# Characterization of Alterations in Glucose and Insulin Metabolism in Prader-Willi Subjects

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**Obesity is a common component of non–insulin-dependent diabetes mellitus (NIDDM) and plays an important role in the development of insulin resistance and hyperinsulinemia. Prader-Willi syndrome (PWS) has been associated with morbid obesity and an increased propensity for early development of NIDDM. It has been assumed that the etiology for this increased rate of NIDDM is related to the morbid obesity and concomitant insulin resistance, but this remains controversial. To shed light on the glucoregulatory mechanisms in PWS, we studied both pediatric and adult PWS patients with normoglycemia. The objectives of our study were (1) to examine glucose, insulin, and C-peptide responses to oral (OGTT) and intravenous (IVGTT) glucose tolerance tests; (2) to characterize acute first- and second-phase insulin secretion during an IVGTT; (3) to assess hepatic insulin extraction (HIE) and insulin clearance (IC) in PWS subjects; and (4) to determine whether β-cell function in PWS is age-dependent. These results in PWS were compared with values obtained in age-, sex-, and body mass index (BMI)-matched non-PWS obese controls. Three groups were studied. Group I consisted of nine PWS subjects under the age of 13 years and 22 age-, sex-, weight-, and puberty stage–matched obese subjects who underwent OGTT. Group II consisted of 14 adult PWS subjects and 10 age-, weight-, and BMI-matched obese adults who underwent OGTT. Group III consisted of nine adult PWS subjects and eight age-, sex-, and weight-matched obese adults who underwent frequently sampled IVGTT (FSIVGTT). During the OGTT in the pediatric group, fasting (86 ± 3 *v* 89 ± 2 mg/dL), peak (144 ± 11 *v* 147 ± 4 mg/dL), and total area under the curve (AUC) (6,984 ± 1,320 *v* 6,963 ± 615 mg/dL · min) glucose levels were not significantly different in PWS versus obese children, respectively. In contrast, fasting (20 ± 6 *v* 37 ± 4 μU/mL), peak (114 ± 24 *v* 214 ± 23 • mU/mL), and total AUC (12,673 ± 2,176 *v* 26,734 ± 2,608 μU/mL μU/mL min) insulin levels were significantly lower in pediatric PWS. During the OGTT in the adult groups, neither fasting insulin (16.7 ± 2.8 *v* 13.5 ± 2.5 μU/mL) nor total AUC for insulin (10,664 ± 1,955 *v* 11,623 ± 1,584 μU/mL · min) were significantly different in adult PWS and obese groups. During the IVGTT in adults, both first-phase (138 ± 42 *v* 454 ± 102 μU/mL · min) and second-phase (295 ± 66 *v* 1,015 ± 231 μU/mL · min) insulin release were significantly reduced in PWS subjects despite similar glucose levels. Similarly, first-phase (8.6 ± 2.3 *v* 21 ± 4.6 ng/dL · min) and second-phase (47 ± 4.6 *v* 75 ± 14 ng/dL · min) C-peptide responses were also significantly reduced in PWS subjects. In contrast, mean HIE and IC was 33% higher in PWS subjects versus obese controls (15.4 ± 1.5 *v* 10.3 ± 1.6). Similarly, poststimulation HIE and IC was significantly greater (5.2 ± 0.8 *v* 2.4 ± 0.4) in the PWS group compared with the obese group ($P < .01$). In summary, this study demonstrates that nondiabetic PWS subjects manifest (1) a reduced β-cell response to glucose stimulation, (2) a significantly increased HIE compared with obese controls, and (3) a dissociation of obesity and insulin resistance, in contrast to normal obese subjects. We conclude that glucoregulatory mechanisms are different in obese PWS versus non-PWS subjects.**



OBESITY is a common component of non–insulin-dependent diabetes mellitus (NIDDM) and plays an important role in the development of insulin resistance and hyperinsulinemia.[1-5] This association of obesity and insulin resistance is frequently seen in NIDDM and in obese individuals with and without impaired glucose tolerance. Insulin resistance and hyperinsulinemia represent early changes in glucose metabolism that may lead to the future development of NIDDM.[6,7]

Prader-Willi syndrome (PWS) is a genetic disease that has been associated with morbid obesity and an increased propensity for early development of NIDDM.[8-10] The true prevalence of the disease in this population is unknown. Previous studies have demonstrated a variable increased prevalence of 7% to 20% compared with the general population prevalence of 5%.[7-9]

Although the etiology of NIDDM in PWS is unknown, it has been assumed to be related to the morbid obesity found in these patients and the concomitant insulin resistance.[9-13] However, the available data are inconsistent. Parra et al[11] demonstrated a hyperinsulinemic response to an oral glucose tolerance test (OGTT) in PWS and obese groups compared with normal-weight controls.[11] Using the intravenous glucose tolerance test (IVGTT), Bier et al[12] demonstrated similar glucose assimilation coefficient (Kg) values between PWS and obese controls. In contrast, two other studies, by Zipf et al[14] and Tomita et al,[15] demonstrated similar insulin response curves in normal-weight and obese PWS subjects in response to protein meal ingestion, whereas obese controls had a significantly higher insulin peak and insulin response. Therefore, there are several disparities in the reported observations regarding insulin/glucose metabolism and insulin action in PWS subjects.

Peripheral insulin levels are determined not only by β-cell secretion but also by hepatic clearance of insulin. Therefore, the liver also plays a major potential role in the development of peripheral hyperinsulinemia. Insulin and C-peptide are secreted in equimolar amounts, but only

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insulin is metabolized by the liver. Thus, the molar ratios of C-peptide and insulin have been used as a noninvasive means of assessing hepatic insulin clearance in this and other studies.[16-19] In this regard, abnormalities in hepatic insulin extraction (HIE) and insulin clearance (IC) are seen in various states of hyperinsulinemia and insulin resistance.[20] To the best of our knowledge, the contribution of HIE and IC to peripheral insulin levels has not been previously examined in the PWS population.

Apart from the potential alterations in insulin metabolism, the differences in insulin secretion and action previously reported in nondiabetic PWS could be partly ascribed to incomplete or nonthorough evaluation of β-cell function in PWS. Therefore, we used two independent studies to examine glucose homeostasis. First, we performed the OGTT to examine changes in glucose, insulin, and C-peptide responses to oral glucose. Second, because previous studies have not addressed the phases of insulin release, we determined the phases of insulin secretion using the IVGTT. This issue is important because an absent or blunted first-phase and/or a decrease in second-phase insulin secretion have been found to be early predictors of impaired glucose tolerance in both insulin-dependent diabetes mellitus and NIDDM.[16-20]

Based on this background, the objectives of the present study were (1) to examine glucose, insulin, and C-peptide responses to OGTT and IVGTT in adult PWS subjects, (2) to characterize the phases of insulin release, (3) to determine the contribution of hepatic insulin clearance to peripheral insulin concentration, and (4) to evaluate the age dependency of the insulin response to an oral glucose challenge. These results in PWS were compared with data from age-, sex-, and body mass index (BMI)-matched non-PWS obese controls.

## SUBJECTS AND METHODS

### *Subjects*

The study subjects comprised three groups. Group I consisted of nine pediatric PWS subjects under the age of 13 years and 22 age-, sex-, weight-, and puberty stage–matched obese subjects who were studied using the OGTT. All pediatric participants were at Tanner stage II-III for sexual maturation. Group II consisted of 14 adult PWS subjects and 10 age-, weight-, and BMI-matched obese adults who underwent an OGTT. Group III contained nine adult PWS subjects and eight age-, sex-, and weight-matched obese adults who underwent an IVGTT. Five PWS subjects and no obese controls from group III were studied in group II. Each participant was nondiabetic as defined by National Diabetes Data Group criteria.[21] All PWS subjects met the established diagnostic criteria for PWS.[22] Each participant had normal cardiac, thyroid, hepatic, and renal function as determined by a thorough history and physical examination and supportive laboratory data where necessary. All non-PWS subjects had stable body weight during the 3 to 6 months before the study. All PWS subjects were weight-gaining or weight-stable. Clinical characteristics are shown in Tables 1 to 3. An age-matched normal-weight control group was included in the tables and figures as a reference. No statistical comparisons were made between this normal-weight group and the two obese groups. A signed informed-consent form approved by the institutional review board was obtained from each subject after the protocol was thoroughly explained.

**Table 1. Group I. Clinical Characteristics of Children With PWS and Healthy Obese Children During OGTT**

| Characteristic | Normal Controls (n = 19) | Obese Controls (n = 22) | PWS Subjects (n = 9) |
|---|---|---|---|
| Age (yr) | 14 ± 0.3 | 10 ± 0.5 | 11.5 ± 1.2 |
| Gender (M/F) | 7/12 | 14/22 | 3/6 |
| Height (m) | 1.6 ± 0.02 | 1.5 ± 0.03 | 1.4 ± 0.05* |
| Weight (kg) | 56 ± 2.1 | 79 ± 4.8 | 72 ± 8.5 |
| BMI (kg/m²) | 21 ± 0.6 | 35.1 ± 1.5 | 35.5 ± 2.3 |
| Tanner puberty stage | 3-4 | 2 | 2-3 |
| Systolic blood pressure | 112 ± 1.8 | 122 ± 3.0 | 117 ± 4.0 |
| Diastolic blood pressure | 72 ± 1.7 | 77 ± 1.5 | 69 ± 4.4 |

NOTE. Values are the mean ± SEM. Normal-weight controls were included as a reference.

*$P < .05$.

### *Study Design*

The subjects reported to the Clinical Research Center of The Ohio State University Hospitals at 8 AM on the day of the study. All subjects ingested their usual diet for 3 consecutive days before the study day. They refrained from strenuous exercise 48 hours before the study day. The studies were performed after a 10- to 12-hour overnight fast, with subjects in the supine position.

Anthropometric measurements were performed on each of the study subjects. These included body weight, height, and BMI. BMI was calculated as body weight in kilograms divided by height in meters squared. Fat-free mass was measured by a bioelectrical impedance analyzer technique.[23] Obesity was defined as a BMI greater than 27 kg/m².

OGTT.

The standard OGTT was performed using 1.75 mg/kg (maximum, 75 g) oral glucose. Biochemical measurements included serum glucose and insulin. Criteria for normal glucose tolerance were determined by the criteria previously established by the NIDDM group.[21]

*IVGTT.* The IVGTT was performed as previously described.[24] On the morning of the study day, two angiocatheters were placed in the antecubital veins, one for administration of glucose and insulin and the other for blood sampling from the contralateral arm. Baseline glucose, insulin, and C-peptide levels were obtained at −20, −5, and 0 minutes. At time 0 minutes, intravenous glucose 0.3 g/kg (50% dextrose water) was administered over a 1-minute period. Both first- and second-phase insulin responses were stud-

**Table 2. Group II: Clinical Characteristics of Adult PWS and Healthy Obese Subjects During OGTT**

| Characteristic | Normal Controls (n = 11) | Obese Controls (n = 10) | PWS Subjects (n = 14) |
|---|---|---|---|
| Age (yr) | 33 ± 2.9 | 33 ± 2.5 | 33 ± 2.9 |
| Gender (M/F) | 1/10 | 0/10 | 5/9 |
| Height (m) | 1.64 ± 0.03 | 1.6 ± 0.02 | 1.48 ± 0.01* |
| Weight (kg) | 61 ± 3.7 | 101 ± 9.0 | 92 ± 6.5 |
| BMI (kg/m²) | 22 ± 0.7 | 39.0 ± 3.0 | 42.0 ± 2.7 |
| Tanner puberty stage | 5 | 5 | 4-5 |

NOTE. Values are the mean ± SEM. Normal-weight controls were included as a reference.

*$P < .05$.

**Table 3. Group III: Clinical Characteristics of Adult PWS and Healthy Obese Subjects During FSIVGTT**

| Characteristic | Normal Controls (n = 11) | Obese Controls (n = 8) | PWS Subjects (n = 9) |
|---|---|---|---|
| Age (yr) | 32 ± 2.8 | 31 ± 2.5 | 25 ± 1.9 |
| Gender (M/F) | 7/4 | 1/7 | 2/7 |
| Height (m) | 1.7 ± 0.02 | 1.6 ± 0.02 | 1.47 ± 0.03* |
| Weight (kg) | 71 ± 2.4 | 80.2 ± 3.4 | 98 ± 9.2 |
| BMI (kg/m$^2$) | 25 ± 0.6 | 30.7 ± 1.4 | 45.5 ± 4.5 |
| Lean body mass (%) | 72 ± 1 | 61.3 ± 2.3 | 56 ± 3.0 |
| Body fat (%) | 28 ± 1.9 | 38.7 ± 2.3 | 44 ± 3.0 |

NOTE. Values are the mean ± SEM. Normal-weight controls were included as a reference.

*$P < .05$.

ied. First-phase insulin secretion was defined as insulin secretion between time 0 to 5 minutes, and second-phase secretion as time 8 to 19 minutes. Blood samples for assay of glucose, insulin, and C-peptide were drawn at frequent intervals during the 20-minute period. The blood samples were centrifuged at 4°C, and sera were stored at −20°C until assayed.

*Chemical analyses.* Serum glucose concentrations were measured by the glucose oxidase method using a glucose analyzer (Beckman Instruments, Fullerton, CA). Serum immunoreactive insulin and C-peptide levels were measured by double-antibody radioimmunoassay technique.[25] The sensitivity of the insulin assay was 2 mU/L serum; intraassay and interassay coefficients of variation (CVs) were 5% and 10%, respectively. The sensitivity of the C-peptide assay was 0.16 nmol/L serum, and intraassay and interassay CVs were 6% and 13%, respectively. There were no significant titers of insulin antibodies in any of our subjects.

### *Calculations and Statistical Analysis*

Results are expressed as the mean ± SEM unless otherwise stated. The areas under the curves (AUCs) were calculated by the trapezoidal rule. The rate of glucose disposal (Kg) was calculated from the natural log transformation of glucose levels from time 8 to 19 minutes during the IVGTT using linear regression analysis.

Basal HIE was calculated as the molar ratio of steady-state C-peptide and insulin concentrations.[26] In the basal, steady state, the kinetics (production/clearance) of insulin and C-peptide are in equilibrium and differences in the half-life values of the two hormones should not influence the estimation of basal HIE and IC. Note that the molar ratios of C-peptide and insulin at steady state reflect HIE and IC in healthy individuals without renal dysfunction. During the IVGTT, the differences in kinetics on insulin and C-peptide would play a role in the determination of HIE in this non–steady state. Therefore, HIE and IC were calculated as the molar ratios of the incremental integrated areas for C-peptide and insulin[17,27] from time 0 to 180 minutes. This time frame includes the return to a new basal, steady state. The incremental integrated molar ratios of insulin and C-peptide are independent of the differences in the half-life values for the two peptides. Although Polonsky and Rubenstein[20] have described the pitfalls and limitations in the use of molar ratios as a reflection of HIE during non–steady state, the use of incremental integrated areas appears to be valid.[27]

Statistical comparison between groups was made by unpaired $t$ test and ANOVA where appropriate. A $P$ value less than .05 was considered statistically significant.

## RESULTS

### *Anthropometric and Clinical Characteristics*

Subjects in group I included 22 obese and nine PWS children matched for age, weight, and puberty stage. Weight tended to be greater in the obese group, but because these subjects were also significantly taller than the PWS group, the BMIs were closely matched (35.1 ± 1.5 *v* 35.5 ± 2.3 kg/m$^2$). Both groups were matched for puberty as clinically defined by Tanner staging, to eliminate the insulin resistance of puberty as a contributing factor to the insulin resistance. Mean systolic (117 ± 4.0 *v* 122 ± 3.0 mm Hg) and mean diastolic (69 ± 4.4 *v* 77 ± 1.5 mm Hg) blood pressures were lower in the pediatric PWS group compared with the obese group, although this did not reach statistical significance.

Subjects in group II were adult PWS subjects and obese controls. In this group, neither weight (92 ± 6.5 *v* 101 ± 9.0 kg) nor BMI (42 ± 2.7 *v* 39 ± 3.0 kg/m$^2$) were significantly different in PWS subjects compared with the obese control group, respectively.

Subjects in group III were matched for age, sex, and weight. The PWS group was significantly shorter than the obese controls (1.47 ± 0.03 *v* 1.6 ± 0.02 m, $P < .001$). There was no difference in weight (98 ± 9 *v* 80 ± 3 Kg), although BMI was significantly higher in PWS subjects compared with obese controls (46 ± 4.5 *v* 31 ± 1.4 Kg/m$^2$, $P < .01$). Lean body mass (56% ± 3% *v* 61% ± 2%) tended to be lower and body fat (44% ± 3% *v* 39% ± 2.3%) tended to be higher in PWS subjects and obese controls, respectively.

### *OGTT in Group I*

During the OGTT in the pediatric group, fasting (86 ± 3 *v* 89 ± 2 mg/dL), peak (144 ± 11 *v* 147 ± 4 mg/dL), and total glucose as measured by the AUC of glucose responses (6,984 ± 1,320 *v* 6,963 ± 615 mg/dL · min) were not significantly different in PWS versus obese children, respectively. In contrast, fasting (20 ± 6 *v* 37 ± 4 μU/mL), peak (114 ± 24 *v* 214 ± 23 μU/dL), and AUC insulin levels (12,673 ± 2,176 *v* 26,734 ± 2,608 μU/mL · min) were significantly lower in PWS versus obese controls (Fig 1).

### *OGTT in Group II*

The OGTT in the adult groups demonstrated no differences in fasting glucose (93.8 ± 9.2 *v* 79.3 ± 2.7 mg/dL) or insulin (16.7 ± 2.8 *v* 13.5 ± 2.5 μU/mL) in PWS and obese adults, respectively. The respective AUC values were similar in PWS and obese groups for glucose (6,138 ± 1,745 *v* 7,568 ± 1,410 mg/dL · min) and insulin (10,664 ± 1,955 *v* 11,623 ± 1,584 μU/mL · min). ANOVA demonstrated no significant differences in glucose or insulin responses (Fig 1).

### *IVGTT in Group III*

During the IVGTT, fasting glucose (78.3 ± 3.5 *v* 78.2 ± 2.0 mg/dL), insulin (6.9 ± 1.1 *v* 9.9 ± 1.4 μU/mL) and C-peptide (2.1 ± 0.7 *v* 2.1 ± 0.3 ng/mL) levels were not different in PWS and obese adult groups. Despite a similar glucose response curve, significant differences in insulin

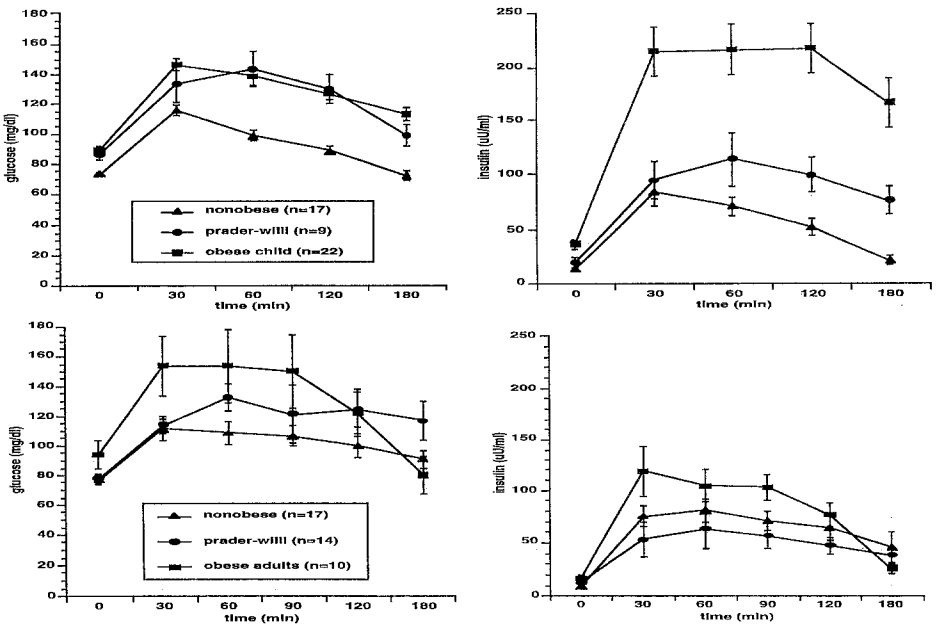


**Fig 1. Glucose and insulin responses to OGTT in the pediatric (left) and adult (right) groups.**

and C-peptide responses to an intravenous glucose load were noted during the IVGTT. The rate of glucose disposal (Kg) tended to be higher in PWS, but differences were not significantly different between the PWS and obese groups (2.08 ± 0.46 *v* 1.87 ± 0.21 %/min). Both first-phase (138 ± 42 *v* 454 ± 102 μU/mL · min) and second-phase (295 ± 66 *v* 1,015 ± 231 μU/mL · min) insulin release were significantly reduced in PWS subjects (Kg). Similarly, first-phase (8.6 ± 2.3 *v* 21 ± 4.6 ng/dL · min) and second-phase (47 ± 4.6 *v* 75 ± 14 ng/dL · min) C-peptide responses were also significantly reduced in PWS subjects. Using the AUC analysis of first- and second-phase glucose and insulin, the insulin to glucose ratios (I/G ratios) were determined. PWS subjects demonstrated reduced I/G ratios during both first-phase (0.23 *v* 0.9) and second-phase (0.14 *v* 0.53) insulin responses compared with the obese group (Fig 2).

### *HIE and IC—Basal and Poststimulation*

Mean HIE and IC were 33% higher in the PWS group compared with the obese control group (15.4 ± 1.5 *v* 10.3 ± 1.6). Following the intravenous glucose load, HIE and IC decreased 66% in the PWS group and 77% in the obese group (5.2 ± 0.8 *v* 2.4 ± 0.4). Poststimulation HIE and IC were also significantly increased in the PWS group compared with the obese group ($P < .01$) (Fig 3).

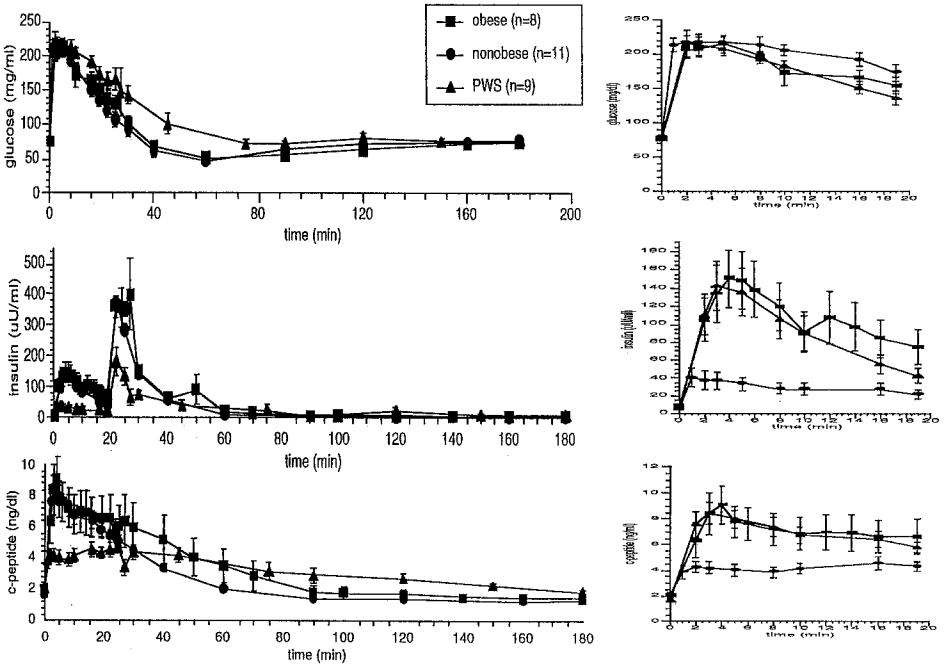


**Fig 2. Glucose, insulin, and C-peptide responses to FSIVGTT in the adult groups.**

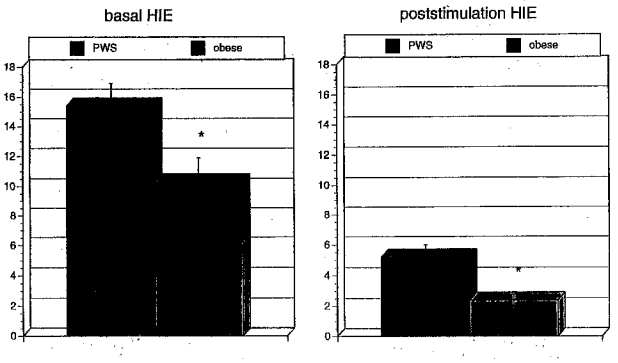


**Fig 3. HIE: the molar ratio of C-peptide and insulin in the basal and poststimulation phase for PWS and obese controls.**

*Correlation Coefficients*

Using univariate regression analysis, weight was significantly correlated with basal insulin level in the normal pediatric obese group ($r = .59$, $P < .003$) but not in the pediatric PWS group. Neither weight nor BMI demonstrated significant correlation with basal insulin ($P > .05$) in the adult PWS or adult obese groups.

## DISCUSSION

PWS is characterized by marked obesity associated with an abnormal appetite,[9] a tendency to gain weight even with normal caloric intake,[9] and an increased prevalence of diabetes mellitus.[8,13] PWS subjects often demonstrate markedly decreased satiety and hyperphagia as a cause of their morbid obesity.[8-13] The hyperphagia of PWS has been thought to be of hypothalamic origin.[28] To provide further insight into glucose homeostasis in PWS, we have carefully and systematically examined β-cell function (insulin and C-peptide) and HIE in PWS.

Our present data in PWS subjects are of interest in several respects. Despite a similar degree of obesity and glucose response, the insulin response to an oral glucose load was significantly lower in the pediatric PWS group compared with the pediatric obese group. Thus, the obese non-PWS pediatric group appeared to be more insulin-resistant than the age- and BMI-matched PWS pediatric group. The adult PWS group demonstrated similar patterns during the OGTT, with intermediate mean glucose and lower insulin responses when compared with both non-obese and obese controls, although these differences were no longer statistically significant. This may be due to the smaller group size or to the effects of aging. Consistent for both the pediatric and adult PWS groups, however, was a delayed peak in glucose and insulin during the OGTT when compared with the obese controls. Although the reason is unclear, the delayed peak of glucose and insulin could be attributed to delayed gastric emptying and/or intestinal glucose absorption. Thus, the OGTT demonstrated both qualitative and quantitative differences in glucose and insulin metabolism in obese PWS subjects compared with obese non-PWS controls.

To further evaluate glucose metabolic differences and to eliminate the effects of incretins and differences in gastric emptying, adult PWS and obese groups underwent an IVGTT. During the IVGTT, we found that glucose responses in PWS and obese subjects were similar. However, first- and second-phase insulin and C-peptide secretion were significantly lower in response to intravenous glucose in PWS, consistent with the OGTT results. A deficiency in this initial phase of insulin release has been shown to affect glucose homeostasis and cause mild prandial hyperglycemia in NIDDM patients,[29] individuals with impaired glucose tolerance, and individuals at risk for NIDDM.[30,31] Because first-phase insulin release is blunted in pre–type I and –type II diabetic patients, we can infer that β-cell dysfunction that can predispose individuals to NIDDM exists in adult PWS subjects.

Serum insulin levels were significantly lower during the OGTT and IVGTT in PWS versus non-PWS subjects with identical glucose levels. Indeed, I/G ratios were reduced in PWS. Furthermore, Kg was slightly greater in PWS than in non-PWS subjects. However, more sophisticated methods, such as the minimal model or the euglycemic/hyperinsulinemic clamp, to accurately quantify the insulin sensitivity in this population will be necessary in future studies.

The reason for β-cell dysfunction in PWS remains unknown; however, several possibilities exist. One possibility is decreased vagal parasympathetic efferent tone to the pancreas, an important component of normal insulin secretion.[32] PWS is characterized by a number of findings suggesting abnormal vagal tone.[9] In this regard, we have previously shown that pancreatic polypeptide secretion, a marker of autonomic nervous system dysfunction, is markedly blunted in the PWS patient.[14,33] In this study and our previous study,[14] we found evidence of a delay in peak glucose and insulin responses, suggesting a possible delay in gastric emptying, another vagally mediated event.

Peripheral insulin levels are determined by β-cell secretion and/or HIE and IC. In this regard, alterations in HIE and IC have been previously demonstrated in individuals with obesity and a predisposition to diabetes.[34-36] We are unaware of any study that has examined HIE and IC in PWS. Thus, the contribution of HIE to peripheral insulin in PWS is unknown. We found that the PWS group had significantly higher HIE and IC during the basal and poststimulation states compared with the obese group. Although the limitations of the use of molar ratios as a reflection of HIE and IC during non–steady state have been examined by several investigators, including Polonsky et al,[20,34] our findings in the non–steady state were consistent with the HIE values during the basal, steady state. To further validate our findings, we believe the use of two-compartment C-peptide kinetics to determine the prehepatic and posthepatic insulin secretion rates and subsequent HIE in PWS subjects will be necessary.

With the degree of obesity seen in the PWS group and their increased tendency for NIDDM, it was unexpected to find a higher HIE in this group compared with both obese and non-obese healthy individuals.[35] In addition, we observed a blunted response of HIE and IC to glucose stimulation in PWS versus obese controls. Normally, HIE decreases with glucose stimulation in humans and experi-

mental animals.[20,35,36] This decrease in HIE during a glucose load has been attributed partly to an incretin effect and the saturation of insulin-binding receptors at the level of the liver. In this study of PWS, we observed the blunted response of HIE to glucose. Although the mechanism is unknown, we believe this may reflect an adaptive mechanism for maintenance of normal hepatic glucose production. Whether differences in the clearance rates of both insulin and C-peptide contributed to the differences in HIE between PWS and non-PWS subjects is uncertain.

In general, obesity in non-PWS subjects has been associated with insulin resistance, hyperinsulinemia, and a reduction in insulin sensitivity.[1-7,34] Several mechanisms for the insulin resistance of obesity have been proposed, including receptor and postreceptor defects. Because morbid obesity is a common component of PWS, we expected an increased insulin secretion and hyperinsulinemia in the PWS group similar to that seen in the non-PWS obese group—but this was not the case. Furthermore, adult PWS subjects in this study tended to have greater body weight, BMI, and percent body fat than the obese controls. We found a dissociation between obesity and insulin/C-peptide responses, as well as HIE and IC, in this study. The etiology for this dissociation of obesity and insulin resistance and IC in PWS is unclear.

Previous studies have demonstrated an inverse relationship between insulin resistance/hyperinsulinemia and upper-body fat distribution.[26,37] The peripheral hyperinsulinemia in upper-body obesity has been ascribed to both β-cell hypersecretion and decreased HIE.[26,37] Previous studies have found that fat distribution in PWS is typically peripheral.[9] Our pilot study in the adult PWS group demonstrated a waist to hip ratio of 0.86, consistent with moderate upper-body obesity. Therefore, moderate upper-body fat distribution alone found in our PWS subjects was not associated with hyperinsulinemia, insulin resistance, or reduced HIE and IC in PWS. The mechanism of the dissociation in PWS remains to be elucidated, possibly by using accurate imaging modalities for visceral adiposity measurements.

In summary, we have characterized glucose homeostasis in PWS subjects. Our findings demonstrate that nondiabetic PWS subjects manifest (1) a reduced β-cell response to glucose stimulation, (2) a significantly increased HIE when compared with obese controls, and (3) a dissociation between obesity and β-cell function and IC, in contrast to normal obese subjects. We conclude that glucoregulatory mechanisms are different in obese PWS versus non-PWS subjects.

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