with Prader-Willi syndrome (<12 yr old) had an LBM that was 81–93% of that found in the children of normal weight, whereas in older patients LBM was only 63–83% of the normative values. Limb areas appeared to be most compromised. In addition, bone mineral content was found to be lower than in the healthy obese and normal weight populations. Notably, Eiholzer and co-workers (32) have shown that, even in the first years of life, children with Prader-Willi syndrome have an abnormally low LBM.

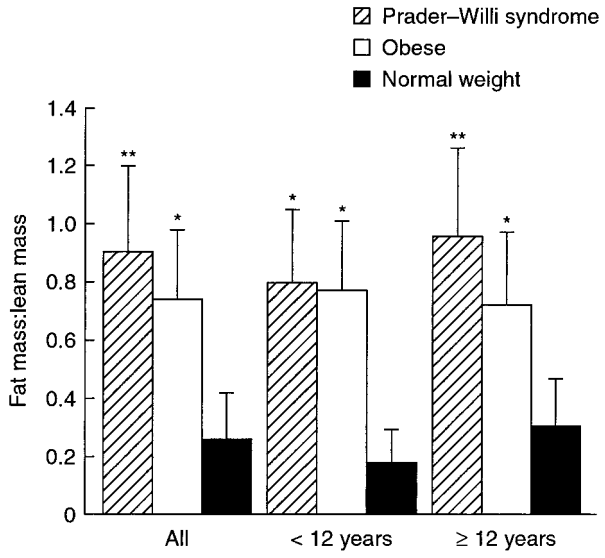

FIG. 2. The ratio of fat mass to lean mass in 27 patients (10 who were younger than 12 yr) with Prader-Willi syndrome (mean age, 14.2 ± 5.1 yr; mean BMI, 27.1 ± 6.6 kg/m^2), 27 obese healthy individuals (mean age, 13.7 ± 4.1 yr; mean BMI, 29.7 ± 5.4 kg/m^2), and 27 healthy individuals of normal weight (mean age, 13.7 ± 4.1 yr; mean BMI, 18.7 ± 2.7 kg/m^2). Values are mean ± SD. *, $P < 0.05$ compared with normal weight group; **, $P < 0.05$ compared with obese group. [Reproduced with permission from: P. Brambilla *et al.*: *Am J Clin Nutr* 65:1369–1374, 1997 (15). © American Society for Clinical Nutrition.]

The low LBM associated with Prader-Willi syndrome is likely to reflect a reduced muscle mass, and thus it may contribute to the observed moderate clinical hypotonia and poor physical performance of these individuals (15, 33). Muscle is a metabolically active tissue, and a small mass of this tissue, in conjunction with reduced physical activity (28), explains the low energy expenditure found in patients with Prader-Willi syndrome (34–37). In one study, patients with the condition expended approximately 50% less energy than healthy obese controls (18).

C. Prognosis

Prader-Willi syndrome is associated with increased morbidity and premature mortality, the main cause of which is thought to be obesity (20, 21). Many of the medical complications of obesity, including type II diabetes mellitus, hypertension, atherosclerosis, hyperlipidemia, compromised cardiopulmonary function, sleep disturbance, and psychological problems, such as depression and lack of self-esteem (38–42), have also been described in Prader-Willi syndrome. Affected individuals are also at risk of developing scoliosis, and this may be a concern when considering GH therapy to improve growth rate. Up to 80% of patients are reported to have a scoliosis exceeding 10°, and 15–20% have clinically significant scoliosis (43). Similarly, the incidence of osteoporosis is higher among patients with Prader-Willi syndrome, to which reduced GH secretion and hypogonadism could contribute (44). Lastly, given their high risk of comorbidity, mental retardation, lack of employment, and limited social and personal relationships, poor quality of life is a major concern for patients with Prader-Willi syndrome (4, 25, 38).

It should be noted, however, that most studies of comorbidity in Prader-Willi syndrome have suffered from limited patient samples and lack of appropriate control groups. In addition, many of these reports date from a period when restricted caloric intake and training of eating habits were not widely accepted control strategies. The literature on this aspect of the disease must therefore be interpreted with care, and high quality epidemiological studies are awaited. In the following sections we review the current literature pertaining to three of the most significant comorbid conditions in Prader-Willi syndrome: glucose intolerance, vascular disease, and respiratory disease.

1. Glucose tolerance. A number of reports suggest that glucose tolerance is abnormal in individuals with Prader-Willi syndrome. Fasting plasma insulin concentration and the insulin response to glucose are often increased in affected individuals, suggesting insulin resistance (45). A reduction in the number of insulin receptors on monocytes has also been described in the syndrome, echoing a similar abnormality seen in patients with simple obesity (46).

The reported prevalence of diabetes mellitus among patients with Prader-Willi syndrome varies. For example, Hall and Smith (17) found that 5 of 14 children with Prader-Willi syndrome had diabetic glucose tolerance and one had diabetes. Similarly, Illig and co-workers (47) reported that 41% of affected patients 15 yr of age and younger (n = 34) had reduced glucose tolerance, of which 21% had diabetes. Diabetes is also common in older patients. In a study involving 23 patients aged 15–41 yr, 17% had diabetes mellitus, the majority of whom required insulin therapy (21). A high incidence of type II diabetes mellitus in adults with Prader-Willi syndrome was also shown by Cassidy *et al.* (48), who studied 22 individuals aged 30–55 yr over a period of 1–12 yr. Nine of the patients (41%) developed diabetes mellitus. Clinically, the diabetes presented as type II, which responded to weight reduction and oral hypoglycemic agents. Finally, in one of the largest surveys to date, the prevalence of diabetes was lower than that described by Cassidy and coworkers. Of 232 adults with Prader-Willi syndrome (age, 16–64 yr), 44 (19%) had diabetes, 29 of whom required insulin (20).

The differing rates of diabetes reported by these authors could result from differences in age and body weight between the study groups. In most of the above studies, however, a large proportion of patients were grossly obese.

In contrast to these reports, some recent studies involving children with Prader-Willi syndrome who were of normal weight or only moderately obese have demonstrated low insulin levels combined with normal serum glucose concentrations (49–52). As subjects with "simple" obesity generally have elevated insulin levels, these results suggest that patients with Prader-Willi syndrome have increased insulin sensitivity, which is different from that of the grossly obese. One interpretation of these findings would be that some degree of GH insufficiency in Prader-Willi syndrome increases insulin sensitivity. Additionally, the high prevalence of diabetes cited in earlier reports may be secondary to gross obesity rather than a feature of the syndrome itself, but this is an area in which more data are needed.

2. Vascular disease. Patients with Prader-Willi syndrome appear to be at high risk of vascular disease. For example, Cassidy and co-workers (48) found that as many as 32% of patients with the condition were hypertensive (n = 22). A lower prevalence of hypertension (17%), however, was observed in a larger-scale survey (20), during which one man experienced a stroke at the age of 24 yr. Again, this study showed that comorbidity was related to weight gain, as hypertension, heart problems, and respiratory difficulties were all correlated with obesity. Several other cases of vascular disease in Prader-Willi syndrome exist in the literature. Advanced coronary atherosclerotic disease, for example, has been described in two patients who were less than 35 yr old (53, 54). One of the original patients described by Prader and co-workers (1) died at the age of 28 yr after developing diabetic vascular complications (55), and a 26-yr-old patient with Prader-Willi syndrome was recently reported to have experienced silent myocardial infarction and hyperlipidemia. The same patient also had rapidly progressive diabetic retinopathy and neuropathy (56). The authors suggested that premature atherosclerotic coronary disease might play an unrecognized role in mortality and morbidity associated with Prader-Willi syndrome. However, their conclusion is based solely on case reports, and controlled data are required before a firm link can be made. Hyperlipidemia may also be a feature of Prader-Willi syndrome, although both normal and elevated lipid levels have been reported (57–60). In a study by l'Allemand and colleagues, 25% of children with Prader-Willi syndrome had elevated levels of low-density lipoprotein cholesterol and apolipoprotein B (61).

3. Respiratory disease. Impaired respiratory function is frequently observed in patients with Prader-Willi syndrome (62). Cassidy and colleagues (48) found that seven of eight affected individuals over the age of 30 yr had restrictive lung disease, and Laurance *et al.* (21) reported that cor pulmonale was the most common cause of death among nine patients with the condition. A further complication seen in affected patients with reduced lung function is hypercapnia (62). Until recently, this was thought to be a secondary effect of respiratory muscle weakness or the result of Pickwickian syndrome brought about by increased abdominal and thoracic fat. However, we and other investigators have now found that affected individuals have an impaired response to short periods of hypercapnia and a reduced ventilatory volume, indicating that the sensitivity of peripheral chemoreceptors to changes in blood oxygen and carbon dioxide is decreased (63–65). Thus, it seems that impaired respiratory function in Prader-Willi syndrome is not caused solely by obesity or muscle weakness.

II. GH Secretory Status in Patients with Prader-Willi Syndrome

There are many data indicating reduced GH secretion in patients with Prader-Willi syndrome. Low peak GH response to stimulation tests, decreased spontaneous GH secretion, and low serum IGF-I levels have been documented in at least 15 studies involving about 300 affected children (Table 2 and Refs. 49, 60, 66–78). Depending on the stimulation test used, 40–100% of children with this condition fulfill the criteria for GH deficiency (GHD), which is generally defined as peak GH levels of less than 10 μg/liter in response to one or two stimulation tests. The majority of affected children also have low GH secretion when measured by frequent blood sampling over 24 h. However, healthy, obese individuals also show reduced GH secretion during provocation tests, when compared with healthy, "lean" controls (79). The cause of reduced GH secretion in obesity is not fully understood and both FFA (80) and insulin have been proposed as mediators of this effect (81). At least one study has shown elevated levels of free IGF-I in individuals with "simple" obesity, suggesting a negative feedback at the pituitary/hypothalamic level (82). However, normal levels of free IGF-I have been found in other studies of subjects with the same condition (83). As a result of these findings, it has been argued that the apparent GH insufficiency in patients with Prader-Willi syndrome simply reflects their obesity. To determine whether this is in fact the case, a detailed comparison of the two conditions with respect to GH-related parameters and clinical features is required.

Firstly, the GH response to GHRH in obese individuals is enhanced by simultaneous administration of a cholinesterase inhibitor, such as pyridostigmine (84). This effect is probably the result of reducing somatostatinergic tone. In contrast, when these agents are coadministered to patients with Prader-Willi syndrome, 13 of 18 still showed a blunted GH response, suggestive of genuine GHD (85). In children with GHD and most, but not all, children with Prader-Willi syndrome (Table 2), serum IGF-I levels are reduced, whereas healthy children with simple obesity have normal or slightly elevated IGF-I levels. Furthermore, the level of IGF-I has been shown to correlate with body mass index (BMI) in obese children (83, 86). This is not the case in children with Prader-Willi syndrome (77), where low IGF-I and GH levels are not limited to those who are severely obese but have also been found in patients who are of normal weight. Lastly, in contrast to healthy obese children (80, 83, 87), depressed levels of IGF-binding protein 3 have been reported in affected individuals (49).

Clinical features of the condition also support the presence of GHD in Prader-Willi syndrome. Both Prader-Willi syndrome and GHD are characterized by short stature, obesity with extra fat deposits over the abdomen, abnormal body composition with reduced muscle mass and decreased bone density, and, in some patients, retarded bone age (8, 16, 88). Conversely, children with simple obesity are often tall for their age and have an increased absolute fat free mass and advanced bone age (89, 90). In summary then, available data suggest that, as a group, patients with Prader-Willi syndrome are GH deficient, although the degree of GHD may vary from mild to severe insufficiency.

The occurrence of reduced GH secretion and hypogonadotropic hypogonadism (see *Section III*) in the majority of children with Prader-Willi syndrome, together with abnormal appetite control and high pain threshold, suggest hypothalamic-pituitary dysfunction. Autopsies of five patients with Prader-Willi syndrome performed by Swaab and coworkers (91) indicated that the paraventricular nucleus was

TABLE 2. Summary of studies assessing GH status in children with Prader-Willi syndrome

Authors, year (ref.)	No. of patients (age in years)	Methods	Results
Fesseler and Bierich, 1983 (66)	12 children	Arginine stimulation test, GHD = peak GH < 10 μg/liter	GHD in 7/12 (58%)
Costeff *et al.*, 1990 (67)	6 (8–11), 5 were of normal wt	Clonidine stimulation test; 24-h GH secretion; somatomedin-C levels	Peak GH response to clonidine below reference range in 4/6; mean GH secretion below reference range in 6/6; somatomedin-C levels in lower reference age in 6/6
Calisti *et al.*, 1991 (68)	5 (5–12)	Insulin tolerance test and L-dopa stimulation tests; GHD = peak GH < 10 μg/liter	Low peak GH in both tests in 2/5
Huw *et al.*, 1992 (69)	11 (8.8 ± 1.2)	Sequential clonidine and arginine test, GHD = peak GH < 10 μg/liter; IGF-I levels	GHD in 10/11 (91%); IGF-I mean SD score, − 1.9 ± 1.3
Cappa *et al.*, 1993 (70)	10 (6–24); 8 obese controls (6–12); 9 short healthy controls (8–13)	GHRH + pyridostigmine stimulation test; IGF-I levels	Peak GH significantly lower in patients and obese controls compared with short healthy controls; IGF-I levels lower in patients than in obese and short controls
Angulo *et al.*, 1996 (71)	44 (2–16), 33 were obese	Insulin tolerance test; clonidine stimulation and L-dopa stimulation tests; GHD = peak GH < 10 μg/liter	GHD by at least two stimulation tests in 40/44 (91%) including 10 nonobese patients
Eiholzer *et al.*, 1998 (49)	19 (0.5–14.6)	IGF-I levels	IGF-I SD score −0.7 ± 0.8
Grosso *et al.*, 1998 (72)	5 (8–11)	Insulin tolerance and clonidine stimulation tests; nocturnal GH secretion	GH peak < 10 μg/liter in response to clonidine and insulin in 3/5; GH secretion below normal in 3/5
Grugni *et al.*, 1998 (73)	22 (13–30); 21 obese controls; 8 short healthy controls	GHRH + pyridostigmine stimulation test; 24-h GH secretion; IGF-I levels	Peak GH and mean spontaneous GH secretion were significantly lower in patients compared with short healthy controls and obese controls. IGF-I levels lower in patients than in the controls
Lindgren *et al.*, 1998 (74)	29 (3–12) 10 obese controls	24-h GH secretion; IGF-I levels	Mean GH 0.7 μg/liter in patients and controls; IGF-I SD score −1.5 in patients and −0.2 in obese controls
Sipilä *et al.*, 1998 (75)	19 children	Clonidine stimulation test	Mean peak GH 3.28 mU/liter; 17/20 (85%) were considered to have severe GHD
Thacker *et al.*, 1998 (76)	16 (2–14)	Arginine and L-dopa stimulation tests in 14; clonidine and L-dopa tests in 1; clonidine test in 1; IGF-I levels in 11	Peak GH < 10 μg/liter; in response to arginine in 10/14 (71%); L-dopa in 12/15 (80%) and clonidine in 2/2
Carrel *et al.*, 1999 (60)	53 (4–16)	Clonidine stimulation test	Reduced GH secretion in all patients; mean peak GH, 2.0 μg/liter
Corrias *et al.*, 2000 (77)	43 (3–22), 7 were of normal weight; 24 obese controls; 25 short healthy controls	Clonidine, GHRH + arginine and GHRH + pyridostigmine stimulation tests; IGF-I levels	Peak GH levels were lower in patients, including those of normal weight, than in short healthy controls. IGF-I levels were lower in patients, regardless of weight, than in short healthy controls
Grugni *et al.*, 2001 (78)	16 (12.7–38.3); 15 obese individuals (12.9–42.9); 8 short healthy children (10.2–14.3)	GH-releasing peptide 6; GHRH + pyridostigmine; IGF-I levels	Peak GH and area under the curve lower in patients with Prader-Willi syndrome than in the control groups for both stimulation tests. IGF-I levels were low in all patients with Prader-Willi syndrome

reduced in size and there were fewer oxytocin-expressing neurons. In a later publication, Swaab (92) identified further irregularities associated with the syndrome. These included a 30% reduction in GHRH-releasing neurons in the nucleus arcuatus, a down-regulation of neuropeptide Y, and a deficiency in vasopressin. Magnetic resonance imaging has also revealed an abnormal bright spot in the posterior pituitary lobe of some affected individuals, which is considered to be a sign of hypothalamic dysfunction (93), and pituitary hypoplasia is frequently observed (94).

III. The Hypothalamic-Pituitary-Gonadal Axis and Sexual Development in Prader-Willi Syndrome

In addition to insufficient GH secretion, the majority of individuals with Prader-Willi syndrome have a dysfunctional hypothalamic-pituitary-gonadal axis, which manifests as retarded or incomplete sexual development. Neonatal hypogonadism is difficult to assess in girls, but boys affected by Prader-Willi syndrome often have small penises and/or undescended testicles, both of which are indications of pre-

natal hypogonadotropic hypogonadism (9). Detailed studies of gonadal structure and function in neonatal and prepubertal patients with Prader-Willi syndrome are lacking.

Puberty is generally delayed in children with Prader-Willi syndrome, and in some individuals it may never occur at all (44, 48), although there have been at least two reported cases of precocious puberty (95, 96). In fact, many children experience premature adrenarche characterized by growth of axillary and pubic hair, this being particularly common in obese individuals (97). In many affected individuals, puberty fails to progress beyond this stage. For example, Greenswag (20) studied a group of 81 females with Prader-Willi syndrome between the ages of 10 and 28 yr. During the study period only 39% of these patients experienced menarche. It seems that very obese girls with Prader-Willi syndrome may be more likely to experience puberty. A possible explanation for this is that aromatization of androgens in the fat tissue of these patients produces sufficient amounts of estrogen to prompt maturation (9). However, even if menses do occur, bleeding is usually irregular, and it is unlikely to be associated with a normal menstrual cycle. Furthermore, spontaneous breast development is difficult to assess in Prader-Willi syndrome because normal glandular development may be confused with increasing fat tissue, particularly in obese girls. Pubertal growth spurt and bone maturation are also compromised in Prader-Willi syndrome. Reduced levels of circulating sex hormones fail to provide the trigger for GH secretion, which may itself be depressed (see *Section II*).

Hypogonadism associated with Prader-Willi syndrome is generally due to insufficient gonadotropin secretion, *i.e.*, hypogonadotropic hypogonadism. In confirmation of this diagnosis, investigators have found that most affected individuals demonstrate a poor response to GnRH (98, 99) that improves after prolonged clomiphene administration. Tolis *et al*. (100) have also observed that repeated administration of GnRH improves LH secretion. These findings point to a hypothalamic dysfunction in the regulation of gonadotropin secretion. However, it should be noted that some individuals showed a normal gonadotropin response to GnRH and that, in our own observations, some males have reached T levels within the normal range.

Wannarachue and Ruvalcaba (101) have also observed patients whose hypogonadism was not classically hypogonadotropic in nature. Of nine females, aged 11–44 yr, only one woman showed a normal LH response to clomiphene administration. Of the two men (age 23 and 28 yr), both had very small testes and elevated LH levels that responded poorly to clomiphene (FSH levels were not reported). The men also had low basal T levels that showed a significant but subnormal response to administration of human CG over 5 d. One of the men had undergone testicular biopsy of both a scrotal and a cryptorchid testis at the age of 15 yr. The microscopic picture was similar in the two biopsies: few germ cells, some thickening of the tubular basement membranes, and seemingly normal Leydig cells. The other man was biopsied at 28 yr of age; atrophy of seminiferous tubules with some hyalinization, thickened basement membranes, and clearly distinguishable Leydig cells were found. In another report of testicular histology, an 8-yr-old boy was found to have no spermatogonia in his cryptorchid testes (102).

These scattered observations in male patients with Prader-Willi syndrome may be the result of hypogonadotropic hypogonadism combined with primary testicular dysgenesis manifesting as very poor spermatogenesis (98). Gonadotropin secretion may improve in early adulthood, leading to atrophy and hyalinization of seminiferous tubules. Furthermore, some male patients have poor Leydig cell function. Hypothetically, in the early years of life, this could be explained by a lack of LH stimulation, but in later years it may be secondary to seminiferous tubular damage caused by present or previous cryptorchidism.

Until recently it was thought that all individuals with Prader-Willi syndrome were sterile. However, we are now aware of two women with Prader-Willi syndrome who have become pregnant (103, 104). In one case, a woman with maternal disomy gave birth to a healthy girl, whereas the other woman, who had a deletion of 15q11-q13, gave birth to a child with Angelman syndrome.

It is possible that the tempo of gonadal maturation varies between individuals, thereby increasing the heterogeneity of patient groups in the various studies. There is some evidence for delayed gonadal maturation, as the normalization of T levels in blood in affected men over the age of 20 yr has been observed (our personal observations). Furthermore, one affected woman, reported to have given birth at the age of 33 yr, had primary amenorrhea until the age of 29 yr (103).

The variation in hypogonadism between individuals with Prader-Willi syndrome remains to be explained.

IV. The Status of Other Hormonal Axes in Prader-Willi Syndrome

Thyroid hormones and baseline TSH levels are normal or slightly elevated (9, 99, 100) in affected patients, although clinically significant thyroid dysfunction has not been documented in Prader-Willi syndrome. Spontaneous cortisol and ACTH levels are usually normal, as is the response to iv ACTH (9, 44, 99), although some authors have reported a subnormal adrenal response to ACTH (105). Basal and TRH-stimulated PRL levels are also within the normal range (99, 100). It has been reported that levels of both dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are elevated in Prader-Willi syndrome (106, 107). In our own unpublished investigations of children aged 3–12 yr, 11 of 23 individuals had elevated levels of DHEAS when compared with the normal range. The three oldest children (11–12 yr of age) had pubic hair growth that was appropriate for their age (stage 2 to 3), while the remaining children with elevated DHEAS levels ($n = 8$) had a BMI above 2 SD scores but no pubertal signs.

V. Endocrine Treatment of Patients with Prader-Willi Syndrome

Currently, there is no cure for Prader-Willi syndrome, but several of the problems associated with the condition can be managed effectively if treatment begins early. This is now

possible with the advent of molecular genetic methods that allow identification of affected children in the neonatal period. If the quality of life of patients with Prader-Willi syndrome is to be improved, a holistic approach to their treatment is needed. Before discussing the potential for endocrine hormone replacement, we describe some of the other therapies that may be required for successful management of the condition.

First, enteral gastric tube feeding is indicated in many neonates with Prader-Willi syndrome. Feeding difficulties commonly occur and may lead to malnutrition if not addressed. Training of balance and motor abilities is also important from an early age, as is physical training to increase muscle strength and energy consumption later in life. Other conditions, such as scoliosis, hyperopia/myopia, and cryptorchidism, should be treated if present. The behavior of affected children may be improved by imposition of regular routines and the strict reinforcement of behavioral limits. Affected children may also benefit from special education. However, the most important aspect of treating Prader-Willi syndrome is control of excessive weight gain, specifically with respect to fat. As we have previously indicated, individuals afflicted by this condition seem to have complications similar to those experienced by healthy obese people. Thus, weight reduction could be expected to have beneficial effects on morbidity and mortality. A strictly controlled diet, in conjunction with eating-habit training and regular exercise, is important from an early age and remains the basis for all therapeutic interventions. It has been noted, however, that early dietary intervention may reduce growth rate (108), possibly by unmasking GHD. To date, appetite suppressants have been mostly unsuccessful in controlling weight gain, as have surgical procedures such as gastric banding, small-intestine bypass, and jaw wiring (9). The various components of medical, psychological, and sociological care required by individuals with Prader-Willi syndrome have been extensively reviewed by Greenswag and Alexander (109).

A. Effects of GH treatment on stature

The GH-deficient state commonly associated with Prader-Willi syndrome, as evidenced by reduced GH secretion, low serum IGF-I levels, and clinical features typical of GHD, has provided a rationale for trials assessing the efficacy of GH treatment. From the current literature, more than 200 children with Prader-Willi syndrome have received GH treatment. The duration of treatment has generally ranged between 6 and 36 months, although some children have received GH for longer periods. To date, three randomized controlled studies have been reported (60, 110, 111).

Longitudinal growth was increased by GH treatment in all studies. A summary of several studies that highlights the change in height SD scores during the first year of treatment is shown in Table 3 (60, 71, 75, 94, 110–113). Initial positive effects on growth velocity appear to be sustained throughout the second year of treatment (Fig. 3). Furthermore, a report involving children treated with GH over a period of 5 yr shows that growth continues to improve with the result that target height SD scores can be reached (114). Long-term efficacy has also recently been reported by Eiholzer and l'Allemand (115) in a study involving 4 yr of treatment.

B. Effects of GH treatment on body composition and muscle function

The effect of GH treatment on body composition in Prader-Willi syndrome has been assessed in several studies (28, 71, 75, 76, 112, 113), two of which were controlled (60, 110) (Table 4). In most of these studies, a controlled diet was initiated before commencement of GH therapy and maintained throughout the trial. The results show that GH treatment leads to an overall improvement in body composition by reducing fat mass and increasing muscle mass (Figs. 4 and 5). A report published at the time of writing supports these data (116). Two years of GH treatment led to a reduction in fat mass and a sustained increase in LBM. Data on the long-term effects of GH on body composition are, however, limited, and recent results show that 5 yr of GH treatment may still be insufficient to normalize LBM (117). Data from other long-term studies do suggest that that GH treatment can help to stabilize BMI (114, 118). Improved motor performance and agility have also been documented in children with Prader-Willi syndrome who received GH (60, 113, 116). Furthermore, some reports suggest that such treatment has beneficial effects on physical appearance, energy, and endurance, thus improving the psychosocial functioning of affected children (70, 76, 112, 113). In a note of caution, it is recognized that many of these observations are based on spontaneous reports by parents and attending physicians; therefore, further studies are required to confirm these particular benefits.

TABLE 3. Summary of studies describing the effects of GH treatment on linear growth during the first year of treatment in children with Prader-Willi syndrome

Authors, year (ref.)	No. of patients (age in years)	Dose of GH quoted (dose in mg/kg/d)	Δ Height SD-score
Angulo *et al.*, 1996 (71)	30 (2–16)	0.2–0.3 mg/kg divided into 3 or 5 doses/wk	1.4[a]
Hauffa 1997 (111)	16 (3–12)	0.15 IU/kg/d (0.05)	1.0
Lindgren *et al.*, 1997 (110)	15 (3–12)	0.1 IU/kg/d (0.03)	1.2
	12 (3–12)	0.2 IU/kg/d (0.07)	1.5
Davies *et al.*, 1998 (112)	25 (4–10)	20 IU/m^2/wk (0.03)	0.6
Eiholzer *et al.*, 1998 (113)	12 (0.6–14.6)	24 IU/m^2/wk (0.04)	0.4–1.2
Sipilä *et al.*, 1998 (75)	19	0.1 IU/kg/d (0.03)	1.2
Carrel *et al.*, 1999 (60)	35 (4–16)	1 mg/m^2/d (0.03)	0.5
Schmidt *et al.*, 2000 (94)	9 (7–16)	14 IU/m^2/wk (0.02)	1.2

[a] 24 months reported.

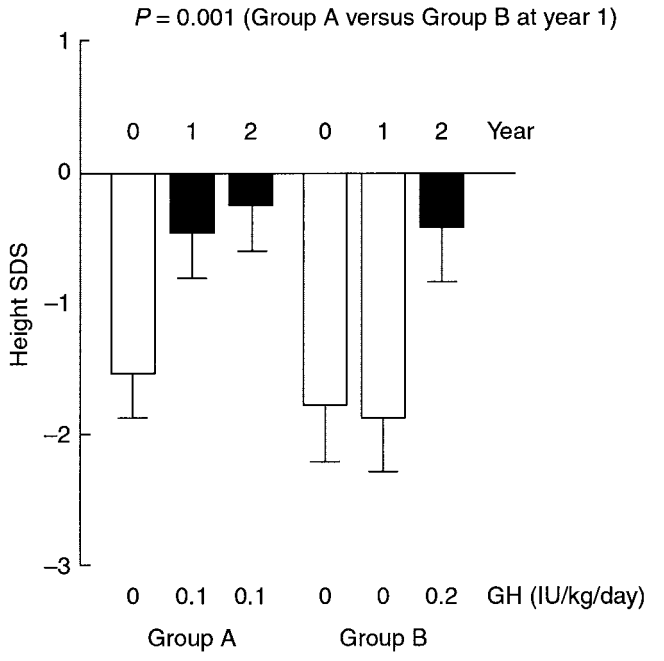

FIG. 3. The effect of GH treatment on height SD score. Group A comprises 15 children with Prader-Willi syndrome treated with GH, 0.1 IU/kg/d (0.33 mg/kg/d) for 2 yr; group B, 12 children with Prader-Willi syndrome who served as a control group during the first year and then were treated with GH, 0.2 IU/kg/d (0.66 mg/kg/d) during the second year of the study. Values are means ± SEM. [Derived from Ref. 110.]

C. Other effects of GH treatment

Two recent studies suggest that GH treatment can improve respiratory function in children with Prader-Willi syndrome. The first study, by Carrel and co-workers (60), showed that such therapy can improve respiratory muscle strength. In the second study, nine children with Prader-Willi syndrome received GH treatment for a period of 6 months (65). Both ventilation and the sensitivity of peripheral chemoreceptors to carbon dioxide increased during the trial, suggesting that GH exerts a direct or indirect effect on the central respiratory regulatory system.

D. Side effects of GH treatment

The reported adverse events during GH treatment of patients with Prader-Willi syndrome are generally similar to those observed during treatment of children with classic GHD, Turner syndrome, or chronic renal insufficiency. Recent studies have shown that insulin levels in children with Prader-Willi syndrome are lower than in obese controls at baseline but increase during GH treatment. Glucose levels tend to remain unchanged or increase within the normal reference range (50, 60). However, considering the limited experience of prolonged GH treatment in these patients and the increased incidence of diabetes mellitus associated with the condition, carbohydrate metabolism (glucose, HbA_{1c}) should be closely monitored in patients receiving GH.

Scoliosis, attributed to a combination of obesity and muscular hypotonia, is common in both children and adolescents with Prader-Willi syndrome. The rapid growth associated with GH may aggravate this spinal deformity; therefore, the occurrence and development of scoliosis should be monitored during therapy. If quantification of scoliosis is difficult, *e.g.*, in advanced obesity, x-ray monitoring should be used. In a controlled, randomized study by Carrel *et al.* (60), 70% of the patients had a mild scoliosis (<20°) that occurred equally between the control and treatment groups. Furthermore, there was no significant worsening of the condition in either group during the 12 months of the study. In a similar study conducted over 1 yr by Lindgren *et al.* (74), no patient in either the control or GH-treated group experienced progression of scoliosis to the severe stage (>20°).

E. Sex hormone replacement therapy

Treatment of hypothalamic-pituitary-gonadal failure in Prader-Willi syndrome remains a controversial issue, and the reader is therefore referred to an in-depth discussion by Lee (44). Most clinicians, however, agree that cryptorchidism should be corrected to enable detection of testicular malignancies (fertility may not be a goal in Prader-Willi syndrome). Yet, in one survey of 99 affected men with cryptorchidism, only 69 (70%) had undergone corrective surgery (20). The true incidence of hypogonadism in adults with Prader-Willi syndrome is unknown but in the same investigation only 41% of males and 18% of females received sex hormone replacement therapy. Sex hormone replacement therapy may be beneficial to hypogonadic patients in a number of ways. Obviously, the development of secondary sexual characteristics would be encouraged, but there is also potential for improvements in bone mineral content and bone mineral density. Possibly as a result of decreased estrogen and androgen production, these parameters are abnormally low in patients with Prader-Willi syndrome from a relatively early age (15, 119).

We have been unable to identify any systematic studies of sex hormone replacement therapy in adolescents or adults with Prader-Willi syndrome. Until such studies are published, these patients should be treated as other hypogonadal individuals. Thus, we suggest that if hypogonadism prevails to the age of 17–18 yr in a man with Prader-Willi syndrome, low doses of T substitution should be offered. Its subsequent effect on activity, strength, endurance, and quality of life should then be followed. If aggressiveness increases, the substitution could be stopped. In female patients, bone mineral density should be monitored during and after adolescence, and estrogen therapy should be considered if it becomes low-normal. In very obese patients, peripheral conversion of adrenal androgens to estrogen might suffice for the basic needs. However, in the increasing number of lean adolescent and adult patients with this syndrome, the estrogen status should be monitored yearly. The need of substitution therapy should be judged individually against the background of the development of bone mineral density, general activity, and quality of life. Given the recent reports of pregnancy in two women with Prader-Willi syndrome, caregivers should be aware of the possible need for contraceptives.

TABLE 4. Summary of studies describing the effects of GH treatment on body composition and muscle function in children with Prader-Willi syndrome

Authors, year (ref.)	No. of patients (age in years)	Dose of GH quoted (dose in mg/kg/d)	Results
Lee *et al.*, 1993 (29)	5 (5.4–13.0)	(0.05)	Total body fat decreased (mean 18%) and LBM increased (12.8–24.3%) significantly in 3 patients after 12 months' GH
Angulo *et al.*, 1996 (71)	30 (2–16)	0.2–0.3 mg/kg divided into 3 or 5 doses/wk	Significant decrease in weight SD score from 3.5 to 2.4 after 2 yr GH
Lindgren *et al.*, 1997 (110)	15 (3–12)	0.1 IU/kg/d (0.03)	Percent body fat decreased by 25% and muscle area of thigh increased significantly after 12 months' GH
	12 (3–12)	0.2 IU/kg/d (0.07)	Percent body fat decreased by 30% and muscle area of thigh increased significantly after 12 months' GH
Davies *et al.*, 1998 (112)	25 (4–10)	20 IU/m^2/wk (0.03)	Significant decrease in fat mass and increase in LBM (mean, 4 kg) after 6 months GH. Children with the greatest percent body fat benefited the most. Several parents reported greater energy and activity in their children
Eiholzer *et al.*, 1998 (113)	12 (0.6–14.6)	24 IU/m^2/wk (0.04)	Weight for height was reduced in obese patients and increased in younger underweight patients after 12 months' GH. Physical performance improved in a subset of patients
Sipilä *et al.*, 1998 (75)	19	0.1 IU/kg/d (0.03)	Weight for height and total body fat decreased after 12 months' GH
Thacker *et al.*, 1998 (76)	7 (5–14)	0.3 mg/kg/wk (0.04)	Many parents noted improved muscle mass and exercise tolerence in their children after 6 months' GH
Carrel *et al.*, 1999 (60)	35 (4–16)	1 mg/m^2/d (0.03)	Significant decrease in fat mass (mean, 8%) and increase in LBM (mean, 5 kg) after 12 months' GH. Improvements also in respiratory muscle strength, physical strength and agility

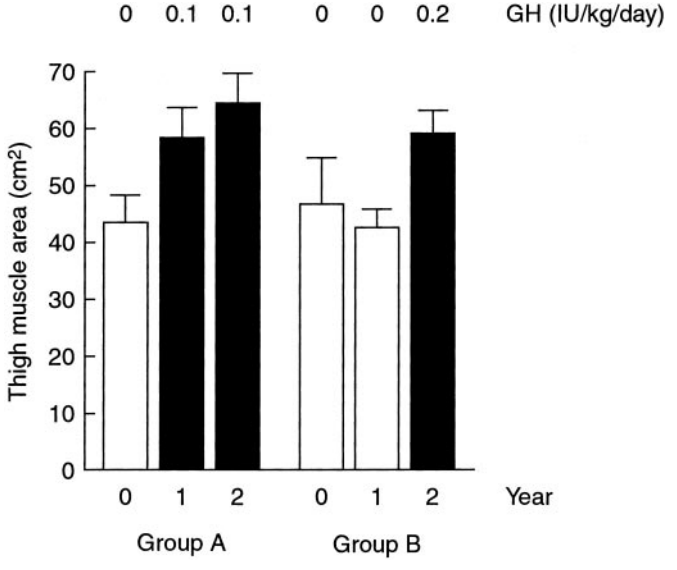

FIG. 4. The effect of GH treatment on muscle area of the thigh. Group A comprises 10 children with Prader-Willi syndrome treated with GH, 0.1 IU/kg/d (0.33 mg/kg/d) for 2 yr; group B, 9 children with Prader-Willi syndrome who served as a control group during the first year and then were treated with GH, 0.2 IU/kg/d (0.66 mg/kg/d) during the second year of the study. Values are means ± SEM. [Derived from Ref. 110.]

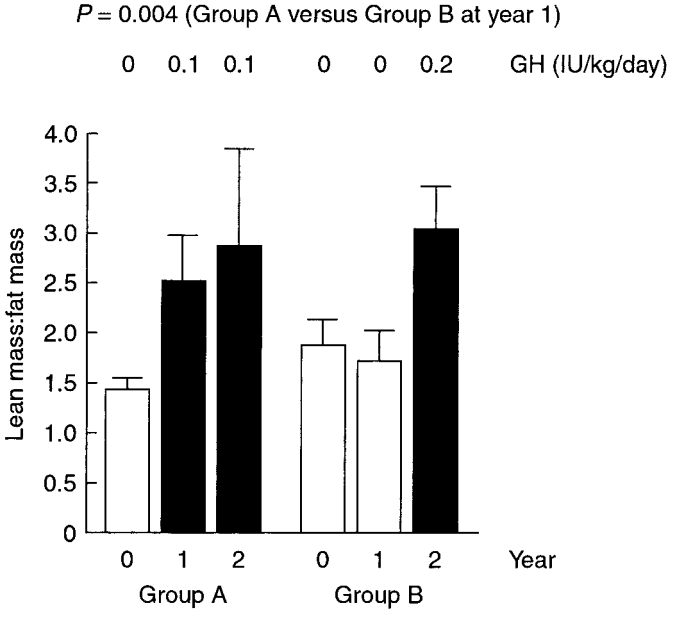

FIG. 5. The effect of GH treatment on the ratio of lean mass to fat mass. Group A comprises 12 children with Prader-Willi syndrome treated with GH, 0.1 IU/kg/d (0.33 mg/kg/d) for 2 yr; group B, 11 children with Prader-Willi syndrome who served as a control group during the first year and then were treated with GH, 0.2 IU/kg/d (0.66 mg/kg/d) during the second year of the study. Values are means ± SEM.

VI. Summary

Prader-Willi syndrome is a disabling condition associated with dysfunction of the hypothalamic-pituitary axis. It is characterized by impaired GH secretion and hypogonadism. Those afflicted by the condition exhibit distinctive abnormalities on chromosome 15, but the link between these and endocrine dysfunction remains unknown.

A growing number of reports describe the use of GH replacement therapy in children with Prader-Willi syndrome. Early studies focused on the beneficial effects of this

treatment on growth. However, it is now clear that GH treatment, when coupled with a strictly controlled diet, may help to reduce obesity and increase muscle mass. As the ultimate goal in the treatment of Prader-Willi syndrome is to reduce future morbidity and mortality, the observed improvement in body composition is, in our opinion, the main reason to use GH treatment in this group of patients. Furthermore, there is some evidence to suggest that GH treatment is associated with improved physical activity and agility in children with Prader-Willi syndrome, and published data suggest that there are few safety risks associated with GH treatment in these patients. Long-term safety studies are required, however, particularly regarding the effects of GH treatment on glucose metabolism and scoliosis.

At present, there are few reports in the literature regarding the use of sex hormone replacement therapy in affected individuals, although it is likely that such treatment would be beneficial in improving secondary sexual characteristics and helping to prevent osteoporosis.

In conclusion, Prader-Willi syndrome is associated with endocrine disorders that are often untreated. It is likely that a more active approach to correction of these hormone deficiencies would benefit individuals with this condition.

Acknowledgments

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