Cardiac, Renal, and Endocrine/Diabetes Mellitus Outcomes in Children With Bardet-Biedl Syndrome

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Summary

- **In pediatric patients with Bardet-Biedl syndrome (BBS) enrolled in the Clinical Registry Investigating BBS (CRIBBS), severity of obesity was associated with increased prevalence of cardiac, endocrine/diabetes, and renal outcomes, demonstrating the need for early identification and management of hyperphagia and obesity in these patients**

Introduction

- BBS is a rare genetic disease characterized by multiorgan involvement including hyperphagia (pathologic, insatiable hunger), severe obesity, renal dysfunction, and visual impairment[1,2]
- These clinical features often develop early in childhood, are progressive, and cause substantial clinical and quality of life burden for patients and their caregivers[1-5]
- Prior research suggests that obesity severity is associated with the development of comorbidities within the overall pediatric population, but its role in the promotion of cardiac, renal, and endocrine/diabetes-related outcomes in children with BBS is poorly understood[6]

Objective

- To examine the prevalence of cardiac, endocrine/diabetes, and renal outcomes in children with BBS with varying levels of obesity severity

Methods

Study design

- Data were collected from patients aged ≤17 years with BBS who were enrolled in CRIBBS, an international registry (NCT02329210) of patients with BBS established in June 2014 by the Marshfield Clinic Research Institute
- After enrollment, annual assessments of patient-reported health outcomes were carried out for a maximum of 8 annual assessments per patient
  - Comorbidity outcomes and weight loss interventions reported at enrollment included both "history of" and "current" status
  - Comorbidity outcomes and weight loss interventions reported during annual follow-up assessments included new occurrences since the last assessment
  - The Hyperphagia Questionnaire was completed by a caregiver at the 4th annual assessment
- Outcomes in the current study included cardiac, endocrine, diabetes, and renal comorbidities reported stratified by weight category (Table 1)
  - For this analysis, patients were required to have ≥1 weight assessment, and those with congenital renal or cardiac conditions were excluded

Table 1. Key Measures Definitions

Outcome	Diagnoses or interventions included
Weight category	Inferred from weight and height-based percentile for children
Hyperphagia	Hyperphagia Questionnaire*
Cardiac†	Heart valve problems,‡ left ventricular hypertrophy, cardiomyopathy, myocardial infarction, heart surgery
Endocrine	Graves disease, Hashimoto thyroiditis, adrenal and pituitary gland disorders, other thyroid problems requiring medication
Diabetes	Diabetes mellitus
Renal§	Renal and kidney disease, diabetes insipidus, vesicoureteral reflex, short-term kidney failure, long-term kidney failure, long-term dialysis, kidney transplant

BMI, body mass index. *The Hyperphagia Questionnaire is a 13-item questionnaire in which each item is rated on a 5-point scale. The questionnaire was completed by caregivers and includes subscales for behavior, drive, and severity. Scores can range from 11 to 55 overall, with higher scores indicating more substantial hyperphagia.[7] †The cardiac outcomes' high-level category includes 3 different subtypes (ie, left ventricular hypertrophy, heart valve issues, and cardiomyopathy) that are indicated by abnormal echocardiography results; thus, abnormal echocardiography results are not considered in the number of cardiac outcomes. ‡Issues with heart valves are not considered in the total number of cardiac outcomes because there is no indication whether the heart valve defect is congenital. §Kidney stones were not included owing to data quality issues.

Analyses

- Weight categorization was based on BMI percentile at the first assessment as follows: underweight or normal weight, overweight, and obesity were defined as BMI <85th, ≥85th to <95th, and ≥95th percentile, respectively
  - Class 1, 2, and 3 obesity were defined as BMI ≥95th to <120% of the 95th percentile, ≥120% to 140% of the 95th percentile, and ≥140% of the 95th percentile, respectively
  - BMI percentiles were based on the World Health Organization BMI growth curves for age and sex
- Descriptive analyses of the proportion of children with any cardiac, endocrine/diabetes, or renal outcomes across all CRIBBS assessments are reported stratified by weight category at first assessment

Results

Population

- A total of 318 children were included in the analysis (Table 2)
  - Most patients were male, White, non-Hispanic, and located in North America
  - Nearly one-third of patients had class 3 (ie, extreme) obesity

Table 2. Patient Demographic and Clinical Characteristics

Parameter	Normal or overweight (n=60)	Obesity class 1 (n=81)	Obesity class 2 (n=77)	Obesity class 3 (n=100)
Age at enrollment, mean (median), y	9.7 (10.0)	8.4 (9.0)	8.4 (8.0)	8.6 (8.0)
Male sex, n (%)	33 (55.0)	49 (60.5)	30 (39.0)	49 (49.0)
Race, n (%)				
White	49 (81.7)	62 (76.5)	53 (68.8)	68 (68.0)
Black	0	2 (2.5)	4 (5.2)	5 (5.0)
Asian	6 (10.0)	4 (4.9)	8 (10.4)	4 (4.0)
Other	4 (6.7)	13 (16.0)	12 (15.6)	22 (22.0)
Unknown	1 (1.7)	0	0	1 (1.0)
Hispanic ethnicity, n (%)	2 (3.3)	8 (9.9)	4 (5.2)	19 (19.0)
Region, n (%)				
Africa	0	2 (2.5)	1 (1.3)	1 (1.0)
Asia	2 (3.3)	1 (1.2)	1 (1.3)	1 (1.0)
Australia	3 (5.0)	6 (7.4)	3 (3.9)	6 (6.0)
Europe	8 (13.3)	13 (16.0)	8 (10.4)	6 (6.0)
North America	46 (76.7)	58 (71.6)	63 (81.8)	84 (84.0)
South America	0	1 (1.2)	1 (1.3)	1 (1.0)
Unknown	1 (1.7)	0	0	1 (1.0)
Follow-up time from enrollment to last weight assessment, mean (median), y	3.6 (3.5)	3.4 (3.0)	3.4 (3.0)	2.9 (3.0)
BMI percentile, mean (median)*	75.9 (83.5)	97.9 (97.8)	99.4 (99.3)	99.8 (99.8)
Hyperphagia Questionnaire completion, n (%)†	12 (20.0)	12 (14.8)	15 (19.5)	7 (7.0)
Total score, mean (median)	19.8 (19.0)	23.0 (21.0)	26.7 (27.0)	25.9 (25.0)
Weight loss intervention				
Weight loss medication, n (%)‡				
Bupropion	1 (1.7)	1 (1.2)	2 (2.6)	2 (2.0)
Liraglutide	0	0	0	1 (1.0)
Metformin	0	5 (6.2)	12 (15.6)	20 (20.0)
Phendimetrazine	0	0	0	-
Phentermine	0	0	0	2 (2.0)
Semaglutide	0	0	0	-
Any of the above	1 (1.7)	5 (6.2)	13 (16.9)	23 (23.0)

BMI, body mass index. *Weight percentiles were calculated according to the formula described on the World Health Organization website for growth curves based on BMI for age and sex.[8] †Hyperphagia Questionnaire scores are taken from the assessment carried out 4 years after enrolment. ‡Weight loss interventions take into account all historical and new uses from enrollment to the last annual assessment, and participants who received investigational medication in the context of a clinical trial were censored at the start of treatment.

Outcomes by obesity class and age group

- Nearly half of all patients (156/318 [49.1%]) reported a health outcome of interest, and the prevalence of any cardiac, endocrine, diabetes, or renal outcome increased with obesity class (Figure 1; Table 3)
  - Cardiac outcomes were reported in 23 patients (7.2%)
  - Endocrine and diabetes-related outcomes were reported in 37 patients (11.6%) and 15 patients (4.7%), respectively
  - Renal outcomes were reported in 125 patients (39.3%)
- Health outcomes occurred early in childhood; among patients aged 0 to <6 years (n=93), outcomes of interest were reported in 46.2%, 48.0%, 52.0%, and 56.7% of those with normal or overweight, obesity class 1, obesity class 2, and obesity class 3, respectively (Figure 2)

Strengths and limitations

- A strength of this analysis is that it used an international sample of patients with BBS from the largest global registry currently available, comprising 607 patients with BBS from 39 countries as of February 2021[9]
- Limitations of the study are that weight-related measures and health outcomes were self-reported and that enrollment in CRIBBS is voluntary

Figure 1. Prevalence of cardiac, endocrine, diabetes, and renal outcomes in the overall population.

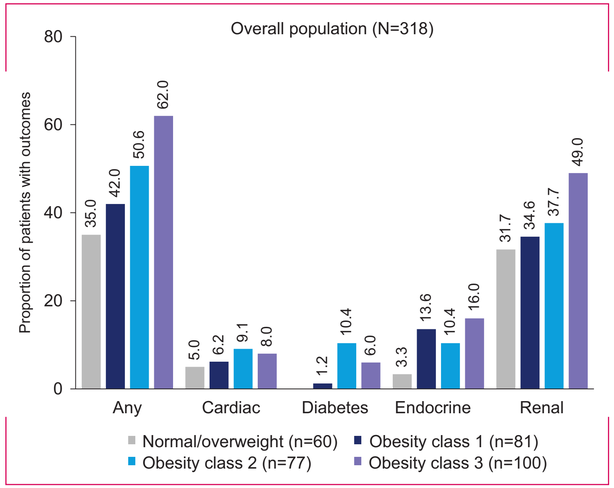
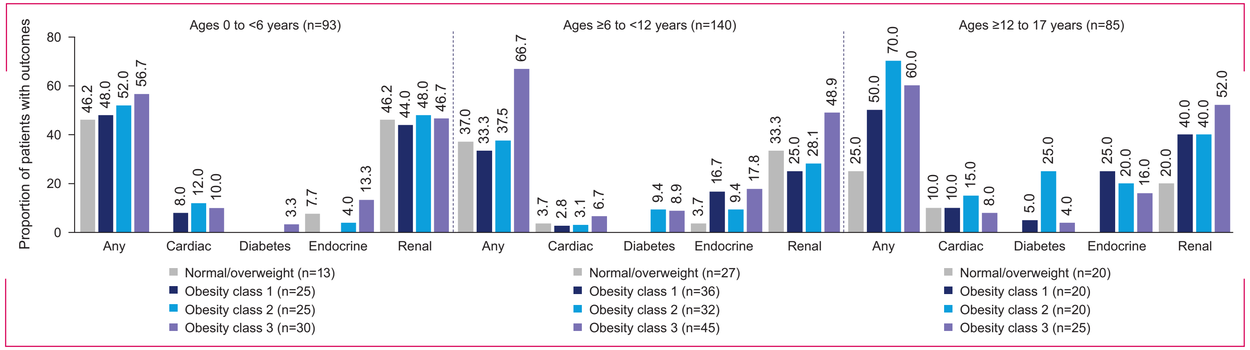


Figure 2. Prevalence of cardiac, endocrine, diabetes, and renal outcomes across age groups.



Conclusions

- This analysis shows that a large proportion of patients with BBS and severe obesity experience cardiac, endocrine, and renal comorbidity outcomes early in life
- Timely diagnosis and early implementation of hyperphagia and weight management strategies in pediatric patients with BBS may reduce the risk and burden associated with cardiac, endocrine/diabetes, and renal comorbidities

Table 3. Cardiac, Endocrine/Diabetes, and Renal Outcomes by Obesity Class

Parameter	Normal or overweight (n=60)	Obesity class 1 (n=81)	Obesity class 2 (n=77)	Obesity class 3 (n=100)
Patients with cardiac outcomes, n (%)	3 (5.0)	5 (6.2)	7 (9.1)	8 (8.0)
Patients with endocrine outcomes, n (%)	2 (3.3)	11 (13.6)	8 (10.4)	16 (16.0)
Patients with diabetes, n (%)	-	1 (1.2)	8 (10.4)	6 (6.0)
Patients with renal outcomes, n (%)	19 (31.7)	28 (34.6)	29 (37.7)	49 (49.0)
Patients with any cardiac, endocrine, diabetes, or renal outcomes, n (%)*	21 (35.0)	34 (42.0)	39 (50.6)	62 (62.0)
By number of distinct outcomes, high-level categories,† mean (median)	1.1 (1.0)	1.3 (1.0)	1.3 (1.0)	1.3 (1.0)
1, n (%)	18 (85.7)	23 (67.6)	30 (76.9)	48 (77.4)
2, n (%)	3 (14.3)	11 (32.4)	5 (12.8)	11 (17.7)
3, n (%)	-	-	4 (10.3)	3 (4.8)
4, n (%)	-	-	-	-
By number of distinct outcomes, low-level categories,‡ mean (median)	1.9 (2.0)	2.1 (2.0)	1.7 (1.0)	2.0 (2.0)
1, n (%)	9 (42.9)	16 (47.1)	25 (64.1)	30 (48.4)
2, n (%)	7 (33.3)	10 (29.4)	6 (15.4)	15 (24.4)
3, n (%)	3 (14.3)	3 (8.8)	6 (15.4)	8 (12.9)
4, n (%)	2 (9.5)	-	-	6 (9.7)
5, n (%)	-	3 (8.8)	-	2 (3.2)
6, n (%)	-	2 (5.9)	1 (2.6)	1 (1.6)
≥7, n (%)	-	-	1 (2.6)	-

*Some patients had outcomes in >1 category. †High-level categories refer to broader outcome categories (ie, cardiac, diabetes, endocrine, or renal comorbidities), and low-level categories refer to all specific diagnoses within each high-level category (listed in Table 1).

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