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Metabolism in Bardet-Biedl Syndrome

## 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:** Describe the endocrine and metabolic characteristics of a large BBS population compared with matched controls.

**Design:** Case-control

**Setting:** Hospital clinic

**Patients:** A clinical/genetic diagnosis of BBS

Intervention: None

**Main outcome measure:** Prevalence of metabolic syndrome

**Results:** One hundred and fifty-two subjects were studied. Eight-four (55.3%) were male and mean ( $\pm$ SD) age was  $33.2\pm 1.0$  years. Compared with age, gender and BMI matched controls, fasting glucose and insulin levels were significantly higher in BBS subjects (glucose: BBS:  $5.2\pm 1.2$ mmol/l vs control  $4.9\pm 0.9$ mmol/l,  $p=0.04$ ; insulin: BBS:  $24.2\pm 17.0$ pmol/l vs control  $14.2\pm 14.8$ pmol/l,  $p<0.001$ ). Serum triglycerides were significantly higher in BBS subjects ( $2.0\pm 1.2$ mmol/l) compared with controls ( $1.3\pm 0.8$ mmol/l  $p<0.001$ ) but total cholesterol/HDL/LDL were similar in both groups. Systolic blood pressure was higher in the BBS group (BBS  $135\pm 18$  mmHg vs controls  $129\pm 16$ mmHg ( $p=0.02$ ). Alanine transaminase (ALT) was raised in 34 (26.8%) BBS subjects, compared to 5 (8.9%) controls ( $p=0.01$ ). The presence of a metabolic syndrome, using IDF criteria, was significantly higher in the BBS group (54.3%) compared to controls (26%  $p<0.001$ ). Twenty-six (19.5%) of BBS males were hypogonadal (serum testosterone  $9.9\pm 5.3$  mmol/l) but significant pituitary abnormalities were uncommon. Subclinical hypothyroidism was present in 24/125 (19.4%) patients with BBS compared with 3/65 (4.6%) controls ( $p=0.01$ ).

**Conclusions:** Insulin resistance and the metabolic syndrome are increased in adult BBS compared with matched controls. Increased subclinical hypothyroidism in the BBS cohort is a novel finding that needs further investigation.

A large case control study examined endocrine and metabolic characteristics in adult Bardet-Biedl syndrome (BBS). Insulin resistance and metabolic syndrome were significantly more prevalent in BBS. .

### INTRODUCTION

Bardet Biedl syndrome (BBS) is a rare autosomal recessive disorder characterised 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 125,000-160,000 in Europe which is equivalent to around 400 cases in the UK (2,3). It is more prevalent in some other countries, attributed to higher levels of consanguinity, with an estimated prevalence in an Arab population of 1 in 13,500 as an example (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 4 of the primary features (polydactyly, obesity, learning disabilities, hypogonadism in males, renal anomalies) or 3 primary features and 2 secondary features must be present. Secondary features include type 2 diabetes mellitus (T2DM), polyuria, polydipsia from nephrogenic diabetes insipidus, hepatic fibrosis, ataxia/poor coordination, mild spasticity, speech disorder/delay, dental crowding/hypodontia/small roots/high arched palate, 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’ as 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 aetiology is unclear. One study from a primarily paediatric cohort (16) found hyperleptinaemia and increased intra-abdominal fat in BBS compared to controls. 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 controls, 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 MRI in 11 children with BBS (18) but again there are no comparable adult data.

We aimed to provide the first detailed case-controlled description of the endocrine and metabolic characteristics from a large BBS adult clinic population.

## METHODS

### Subjects

Patients with BBS were identified through the BBS Multi-disciplinary Team clinics at Guy’s & St Thomas’ Hospitals NHS Foundation Trust (GSTT) and University Hospitals Birmingham NHS Foundation Trust (UHB), UK, 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 where possible. Each patient attending the BBS clinic is assessed by an endocrinologist, nephrologist, clinical geneticist, ophthalmologist and dietician.

Control subjects were identified from an obesity clinic at GSTT (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 CKD stages 3-5, so formal comparison analyses for CKD between BBS and controls were not performed but the distribution of CKD is described in the results for information. All studies were approved by Dulwich Ethics Committee, South-East London or the Royal Marsden

Research Ethics Committee. Informed consent was collected from control participants. Data collected from BBS patients were part of routine clinical care and specific informed consent was not required. Controls were matched with BBS subjects 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 sample. Full blood count, renal and liver function tests, thyroid function tests, lipid profile, glucose and insulin were all measured in the fasted state. Serum insulin was measured using a chemiluminometric sandwich immunoassay (Advia Centaur, Siemens). Anthropometric measurements were taken with participants wearing light clothing. Waist circumference was measured at the level of the iliac crest in expiration. Body mass index (BMI) was calculated as kilogram per square metre. Obesity was defined as  $BMI > 30 \text{ kg/m}^2$ . Blood pressure was taken once in the seated position.

The International Diabetes Federation (IDF) criteria were used to identify metabolic syndrome. This defines metabolic syndrome as central obesity (measured by ethnicity specific values for waist circumference) and any two of the following: raised triglycerides ( $> 1.7 \text{ mmol/l}$ ), reduced HDL cholesterol ( $< 1.03 \text{ mmol/l}$  in males,  $< 1.29 \text{ mmol/l}$  in females), raised blood pressure (systolic  $> 130 \text{ mmHg}$  or diastolic  $> 85 \text{ mmHg}$ ) and raised plasma fasting glucose ( $> 5.6 \text{ mmol/l}$ ) or if the patients are already on treatment for any of these factors (19). Levels of liver transaminases above the local laboratory reference range were used as an indication for biochemical evidence of NAFLD, if no other diagnosis was clinically apparent. Subclinical hypothyroidism was identified if thyroid stimulating hormone (TSH) levels were raised but serum free thyroxine (T4) levels were within the normal laboratory reference range.

Presence of hypogonadism in our BBS group was defined by characteristic clinical signs and symptoms accompanied by low total testosterone and abnormal luteinizing hormone (LH)/follicle stimulating hormone (FSH). Sex hormone binding globulin (SHBG) and free testosterone were measured.

For a sub-group 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 BBS 10 mutations due to the small numbers in each group.

### **Statistical Analysis**

Data were analysed using the IBM SPSS Statistics (Version 19.0 for Windows, Armonk, NY: IBM Corp). Student's t-test was used for continuous variables which 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. A Data that were normally distributed are presented as mean  $\pm$  standard deviation (SD). Chi squared test was used for frequencies. Two-tailed p-values were considered significant at  $< 0.05$ .

## **RESULTS**

### **Demographics & Clinical characteristics**

One hundred and fifty-two subjects with BBS were included. Eighty-four (55.3%) were male. Mean age was  $33.2 \pm 11.8$  years (range 16-58 years) and BMI  $35.7 \pm 7.8 \text{ kg/m}^2$  (range 19.2-57). Figure 1 shows the BBS subjects categorised by BMI. Overall, 102 (76.3%) BBS subjects were obese (74.1% of females and 78.1% of males). One patient had a previous gastric band but otherwise no BBS patients took weight loss medication. One hundred and twenty-six (82.9%) patients were white Caucasian. 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).

Controls consisted of 103 individuals who were matched for age, sex and BMI with 48 (46.6%) males, a mean age of  $32.5 \pm 8.0$  years (range 16-52 years) and a mean BMI of  $34.2 \pm 9.1 \text{ kg/m}^2$  (range 20.1-54.8). Sixty-two (60.1%) controls were white Caucasian (Table 2).

Clinical and biochemical characteristics were compared between BBS subjects and matched controls (Table 3). Fasting glucose (BBS  $5.2 \pm 1.2$  vs control  $4.9 \pm 0.9$  mmol/l,  $p=0.04$ ) insulin ( $24.2 \pm 17.0$  vs  $14.2 \pm 14.8$  pmol/l,  $p<0.001$ ) and HOMA IR ( $5.55 \pm 4.14$  vs  $3.09 \pm 4.53$ ,  $p=0.003$ ) were significantly higher in the BBS group compared with the non-BBS group. These were unadjusted comparisons. Glycated haemoglobin was not different between the 2 groups, although the BBS group had 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, high density lipoprotein (HDL) cholesterol or low density lipoprotein (LDL) cholesterol between the two groups. However, serum triglycerides were significantly higher in the BBS group ( $2.0 \pm 1.2$  mmol/l) compared with controls ( $1.3 \pm 0.8$  mmol/l  $p<0.001$ ). Systolic blood pressure was higher in the BBS group (BBS  $135.2 \pm 18.3$  mmHg vs controls  $129.0 \pm 16.1$  mmHg ( $p=0.02$ ). Nine BBS patients were taking anti-hypertensive medication compared with none in the control group. Alanine transaminase (ALT) was raised above the reference range in 34 (26.8%) individuals with BBS, compared to five (8.9%) controls ( $p=0.01$ ). The presence of a metabolic syndrome, using IDF criteria, was significantly higher in the BBS group (54.3%) compared to controls (26%  $p<0.001$ ). The individual features of the metabolic syndrome are also shown in table 3. BBS subject had significantly increased frequency of all features of the metabolic syndrome except for HDL cholesterol (table 3).

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

Twenty-four (15.8%) BBS patients had T2DM and 1 patient had type 1 diabetes. Of those with T2DM, 13 were male and 11 were female with a mean age of  $40.4 \pm 9.6$  years. Management of T2DM was as follows: 6 patients were diet controlled, 8 were taking metformin and 10 used insulin to manage their diabetes. The mean HbA1c of those with T2DM was  $62 \pm 28$  mmol/mol ( $7.8 \pm 4.8\%$ ).

One hundred and two BBS patients (78.4%) had normal pituitary function. Of the remaining patients, 15 (11.5%) had an isolated low IGF-1, 5 had mild hyperprolactinaemia (prolactin  $<1000$  mIU/l) and 7 had isolated low prolactin. One patient had significant hyperprolactinemia (prolactin of 6391 IU/ml (102-496 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%), ten (6.5%) had hypothyroidism and one had hyperthyroidism. There were 24/125 (19.4%) BBS patients with subclinical hypothyroidism compared with 3/65 (4.6%) controls ( $p=0.01$ ).



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 (Figure 2). In the control cohort, no patients had Stage 5 or 4 CKD, 1 (1.2%) Stage 3 CKD, 31 (38.3%) Stage 2 CKD and 49 (60.5%) 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 BBS1 and BBS10 mutations due to small numbers in the sub-groups. Compared with BBS1 subjects, BBS10 mutation was associated with a trend towards increased diastolic blood pressure (BBS1  $81.4 \pm 9.4$  v BBS10  $89.1 \pm 8.4$  mmHg  $p=0.05$ ), increased HOMA-IR (BBS1  $5.8 \pm 4.3$  v BBS10  $12.4 \pm 4$   $p=0.02$ ) and increased triglycerides (BBS1  $1.71 \pm 0.8$  v BBS10  $2.7 \pm 1.5$  mmol/l  $p=0.03$ ) despite a younger age in our study group (BBS1  $35 \pm 11.2$  v  $27.7 \pm 11.3$  years  $p=0.02$ ). BBS10 subjects also had a higher prevalence of hypogonadism (BBS1 6 (10.5%) v BBS10 6 (42%)  $p=0.01$ ).

## DISCUSSION

To our knowledge, this is the most detailed endocrine and metabolic characterisation undertaken to date of a large adult BBS population. Our data also provide the first robust confirmation that the metabolic syndrome is more prevalent in BBS compared to matched controls 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 novel data showing increased subclinical hypothyroidism in BBS.

Data from a cohort study that followed 46 BBS subjects over a prolonged time 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 BBS subjects (20,21). However, these were small studies (three cases in one study) and they also had discrepant findings. One study showed that in 33 BBS patients with an average age of 26.3 years, hypertension and dyslipidaemia were common, with six per cent having overt diabetes.

Case-control data in a predominantly pediatric population have shown that at a mean age of 14 years, BBS subjects 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 BBS subjects, despite anti-hypertensive medication in a small number. Raised systolic blood pressure in the BBS group is a novel finding. This 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 had marked fasting hyperinsulinemia compared to matched controls. In the case control study by Feuillan et al. BBS subjects showed a trend towards higher fasting insulin but this did not reach statistical significance, with fasting glucose similar in both groups. These are important data taken together, suggesting that hyperinsulinemia starts at an early age in BBS and by a subject's third decade, hyperinsulinemia is more pronounced and fasting glucose is raised, although still within the non-diabetic 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 BBS subjects until, as suggested by the cohort study above, 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., 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. This subsequently increases the prevalence of T2DM and cardiovascular mortality. BBS subjects are known to have hyperleptinemia and are likely to have leptin resistance (23). This may be mediated by impaired leptin receptor trafficking and signalling, resulting from altered or deficient BBS proteins (24). Leptin has an overall effect of decreasing bodyweight, 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 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 beta cell ciliary dysfunction is associated with disruption in insulin secretion/signalling and that the BBS protein/insulin receptor interaction has consequences on whole body insulin action and glucose metabolism (26,27). Intriguingly, not all BBS mutations may cause insulin resistance, with data suggesting BBS12 mutations associated with improved insulin sensitivity and glucose utilization (28).

The prevalence of overt diabetes in our study with mean age of 33 years was around 15%, compared to 6% in a younger population (mean age 26.3 years) (21) and 48% in BBS subjects 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 30's 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). It reported evidence of hyperprolactinaemia, 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 one enlarged pituitary gland. A further two case reports have described full dynamic endocrinological evaluations in single adults BBS patients, with both showing secondary hypogonadism but no other specific abnormalities (29,30). Our data do not suggest widespread pituitary hormone abnormalities in adult BBS subjects. Significant hyperprolactinaemia 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 paediatric study.

Hypogonadism however was common, and this is in keeping with previous reports (7). The aetiology was secondary hypogonadism in the majority of cases, most of which had been relatively asymptomatic and unrecognised before attending the specialised 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 replace asymptomatic BBS men with testosterone. Future studies will be useful in determining whether testosterone replacement in BBS men with secondary hypogonadism will improve metabolic parameters including body composition and quality of life.

Diabetes insipidus is considered an established feature of BBS. Our results suggest that significant DI in adults is a rare occurrence and when present, it is likely to reflect a lack of renal responsiveness to DDAVP 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 pre-cursor to overt hypothyroidism in most cases, is primary in aetiology and usually related to autoimmune thyroid disease. Further work will need to be done 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 symptomatology, ascertain the presence or otherwise of thyroid autoimmunity and then consider monitoring or a trial of 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 chronic kidney disease (CKD) was similar to previous cohorts, although it is of interest that stage 1 and 2 CKD were not different from obese controls. Nephrogenic diabetes insipidus is not a widely recognised feature of BBS, and there were only 2 cases in our cohort and both 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.

With regards to the gene mutations in Bardet Biedl syndrome, 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 Caucasians in our study population. Previous studies have confirmed that within a multi-ethnic cohort, a number of novel gene mutations are observed and the spectrum of clinical characteristics can overlap with those of other ciliopathies, namely Alstrom and McKusick-Kauffman syndromes (33).

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

We performed a limited unadjusted sub-study 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. 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. suggesting lower HOMA-IR, serum leptin, BMI and abdominal fat in *BBS1* compared with *BBS10* mutations (16). We acknowledge that differences in clinical manifestation/ severity may occur with different BBS mutations and 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 (eg 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 with regards to 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 BBS participants were also taken as part of routine clinical care, and hence were not measured on multiple occasions. Body mass index alone as a measure of obesity has limitations and future work to compare other parameters such as serum leptin, would be informative.

To conclude, our study reports increased prevalence of insulin resistance and the metabolic syndrome in adult BBS subjects compared to matched controls. Overt diabetes had not yet developed in many subjects and this may represent an opportunity to intervene with lifestyle measures. Subclinical hypothyroidism was a novel finding that will need further exploration.

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Disclosure statement:

The authors have nothing to disclose

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Figure 1 Bardet-Biedl (BBS) subjects stratified according to gender and body mass index (BMI)

Figure 2 Bardet-Biedl syndrome (BBS) patients and controls stratified according to chronic kidney disease stage

Table 1 Gene mutations in 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*	2 (<1%)
MKKS	1 (<1%)

BBS2 BBS5	1 (<1%)
Not known**	30 (19.7%)

\*MKKS: McKusick-Kaufman Syndrome

\*\* None of the current known gene mutations found

Table 2 Demographic details of BBS and control subjects

	BBS Mean $\pm$ SD	Control Mean $\pm$ SD	p value
Age (years)	33.2 $\pm$ 11.8	32.5 $\pm$ 7.8	0.75
BMI (kg/m <sup>2</sup> )	35.7 $\pm$ 8.0	34.2 $\pm$ 9.1	0.13
Sex (% male)	55.3% (84)	46.6% (48)	0.17

Table 3 Clinical Features of Bardet-Biedl (BBS) subjects compared to age, sex and body mass index (BMI) matched controls.

Variable	BBS subjects (n) Mean $\pm$ SD	Control subjects (n) Mean $\pm$ SD	p value
Fasting glucose (mmol/L)	5.2 $\pm$ 1.2 (109)	4.9 $\pm$ 0.9 (98)	<b>0.04</b>
Fasting insulin (pmol/L)	24.2 $\pm$ 17.0 (46)	14.2 $\pm$ 14.8 (78)	<b>&lt;0.001</b>
HOMA-IR	5.55 $\pm$ 4.14 (46)	3.09 $\pm$ 4.53 (78)	<b>0.003</b>
HbA1c (mmol/mol (%))	42 $\pm$ 15 (6.0 $\pm$ 1.4) (101)	40 $\pm$ 10 (5.8 $\pm$ 0.9) (60)	0.37
Cholesterol (mmol/L)	4.9 $\pm$ 1.0 (129)	4.8 $\pm$ 0.9 (88)	0.78
HDL Cholesterol (mmol/L)	1.2 $\pm$ 0.3 (126)	1.2 $\pm$ 0.4 (87)	0.47
LDL Cholesterol (mmol/L)	2.8 $\pm$ 0.9 (84)	2.9 $\pm$ 0.9 (87)	0.21
Triglycerides (mmol/L)	2.0 $\pm$ 1.2 (130)	1.3 $\pm$ 0.8 (88)	<b>&lt;0.001</b>
Systolic BP (mmHg)	135.2 $\pm$ 18.3 (100)	129.0 $\pm$ 16.1 (67)	<b>0.02</b>
Diastolic BP (mmHg)	81.4 $\pm$ 11.4 (100)	80.3 $\pm$ 11.6 (70)	0.55
Prevalence of metabolic syndrome	54.3% (63/116)	26% (26/100)	<b>&lt;0.001</b>
Prevalence of subclinical hypothyroidism	19.4% (24/124)	4.6% (3/65)	<b>0.01</b>
Prevalence of hypogonadism	19.5% (26/133) Primary 15.4% (4/26) Secondary 84.6% (22/26)	not available	Not available
Raised alanine transaminase (ALT)	26.8% (34/127)	8.9% (5/56)	<b>0.01</b>
Metabolic Syndrome parameters			
Central obesity	77% (101/131)	60% (62/103)	<b>0.006</b>
Raised triglycerides (>1.7mmol/L)	55% (71/130)	21% (18/88)	<b>&lt;0.0001</b>
Reduced HDL cholesterol (<1.03mmol/L in males, <1.29mmol/L in females)	40% (51/126)	45% (39/87)	0.53
Hypertension (systolic >135mmHg or diastolic >85mmHg)	67% (67/100)	43% (30/70)	<b>0.002</b>
Raised fasting plasma glucose (>5.6mmol/L)	26% (28/109)	8% (8/98)	<b>0.0008</b>

Table 4 Comparison of common genotypes and their endocrine and metabolic characteristics

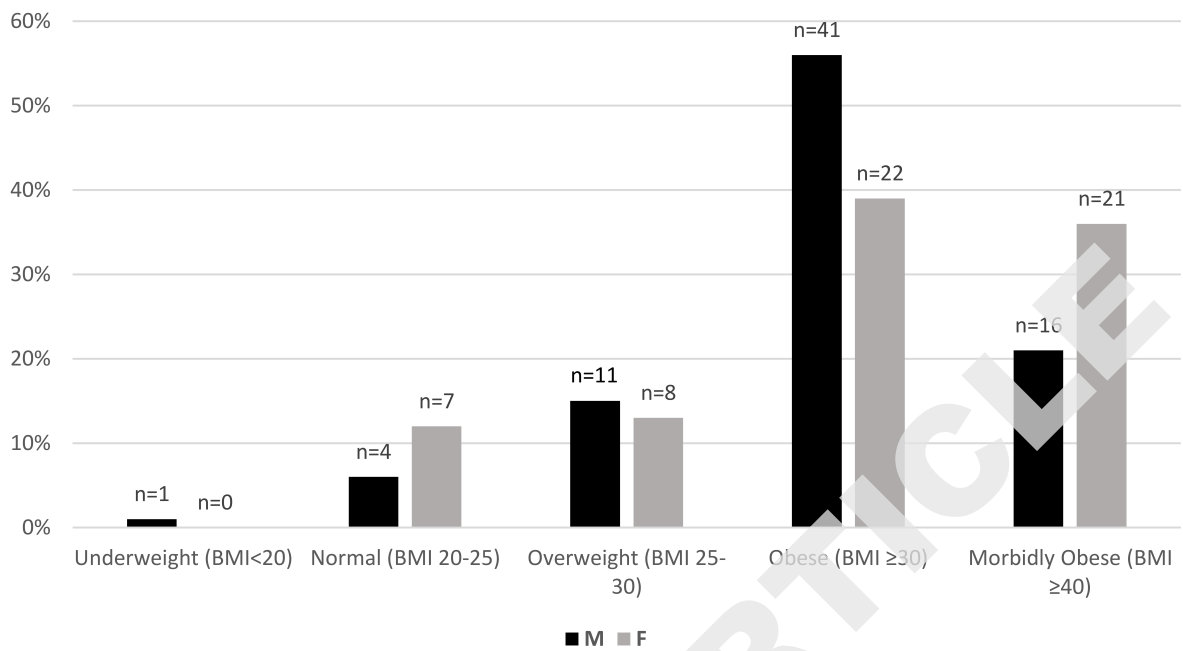
	BBS1 n=57	BBS2 n=10	BBS10 n=14	BBS12 n=4	p value*
Male n (%)	31 (54)	6 (60)	11 (79)	3 (75)	0.1
Age (years)	35 $\pm$ 11.2	36.6 $\pm$ 12.3	27.2 $\pm$ 11.3	30 $\pm$ 12.3	<b>0.02</b>
BMI (kg/m <sup>2</sup> )	34.2 $\pm$ 7.1	41.5 $\pm$ 9.8	36.9 $\pm$ 8.7	35.8 $\pm$ 6.8	0.31
Systolic BP (mmHg)	135.1 $\pm$ 13.3	139.3 $\pm$ 18.7	145.4 $\pm$ 24.9	137.7 $\pm$ 17.5	0.27
Diastolic BP (mmHg)	81.4 $\pm$ 9.4	87.2 $\pm$ 9.6	89.1 $\pm$ 8.4	78.7 $\pm$ 7.6	0.05
HOMA-IR	5.8 $\pm$ 4.3	7.1 $\pm$ 1	12.4 $\pm$ 4.0	4.4 $\pm$ 1	<b>0.02</b>
Triglycerides (mmol/l)	1.7 $\pm$ 0.8	2.6 $\pm$ 1.2	2.7 $\pm$ 1.5	2.7 $\pm$ 1.8	<b>0.03</b>
Metabolic syndrome present n	27 (47.3)	7 (70)	11 (78)	2 (50)	<b>0.04</b>

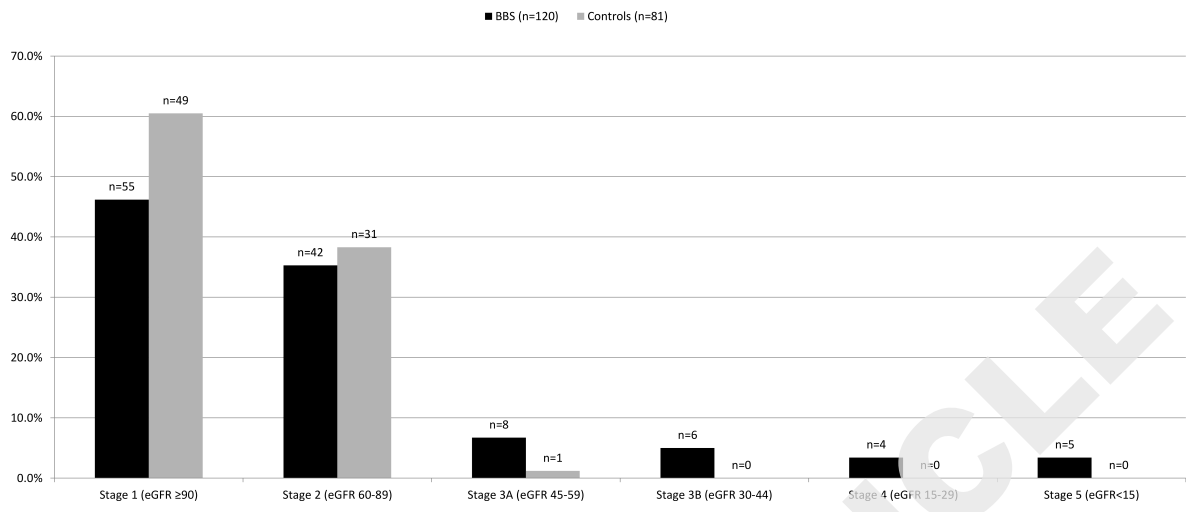


(%)					
Hypothyroidism or Subclinical hypothyroidism n (%)	9 (15.7)	3 (30%)	4 (28%)	2 (50%)	0.3
Hypogonadism n (%)	6 (10.5)	2 (20)	6 (42)	0	<b>0.01</b>

\*Comparison between BBS1 and BBS10 mutations only

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