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Carbohydrate Metabolism Is Not Impaired after 3 Years of Growth Hormone Therapy in Children with Prader-Willi Syndrome

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Key Words

Prader-Labhart-Willi syndrome · Obesity · Insulin · Body composition · Growth hormone therapy · Oral glucose tolerance test · Quick insulin check index

Abstract

Background/Aim: In children with Prader-Labhart-Willi syndrome (PWS), the insulin secretion is reduced, despite obesity, being ascribed to the growth hormone (GH) deficiency of hypothalamic origin. Besides, an increased prevalence of diabetes mellitus was described in this syndrome. Hence, we addressed the questions of how body composition and insulin secretion are interrelated and what impact GH therapy has on the carbohydrate metabolism in PWS. ***Methods:*** We measured weight, lean and fat mass (by dual-energy X-ray absorptiometry), triglycerides, HbA_{1c}, and fasting insulin and glucose levels in 17 children (age range 1.5–14.6 years) with PWS to examine whether the carbohydrate metabolism is altered during 36 months of therapy with 8 mg GH/m^2 body surface/week. In a subgroup of 8 children, the insulin secretion was longitudinally assayed during oral glucose tolerance at 0 and 12 months of therapy. ***Results:*** Before therapy, the insulin secretion was lower and markedly delayed as compared with reference data and did not rise during therapy. The glucose tolerance was impaired in 2 of 12 children examined by oral glucose tolerance test before therapy and normalized during therapy. Fasting insulin and insulin resistance being normal at the beginning, significantly increased at 12 months and returned to initial levels at 36 months of GH therapy. Fasting glucose as well as HbA_{1c} and triglyceride levels were always normal. The fat mass before GH therapy was increased (39.5%) and dropped into the upper normal range (28.3%) during 3 years of therapy, being correlated with fasting insulin concentration and indices of insulin sensitivity before and after 1 year of therapy. ***Conclusions:*** Children with PWS are characterized by an intact insulin sensitivity with a decrease and a delay of insulin secretion, regardless of moderate obesity or GH treatment. In the present setting, the carbohydrate metabolism is not impaired by GH therapy, but by the excessively increased fat mass.

Introduction

Impaired glucose tolerance as well as an early and more frequent manifestation of diabetes mellitus were often described in individuals with Prader-Labhart-Willi syn-

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Table 1. Individual data of patients at the beginning of therapy

Patient No.	Sex	Pubertal stage Borg	Age years	Bone age years	Weight for height SDS [25]	BMI SDS [25]	Lean mass z-score [19]	Relative fat %	Fasting insulin SDS [27]
7[a, b]	male	1	1.5	0.75	–2.47	–2.38	–[a]	10.0	–0.7
8[b, c]	male	1	1.8	1.3	–0.64	–0.29	–0.39	28.3[e]	–0.6
9[b]	male	1	3	2	–1.24	–0.84	–1.18	23.6	–0.7
10	male	1	4.1	2	–2.78	–2.11	–1.49	21.0	–0.7
11[b, c]	female	1	3.7	2.3	4.14	4.31	–0.73	43.1[e]	–0.9
12	male	1	6.7	6.3	3	2.91	–2.62	44.0[e]	–1.0
13[b, c]	female	1	5	4.3	3.16	2.88	0.17	30.6[e]	–0.2
14	female	1	6.8	6.5	6.38	5.47	–1.86	54.2[e]	–1.1
15[b, c]	male	1	6.8	5	4.37	4.07	–1.22	43.3[e]	–0.5
16[c]	male	1	7	7.8	4.34	3.99	–1.68	43.3[e]	0.2
17	female	1	7.1	5.8	0.84	0.54	–2.42	42.6[e]	0.1
18[b, c]	male	1	9.5	9.5	3.76	2.45	–2.81	47.7[e]	1.2
19	female	2	11.1	11	5.31	4.67	–0.19	50.0[e]	–1.2
20[c]	female	3	9	11.5	6.29	5.9	n.d.	–[e, f]	0.6
21[b, d]	female	2–3	13.3	13	4.31	1.45	–2.50	53.4[e]	–1.9
22[b, d]	male	3	13.5	14.5	12.04	9.74	–0.97	60.5[e]	4.3
23[b, c, d]	female	2–3	14.6	12.5	1.57	–0.17	–1.54	36.1[e]	–2.3
Mean ± SEM			7.3 ± 1.0	6.8 ± 1.1	3.1 ± 0.9	2.5 ± 0.8	–1.4 ± 0.2	39.5 ± 3.4	–0.32 ± 0.35
Median		1	6.8	6.3	3.8	2.88	–1.49	43.2	–0.68
Range		1–3	1.5–14.6	0.8–14.5	–2.8 to 12.0	–2.4 to 9.7	–2.8 to 0.2	10.0–60.5	–2.3 to 4.3

B = Breast stage in female patients (Tanner); G = genital stage in male patients.

[a] Initial body composition assessed by a different DEXA device (Lunar®) in this boy; substitution with 50 µg *L*-thyroxine.

[b] Fasting insulin and glucose longitudinally assessed up to 3 years of GH therapy.

[c] OGTT performed before and after 1 year of therapy.

[d] Substitution with steroid hormones >14 months after start of therapy: No. 21 at 14.5 years with ethinyl estradiol 10 µg; No. 22 at 14.8 years with testosterone enanthate 100 mg i.m. 3 weekly, and No. 23 at 16.6 years with Trisequens® (2 mg estradiol, 1mg norethisterone acetate)

[e] % fat >95th percentile [26].

[f] Obesity assessed by skinfold SDS >2 [25].

drome (PWS) [1–5]. To date, however, the precise aetiology of diabetes in PWS remains unknown, and it is defined neither as type 1 nor type 2 [6]. High fasting insulin levels [7] and the increased insulin response in an oral glucose tolerance test (OGTT) [1, 3] implied that these patients were insulin resistant [4]. A reduced number of insulin receptors on monocytes in PWS substantiated this assumption [8]. Yet, in most of the studies, the patients were grossly obese, a condition typically generating an increased insulin resistance [9].

In spite of this, recent studies [10] found decreased fasting insulin levels and, on intravenous glucose tolerance testing, a reduced insulin response of beta cells in PWS children [11] and adults [12]. This was ascribed to the growth hormone (GH) deficiency (GHD) of hypothalamic origin [11] which might also account for the delay and decrease of the insulin response to an oral glucose load in PWS observed by the group of Zipf [12]. There is recent evidence of beneficial effects of a GH therapy [13–15], increasing lean mass and decreasing relative fat mass. However, the rise in circulating GH decreases the insulin sensitivity, as described in patients without PWS under GH therapy [16, 17]. In addition, a recent study [18] has warned that the manifestation of diabetes mellitus is accelerated by GH therapy in predisposed individuals, especially in those having PWS. Therefore, we investigated carbohydrate metabolism in children with PWS during 3 years of GH therapy, using the following approach: (1) Are there alterations of insulin secretion or sensitivity in PWS, estimated by simple measures includ-

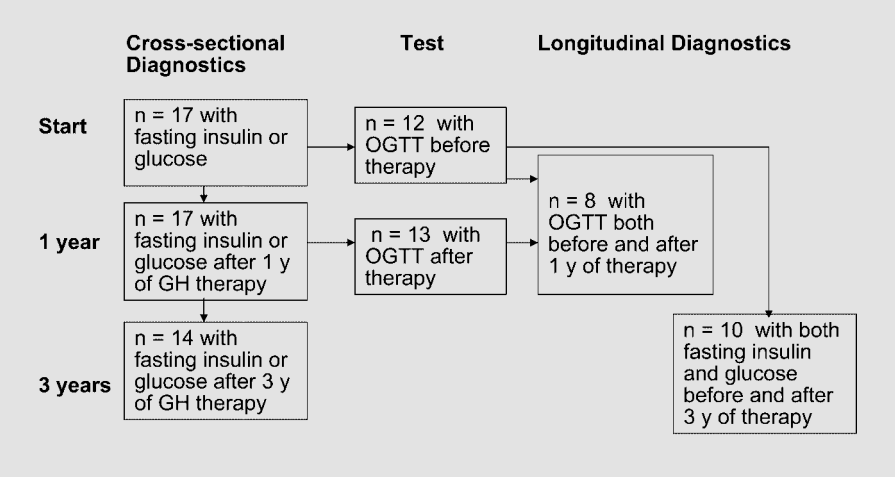

Fig. 1. Schematic presentation of monitoring of the carbohydrate metabolism in a total of 17 patients with PWS before and during GH therapy (see Patients and Methods).

ing OGTT, fasting insulin, and glucose? (2) Are these potential alterations associated with fat or lean mass? (3) Do 3 years of GH treatment change parameters of the carbohydrate metabolism such as insulin sensitivity or secretion and glucose tolerance? The observation period is based on the results of several studies demonstrating that a steady state of body composition is reached in the 3rd year of GH therapy [19, 20].

Patients and Methods

Patients

Seventeen children with PWS, documented by deletion or uniparental disomy of chromosome 15, were studied prospectively (table 1). The study sample is part of a larger group of patients for which data on body composition, growth, and metabolic changes during GH therapy were previously described [19, 21–23]. The children were treated with 8 mg/m^2 body surface/week (~0.037 mg/kg/day) recombinant GH (Pharmacia & Upjohn, Dübendorf, Switzerland), administered in daily subcutaneous injections. The study had been approved by the Ethics Committee of the Children's University Hospital of Zürich, and informed consent had been obtained from the parents. No additional medication was administered besides substitution for hypothyroidism in a 1.5-year-old boy (*L*-thyroxine 50 μg; No. 7 in table 1) and for hypogonadism in 3 adolescents after more than 14 months of GH therapy (Nos. 21–23 in table 1). The patients were advised to continue their diets, adapted to the recommendations of the Prader-Willi Syndrome Association of the USA [24]. The food intake was monitored by records; in general, the energy intake (median 11.3, range 8–13.4 kcal/cm height) was 20–40% below the recommendations for healthy children of the same age.

Height, weight, and body mass index (BMI) were assessed 6 monthly by the same investigator (U.E.) according to standard techniques [25] and are given as standard deviation (SD) scores (SDS; individual value – reference mean, divided by SD) to adjust data for age and sex, using the first Zürich longitudinal study [25], and data on BMI were kindly provided by the authors [25].

The body composition was determined by dual-energy X-ray absorptiometry (DEXA) in 16 patients (not in patient No. 20, table 1), as described recently [19]. Obesity was defined as relative fat mass (kg fat/kg total weight × 100) above percentile 95 of age- and sex-dependent Netherlands' reference data [26]. Since the relative fat mass may be biased by the reduced lean mass observed in PWS [13, 19], lean and fat masses were also separately provided as SDS based on prediction models established in Caucasian US American children. Missing values were not due to a specific selection of patients or dropouts, but to shortage of serum as a result of the difficulties encountered during veinipuncture of young or very obese PWS children or to uncompleted investigation intervals as a consequence of delayed start of therapy (patient Nos. 12, 19, and 20 missing at 36 months). Therefore, complete longitudinal investigations on insulin sensitivity parameters could be assessed only in 10 patients, and OGTTs were performed only in 8 patients both before and during therapy (fig. 1). The clinical data of these subgroups did not significantly differ from the whole group.

As published previously [10], fasting insulin levels were compared to reference data of Lautala et al. [27], obtained by a dextran-coated charcoal radio-immunoassay of insulin with polyconal antibodies in a population-based study in Finnish children, age range 3–18 years, with a normal prevalence of overweight (10%), as defined by skinfolds and BMI. Since an appropriate control group with the same disturbances of body composition as in PWS was lacking, the insulin levels were also compared to obese American Caucasian children, age range 8.2 ± 1.4 years, with a lower degree of obesity (33.9 ± 12.8% relative fat mass, assessed by the same DEXA device, QDR 2000; Hologic, Bedford, Mass., USA). Fasting insulin was measured by a similar immunometric sandwich assay (Immulite 2900; Diagnostic Products Corporation, Los Angeles, Calif., USA) as in PWS [28].

The standard OGTT was performed in 13 patients before and in 12 children after 12 months of therapy, using 50 g glucose/m^2 body surface, maximum 75 g. This dose corresponds closely to the WHO standard of 1.75 g/kg [29]. The OGTT was evaluated according to

Table 2. Parameters of body composition and metabolism

	BMI SDS	Fat mass SDS	Lean mass SDS	Relative fat %	Triglycerides mmol/l	HbA_{1c} %	Fasting glucose mmol/l	Fasting insulin [a] pmol/l
Before GH therapy (n = 17)								
Mean ± SEM	2.5 ± 0.8	1.18 ± 0.45	−1.4 ± 0.2	39.5 ± 3.4	0.88 ± 0.05	4.66 ± 0.1	4.1 ± 0.10	28.1
Range								14–251
12 months on GH (n = 17)								
Mean ± SEM	1.5 ± 0.9*	0.08 ± 0.46*	−0.85 ± 0.3*	30.3 ± 2.6**	0.91 ± 0.09 (n.s.)	5.10 ± 0.1**	4.3 ± 0.1 (n.s.)	54.1**
Range								16–212
36 months on GH (n = 14)								
Mean ± SEM	1.0 ± 0.4 (n.s.)	0.24 ± 0.23 (n.s.)	−1.1 ± 0.4 (n.s.)	28.3 ± 2.0*	0.74 ± 0.06 (n.s.)	4.95 ± 0.2 (n.s)	4.1 ± 0.2 (n.s.)	24.6 (n.s)
Range								9–63
Reference range	−2 to 2 SD [25]	−2 to 2 SD [19]	−2 to 2 SD [19]	16–30 [26]	0.35–1.55 [22]	3.8–6.0	3.8–6.4	<7–122 [27]

* $p < 0.05$, ** $p < 0.01$: significant change versus baseline data. n.s. = not significant.

[a] Given as median and range.

criteria of the WHO [6] and the German Society for Paediatric Diabetology [30]. The results of the study group were compared with reference data obtained by Deschamps et al. [31] in 158 obese children (age range 0.3–15 years, weight for height >2 SD, 88 boys and 70 girls) and in 70 normal lean children, matched for age and sex. Glucose was measured in plasma and insulin by competitive radioimmunoassay with polyclonal antibody according to the Yalow and Berson method.

Biochemical Analyses

Accuracy and precision of all analyses were accepted by approved external quality control. Serum insulin was measured by an enzyme-linked immunosorbent assay (Tosoh, Tokyo, Japan), serum glucose by the standard hexokinase method, HbA_{1c} by DCA 2000 (Bayer, Zürich, Switzerland), and triglycerides enzymatically on a Hitachi 717 or 917 analyzer (Boehringer Mannheim, Germany). After 1997, the fasting morning levels of metabolic parameters were monitored using the following methods: serum insulin was determined by an immunometric sandwich chemiluminescent assay (Access; Beckmann, Zürich, Switzerland) and HbA_{1c} by immunological quantification (Roche, Rotkreuz, Switzerland). The results of old and new assay systems were similar, as documented by the external quality control and by the use of identical normal ranges.

Predictors of Insulin Sensitivity

The insulin sensitivity was estimated by two models, based on fasting levels of insulin and glucose: the quick insulin check index [QUICKI = $1/\log (Insulin_0\ (mU/l)) + \log (glucose_0\ (mg/dl))$] [32] and the simple insulin-glucose ratio (IGR) [31], the reciprocal value of sensitivity. It has been emphasized recently that these parameters are useful in examining the insulin sensitivity in clinical studies [28, 33], as long as overt diabetes has not yet set in [34]. Own results were compared with QUICKI assessed in the same group of slightly obese children as described for fasting insulin [28] and in healthy lean children (age 9.85 ± 1.16 years) [33]; in this latter study, fasting glucose and insulin (Immulite 2,900 immunoassay; Diagnostic Products Corporation) were measured in plasma.

Predictors of Insulin Secretion

Two predictors of insulin secretion, recently tested in non-diabetic adults, were shown to be closely correlated with the gold standard, the insulin secretion in the hyperglycaemic clamp [35]. As a result, the insulin secretion can be represented either by the area under the curve of insulin divided by the area under the curve of glucose, AUC_{Ins}/AUC_{Gluc}, ($r = 0.71$), or, in analogy to the 1st and 2nd phase of hyperglycaemic clamp, the insulin secretion can be represented by two prediction equations from the first and second phase of the OGTT: 1st PhIns = $1{,}283 + 1.829 \cdot Ins_{30} - 138.7 \cdot Gluc_{30} + 3.772 \cdot Ins_0$ (pmol/l) and 2nd PhIns = $287 + 0.4164 \cdot Ins_{30} - 26.07 \cdot Gluc_{30} + 0.9226 \cdot Ins_0$ (pmol/l), both correlating with insulin secretion in the hyperglycaemic clamp ($r = 0.78$ and 0.79, respectively) [35]. The data of all predictors are provided in the same units as proposed by the original references.

Statistics

All own results are indicated in SI units as mean values and standard errors of the mean (SEM) except for the presentation of insulin levels and of their individual follow-up courses in which median values are used. The changes induced by GH therapy after 12 and 36 months were tested by the non-parametric Wilcoxon signed-ranks test for paired samples, and p-values <0.05 were considered significant. Linear correlations were tested by Pearson's test (SPSS 8.0) and corrected by age and sex, if appropriate, in partial correlations. All data were processed by GAS 3.3 of the Institute for Medical Informatics (IMI, Zürich, Switzerland).

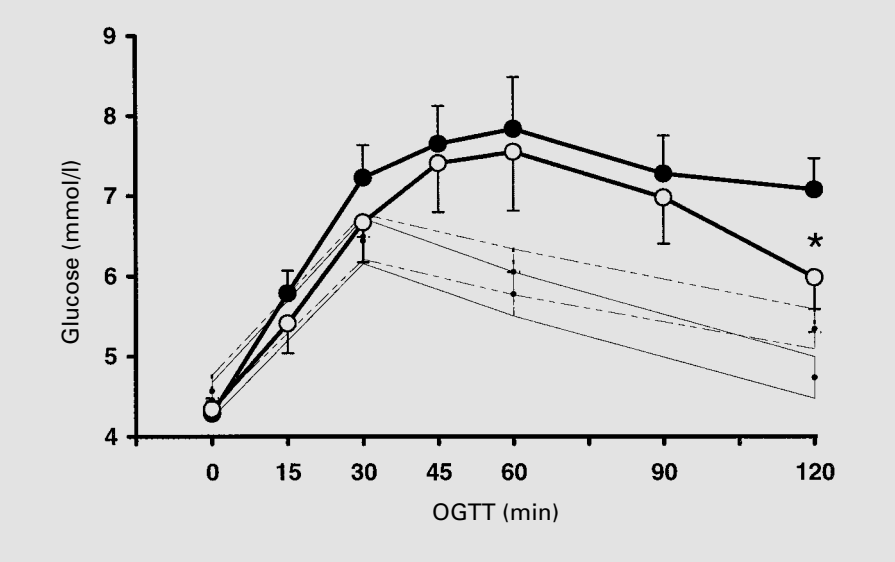

Fig. 2. Serum glucose levels (mean ± SEM) on OGTT in 8 children with PWS before (dark circles) and after (open circles) 12 months as compared with reference data (–1 to 1 SEM) of normal-weight (continuous fine lines) and obese (broken fine lines) children [31].

Results

Metabolic Follow-Up before and during GH Therapy

Only HbA_{1c} clearly increased (table 2), but nevertheless was normal in all patients during GH therapy. Fasting glucose and triglycerides, on the contrary, did not significantly change and remained normal. Before therapy, fasting insulin levels, on average (table 2), were slightly lower than published data in healthy children (mean 51.1 pmol/l) [27] and clearly lower than in less obese Caucasian children (73.9 pmol/l on average). Decreased insulin levels were found not only in young underweight children (Nos. 7–10, table 1), but also in pubertal overweight children with PWS (Nos. 21 and 23, table 1). Except in 1 pubertal boy with extreme obesity (No. 22, table 1), the insulin levels actually were not increased in the 9 obese children with PWS (table 1), unlike in healthy obese children [28, 31].

After 12 months of GH therapy, the fasting insulin concentrations significantly rose, independent of age or fat mass, but returned to initial levels after 36 months, and formerly high insulin levels went down to the normal range (table 2). Notably, all 6 patients who were still obese after 36 months of GH therapy had low insulin levels (data not shown).

OGTT and Insulin Secretion

The glucose tolerance was normal but above the average of reference children (fig. 2). After 1 year of therapy with GH, only the glucose level after 2 h had significantly decreased, and neither the AUC of glucose (14.0 ± 0.7 mmol/l h and, after 1 year, 13.2 ± 0.9 mmol/l h) nor the glucose concentration at any other time of OGTT (fig. 2) was significantly altered by GH treatment. However, a glucose intolerance was established in 2 prepubertal obese boys at baseline which normalized during GH therapy.

The insulin secretion on OGTT (fig. 3, table 3) was normal and even lower as compared with reference data of obese children [31]. There was a biphasic insulin secretion with a low release during the first part of the OGTT and with higher levels than observed in healthy lean children during the second part. It was remarkable that in PWS children the individual maximum of insulin secretion occurred between 60 and 90 (75 ± 12) min and, therefore, was delayed as compared with healthy lean and obese children (maximum between 30 and 45 min). This pattern with a delayed maximal peak did not change during GH treatment. In contrast, the estimate of first-phase insulin secretion significantly increased during GH therapy, while the second-phase insulin secretion remained unchanged. The total insulin secretion on OGTT slightly but not significantly increased following GH therapy (table 3).

Insulin Sensitivity

Both indices of insulin sensitivity showed the same pattern (fig. 4, table 3). Before GH therapy, children with PWS were characterized by a particular sensitivity to insulin action, in relation to the increased relative fat mass: the IGR was normal (mean in lean children 0.1)

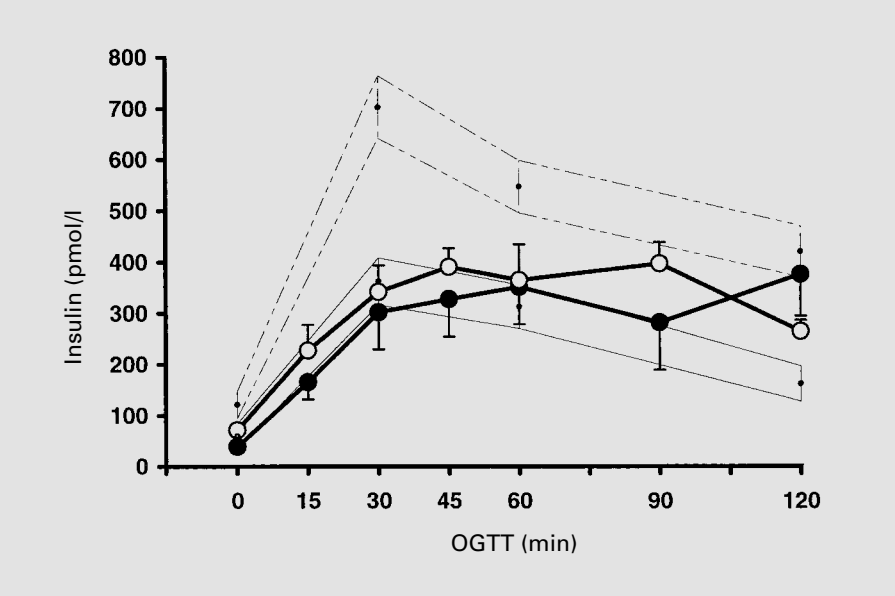

Fig. 3. Serum insulin levels (mean ± SEM) on OGTT in 8 children with PWS before (dark circles) and after (open circles) 12 months as compared with reference data (–1 to 1 SEM) of normal-weight (continuous fine lines) and obese (broken fine lines) children [31].

Table 3. Predictors of insulin sensitivity or of insulin secretion (mean ± SEM)

Therapy	n	IGR	QUICKI	n	1st PhIns	2nd PhIns	AUC_{Ins}/AUC_{Gluc}
Before GH therapy	17	0.09 ± 0.03	0.40 ± 0.02	8	982 ± 145	261 ± 34	40.7 ± 23.4
12 months on GH therapy	17	0.15 ± 0.03*	0.35 ± 0.01*	8	1,255 ± 99*	322 ± 24 (n.s.)	48.2 ± 11.3 (n.s.)
36 months on GH therapy	14	0.07 ± 0.01 (n.s.)	0.38 ± 0.01 (n.s.)	n.d.	–	–	–

n.d. = Not determined.

IGR = Insulin/glucose ratio = insulin (mU/l): glucose (mg/dl) [31]; QUICKI = insulin sensitivity = $1/\log [insulin_0 (mU/l]) + \log [glucose_0 (mg/dl])$ [32, 33]; 1stPhIns = first-phase insulin secretion estimated by OGTT = $1{,}283 + 1.829 \cdot Ins_{30} - 138.7 \cdot Gluc_{30} + 3.772 \cdot Ins_0$ (pmol/l) [35]; 2ndPhIns = second-phase insulin secretion estimated by OGTT = $287 + 0.4164 \cdot Ins_{30} - 26.07 \cdot Gluc_{30} + 0.9226 \cdot Ins_0$ (pmol/l) [35]; AUC_{Ins}/AUC_{Gluc} = molar ratio of AUC_{Ins} and glucose AUC during OGTT (pmol/mmol) [35].

* $p < 0.05$: significant change versus baseline data by paired Wilcoxon test.

[31], and the mean QUICKI was above the published average in healthy children, being 0.339 ± 0.02 [33] or, in obese children, 0.36 ± 0.04 [28] or, in lean adults, 0.38 ± 0.03 [32]. Only 1 child with gross obesity (No. 22, table 1; BMI 42 kg/m^2) was insulin resistant. During GH therapy, the insulin sensitivity significantly decreased, but returned to initial levels after 36 months.

Correlations of Metabolic Parameters with Body Composition

Since several parameters were closely related to age and gender, all regressions were corrected using partial correlations controlling for age and gender. There was a significantly negative partial correlation between glucose levels and lean mass after 12 months ($r = -0.61$, $p < 0.05$), but no correlation with the fat mass at any time.

Before therapy, insulin sensitivity and fasting insulin were significantly correlated with absolute fat mass (fasting insulin: r = 0.831, IGR: r = 0.874, and QUICKI: r = –0.80; all $p < 0.001$), but to a lower degree with percentage of fat (fasting insulin: r = 0.558, p = 0.038; IGR: r = 0.622, p = 0.023; QUICKI: r = –0.753, p = 0.002). The insulin secretion parameters such as AUC_{Ins}/AUC_{Gluc} were even more closely correlated with absolute fat mass (r = 0.914

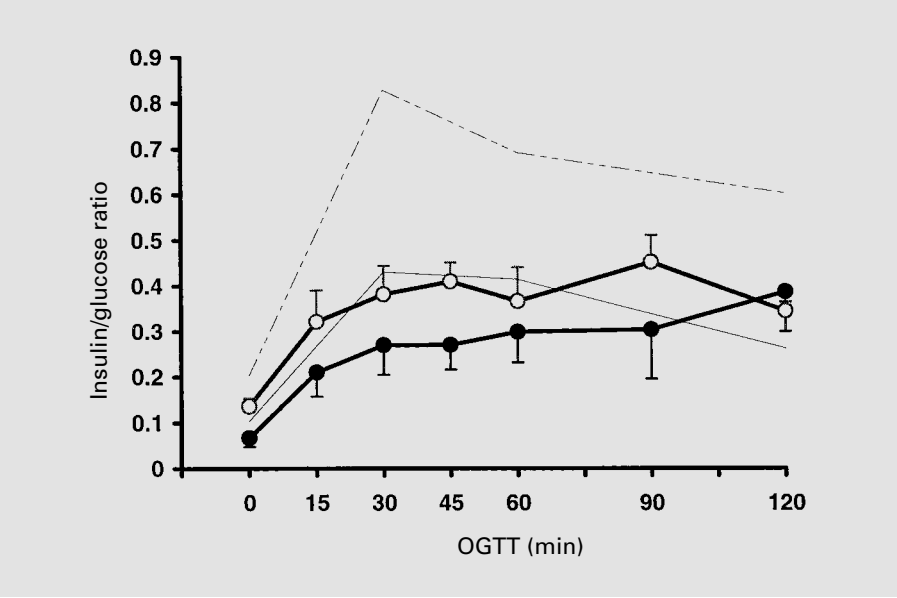

Fig. 4. Serum insulin/glucose ratio (mean ± SEM) on oral glucose tolerance test in 8 children with PWS before (dark circles) and after (open circles) 12 months as compared with reference data of normal-weight (continuous fine line, mean) and obese (broken fine line, mean) children [31].

and 0.926, $p < 0.0001$, respectively). Both 1st-phase and 2nd-phase insulin yielded similar positive correlations with fat mass ($r = 0.914$ and 0.913, respectively; $p < 0.0001$).

After 12 months of GH-therapy, two parameters of insulin sensitivity still correlated with absolute fat mass (fasting insulin: $r = 0.729$, $p = 0.011$; IGR: $r = 0.856$, $p = 0.003$); the QUICKI, however showed only a trend which was not significant due to the small number ($r = -0.368$, $p = 0.31$). Similarly, only a trend of insulin secretion, as assessed by AUC_{Ins}/AUC_{Gluc}, to correlate with relative fat mass was detectable ($r = 0.602$, $p = 0.066$) during GH therapy.

Discussion

In markedly obese children and adults with PWS, insulin resistance, impaired glucose tolerance, as well as overt diabetes mellitus were held to be common complications [1, 3, 4]. Although more recent studies revealed that insulin levels are low or normal [10–12], at least in children, there actually is concern about an accelerated manifestation of diabetes mellitus during GH therapy [18]. This limitation could restrict the otherwise beneficial treatment with GH [13, 14, 36] in PWS. For the patients investigated in the present study, the long-term efficacy of GH on body composition, growth, and other parameters [15, 19, 21, 22] has been shown recently. The actual data for the first time document that, in children with PWS, 3 years of therapy with 8 mg GH/m^2 body surface/week do not impair carbohydrate metabolism, but rather counteract a potential GH-induced insulin resistance by increasing lean mass and decreasing fat tissue [11, 19, 22]. The observed increase in fasting insulin and also the observed decrease in insulin sensitivity are only transient.

At baseline, our findings on normal fasting glucose and glucose tolerance, on average, in children and adolescents with PWS are in line with results of other recent studies [11–13, 37]. However, we as well as others [13] found single individuals, up to 10%, with a reduced glucose tolerance.

During 1–3 years on GH therapy, the mean blood glucose levels after an oral glucose load did not increase significantly, neither in this nor in any other study [11, 36, 38, 39]. In general, the glucose assimilation in PWS does not differ from that of healthy obese controls, children [11] and adults [12] alike. Yet, overt diabetes during GH therapy developed in 3 out of 138 children investigated in different studies [11, 13, 36–40] and was normalized after discontinuation of treatment [11, 38]. The main risk factor to develop diabetes was obesity itself [11]. In the present study, the HbA_{1c} levels were normal before and during GH therapy, nevertheless showing a significant rise. Thus, GH therapy only slightly and reversibly alters the glucose metabolism.

At baseline, fasting insulin is decreased or normal in PWS, not only in the present, but also in other studies [10, 11, 13, 37, 39], reflecting the high insulin sensitivity encountered in the children with PWS, because they have GHD. This finding differs from the elevated insulin levels described in children with non-syndromal obesity [31]. During GH therapy, however, the fasting insulin levels slightly increased in children with PWS during 1 [11, 13, 38–40] or 2 years of GH therapy [37]. But, after this transient rise, insulin declined during the 2nd year of treatment [41] and, as we observed in the present study, remained at pretherapy levels during the 3rd year of GH therapy. The insulin sensitivity seems to be fully preserved under GH therapy, since its surrogate parameters IGR [31] and QUICKI [32] apparently remain in the normal range [28, 32, 33]. The normal triglyceride levels document the absence of hyperinsulinism and its metabolic consequences in these patients [22] as well as in adult women with PWS [42]. These findings are all the more remarkable, as GH therapy has previously been shown to induce insulin resistance both in GHD [16] and normal short-statured patients [17]. Nevertheless, high fasting insulin levels were occasionally found in very obese children in the present and in other studies [3, 12, 38], regardless of GH treatment. This finding is compatible with the postulated critical cutoff of elevated fat mass, above a BMI exceeding 26 kg/m^2, which has been shown to enhance the insulin secretion in simple obesity and even in GHD [43, 44]. Therefore, extreme obesity may impair the carbohydrate metabolism and may lead to overt diabetes in PWS. This is corroborated by our finding that the fat mass is significantly correlated with insulin sensitivity and insulin secretion before GH substitution. Also during GH therapy, some parameters of insulin sensitivity remain correlated with fat mass. The marked reduction of fat tissue, together with the GH-induced increase of lean mass [19], ultimately contributes to enhance peripheral glucose uptake, as it is documented by the improved glucose levels 2 h after glucose load.

The insulin secretion during intravenous glucose tolerance testing [11] and OGTT [12] not only was distinctively reduced as compared with that of obese controls or, in the present work, in relation to the 2- to 2.5-fold elevation seen during OGTT in non-syndromal obese children [31], but also showed the abnormal and delayed pattern of insulin release in children with PWS. Mainly the first-phase insulin secretion during OGTT was reduced. This phenomenon was previously described by others [12] and, in part, can be ascribed to the hypothalamic GHD. In fact, as shown here and by Lindgren et al. [11], treatment with GH significantly enhances the first-phase insulin secretion in children with PWS. The present data, in contrast, imply that GHD is not responsible for the delay of insulin secretion in PWS, because it remained unchanged during substitution with GH. In this context, it was also speculated [12] that a prolonged eating drive [45, 46] or a delayed gastric emptying as well as an impaired vagal tone [12, 47] account for the delayed and diminished insulin response to oral glucose load in PWS. The vagal parasympathetic efferent tone to the pancreas is an important component of a normal insulin secretion and may be decreased in PWS patients. This syndrome is characterized by a number of findings suggesting an abnormal vagal tone. In this regard, it has been previously shown that pancreatic polypeptide secretion, a marker of autonomic nervous system dysfunction, is markedly blunted in the PWS patient [12, 47].

The reduction of first-phase insulin secretion on OGTT can be considered one of at least two mechanisms which induce overt diabetes in PWS patients. Under experimental reduction of the early phase of insulin release on OGTT, a late hyperinsulinaemia and a glucose intolerance were induced, as reviewed by Gerich [48]. Therefore, basically, an impaired early insulin release may be the reason for the development of this particular type-2-like diabetes in PWS patients [12]. Moreover, the manifestation of diabetes may be precipitated by a considerable excess of fat mass, ultimately causing additional insulin resistance [11].

In summary, the baseline metabolic situation in PWS is characterized first by hypothalamic GHD and second by an additional decrease and delay of insulin secretion. Since the present and other studies [42] did show that insulin resistance is not increased in this form of syndromal obesity, no specific risk is induced by GH therapy. Only in extremely obese patients with PWS, or in rapid weight gain, the risk to manifest diabetes seems to be increased. Therefore, in these patients GH therapy should not be started. Regardless of GH therapy, which, in our hands, did not impair insulin secretion and sensitivity, the carbohydrate metabolism in PWS always has to be closely monitored, because excessive adiposity may further disturb the metabolic balance. Body weight and height, body composition (by skinfolds or DEXA), fasting glucose, fasting insulin, HbA_{1c}, and insulin-like growth factor I should be regularly assessed during GH therapy in PWS patients in order to monitor side effects and carbohydrate metabolism.

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