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Metabolic syndrome in children with Prader–Willi syndrome: The effect of obesity

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Abstract *Background and aims:* Prader–Willi syndrome (PWS), the most frequent syndromic obesity, is associated with elevated morbidity and mortality in pediatric and adult ages. In PWS, the presence of metabolic syndrome (MS) has not yet been established. The aim of the study was to estimate the frequency of MS and its components in pediatric subjects according to obesity status.

Methods and results: A cross-sectional study was performed in 109 PWS children aged 2–18 years (50 obese and 59 non-obese) and in 96 simple obese controls matched for age, gender, and also for BMI with obese PWS. Obesity was defined when SDS-BMI was >2.

Non-obese PWS showed significantly lower frequency of hypertension (12%) than obese PWS (32%) and obese controls (35%)($p = 0.003$). The same was observed for low HDL-cholesterol (3% vs 18% and 24%, $p = 0.001$) and high triglycerides (7% vs 23% and 16%, $p = 0.026$). Frequency of

Abbreviations: PWS, Prader–Willi syndrome; UPD, uniparental disomy; DM2, type 2 diabetes mellitus; CVD, cardiovascular disease; MS, metabolic syndrome; GH, growth hormone; BMI, body mass index; CDC, Centre for Disease Control and Prevention; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-index, homeostasis model assessment index; IGT, impaired glucose tolerance; IQR, interquartile range; SDS, standard deviation score.

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altered glucose metabolism was not different among groups (2% vs 10% and 5%), but type 2 diabetes (four cases) was present only in obese PWS. Non-obese PWS showed lower insulin and HOMA-index respect to obese PWS and obese controls ($p \leq 0.017$). Overall MS frequency in PWS was 7.3%. None of the non-obese PWS showed MS compared with 16% of obese PWS and controls ($p < 0.001$). When obesity was excluded from the analysis, a significantly lower frequency for clustering of $\geq$2 factors was still found in non-obese PWS ($p = 0.035$).
Conclusion: Non-obese PWS showed low frequency of MS and its components, while that observed in obese PWS was very close to those of obese controls, suggesting the crucial role of obesity status. Prevention of obesity onset remains the most important goal of PWS treatment. Early identification of MS could be helpful to improve morbidity and mortality in such patients.

Introduction

Prader—Willi syndrome (PWS) is a complex multisystem disorder due to the absent expression of the paternally active genes in the PWS critical region on chromosome 15 [1]. PWS is the most frequent cause of syndromic obesity and occurs in 1 in 25,000 live births [2]. Its major clinical features include muscular hypotonia, childhood-onset obesity, short stature, small hands and feet, sleep disorders, developmental delay, and hypogonadism. The syndrome is characterized by hyperphagia and weight gain between the ages of 1 and 6 years, leading most PWS subjects to develop morbid obesity [3]. It was shown that early PWS diagnosis can prevent obesity [4]. In this respect, PWS harbor a higher fat mass than simple obesity, under the same degree of weight excess, both in children and in adults [5,6]. Patients with PWS die prematurely from complications conventionally related to obesity, including type 2 diabetes mellitus (DM2), arterial hypertension, sleep apnea, respiratory insufficiency and cardiovascular disease (CVD) [7].

The etiology of the increased mortality seen in PWS [7] is not completely known. In this context, the metabolic syndrome (MS) is a strong risk factor for atherosclerotic CVD and DM2 [8], and MS might be one of the mechanisms responsible for excessive mortality in PWS. The metabolic profile of PWS patients, however, is usually more favorable than that in simple obese subjects [9]. Although there is marked fat accumulation, the identification of an atypically reduced visceral fat depot in obese PWS females has been advocated to explain a healthier lipid profile and higher insulin sensitivity, compared with matched obese population [10]. Nevertheless, data on fatness patterning in PWS are still conflicting [11,12]. In addition, it has previously been demonstrated that several cardiovascular risk factors are already present in pre-pubertal children with PWS [13].

No data are currently available on the frequency of MS in PWS. As there is evidence that MS development has its origin in children and adolescents, driven by the growing obesity epidemic in the young population [14], we sought to estimate the presence of MS in a large cohort of children and adolescents with genetically confirmed PWS. We also looked for metabolic differences between obese and non-obese PWS subjects, and between obese PWS and simple obese peers.

Methods

Study population

One hundred and nine PWS patients 2—18 years old, 58 males and 51 females, were studied (Table 1). Subjects were divided according to the presence of obesity (see below) in obese and non-obese PWS. All patients showed the typical PWS clinical phenotype [15]. Concerning genetic abnormalities distribution, cytogenetic analysis was performed in all subjects and PWS were classified into three groups: 58 of them had interstitial deletion of the proximal long arm of chromosome 15 (del15q11-q13) (DELETED), 31 subjects presented uniparental maternal disomy for chromosome 15 (UPD15), while a positive methylation test was demonstrated in the remaining 20 PWS but the underlying genetic defect was not identified. At the time of the study, four subjects had DM2 (two males and two females, all of them obese and older than 10 years of age), two of them were treated with insulin and metformin, and the other two with metformin alone. At the time of the study, four of the 23 hypertensive patients were treated with loop diuretics ($n = 2$), angiotensin-converting enzyme inhibitor ($n = 1$), and angiotensin receptor blocker ($n = 1$). Sixty-nine subjects were treated with growth hormone (GH) from at least 6 months at the moment of the study or had been treated for at least 6 months in the last 3 years. Mean duration of GH treatment was 4.4 years (range 0.5—14.0 years) and mean age at start was 5.6 years (range 0.6—16.7 years).

As the obese control group, a sample of 96 children and adolescents (50 males) was considered, chosen among those followed at the Pediatric Department of San Raffaele Institute, Milan, and matched to obese PWS for gender, age (within 1 year) and body mass index (BMI) (within 1 kg/m^2) (Table 1).

The study protocol was approved by the ad hoc Ethical Committee of the Istituto Auxologico Italiano Foundation. Written informed consent from parents and written assent from children and adolescents (when appropriate) were obtained.

Anthropometric and blood pressure measurements

Physical examination included determination of height and weight. Standing height was determined by a Harpenden Stadiometer (Holtain Limited, Crymych, Dyfed, UK). Body

Table 1 Measurements of PWS and obese control children.

	Obese PWS ($n = 50$)[a]	Non-obese PWS ($n = 59$)	Obese controls ($n = 96$)[a]
Gender (M/F)[b]	27/23	31/28	50/46
Age (years)	11.0 (8.1)	10.5 (6.0)	10.0 (5.8)
Weight (kg)	60.8 (54.0)	36.2 (29.5)*	58.5 (40.0)
SDS-weight	2.31 (1.24)**	0.43 (1.62)**	2.65 (0.72)**
Height (m)	1.39 (0.29)	1.32 (0.29)*	1.44 (0.30)
SDS-height	−0.87 (1.79)	−0.89 (1.50)	0.82 (1.54)*
BMI (kg/m^2)	32.5 (13.3)	19.8 (6.6)*	29.6 (7.3)
SDS-BMI	2.52 (0.50)	1.14 (1.40)*	2.46 (0.46)
Glucose (mg/dL)	80 (13)	77 (14)	84 (9)*
Insulin (mU/L)	11 (14)	7 (6)*	11 (10)
HOMA-index	2.8 (3.3)	1.2 (1.4)*	2.3 (2.2)
Triglycerides (mg/dL)	90 (50)	66 (38)*	84 (50)
HDL-cholesterol (mg/dL)	48 (14)	59 (19)*	46 (14)
Systolic BP (mm Hg)	112 (20)	105 (22)*	120 (19)
SDS-systolic BP	1.03 (1.79)	0.20 (1.63)*	1.20 (1.48)
Diastolic BP (mm Hg)	70 (15)	60 (14)*	70 (17)
SDS-diastolic BP	0.93 (1.02)	0.31 (1.18)*	0.62 (1.24)
Treatment with GH (yes/no)	40/10	29/30	

Data are shown as median (IQR). SDS, standard deviation score; PWS, Prader–Willi syndrome; IQR, inter-quartile range; BMI, body mass index; HOMA-index, homeostasis model assessment index; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure.

[a] Obesity was defined when SDS-BMI was >2.

[b] $p = 0.98$ (Fisher's exact test).

* $p < 0.017$ vs all groups (Wilcoxon–Mann–Whitney test with Bonferroni's correction for three groups).

** $p < 0.017$ among each group (Wilcoxon–Mann–Whitney test with Bonferroni's correction for three groups).

weight was measured to the nearest 0.1 kg, by using standard equipment. BMI was defined as weight in kilograms divided by the square of height in meters. The published CDC standards for age- and gender-specific weight, height and BMI percentiles were used for calculating standard deviation score (SDS) as well as for classifying PWS subjects as non-obese (BMI < 2.0 SDS) or obese (BMI > 2.0 SDS) [16]. Diastolic and systolic blood pressure (BP) were measured to the nearest 2 mmHg in the supine position after 5 min rest, using a standard mercury sphygmomanometer with appropriate sized cuff. The average of three measurements on different days was used.

Laboratory analyses

The subjects were evaluated after a 12-h overnight fast. Baseline blood samples were drawn by venipuncture for determination of glucose, insulin, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides. Enzymatic methods (Roche Molecular Biochemicals, Mannheim, Germany) were used for measurement of blood glucose, total cholesterol, HDL-cholesterol and triglycerides. Serum insulin levels were measured by chemiluminescence (Immulite 2000). Insulin resistance was measured by homeostasis model assessment (HOMA-index), calculated as insulin (μU/mL) × [blood glucose (mmoL/L)/22.5] [17]. All PWS subjects and obese controls performed an oral glucose tolerance test.

Metabolic syndrome

According to Weiss et al. [14], we defined subjects with MS as having ≥3 of the following parameters: obesity, high systolic BP or diastolic BP, high triglycerides, low HDL-C and impaired glucose tolerance (IGT) or DM2. Obesity was defined when SDS-BMI was >2. Hypertension was defined as values of systolic or diastolic BP ≥95th percentile for age, sex and height [18] or when any antihypertensive drugs were being used. Hypertriglyceridemia was defined as a value of triglycerides ≥95th percentile for gender and age and low HDL-C as a value of HDL-C ≤5th percentile for gender and age. These percentiles were calculated for subjects aged 2–11 years according to the National Cholesterol Education Program [19], and for subjects of 12 years and older from Jolliffe and Ianssen [20]. Impaired glucose tolerance (IGT) and type 2 diabetes mellitus (DM2) were defined on the basis of the following glucose (mg/dl) cut-off points: IGT if fasting glucose >100 and <126 or if >140 and <200 at 120 min after oral glucose tolerance test; DM2 if fasting glucose >126 or if >200 at 120 min after oral glucose tolerance test [21].

Statistical analysis

Values of continuous variables are given as median and inter-quartile range (IQR) because of skewed distributions. IQR are calculated as the difference between the 75th and 25th percentiles. Values of categorical variables are given as the number or percentage of subjects with the characteristic of interest. Between-group comparisons (obese PWS vs non-obese PWS and vs obese controls) of continuous variables were performed with the Wilcoxon–Mann–Whitney test with Bonferroni's correction for three groups. Between-group comparisons of categorical variables were performed with the Fisher's exact test. Exact logistic regression was used to test whether the odds of the

metabolic syndrome (1 = yes, 0 = no) and its components except obesity (hypertension, hypertriglyceridemia, low HDL-C, IGT or DM2, all coded as 1 = yes, 0 = no) differ in obese PWS and non-obese PWS vs obese control subjects [22]. Exact logistic regression was also used to test whether HOMA-index, evaluated as continuous predictor, was a risk factor for the metabolic syndrome in addition to being obese PWS vs non-obese PWS. Linearity of the HOMA-index logit was ascertained using lowess plots and multivariable fractional polynomials [23].

Exact logistic regression was also used to test whether the odds of the metabolic syndrome (1 = yes, 0 = no) and its components differed in UDP15 vs DELETED PWS subjects. We also used exact logistic regression to evaluated the effect of previous or current GH treatment on the odds of the MS and its components in obese vs non-obese PWS.

Results

The measurements of the study subjects are given in Table 1. Obese PWS were compared with non-obese PWS (matched for age and gender) and with obese controls (matched for gender, age and BMI). Non-obese PWS showed lower weight, SDS-weight, height, BMI and SDS-BMI than obese PWS and controls. Weight, height and BMI were similar between obese PWS and obese controls, while SDS-weight was lower in obese PWS.

GH treated PWS showed a lower SDS-BMI (1.7(1.4), median (IQR)) at the moment of the study as compared with non-treated PWS (2.1(0.9)) ($p < 0.0001$). In treated PWS, SDS-BMI significantly increased with respect to the moment of GH start (0.9(1.7)) ($p < 0.0001$).

Glucose levels were lower in both PWS groups as compared to obese controls ($p \leq 0.017$). Non-obese PWS showed lower insulin, HOMA-index, triglycerides, systolic BP, SDS-systolic BP, diastolic BP and SDS-diastolic BP and higher HDL-C with respect to obese PWS and obese controls ($p \leq 0.017$). No differences were present between obese PWS and obese controls for insulin, HOMA-index, triglycerides, systolic and diastolic BP and HDL-C.

The frequency of the metabolic syndrome and its components is given in Table 2 and Fig. 1. Non-obese PWS showed lower frequency of hypertension, low HDL-C, high triglycerides and MS as compared with both obese PWS and obese controls. When obesity was excluded from the score of the metabolic syndrome, a significantly lower frequency of clustering for two or more factors was still found in non-obese PWS. No difference was detectable between obese PWS and obese controls for the frequency of MS and all its components.

The odds of the metabolic syndrome and its components for non-obese PWS and obese PWS vs obese controls are given in Table 3. Non-obese PWS had lower odds of hypertension, high triglycerides, low HDL-C and metabolic syndrome as compared to obese PWS and controls.

At multivariable analysis, HOMA-index in PWS was associated, independently from obesity, with high triglycerides (multivariable OR = 1.34, exact 95%CI 1.05—1.80, exact-p = 0.016) and low HDL-C (multivariable OR = 1.31, exact 95%CI 1.01—1.78, exact-p = 0.038), while it was not associated with hypertension (multivariable OR = 1.19, exact 95%CI 0.96—1.50, exact-p = 0.12), altered glucose metabolism (multivariable OR = 1.11, exact 95%CI 0.81—1.46, exact-p = 0.46) and the MS diagnosis (multivariable OR = 1.27, exact 95%CI 0.98—1.75, exact-p = 0.08).

Table 2 Frequency of the metabolic syndrome and its components in obese PWS, non-obese PWS and obese control children.

	Obese PWS (n = 50)	Non-obese PWS (n = 59)	Obese controls (n = 96)	p-value[a]
Obesity[b]	50	0	96	<0.001
Low HDL-C	9	2	23	0.001
Hypertriglyceridemia	13	4	15	0.026
Hypertension	16	7	34	0.003
IGT or DM2	5	1	5	0.167
MS score = 0	0	47	0	<0.001
MS score = 1	21	10	37	0.005
MS score = 2	21	2	44	<0.001
MS score = 3	3	0	12	0.007
MS score = 4	4	0	3	0.055
MS score = 5	1	0	0	0.244
MS score ≥ 3	**8**	**0**	**15**	**0.001**
MS score = 0 w/o obesity	21	47	37	<0.001
MS score = 1 w/o obesity	21	10	44	<0.001
MS score = 2 w/o obesity	3	2	12	0.123
MS score = 3 w/o obesity	4	0	3	0.055
MS score = 4 w/o obesity	1	0	0	0.244
MS score ≥2 w/o obesity	**8**	**2**	**15**	**0.035**

PWS, Prader—Willi syndrome; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; DM2, type 2 diabetes; MS, metabolic syndrome; w/o, without. In bold: frequency and p value in groups when MS score was ≥3 including obesity and when MS score was ≥2 excluding obesity.

[a] Fisher's exact test (non-obese PWS vs all).

[b] Obesity was defined when SDS-BMI was >2.

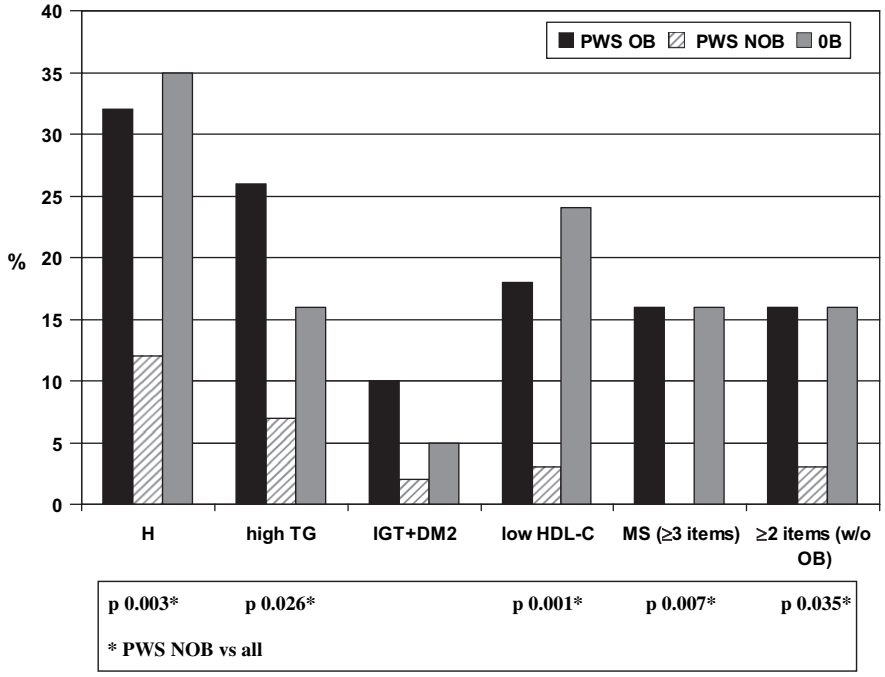

Figure 1 Percentages of subjects with hypertension, hypertriglyceridemia, impaired glucose tolerance (IGT) or diabetes (DM2), low HDL-C, and metabolic syndrome (≥3 parameters including obesity) or ≥2 items (excluding obesity) in the study population. Obesity was defined when SDS-BMI was >2. PWS OB, obese PWS; PWS NOB, non-obese PWS; OB, obese controls; H, hypertension; TG, triglycerides; IGT, impaired glucose tolerance; DM2, type 2 diabetes; HDL-C, high-density lipoprotein cholesterol; MS, metabolic syndrome; ≥2 items, ≥2 parameters excluding obesity; w/o OB, without obesity.

The odds of the MS and its components for UDP15 vs DELETED PWS are given in Table 4. None of these parameters was different between groups.

According to GH treatment, 40 out of 69 treated patients were obese while 29 were non-obese. An effect of GH treatment on the frequency of MS components, independent from obesity status, was absent, except for a lower risk of hypertriglyceridemia in treated subjects ($p = 0.002$) (Table 5).

Discussion

A mortality rate of 3% a year across all ages and about 7% a year in those over 30 years of age has been reported in patients with PWS [2]. Complications associated with obesity are recognized as the main risk factors for death during the life-span of patients with PWS [24], while acute respiratory illness and gastroenteritis seem to be the major causes of sudden death in children [25]. PWS adults are prone to premature death from cardiovascular and pulmonary problems as well as from disorders associated with DM2 [26]. Early development of myocardial infarction, congestive heart failure and stroke have been reported in PWS subjects [27—29]. In addition, impaired microvascular function and subnormal exercise capacity have been demonstrated in young adults without ischaemic symptoms [30].

Factors that determine the evolution to CVD and metabolic complications in these patients are not fully clarified. In non-PWS populations, MS has been specifically associated with coronary heart disease and DM2 [31]. There is

Table 3 Odds of the metabolic syndrome and its components in non-obese and obese PWS children vs obese controls. Obesity was defined when SDS-BMI was >2.

	Non-obese PWS			Obese PWS		
	OR[a]	Exact-95%CI	Exact-*p*	OR[a]	Exact-95%CI	Exact-*p*
Hypertension	0.29	0.09—0.84	0.019	1.16	0.53—2.60	0.824
Hypertriglyceridemia	0.21	0.05—0.75	0.012	0.53	0.21—1.34	0.199
Low HDL-C	0.16	0.02—0.84	0.026	1.43	0.57—3.86	0.544
IGT or DM2	0.15	0.03—1.48	0.139	0.50	0.11—2.30	0.450
MS	0.07	0.00—0.45	0.003	0.97	0.35—2.87	1.000

PWS, Prader—Willi syndrome; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; DM2, type 2 diabetes; MS, metabolic syndrome; CI, confidence interval.
[a] Odds = 1 for obese controls.

Table 4 Odds of the metabolic syndrome and its components in UDP15 ($n = 31$) vs DELETED ($n = 58$) PWS children.[a]

	UDP15		
	OR	Exact-95%CI	Exact-*p*
Obesity[b]	0.83	0.31—2.18	0.848
Hypertension	0.31	0.05—1.24	0.117
Hypertriglyceridemia	0.18	0.01—1.45	0.150
Low HDL-C	1.28	0.24—5.94	0.967
IGT or DM2	1.26	0.10—11.6	1.000
MS	0.26	0.00—2.00	0.221

PWS, Prader—Willi syndrome; UPD, uniparental disomy; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; DM2, type 2 diabetes; MS, metabolic syndrome.
[a] Odds = 1 for deleted PWS.
[b] Obesity was defined when SDS-BMI was >2.

evidence that the development of the MS has its origin in childhood [32]. Previous observations reported that MS has a high prevalence both in children and adolescents [33], even among subjects as young as 9 years [34]. As far as PWS is concerned, it was suggested that in older children and adolescents obesity can lead to MS [35]. Thus, it is conceivable that MS may be involved in the pathogenesis of morbidity and early mortality in PWS. Nevertheless, it has to be questioned whether the metabolic profile of PWS subjects is comparable to what is observed in patients with essential obesity. In this respect, insulin resistance is thought to be the cardinal mechanism underlying the MS [36]. Individuals with PWS, however, seem to have a lower risk for insulin resistance than simple obese subjects, both in children and in adults [9,37]. Moreover, the bulk of evidence showed that insulin levels are relatively low in the majority of PWS patients [38]. In this light, the question arises as to whether there is the same pathogenetic relationship between CVD and the development of MS in PWS as in non-syndromic obesity.

Table 5 Effect of GH treatment on the prevalence of MS components in obese PWS ($n = 50$) vs non-obese PWS children ($n = 59$). Obesity was defined when SDS-BMI was >2.

	OR	Exact-95%CI	Exact-*p*
Hypertension			
Obese PWS	3.25	1.10—10.50	0.030
Treatment with GH	0.38	0.13—1.13	0.087
Hypertriglyceridemia			
Obese PWS	4.59	1.20—22.10	0.022
Treatment with GH	0.16	0.04—0.56	0.002
Low HDL-C			
Obese PWS	5.84	1.13—58.32	0.032
Treatment with GH	0.64	0.14—2.99	0.716
IGT or DM2			
Obese PWS	6.35	0.67—310.80	0.139
Treatment with GH	1.16	0.15—13.8	1.000

PWS, Prader—Willi syndrome; GH, growth hormone; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; DM2, type 2 diabetes; CI, confidence interval.

Our study is the first to document the frequency of MS in a representative sample of children and adolescents with PWS. Altogether, the number of PWS patients who were diagnosed with the MS was 7.3%. However, our PWS population included both obese and non-obese subjects. Because the presence of MS increases with obesity [14,39], we compared the metabolic profile of obese PWS with those observed in non-obese PWS and obese controls. We found that non-obese PWS showed a more favorable metabolic status (lower insulin, HOMA-index, triglycerides, systolic and diastolic BP, and higher HDL-C), a lower frequency of hypertension, low HDL-C and high triglycerides. Consequently, we did not find any subject with MS among non-obese PWS, which was different from obese PWS and obese controls. Even the frequency of glucose homeostasis alterations seems to be reduced in non-obese PWS and none of them showed DM2, but the small number of affected patients limits the statistical analysis. On the contrary, obese PWS presented a metabolic pattern very similar to that of obese controls. The only exception is represented by reduced fasting glucose levels, which could be a characteristic of the whole PWS population. Moreover, when the presence of obesity was excluded from the analysis and the frequency of ≥ 2 altered parameters was considered, a significantly lower frequency in the clustering of metabolic risk factors was still present in the non-obese PWS group as compared to both obese groups, thus confirming the main role played by obesity status in this field.

Therefore, the key point seems to be the definition used for MS estimation. We adopted the MS definition proposed by Weiss et al. [14] which utilizes BMI (i.e., obesity) instead of central obesity markers (i.e., waist circumference). Other MS definitions based on waist circumference were not applicable in our PWS population due to the lack of such data in the majority of our patients. Moreover, it has to be discussed whether waist circumference really represents abdominal adiposity in subjects with unusual body proportions like those of PWS [5]. However, on the basis of the adopted MS definition, obese PWS showed the same MS frequency as obese controls (16%), and similar frequencies to those observed in previous reports in the pediatric age [39,40].

An interesting finding is the lack of importance of insulin resistance in the prediction of MS when the obese condition in PWS is considered, and we can demonstrate its effect only on lipid abnormalities. This could suggest a different role of insulin in the pathogenesis of metabolic alterations in PWS as compared to simple obesity. However, a clear relationship between obesity status and insulin levels was still detectable in PWS, as obese subjects showed higher insulin levels and HOMA-index than non-obese subjects, and therefore this point deserves further study.

We did not find any difference in the metabolic profile according to the genetic pattern, suggesting that deleted subjects and those with UPD15 show a similar clinical outcome.

Finally, a lower risk for high triglycerides was found in GH treated PWS subjects, confirming the metabolic role of GH treatment in such patients. GH treatment seems also to have some benefit for obesity development prevention.

In conclusion, to the best of our knowledge this is the first study assessing MS frequency in PWS children and adolescents, with and without obesity. Overall, our findings suggest the main role that obesity status plays on the individual metabolic risk clustering in the PWS population, and thus confirm that improvement in weight control remains the most important goal of any PWS treatment program. In addition, screening for associated MS should be a routine element of care and treatment for all children with PWS, especially in obese subjects. Early identification and treatment of MS could be helpful to improve morbidity and mortality in these patients. Additional research is needed to better understand the role of MS in the natural history of Prader—Willi syndrome, particularly in adult patients.

Conflict of interest

None.

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