Published in final edited form as:
J Pediatr. 2006 January ; 148(1): 23–29.

INSULIN DYNAMICS PREDICT BODY MASS INDEX AND Z-SCORE RESPONSE TO INSULIN SUPPRESSION OR SENSITIZATION PHARMACOTHERAPY IN OBESE CHILDREN

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Presented in part at the North American Association for the Study of Obesity, Las Vegas, NV, November 2004.

Abstract

Objective—To assess the use of oral glucose tolerance testing (OGTT) to predict efficacy of insulin sensitization (metformin) or suppression (octreotide) because insulin resistance and insulin hypersecretion may impact pharmacotherapeutic efficacy in obese children.

Study design—Forty-three and 24 obese children, with and without central nervous system (CNS) insult, underwent OGTT. Insulin sensitivity was expressed as composite insulin sensitivity index (CISI), and secretion as corrected insulin response (CIRgp). Those without CNS insult received metformin (weight-based dosing) for 6 to 16 months. Those with CNS insult received octreotide SQ 15 μg/kg/d for 6 months. Body mass index (BMI) and z-score responses were modeled using CIRgp and CISI.

Results—Metformin: With CIRgp and CISI = 1, BMI z-score in white children declined by 0.23 over the first 4 months ($P < .001$), and by 0.14 over the next year ($P = .33$). Each 2-fold increase in CIRgp or CISI attenuated BMI z-score reduction, but with wide uncertainty ($P = .24$). Black children exhibited little response. Octreotide: With CIRgp and CISI = 1, BMI z-score decreased by 0.23 in the first 4 months ($P = .052$). Efficacy was dependent on an interaction between CIRgp and CISI ($P = .051$).

Conclusions—Efficacy of metformin was predicted by pretreatment insulin resistance. Efficacy of octreotide was predicted by insulin hypersecretion and sensitivity.

Keywords

BMI Body mass index; CIRgp Corrected Insulin Response; CISI Composite Insulin Sensitivity Index; CNS Central nervous system; GLP-1 Glucagon-like peptide-1; OGTT Oral glucose tolerance testing; UCSF University of California San Francisco; U.T. University of Tennessee

Obesity is not one disease, but rather a phenotype of many different diseases.[1,2] When targeted to the specific pathology, pharmacotherapy, such as leptin for leptin deficiency,[3] can be effective. However, when therapy is not targeted, efficacy tends to be suboptimal.[4] Indeed, pharmacotherapies for childhood obesity have been shown to possess variable inter-individual

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Supported in part by GCRC M01-RR00211, University of Tennessee, Memphis, and PCRC 5 M01 RR-01271, University of California, San Francisco, with funds provided by the National Center for Research Resources, U.S. Public Health Service.

responsiveness.[5–8] A corollary is that determining the causes of specific types of obesity may lead to effective therapies that target the specific causes. Such strategies must currently rely on the use of pretreatment "predictor variables."

Insulin is an important factor in the genesis of childhood obesity. Most obese children have hyperinsulinemia.[9] There are two forms of euglycemic hyperinsulinemia: (1) fasting hyperinsulinemia caused by defective hepatic and muscle insulin signal transduction, a manifestation of what is commonly called "insulin resistance"[10–12]; and (2) glucose-stimulated hyperinsulinemia, also termed "insulin hypersecretion," which occurs as a result of neural dysregulation of the β-cell as seen in subjects with hypothalamic obesity caused by central nervous system (CNS) insult.[13,14] We have previously demonstrated in obese children that insulin secretion and insulin sensitivity are distinct phenomena and are predicted both by race and cause.[15]

The biguanide metformin, an insulin sensitizer, has been used to promote weight loss in obese adolescents.[5,6,16–19] The standard deviation of body mass index (BMI) and BMI z-score change in these studies, however, is equivalent to the magnitude of the response, indicating considerable variability in efficacy. Similarly, we have reported that the somatostatin analog octreotide suppresses insulin secretion and promotes BMI loss in patients with hypothalamic obesity[20,21] but with variable efficacy. We postulated that the pretreatment insulin dynamics in these patients reflected the cause of their obesity and might be used as a predictor of weight response to pharmacotherapy. We therefore modeled the changes in BMI and BMI z-score in obese children receiving metformin or octreotide on the basis of their pretreatment insulin sensitivity and secretion.

METHODS

Patients were subjects within 3 individual studies performed at the University of Tennessee (U.T.) General Clinical Research Center and the University of California San Francisco (UCSF) Pediatric Clinical Research Center. Institutional Review Board and Scientific Advisory Committee approvals were obtained at each site. For the metformin study, inclusion criteria were as follows age 2 to 18 years, BMI (defined as weight ÷ height^2 [kg/m^2]) above the 95th percentile for the BMI-for-age curve (Centers for Disease Control and Prevention, 1999), continued BMI gain for at least 3 months after outpatient exercise and nutritional counseling, and desire by the patient and parent to try adjunct pharmacotherapy. Exclusion criteria included voluntary weight maintenance or loss for the 3 months before initiation of pharmacotherapy, diabetes mellitus, kidney or liver disease (or significant elevation of liver enzymes greater than 3 times the upper limit of normal), history of CNS insult, antidepressant medication, or any glucocorticoid therapy. For the two octreotide studies reported previously,[20,21] inclusion criteria were age 8 to 18 years, and intractable weight gain after CNS insult (surgery or cranial radiation for brain tumor or cranial radiation for acute lymphoblastic leukemia). Exclusion criteria included diabetes mellitus, kidney or liver disease, antidepressant medication, or receipt of supraphysiological doses of glucocorticoid therapy (greater than 11 mg/m^2/d). Only 2 of 24 subjects were black, and exclusion of their data did not alter the analysis, so they are included for completeness. Sex (male/female) and pubertal status (prepubertal [Tanner I] or no sex hormone replacement/pubertal [Tanner II–V] or sex hormone replacement) were also documented.[22,23]

Informed consent was obtained from each subject and parent. Subjects were counseled to continue their routine caloric intake in the days before the oral glucose tolerance test (OGTT). Recruited subjects were admitted to either the U.T. GCRC or UCSF PCRC after an overnight fasted state. Subjects underwent a 3-hour OGTT.[24] Each subject drank 1.75 gm/kg dextrose

(maximum 75 gm), and blood samples for glucose and insulin were obtained at 0, 30, 60, 90, 120, and 180 minutes.[25]

Subjects without CNS insult (n = 45) received oral metformin on the basis of weight (30–50 kg, 500 mg 2 times daily; 50 to 70 kg, 500 in AM, to 1000 mg in PM; > 70 kg, 1000 mg 2 times daily), along with a daily multivitamin tablet to protect against lactic acidosis.[26] Height and weight were monitored every 3 months, with a period of study that ranged from 6 to 16 months. Subjects with CNS insult (n = 24) received subcutaneous octreotide for 6 months on the basis of weight, with an escalating dose of 5 μg/kg/d divided 3 times daily for the first 2 months, 10 μg/kg/d divided 3 times daily for the second 2 months and 15 μg/kg/d for the final 2 months. Height and weight were monitored every 2 months.

Chemical Analyses

Plasma glucose concentrations were measured by the glucose oxidase method.[27] Plasma insulin concentrations were measured by radioimmunoassay at each site. The interassay and intraassay coefficients of variation were 9.2% and 4.5%, and 8.4% and 4.3% at U.T. and UCSF, respectively.

Insulin Indexes

From the pretreatment OGTT, the following insulin indexes were obtained or computed:

Corrected Insulin Response at Glucose Peak (CIRgp),[25] an indicator of β-cell activity: the higher the CIRgp, the greater the insulin secretion for the same glucose stimulus.

$$CIR_{gp} = \frac{(Insulin_{glupeak} \times 100)}{(Glu_{glupeak} \times [Glu_{glupeak} - 70])}$$

Composite Insulin Sensitivity Index (CISI),[28] a measure of insulin sensitivity obtained from the OGTT: the higher the CISI, the higher the insulin sensitivity.

$$CISI = \frac{10000}{\sqrt{(FI \times FG \times [mean\ insulin_{(0-120min)}] \times [mean\ glucose_{(0-120min)}])}}$$

Statistical Analysis

There were 45 patients who received metformin. Of these, 43 were categorized by race as either white or black. There was one Asian and one Pacific Islander; these 2 patients were excluded from the final analysis. Of the 24 patients with CNS insult receiving octreotide, 22 were white. Although 2 subjects were black, their exclusion did not alter the results, so they are included for completeness.

The insulin indices CIRgp and CISI were both skewed, so they were transformed by logarithm base 2 for all analyses. BMI and BMI z-score in subjects receiving metformin or octreotide therapy were modeled over time using linear regression with random intercepts and slopes for each person.[29] The effect of treatment was modeled as an initial rate of change over the first 4 months of treatment, followed by a different rate of change over the next 12 months for metformin; and up to 6 months for octreotide, after which treatment was discontinued per protocol. Pretreatment CIRgp and CISI, race, sex, and pubertal status were assessed to determine if they modified the estimated rates of change. Because the effects of several predictors appeared to differ by race for metformin treatment, separate models of white children and black children are presented. Graphical assessment of residuals did not show any overly-influential points that would invalidate the models.

RESULTS

Demographics, anthropometrics, and baseline insulin dynamics of the patients who received metformin or octreotide are listed in Table I. As denoted previously, black children exhibited higher CIRgp and lower CISI than did white children, despite similar BMIs and BMI z-scores.[15]

Metformin

Multiple linear regression modeling for white children (n = 26) is shown in Table II*A* and *B*. We found a diphasic response curve, which altered its trajectory at the month 4 time point; therefore the model includes separate estimates of predictors' effects for the first 4 months, and the next 12 months. For a pubertal white female with a CIRgp of 1.0 and a CISI of 1.0, the average BMI and z-score change was − 2.7 kg/m^2 and − 0.23, respectively, over the first 4 months ($P < .001$). The rates of change then reduced to − 1.6 kg/m^2/yr and − 0.14/yr for the next 12 months ($P = .32, .33$). Increasing insulin sensitivity (eg, doubling the CISI) mitigated the BMI response to metformin ($P = .027$), although its effect on BMI z-score was not as robust ($P = .24$). Results for doubling the CISI were similar for the less biologically rigorous outcomes of raw and percent change in weight: +0.6 kg ($P = .023$) and +0.9% ($P = .009$). Male sex attenuated metformin efficacy ($P = .013$). Prepubertal status accentuated metformin efficacy ($P = .023$).

Multiple linear regression modeling in black children (n = 17) is shown in Table II*C* and *D*. There did not appear to be significant improvement in either BMI or BMI z-score in this population in the first 4 months or in the next year, although a higher CIRgp appeared to predict better response. This also held for raw and percent change in weight: − 0.7 kg ($P = .032$) and − 1.3% ($P = .009$) per doubling of CIRgp.

Octreotide

Multiple linear regression modeling in obese children with CNS insult receiving octreotide for the first 4 months (n = 24) is shown in Table III*A* and *B*. Estimates for rate of change in the succeeding 2 months were highly variable and are not reported. For a pubertal or sex hormone-supplemented female with a CIRgp of 1.0 and a CISI of 1.0, the rate of BMI and z-score decrements were 4.3 kg/m^2 ($P = .014$) and 0.23 ($P = .052$), respectively, over 4 months. Interestingly, for every doubling of the CIRgp with CISI = 1.0, the change in BMI and BMI z-score was severely mitigated ($P < .001$ and .036, respectively); whereas for every doubling of the CISI with CIRgp = 1.0, mitigation was much less. Finally, there was a strong interaction between CIRgp and CISI in this analysis (BMI: $P = .001$; BMI z-score: $P = .051$), such that doublings of both CIRgp and CISI reduced the BMI and z-score response less than did a doubling of CIRgp alone with an unchanged CISI, suggesting greater efficacy of octreotide in subjects who were insulin hypersecretors but remained insulin sensitive. Sex and pubertal status did not appear to have meaningful effects on response to octreotide therapy, although there was some indication that males did not reduce BMI z-score as rapidly as females.

DISCUSSION

Insulin promotes adipogenesis and weight gain through effects mediated directly at the adipocyte. Specifically, insulin up-regulates Glut4, acetyl-CoA carboxylase, fatty acid synthase, and lipoprotein lipase.[30] Insulin resistance caused by hepatic/muscle dysfunction promotes reflex hyperinsulinemia and can promote the metabolic syndrome in children.[31, 32] Insulin hypersecretion caused by CNS/pancreatic dysfunction is less common and usually exists as an effector of "hypothalamic obesity" because of brain tumor or cranial radiation.[33] We have previously shown that these two insulin disorders can be dissociated from each

other by assessing the insulin response to OGTT and measuring insulin secretion with the CIRgp and insulin sensitivity with the CISI.[15] We have also shown that insulin hypersecretion is the predominant insulin abnormality both in obese black children, and in children with hypothalamic obesity.[15]

Previous studies of pharmacotherapy in obese children have yielded considerable variability in efficacy. We postulated that insulin dynamics might offer a method for "triaging" patients to therapy on the basis of the cause of their obesity. Therefore we evaluated patients within clinical observational protocols who had received metformin for insulin resistance and octreotide for insulin hypersecretion. Although these studies are suboptimal because of their open-label nature, possible placebo effects, and inconsistent compliance, the ability of an a priori pretreatment metabolic parameter variable to distinguish the clinical response validates this approach. By using multiple linear regression analysis, we were able to determine which of the different predictor variables modified the efficacy of each medication. In addition to insulin dynamics, demographic variables such as age, sex, pubertal status, and initial BMI and z-score were also evaluated but were not as predictive.

Metformin improves insulin sensitivity, predictably decreases fasting hyperinsulinemia, and prevents the onset of type 2 diabetes mellitus[34] but demonstrates variable efficacy in promoting weight loss in adults.[17,35] The mechanism of action of metformin on body weight remains unclear. Although some postulate that metformin promotes weight loss though a primary anorectic effect,[36] it is more likely that the decline in caloric intake observed with metformin is related to its reduction in insulin resistance through its enhancement of hepatic glucose turnover, reduction of hepatic glucose output[37,38] and through its actions on hepatic AMP kinase.[39] Another possible mechanism of metformin action is through central effects on glucagon-like peptide-1 (GLP-1),[40] which would reduce food intake.

In white children, metformin was effective in promoting loss of BMI and BMI z-score, provided that the patient was insulin resistant (ie, a low CISI) but not an insulin hypersecretor. As the CISI increased, the effect of metformin was mitigated. Most of the response was achieved in the first 4 months of therapy, but a beneficial effect was observed for the next year as well. Interestingly, metformin had greater effect in females than in males. Our results suggest efficacy of metformin in prepubertal children with severe obesity caused by insulin resistance. Most practitioners have reserved metformin for treatment of adolescents only, because its current Food and Drug Administration indication in pediatric type 2 diabetes mellitus extends down to 10 years of age.

Octreotide binds to a somatostatin receptor on the β-cell membrane,[41] which is coupled to a voltage-gated calcium channel, which limits its opening, thus attenuating insulin release.[42–44] Insulin suppression using octreotide has been shown to be effective in reducing BMI in children with hypothalamic obesity caused by CNS insult[20,21]; however, patients have demonstrated variable responsiveness. The results of this study demonstrate that both insulin hypersecretion and insulin sensitivity (as measured by CIRgp and CISI) are necessary to predict a beneficial BMI response to octreotide.

Studies by Bergman et al[45] using intravenous glucose tolerance testing have suggested that insulin secretion is merely an epiphenomenon of insulin resistance, obeying a hyperbolic relationship known as the "disposition index." However, the intravenous glucose tolerance testing does not take into account other stimuli to β-cell insulin release, such as vagal innervation[46] and intestinal incretins such as GLP-1,[47] which would only activate with an oral challenge. By performing OGTT, we have shown that insulin hypersecretion is a phenomenon that is separate and distinct from insulin resistance.[15] This study also supports this contention,

in that metformin's efficacy on BMI reduction is predicted by insulin resistance, whereas octreotide's efficacy is predicted by both insulin hypersecretion and insulin sensitivity.

With our data, an adjusted disposition index can be defined such that when logarithmically transformed, it would equal the sum of log(CIRgp) and log(CISI). This implies that it would work well in the models of Tables II and III when the coefficients shown for CIRgp and CISI are approximately equal and there is no interaction between the 2. This appears to be the case in Table II*B* and *D* but is suspect for II, *C*, and clearly violated for II, *A* (because the coefficients differ) and III, *A* and *B* (because of the interaction between CIRgp and CISI).

One conundrum posed by these results is that despite marked insulin resistance (mean CISI of 1.6), black children did not respond to metformin with BMI or BMI z-score reduction.[48] Other investigators have documented excessive insulin secretion[49,50] and defective insulin clearance[51] in black children, which is not explained by either the degree of insulin sensitivity or adiposity. Although the reasons for this are still not completely clear, our previous study demonstrated that when controlled for the degree of insulin secretion, the difference in insulin resistance between black and white children is obviated, but when controlled for the degree of insulin resistance, the difference in insulin secretion between the 2 races remains dichotomous.[15] This suggests that the primary defect in black children is actually insulin hypersecretion, and that insulin resistance may be an epiphenomenon. We have previously shown that obese black adults have an accentuated GLP-1 response to OGTT,[52,53] which may account for the insulin hypersecretion directly at the β-cell, and would not be amenable to metformin therapy, whose primary effects are on the liver. Other possible reasons for this racial dichotomy in efficacy include differences in dietary choices or compliance with medication.

Lifestyle intervention continues to be the standard of care for pediatric obesity and should remain the initial option for therapy. However, the results of most studies suggest that efficacies of lifestyle approaches are quite variable. We have noted that individual differences in insulin dynamics may also contribute to this variability.[54] Our results support the concept of using the OGTT with insulin dynamics to discern both insulin hypersecretion and resistance and as a method for directing adjunct pharmacotherapeutic decisions in obese children who have not responded to lifestyle intervention alone. However, before OGTT with insulin dynamics can be proposed as a clinical tool for general use, randomized controlled trials of pharmacotherapy in childhood obesity will be required. Neither metformin nor octreotide has been approved by the FDA for the treatment of pediatric obesity. However, a randomized controlled study of metformin efficacy with pre-hoc insulin dynamics is currently ongoing within the Glaser Pediatric Research Network, as is a study of efficacy of the long-acting octreotide-LAR in hypothalamic obesity conducted by its manufacturer.

Last, our results suggest a "decision-tree" evaluation point in the workup and treatment of obese children. It is clear that "one size does not fit all" when it comes to obesity therapy. There is clearly a role for pharmacotherapy in select patients, and it appears that assessing the biologic mechanism of the weight gain is an important consideration in terms of predicting response. Assessing insulin dynamics by OGTT is simple, relatively inexpensive, and prescient in terms of understanding the causes of obesity and targeting of patients with available medical therapies.

Acknowledgements

We acknowledge the administrative assistance of Faith Sanders. The authors would like to thank the nurses of the LeBonheur Children's Medical Center CRC/Metabolic Unit and of the UCSF PCRC for their assistance in the enactment of these studies. The authors acknowledge the support of Novartis Pharmaceuticals Corp. in providing octreotide.

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Table I

Demographics, anthropometrics, and insulin dynamics of subjects treated with metformin or octreotide (±SD)

	Total	White	Black
Metformin			
N	45	26	17
Age	12.5 ± 3.6 yr (range 2–18)	12.2 ± 3.8 yr (range 2–17)	13.1 ± 3.1 yr (range 6–18)
Sex	34F, 11M	20F, 6M	14F, 3M
Puberty	12 prepubertal, 33 pubertal	7 prepubertal, 19 pubertal	3 prepubertal, 14 pubertal
BMI (kg/m^2)	38.2 ± 7.7 kg/m^2	37.2 ± 7.2 kg/m^2	39.8 ± 8.4 kg/m^2
BMI z-score	2.62 ± 0.58	2.64 ± 0.70	2.59 ± 0.36
CIRgp (secretion)	2.90 ± 3.33	2.22 ± 1.31	4.00 ± 5.03*
CISI (sensitivity)	2.22 ± 1.70	2.66 ± 1.96	1.60 ± 1.03*
Octreotide			
N	24	22	2
Age	14.6 yr (range 9–18)	14.6 yr (range 9–18)	13.9 yr (range 12–15)
Sex	11F, 13M	10F, 12M	1F, 1M
Puberty	7 prepubertal, 3 pubertal, 14 sex hormone replaced	6 prepubertal, 3 pubertal, 13 sex hormone replaced	1 prepubertal, 1 sex hormone replaced
BMI (kg/m^2)	37.2 ± 6.3 kg/m^2	36.6 ± 5.9 kg/m^2	43.6 ± 10.1 kg/m^2
BMI z-score	2.43 ± 0.34	2.39 ± 0.32	2.75 ± 0.42
CIRgp (secretion)	2.53 ± 1.28	2.46 ± 1.31	3.28 ± 0.09
CISI (sensitivity)	2.40 ± 0.99	2.25 ± 0.89	4.04 ± 0.18

* $P < .05$, black vs white.

Table II, A

Modeling of changes in BMI with metformin therapy in 26 white children

Parameter	ΔBMI (kg/m^2) First 4 months	95% CI	*P*	ΔBMI (kg/m^2) Next 12 months	95% CI	*P*
Baseline (CIRgp 1, CISI 1, female, pubertal)	− 2.7	− 4.0, − 1.5	<.001	− 1.6	− 4.8, +1.6	.32
Modifications to the above effects						
For every doubling of CIRgp (secretion)	− 0.1	− 0.8, +0.6	.78	− 0.1	− 1.7, +1.6	.94
For every doubling of CISI (sensitivity)	+0.7	+0.1, +1.4	.027	+0.6	1.2, +2.3	.52
Male sex	− 0.2	− 1.7, +1.4	− .82	− 2.4	− 6.0, +1.3	.19
Prepubertal	− 0.3	− 1.7, +1.1	.68	− 0.5	− 3.8, +2.8	.76

Table II, B

Modeling of changes in BMI z-score with metformin therapy in 26 white children

Parameter	ΔBMI z-score First 4 months	95% CI	*P*	ΔBMI z-score Next 12 months	95% CI	*P*
Baseline (CIRgp 1, CISI 1, female, pubertal)	− 0.23	− 0.36, − 0.11	<.001	− 0.14	− 0.44, +0.15	.33
Modifications to the above effects						
For every doubling of CIRgp (secretion)	+0.03	− 0.03, +0.10	.30	− 0.02	− 0.17, +0.13	.78
For every doubling of CISI (sensitivity)	+0.04	− 0.03, +0.10	.24	− 0.02	− 0.19, +0.14	.78
Male sex	+0.19	+0.04, +0.35	.013	+0.12	− 0.21, +0.46	.46
Prepubertal	− 0.16	− 0.30, − 0.02	.023	− 0.21	− 0.51, +0.08	.15

Table II, C

Modeling of changes in BMI with metformin therapy in 17 black children

Parameter	ΔBMI (kg/m^2) First 4 months	95% CI	*P*	ΔBMI (kg/m^2) Next 12 months	95% CI	*P*
Baseline (CIRgp 1, CISI 1, female, pubertal)	+0.5	− 1.3, +2.4	.57	+4.6	− 0.8, +10.0	.09
Modifications to the above effects						
For every doubling of CIRgp (secretion)	− 1.0	− 1.9, − 0.1	.025	− 0.6	− 3.1, +2.0	.64
For every doubling of CISI (sensitivity)	− 0.7	− 2.0, +0.5	.23	− 2.2	− 5.5, +1.2	.18
Male sex	+3.1	− 1.6, +7.8	.18	− 18.0	− 45.8, +9.8	.18
Prepubertal	+2.6	+0.6, +4.6	.01	− 1.3	− 6.8, +4.2	.63

Table II, D

Modeling of changes in BMI z-score with metformin therapy in 17 black children

Parameter	ΔBMI z-score First 4 months	95% CI	*P*	ΔBMI z-score Next 12 months	95% CI	*P*
Baseline (CIRgp 1, CISI 1, female, pubertal)	− 0.04	− 0.17, +0.09	.55	+0.12	− 0.27, +0.51	.53
Modifications to the above effects						
For every doubling of CIRgp (secretion)	− 0.04	− 0.10, +0.02	.18	− 0.04	− 0.22, +0.15	.68
For every doubling of CISI (sensitivity)	− 0.04	− 0.13, +0.05	.34	− 0.09	− 0.34, +0.17	.47
Male sex	+0.21	− 0.14, +0.56	.21	− 0.58	− 2.68, +1.52	.56
Prepubertal	+0.11	− 0.04, +0.25	.13	− 0.07	− 0.48, +0.34	.73

Table III, A

Modeling of changes in BMI with octreotide therapy in 24 patients with hypothalamic obesity

Parameter	ΔBMI in 4 months	95% CI	*P*
Baseline (CIRgp 1, CISI 1, female, pubertal)	− 4.3	− 7.7, − 1.0	.014
Modifications to the above effects			
For every doubling of CIRgp (secretion)	+4.8	+2.3, +7.4	<.001
For every doubling of CISI (sensitivity)	+ 2.0	− 0.3, +4.2	.086
CIRgp × CISI interaction	− 3.4	− 5.3, +1.6	.001
Male sex	+0.8	− 0.6, +2.3	.25
Prepubertal or no sex hormone	+0.8	− 0.9, +2.4	.35

Table III, B

Modeling of changes in BMI z-score with octreotide therapy in 24 patients with hypothalamic obesity

Parameter	ΔBMI z-score in 4 months	95% CI	*P*
Baseline (CIRgp 1, CISI 1, female, pubertal)	− 0.23	− 0.47, 0.00	.052
Modifications to the above effects			
For every doubling of CIRgp (secretion)	+0.19	+0.01, +0.37	.036
For every doubling of CISI (sensitivity)	+ 0.07	− 0.09, +0.23	.35
CIRgp × CISI interaction	− 0.13	− 0.27, 0.00	.051
Male sex	+0.10	0.01, +0.20	.067
Prepubertal or no sex hormone	0.00	− 0.12, +0.12	.99