Impact of Setmelanotide on Metabolic Syndrome Risk Score in Pediatric Patients With Acquired Hypothalamic Obesity

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Introduction

- Patients with acquired hypothalamic obesity (aHO) experience accelerated weight gain resulting from damage to the hypothalamus that may impair melanocortin-4 receptor pathway signaling[1-3]
- Sustained obesity can lead to increased rates of metabolic syndrome, which is associated with a significantly increased risk of developing cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM)[4,5]
  - The metabolic syndrome severity based on body mass index (MetS-Z-BMI) score is a practical measurement that positively correlates with long-term risk of T2DM and CVD[5]
  - A 1.0-point increase in MetS-Z-BMI score in childhood increases the chance of future CVD and T2DM by 9.8 and 2.7 times, respectively[4]
  - The MetS-Z-BMI score has not yet been assessed in the pediatric aHO population
- Treatment with the melanocortin-4 receptor agonist setmelanotide in a Phase 2 trial reduced bodyweight and hunger in patients with aHO[6]; setmelanotide is now being studied in a Phase 3 clinical trial in patients with aHO

Objective

- To determine the MetS-Z-BMI score–based CVD and T2DM risks in pediatric patients with aHO and to evaluate the effect of 1 year of continued setmelanotide on the risk of developing of metabolic syndrome

Methods

- Metabolic parameters from pediatric patients (aged 6 to <18 years) in a Phase 2 trial of patients with aHO (NCT04725240) and a long-term extension trial (NCT03651765) were used to calculate MetS-Z-BMI score change after 52 weeks of continuous setmelanotide treatment
  - Metabolic parameters collected included weight and waist circumference, glucose metabolism, triglycerides, high-density lipoprotein cholesterol, and diastolic and systolic blood pressure
  - Only pediatric patients with all data necessary to calculate MetS-Z-BMI score (ie, race/ethnicity and metabolic measurements at baseline and Week 52) could be evaluated
- Calculations for the MetS-Z-BMI scores were performed accounting for patient age, sex, and race/ethnicity using previously established formulas (see QR codes)[7,8]
  - MetS-Z-BMI score can be calculated as follows: (Overall constant) + BMI × (BMI constant) - HDL × (HDL constant) + SBP × (SBP constant) +ln(tryglyceride) × (tryglyceride constant) + glucose × (glucose constant)[7,8]
  - BMI Z score served as the weight-based measure in this analysis and was calculated using Centers for Disease Control and Prevention criteria[9]

Gurka et al. 2012[7]

Gurka et al. 2014[8]

Results

Patient Demographics and Baseline Characteristics

- Of 12 patients with BMI data available at baseline and 52 weeks, 3 did not meet the criteria or have all data necessary for analysis
  - One patient was not able to be analyzed because there is not a specific published MetS-Z-BMI score calculation available for their identified race at this time (Pacific Islander/Hawaiian)
  - Two patients were excluded because of nonadherence to setmelanotide treatment
- In the 9 evaluable patients, the mean (standard deviation [SD]) MetS-Z-BMI score at baseline was 1.05 (0.78), indicating overall increased risk of CVD and T2DM corresponding to a 10.2-fold increased risk of developing CVD and a 2.8-fold increased risk of developing T2DM versus the risk that would be predicted for a reference US population (Table)
  - The comorbidities reported at baseline were insulin resistance (n=2) and metabolic dysfunction–associated fatty liver disease (n=2)
- Individual MetS-Z-BMI scores ranged from −0.17 to 1.86 (Figure 1)

Table. Demographics and Baseline Characteristics of Evaluable Patients (n=9)

	Value
Age, mean (SD), y	11.3 (3.2)
Age range, y	6-16
Sex, n (%)	
Female	3 (33.3)
Male	6 (66.6)
Tumor type, n (%)	
Craniopharyngioma	7 (77.7)
Hypothalamic hamartoma	2 (22.2)
Hypothalamic involvement	
Unilateral	2 (22.2)
Bilateral	7 (77.7)
Weight, mean (SD), kg	90.4 (33.8)
BMI, mean (SD), kg/m^2	35.7 (6.4)
BMI Z score (CDC), mean (SD)	2.6 (0.2)
SBP, mean (SD), mm Hg	110.3 (7.5)
HDL, mean (SD), mg/dL	45.3 (26.7)
Triglycerides, mean (SD), mg/dL	143.3 (77.2)
Fasting glucose, mean (SD), mg/dL	85.5 (8.8)
MetS-Z-BMI score, mean (SD)	1.05 (0.78)
CVD OR, mean (SD)	10.2 (7.6)
T2DM OR, mean (SD)	2.8 (2.1)
Insulin resistance, n (%)	2 (22.2)
MAFLD, n (%)	2 (22.2)

BMI, body mass index; CDC, Centers for Disease Control and Prevention; CVD, cardiovascular disease; HDL, high-density lipoprotein; MAFLD, metabolic dysfunction–associated fatty liver disease; MetS-Z-BMI, metabolic syndrome severity based on BMI; SBP, systolic blood pressure; SD, standard deviation; OR, odds ratio; T2DM, type 2 diabetes mellitus.

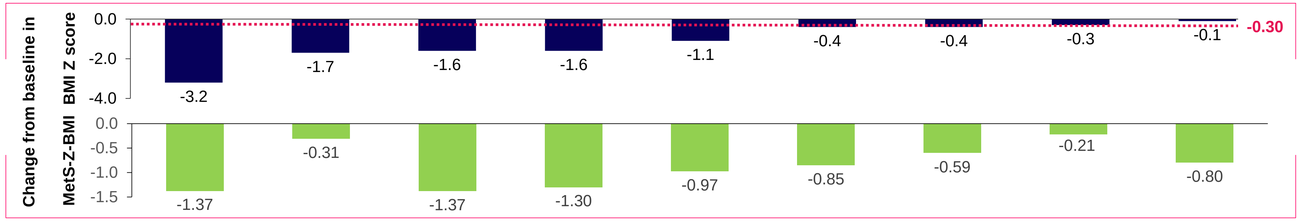
- After 52 weeks of setmelanotide, all patients exhibited a reduction in MetS-Z-BMI score, with a mean (SD) reduction to 0.18 (0.76) (P=0.0004 [2-tailed paired t test])
  - Individual MetS-Z-BMI score change ranged from −0.21 to −1.37 (Figure 2)
  - The mean (SD) change in BMI Z score was −1.16 (0.99)
- Regardless of sex or hypothalamic involvement, both subgroups exhibited a mean reduction in MetS-Z-BMI score (Figure 3)

Figure 1. Individual Baseline Characteristics and MetS-Z-BMI Score–Predicted Comorbidity Odds Ratio

Patient no.	1	2	3	4	5	6	7	8	9
Age	6	16	9	15	14	9	10	12	11
Sex	M	F	F	M	M	M	F	M	M
HI	Unilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Unilateral
Comorbidities	No	No	No	Yes*	No	Yes†	Yes‡	No	No
BMI Z score (CDC)	2.4	2.4	2.6	2.7	2.6	2.7	2.9	2.2	2.6
MetS-Z-BMI score	0.59	-0.17	1.07	1.75	1.73	1.86	1.71	0.83	0.04
CVD OR	5.7	-1.6	10.5	17.1	17	18.2	16.7	8.1	0.4
T2DM OR	1.6	-0.4	2.9	4.7	4.7	5	4.6	2.2	0.1

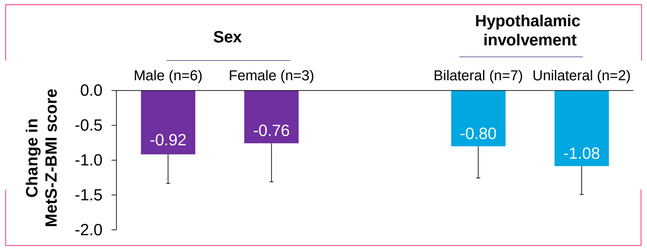
*MAFLD. †Insulin resistance and MAFLD. ‡Insulin resistance. BMI, body mass index; CDC, Centers for Disease Control and Prevention; CVD, cardiovascular disease; HI, hypothalamic involvement; MAFLD, metabolic dysfunction–associated fatty liver disease; MetS-Z-BMI, metabolic syndrome severity based on BMI; OR, odds ratio; T2DM, type 2 diabetes mellitus.

Figure 2. Individual Changes in BMI Z Score and MetS-Z-BMI Score at 52 Weeks



Minimum clinically important difference indicated by red broken line. BMI, body mass index; MetS-Z-BMI, metabolic syndrome severity based on BMI.

Figure 3. Mean Change From Baseline in MetS-Z-BMI Score at 52 Weeks by Sex and Hypothalamic Involvement



Error bars are the standard deviation. MetS-Z-BMI, metabolic syndrome severity based on body mass index.

Safety

- All 9 patients included in this analysis experienced an adverse event
  - No patients experienced a serious adverse event in the primary study or in the long-term extension, and no new safety signals were identified during the long-term extension

Limitations

- Limitations include that these analyses were post hoc in nature, lacked a placebo control, and were performed within a small sample size

Conclusions

- One year of setmelanotide treatment was associated with a reduction in MetS-Z-BMI score in all pediatric patients with aHO
- These data suggest a potential benefit of setmelanotide beyond weight loss alone and that early initiation of treatment may reduce the risk of developing metabolic syndrome, T2DM, and CVD

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