The Endocrine and Metabolic Characteristics of a Large Bardet-Biedl Syndrome Clinic Population

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Context: Bardet-Biedl syndrome (BBS) is a rare autosomal recessive disorder in which previous reports have described obesity and a metabolic syndrome.

Objective: We describe the endocrine and metabolic characteristics of a large BBS population compared with matched control subjects.

Design: We performed a case-control study.

Setting: This study was performed at a hospital clinic.

Patients: Study patients had a clinical or genetic diagnosis of BBS.

Main Outcome Measurements: Our study determined the prevalence of a metabolic syndrome in our cohort.

Results: A total of 152 subjects were studied. Eighty-four (55.3%) were male. Mean (± standard deviation) age was 33.2 ± 1.0 years. Compared with age-, sex-, and body mass index–matched control subjects, fasting glucose and insulin levels were significantly higher in subjects with BBS (glucose: BBS, 5.2 ± 1.2 mmol/L vs control, 4.9 ± 0.9 mmol/L, $P = 0.04$; insulin: BBS, 24.2 ± 17.0 pmol/L vs control, 14.2 ± 14.8 pmol/L, $P < 0.001$). Serum triglycerides were significantly higher in subjects with BBS (2.0 ± 1.2 mmol/L) compared with control subjects (1.3 ± 0.8 mmol/L; $P < 0.001$), but total cholesterol, high-density lipoprotein, and low-density lipoprotein were similar in both groups. Systolic blood pressure was higher in the BBS group (BBS, 135 ± 18 mm Hg vs control subjects, 129 ± 16 mm Hg; $P = 0.02$). Alanine transaminase was raised in 34 (26.8%) subjects with BBS, compared with five (8.9%) control subjects ($P = 0.01$). The rate of metabolic syndrome, determined using International Diabetes Federation criteria, was significantly higher in the BBS group (54.3%) compared with control subjects (26% $P < 0.001$). Twenty-six (19.5%) of male subjects with BBS were hypogonadal (serum testosterone, 9.9 ± 5.3 mmol/L), but significant pituitary abnormalities were uncommon. Subclinical hypothyroidism was present in 24 of 125 (19.4%) patients with BBS, compared with 3 of 65 (4.6%) control subjects ($P = 0.01$).

Conclusions: Insulin resistance and the metabolic syndrome are increased in adult patients with BBS compared with matched control subjects. Increased subclinical hypothyroidism in the BBS cohort needs further investigation. **(*J Clin Endocrinol Metab* 103: 1834–1841, 2018)**

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Abbreviations: BBS, Bardet-Biedl syndrome; BMI, body mass index; CKD, chronic kidney disease; DI, diabetes insipidus; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; MRI, magnetic resonance imaging; T2DM, type 2 diabetes mellitus.

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive disorder characterized by a pleiotropic phenotype including obesity, rod cone dystrophy, polydactyly, hypogonadism, renal abnormalities, and cognitive impairment (1).

The prevalence of BBS is estimated to be 1 in 125,000 to 160,000 in Europe, which is equivalent to around 400 cases in the United Kingdom (2, 3). It is more prevalent in some other countries (*e.g.*, there is an estimated prevalence in an Arab population of 1 in 13,500); this increased prevalence has been attributed to higher levels of consanguinity (4). There is a high prevalence of BBS in Newfoundland (1 in 18,000), which is thought to be due to the geographical and cultural isolation of this community, high levels of kinship, and founder effects (5, 6).

The diagnosis of BBS is clinical, and at least four of the primary features (polydactyly, obesity, learning disabilities, hypogonadism in male patients, renal anomalies) or three primary features and two secondary features must be present. Secondary features include type 2 diabetes mellitus (T2DM), polyuria, polydipsia from nephrogenic diabetes insipidus (DI), hepatic fibrosis, ataxia/poor coordination, mild spasticity, speech disorder/delay, dental crowding/hypodontia/small roots/high arched palate, and left ventricular hypertrophy/congenital heart disease (7). The diagnosis can be confirmed with direct genetic sequencing in 80% of patients (8). To date, 22 BBS genes on multiple loci have been discovered (9–12), with the most common gene mutations, BBS1 and BBS10, accounting for 23.2% and 20% of cases, respectively (1, 6). BBS is part of the family of "ciliopathies"; these genes encode proteins involved in the function and maintenance of primary cilia (13–15).

Obesity is an important cause of morbidity in BBS, but the etiology is unclear. One study from a primarily pediatric cohort (16) found hyperleptinemia and increased intra-abdominal fat in subjects with BBS compared with control subjects. A predisposition to central obesity may be associated with increased metabolic syndrome, but there are currently few data in adults, with at least one study finding normal fasting insulin resistance (16). Another study reported that 20 patients with BBS had a similar basal metabolic rate and energy intake when compared with body mass index (BMI)-matched control subjects, but the physical activity level of the patients with BBS was lower (17). Further research into other endocrine features of BBS found a high frequency of pituitary abnormalities on magnetic resonance imaging (MRI) in 11 children with BBS (18), but there are no comparable adult data.

We provide a detailed case-controlled description of the endocrine and metabolic characteristics from a large clinic population of adults with BBS.

Materials and Methods

Subjects

Patients with BBS were identified through the BBS Multidisciplinary Team clinics at Guy's & St Thomas' Hospitals NHS Foundation Trust and University Hospitals Birmingham NHS Foundation Trust, the two main specialist clinics in England for adults with BBS. The BBS diagnosis was made on clinical grounds using established criteria (7), and samples for genetic analysis were taken when possible. Each patient attending the BBS clinic is assessed by an endocrinologist, a nephrologist, a clinical geneticist, an ophthalmologist, and a dietician.

Control subjects were identified from an obesity clinic at Guy's & St Thomas' Hospitals NHS Foundation Trust (n = 32; 31% of total) and from participants in other research studies undertaken by King's Diabetes Research group, King's College London, involving neuro-imaging and appetite (n = 71). The research studies excluded chronic kidney disease (CKD) stages 3 to 5. Formal comparison analyses for CKD between subjects with BBS and control subjects were not performed, but the distribution of CKD is described in the Results. All studies were approved by the Dulwich Ethics Committee, South-East London or by the Royal Marsden Research Ethics Committee. Informed consent was obtained from participants in the control group. Data collected from patients with BBS were part of routine clinical care, and specific informed consent was not required. Control subjects were matched with patients with BBS by age, sex, and BMI using frequency matching. The case-control comparison was not ethnicity specific.

Clinical and laboratory assessment

Blood samples were taken after a 9-hour fast. Morning medications were omitted until after the samples were taken. Full blood count, renal and liver function tests, thyroid function tests, lipid profile, glucose, and insulin were measured in the fasted state. Serum insulin was measured using a chemiluminometric sandwich immunoassay (Advia Centaur; Siemens Healthcare Diagnostics Ltd, Camberley, UK). Anthropometric measurements were taken with participants wearing light clothing. Waist circumference was measured at the level of the iliac crest on expiration. BMI was calculated as kilogram per square meter. Obesity was defined as BMI >30 kg/m^2. Blood pressure was taken once in the seated position.

International Diabetes Federation criteria were used to identify metabolic syndrome. These criteria define metabolic syndrome as central obesity (measured by ethnicity-specific values for waist circumference) and any two of the following: raised triglycerides (>1.7 mmol/L), reduced high-density lipoprotein cholesterol (HDL-C) (<1.03 mmol/L in male subjects, <1.29 mmol/L in female subjects), raised blood pressure (systolic >130 mm Hg or diastolic >85 mm Hg), and raised plasma fasting glucose (>5.6 mmol/L) or if the patients were on treatment for any of these factors (19). Levels of liver transaminases above the local laboratory reference range were used as an indication of biochemical evidence of nonalcoholic fatty liver disease if no other diagnosis was clinically apparent. Subclinical hypothyroidism was identified if thyroid-stimulating hormone levels were raised but if serum-free thyroxine levels were within the normal laboratory reference range.

The presence of hypogonadism in our BBS group was defined by characteristic clinical signs and symptoms accompanied by

low total testosterone and abnormal luteinizing hormone/follicle-stimulating hormone. Sex hormone-binding globulin and free testosterone were measured.

For a subgroup of subjects (n = 85), the endocrine and metabolic characteristics for the four most common mutations were described. Unadjusted comparisons were only made between BBS1 and BBS10 mutations due to the small numbers in each group.

Statistical analysis

Data were analyzed using the SPSS Statistics (Version 19.0 for Windows; IBM, Armonk, NY). Student's *t* test was used for continuous variables that showed a normal distribution, and the Mann-Whitney *U* test was used for continuous variables that did not show a normal distribution after log transformation. Data that were normally distributed are presented as mean ± standard deviation. A χ^2 test was used for frequencies. Two-tailed *P* values were considered significant at <0.05.

Results

Demographics and clinical characteristics

A total of 152 subjects with BBS were included in the study. Eighty-four (55.3%) were male. Mean age was 33.2 ± 11.8 years (range, 16–58 years), and mean BMI was 35.7 ± 7.8 kg/m^2 (range, 19.2–57 kg/m^2). Fig. 1 shows the subjects with BBS categorized by BMI. Overall, 102 (76.3%) subjects with BBS were obese (74.1% of female subjects and 78.1% of male subjects). One patient had a previous gastric band, but otherwise no patients with BBS took weight loss medication. One hundred twenty-six (82.9%) patients were white. The majority of subjects with known mutations (n = 108) had the BBS1 mutation [71 subjects (46.7%)], with 17 subjects (11.1%) carrying the BBS2 mutation and 20 subjects (14.4%) carrying the BBS10 mutation (Table 1).

The control group consisted of 103 individuals who were matched for age, sex, and BMI. Mean age was 32.5 ± 8.0 years (range, 16 to 52 years), and mean BMI was 34.2 ± 9.1 kg/m^2 (range, 20.1 to 54.8 kg/m^2). Sixty-two (60.1%) control subjects were white, and 48 (46.6%) were male (Table 2).

Clinical and biochemical characteristics were compared between subjects with BBS and matched control subjects (Table 3). Fasting glucose (BBS 5.2 ± 1.2 mmol/L vs control 4.9 ± 0.9 mmol/L; $P = 0.04$) insulin (24.2 ± 17.0 vs 14.2 ± 14.8 pmol/L; $P < 0.001$), and homeostatic model assessment of insulin resistance (HOMA-IR) (5.55 ± 4.14 vs 3.09 ± 4.53; $P = 0.003$) were significantly higher in the BBS group compared with the control group. These were unadjusted comparisons. Glycated hemoglobin was not different between the two groups, although the BBS group had a mean HbA1c that was within the range for impaired glucose tolerance. Subjects with known diabetes (n = 25) were excluded from glucose/insulin/HOMA-IR/HbA1c analyses but were included in all other analyses.

There was no difference in total cholesterol, HDL-C, or low-density lipoprotein cholesterol between the two groups. However, serum triglycerides were significantly higher in the BBS group (2.0 ± 1.2 mmol/L) compared with the control group (1.3 ± 0.8 mmol/L; $P < 0.001$). Systolic blood pressure was higher in the BBS group (BBS, 135.2 ± 18.3 mm Hg vs controls, 129.0 ± 16.1 mm Hg; $P = 0.02$). Nine patients with BBS were taking antihypertensive medication, compared with zero patients in the control group. Alanine transaminase was raised above the reference range in 34 (26.8%) individuals with BBS, compared with five (8.9%) control subjects ($P = 0.01$). The presence of a metabolic syndrome, using International Diabetes Federation criteria, was significantly higher in the BBS group (54.3%) compared with control subjects (26%; $P < 0.001$). The individual features of the metabolic syndrome are shown in Table 3. Subjects with

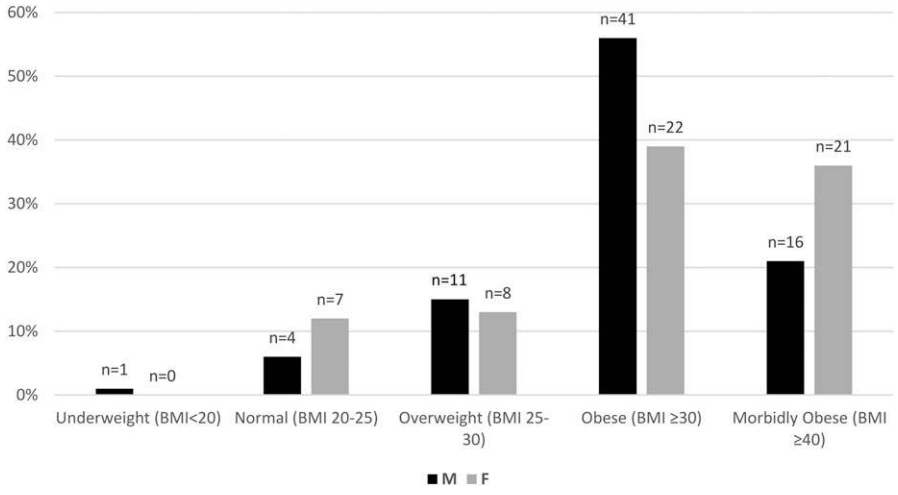

Figure 1. Subjects with BBS stratified according to sex and BMI.

Table 1. Gene Mutations in the BBS Group

Gene Mutation	n (%)
BBS1	71 (46.7)
BBS2	17 (11.1)
BBS8	1 (<1)
BBS9	1 (<1)
BBS10	20 (13.1)
BBS12	8 (<1)
BBS6MKKS[a]	2 (<1)
MKKS	1 (<1)
BBS2 BBS5	1 (<1)
Not known[b]	30 (19.7)

[a]McKusick-Kaufman syndrome.

[b]None of the current known gene mutations was found.

BBS had significantly increased frequency of all features of the metabolic syndrome except for HDL-C (Table 3).

Polycystic ovary syndrome was present in 10 of 68 (14.7%) female subjects with BBS. Two female subjects with BBS were known to have given birth to healthy infants, and four male subjects with BBS had fathered children. Twenty-six (19.5%) male subjects were hypogonadal (primary in four patients and secondary in 22 patients, one secondary to raised prolactin as described below, with normal/low gonadotrophins in the others). Sex hormone binding globulin was low in 96.1% (25/26) of the clinically hypogonadal patients. All patients were assessed thoroughly clinically and biochemically for DI, and two (0.01%) patients were confirmed to have an established diagnosis of nephrogenic DI.

Twenty-four (15.8%) patients with BBS had T2DM, and one patient with BBS had type 1 diabetes. Of those with T2DM, 13 were male and 11 were female, with a mean age of 40.4 ± 9.6 years. Management of T2DM was as follows: six patients were diet controlled, eight were taking metformin, and 10 used insulin to manage their diabetes. The mean HbA1c of subjects with T2DM was 62 ± 28 mmol/mol (7.8 ± 4.8%).

A total of 152 patients with BBS (78.4%) had normal pituitary function. Of the remaining patients, 15 (11.5%) had an isolated low IGF-1, five had mild hyperprolactinemia (prolactin <1000 mIU/L), and seven had isolated low prolactin. One patient had significant hyperprolactinemia (prolactin of 6391 IU/mL (102 to 496 IU/mL) with suppressed gonadotrophins and total testosterone of 3.5 nmol/L. A subsequent MRI showed pituitary hypoplasia.

Most BBS subjects were euthyroid (77.0%). Among these subjects, 10 (6.5%) had hypothyroidism, and one had hyperthyroidism. There were 24 of 125 (19.4%) patients with BBS with subclinical hypothyroidism compared with 3 of 65 (4.6%) control subjects ($P = 0.01$).

Four (3.9%) patients had stage 5 CKD, 4 (3.9%) stage 4 CKD and 14 (13.7%) stage 3 CKD. An additional four patients had functioning renal transplants (Fig. 2). In the control cohort, no patients had stage 5 or 4 CKD, one (1.2%) had stage 3 CKD, 31 (38.3%) had stage 2 CKD, and 49 (60.5%) had stage 1 CKD.

The main endocrine and metabolic features of the most common mutations are shown in Table 4. Unadjusted comparisons were only performed between the BBS1 and BBS10 mutations due to small numbers in the subgroups. The BBS10 mutation was associated with a trend toward increased diastolic blood pressure (BBS1, 81.4 ± 9.4 vs BBS10, 89.1 ± 8.4 mm Hg; $P = 0.05$), increased HOMA-IR (BBS1, 5.8 ± 4.3 vs BBS10, 12.4 ± 4; $P = 0.02$), and increased triglycerides (BBS1, 1.71 ± 0.8 vs BBS10, 2.7 ± 1.5 mmol/L; $P = 0.03$) despite a younger age in our study group (BBS1, 35 ± 11.2 vs 27.7 ± 11.3 years; $P = 0.02$). Subjects with BBS10 also had a higher prevalence of hypogonadism [BBS1, n = 6 (10.5%) vs BBS10, n = 6 (42%); $P = 0.01$].

Discussion

Our data provide robust confirmation that the metabolic syndrome is more prevalent in subjects with BBS compared with matched control subjects and is in keeping with increased cardiovascular mortality. Specifically, fasting blood glucose, triglycerides, and systolic blood pressure were raised in the BBS group, and overall insulin resistance was higher. Contrary to previous reports, global pituitary dysfunction is uncommon, but there is an increased prevalence of male hypogonadism. We also report data showing increased subclinical hypothyroidism in subjects with BBS.

Data from a cohort study that followed 46 subjects with BBS over a prolonged period showed that 48% developed T2DM at a mean age of 43 years (5). Cardiovascular mortality was also increased, with median survival of 63 years. Increased prevalence of metabolic syndrome has been suggested in case series and cross-sectional data, describing the metabolic syndrome or its components, in adult subjects with BBS (20, 21). However, these were small studies (three cases in one study), and they also had discrepant findings. One study showed that hypertension and dyslipidemia were common in 33

Table 2. Demographic Details of Patients With BBS and Control Subjects

	BBS (Mean ± SD)	Control (Mean ± SD)	*P* Value
Age, y	33.2 ± 11.8	32.5 ± 7.8	0.75
BMI, kg/m^2	35.7 ± 8.0	34.2 ± 9.1	0.13
Sex, % male	55.3% (n = 84)	46.6% (n = 48)	0.17

Abbreviations: SD, standard deviation.

Table 3. Clinical Features of Subjects With BBS Compared With Age-, Sex-, and BMI-Matched Control Subjects

	BBS		Control		
Variable	**n**	**Mean ± SD**	**n**	**Mean ± SD**	***P* Value**
Fasting glucose, mmol/L	109	5.2 ± 1.2	98	4.9 ± 0.9	**0.04**
Fasting insulin, pmol/L	46	24.2 ± 17.0	78	14.2 ± 14.8	**<0.001**
HOMA-IR	46	5.55 ± 4.14	78	3.09 ± 4.53	**0.003**
HbA1c, mmol/mol (%)	10	42 ± 15 (6.0 ± 1.4)	60	40 ± 10 (5.8 ± 0.9)	0.37
Cholesterol, mmol/L	129	4.9 ± 1.0	88	4.8 ± 0.9	0.78
HDL-C, mmol/L	126	1.2 ± 0.3	87	1.2 ± 0.4	0.47
LDL-C, mmol/L	2.8 ± 0.9 (84)		2.9 ± 0.9 (87)		0.21
Triglycerides, mmol/L	130	2.0 ± 1.2	88	1.3 ± 0.8	**<0.001**
Systolic BP, mm Hg	100	135.2 ± 18.3	67	129.0 ± 16.1	**0.02**
Diastolic BP, mm Hg	100	81.4 ± 11.4	70	80.3 ± 11.6	0.55
Prevalence of metabolic syndrome, %	54.3 (63/116)		26% (26/100)		**<0.001**
Prevalence of subclinical hypothyroidism, %	19.4 (24/124)		4.6% (3/65)		**0.01**
Prevalence of hypogonadism, %	19.5 (26/133)		NA		NA
Primary	15.4 (4/26)				
Secondary	84.6 (22/26)				
Raised ALT, %	26.8 (34/127)		8.9 (5/56)		**0.01**
Metabolic syndrome parameters					
Central obesity, %	77 (101/131)		60 (62/103)		**0.006**
Raised triglycerides (>1.7 mmol/L), %	55 (71/130)		21 (18/88)		**<0.0001**
Reduced HDL-C (<1.03 mmol/L in male subjects, <1.29 mmol/L in female subjects), %	40 (51/126)		45 (39/87)		0.53
Hypertension (systolic >135 mm Hg or diastolic >85 mm Hg), %	67 (67/100)		43 (30/70)		**0.002**
Raised fasting plasma glucose (>5.6 mmol/L), %	26 (28/109)		8 (8/98)		**0.0008**

Boldface indicates *P* values <0.05 that are considered significant.

Abbreviations: ALT, alanine transaminase; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; NA, not available.

patients with BBS with an average age of 26.3 years, with 6% having overt diabetes.

Case-control data in a predominantly pediatric population have shown that, at a mean age of 14 years, subjects with BBS had increased visceral adiposity, raised diastolic blood pressure, and hypertriglyceridemia (16). Our study shows higher triglycerides, systolic blood pressure, and fasting blood glucose in adult subjects with BBS despite antihypertensive medication in a small number. Raised systolic blood pressure in the BBS group may be related to insulin resistance, but it is also possible that BBS proteins are associated with blood pressure control. Rodent data have implicated BBS genes in the regulation of vascular function (22).

Subjects with BBS had marked fasting hyperinsulinemia compared with matched control subjects. In the case-control study by Feuillan *et al.* (16), subjects with BBS showed a trend toward higher fasting insulin, but this did not reach statistical significance, with fasting glucose similar in both groups. Taken together, these data suggest that hyperinsulinemia starts at an early age in BBS and that by a subject's third decade, hyperinsulinemia is

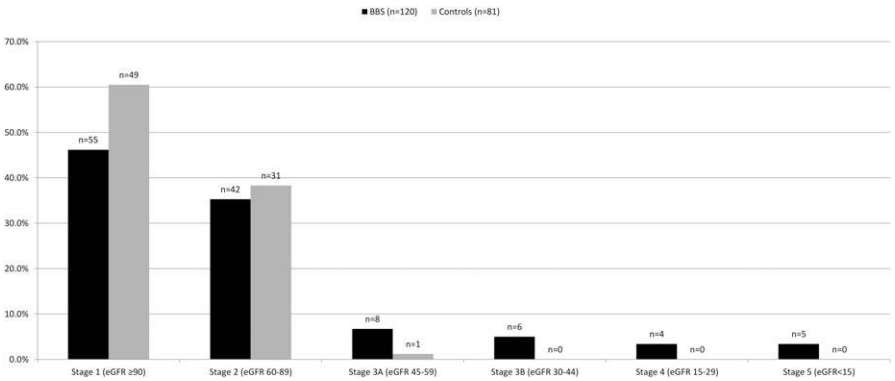

Figure 2. Patients with BBS and control subjects stratified according to CKD stage.

Table 4. Comparison of Common Genotypes and Their Endocrine and Metabolic Characteristics

	BBS1 (n = 57)	BBS2 (n = 10)	BBS10 (n = 14)	BBS12 (n = 4)	*P* Value[a]
Male, n (%)	31 (54)	6 (60)	11 (79)	3 (75)	0.1
Age, y	35 ± 11.2	36.6 ± 12.3	27.2 ± 11.3	30 ± 12.3	**0.02**
BMI, kg/m^2	34.2 ± 7.1	41.5 ± 9.8	36.9 ± 8.7	35.8 ± 6.8	0.31
Systolic BP, mm Hg	135.1 ± 13.3	139.3 ± 18.7	145.4 ± 24.9	137.7 ± 17.5	0.27
Diastolic BP, mm Hg	81.4 ± 9.4	87.2 ± 9.6	89.1 ± 8.4	78.7 ± 7.6	0.05
HOMA-IR	5.8 ± 4.3	7.1 ± 1	12.4 ± 4.0	4.4 ± 1	**0.02**
Triglycerides, mmol/L	1.7 ± 0.8	2.6 ± 1.2	2.7 ± 1.5	2.7 ± 1.8	**0.03**
Metabolic syndrome present, n (%)	27 (47.3)	7 (70)	11 (78)	2 (50)	**0.04**
Hypothyroidism or subclinical hypothyroidism, n (%)	9 (15.7)	3 (30%)	4 (28%)	2 (50%)	0.3
Hypogonadism, n (%)	6 (10.5)	2 (20)	6 (42)	0	**0.01**

Boldface indicates *P* values <0.05 that are considered significant.

Abbreviations: BP, blood pressure.

[a]Comparison between BBS1 and BBS10 mutations only.

more pronounced and fasting glucose is raised, although these values are still within the nondiabetic range. Insulin resistance is the common feature that links the different components of the metabolic syndrome, and this appears to increase steadily throughout adulthood in subjects with BBS until, as suggested by the Feuillan *et al.* study (16), they may decompensate by their fourth decade and develop overt T2DM. The careful case-control matching of our study, together with findings from Feuillan *et al.* (16), suggest that progression of hyperinsulinemia to T2DM is above and beyond what would be expected from obesity alone.

The reasons for this are not clear. It is known that adipose tissue partitioning is abnormal in BBS from an early age, and the predisposition to visceral adiposity may lead to increased features of metabolic syndrome as an adult, increasing the prevalence of T2DM and cardiovascular mortality. Subjects with BBS are known to have hyperleptinemia and are likely to have leptin resistance (23). This may be mediated by impaired leptin receptor trafficking and signaling resulting from altered or deficient BBS proteins (24). Leptin has an overall effect of decreasing body weight, and *db/db* (leptin-receptor)-deficient mice have increased subcutaneous and visceral adipose compartments (25). Predisposition to increased visceral adipose tissue is also likely to be genetically determined, as is found in certain ethnic groups, although the exact mechanisms have yet to be elucidated.

Alternative mechanisms for insulin resistance in BBS may be related to the requirement of BBS proteins to regulate the trafficking of insulin receptors. Recent data using knockout mouse models have shown that β-cell ciliary dysfunction is associated with disruption in insulin secretion/signaling and that the BBS protein/insulin receptor interaction has consequences on whole body insulin action and glucose metabolism (26, 27). Not all BBS mutations cause insulin resistance, with data suggesting that BBS12 mutations are associated with improved insulin sensitivity and glucose utilization (28).

The prevalence of overt diabetes in our study with mean age of 33 years was ~15%, compared with 6% in a younger population (mean age, 26.3 years) (21) and 48% in subjects with BBS a decade older (5). Diabetes was managed with diet or metformin in many cases. The approximate tripling of the incidence of diabetes in a decade from the early thirties is useful clinical information and may represent an opportunity to prevent the onset of T2DM with lifestyle modification.

Another small study in pediatric patients of Turkish origin found a high incidence of pituitary hormone abnormalities (18). This study reported evidence of hyperprolactinemia, primary and secondary hypogonadism, one case of precocious puberty, and one case of growth hormone deficiency requiring treatment. MRI pituitary scans were performed in all subjects and showed abnormalities in 63%, including pituitary hypoplasia, Rathke's cyst, and an enlarged pituitary gland. Two other case reports have described full dynamic endocrinological evaluations in single adult patients with BBS, with both showing secondary hypogonadism but no other specific abnormalities (29, 30). Our data do not suggest widespread pituitary hormone abnormalities in adult subjects with BBS. Significant hyperprolactinemia was only found in one subject in whom MRI showed pituitary hypoplasia. MRI scans were not performed in the remainder of our subjects, so it is not possible to confirm or refute the findings in the above pediatric study.

Hypogonadism was common, and this is in keeping with previous reports (7). The etiology was secondary hypogonadism in the majority of cases, most of which had been relatively asymptomatic and unrecognized before attending the specialized clinic. Most male subjects also had accompanying microgenitalia. The mechanism for secondary hypogonadism is unknown, but gonadotrophin

deficiency and obesity-related hypogonadism are likely to be contributory factors. Our clinical practice has been not to use testosterone replacement to treat asymptomatic men with BBS. Future studies will be useful in determining whether testosterone replacement in men with BBS with secondary hypogonadism will improve metabolic parameters, including body composition and quality of life.

DI is considered an established feature of BBS. Our results suggest that significant DI in adults is a rare occurrence and, when present, is likely to reflect a lack of renal responsiveness to desmopressin due to nephrogenic rather than cranial DI.

The increased prevalence of subclinical hypothyroidism was an unexpected finding. To our knowledge, this has not been previously described. Outside BBS, subclinical hypothyroidism is the precursor to overt hypothyroidism in most cases, is primary in etiology, and is usually related to autoimmune thyroid disease. Further work is needed to assess whether thyroid autoimmunity is increased in BBS. Our data suggest that it is useful to check thyroid function periodically in people with BBS. If abnormal results are found, our usual practice would be to assess symptomology, ascertain the presence or absence of thyroid autoimmunity, and then consider monitoring or treatment with levothyroxine. Subclinical hypothyroidism has been associated with increased prevalence of the metabolic syndrome and central obesity, although the data are heterogeneous and sometimes conflicting (31, 32).

The prevalence of CKD was similar to previous cohorts, although stage 1 and 2 CKD were not different from obese control subjects. Nephrogenic DI is not a widely recognized feature of BBS; there were only two cases in our cohort, and both cases were diagnosed in childhood. Our subjects were all thoroughly evaluated by an endocrinologist and a nephrologist, and we feel that this is likely to be an accurate prevalence.

Regarding the gene mutations in BBS, the majority of patients (61.1%) fell in the *BBS1* or *BBS10* categories, closely followed by mutations in *BBS2*. This order of the number of cases of BBS attributable to each mutation is reflected in previous studies (1). There was a high prevalence of BBS1 M390R mutations (80%) within the BBS1 cohort, which reflects the high frequency of white subjects in our study population. Previous studies have confirmed that, within a multiethnic cohort, a number of novel gene mutations are observed, and the spectrum of clinical characteristics can overlap with those of other ciliopathies (*e.g.*, Alstrom and McKusick-Kauffman syndromes) (33).

Further data from our group have shown that patients with missense mutations in the BBS1 gene have lower cardiovascular risk markers (hypertension, hyperlipidemia, impaired glucose tolerance) than BBS10 or other BBS1 mutations (34).

We performed a limited unadjusted substudy analysis between the two most common mutations (BBS1 and BBS10) and found that insulin resistance and features of the metabolic syndrome were increased in the BBS10 group despite a younger age in this group. Although numbers in the groups were small, our data suggest that hypogonadism was also increased in the BBS10 group, despite similar BMI, which may be a contributing factor in the increased metabolic disruption seen in this group. These data are also in keeping with data from Feuillan *et al.* (16), suggesting lower HOMA-IR, serum leptin, BMI, and abdominal fat in BBS1 compared with BBS10 mutations. We acknowledge that differences in clinical manifestation and severity may occur with different BBS mutations. Longer-term prospective studies allowing for the effect of interventions and medication may provide further understanding of the mechanisms of development of endocrine and metabolic adverse features. Recognition of the prevalence of these complications will inform the development of clinical interventions (*e.g.*, weight management, thyroid hormone use) that may be of value in managing the patient with BBS.

Our study has some limitations. We did not collect detailed information about dietary intake and hence were not able to adjust for this in our analyses. Data for fasting samples were collected within the setting of routine clinic care, and, although patients were given standard instructions for fasting samples, this was not performed within a research setting. Blood pressure measurements for participants with BBS were also taken as part of routine clinical care and hence were not measured on multiple occasions. BMI alone as a measure of obesity has limitations, and future work to compare other parameters, such as serum leptin, would be informative.

In summary, our study reports increased prevalence of insulin resistance and the metabolic syndrome in adult subjects with BBS compared with matched control subjects. Overt diabetes had not yet developed in many subjects, and this may represent an opportunity to intervene with lifestyle measures. The finding of subclinical hypothyroidism needs further exploration.

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