Current Diabetes Reports (2020) 20: 7
https://doi.org/10.1007/s11892-020-1284-5

OTHER FORMS OF DIABETES AND ITS COMPLICATIONS (J J NOLAN AND H THABIT, SECTION EDITORS)

Update on Diabetes Mellitus and Glucose Metabolism Alterations in Prader-Willi Syndrome

Antonino Crinò[1] · Graziano Grugni[2]

Published online: 6 February 2020

Abstract

Purpose of Review This review summarizes our current knowledge on type 2 diabetes mellitus (T2DM) and glucose metabolism alterations in Prader-Willi syndrome (PWS), the most common syndromic cause of obesity, and serves as a guide for future research and current best practice.

Recent Findings Diabetes occurs in 10–25% of PWS patients, usually in adulthood. Severe obesity is a significant risk factor for developing of T2DM in PWS. Paradoxically, despite severe obesity, a relative hypoinsulinemia, without the expected insulin resistance, is frequently observed in PWS. The majority of PWS subjects with T2DM are asymptomatic and diabetes-related complications are infrequent. Long-term growth hormone therapy does not adversely influence glucose homeostasis in all ages, if weight gain does not occur.

Summary Early intervention to prevent obesity and the regular monitoring of glucose levels are recommended in PWS subjects. However, further studies are required to better understand the physiopathological mechanisms of T2DM in these patients.

Keywords Prader-Willi syndrome · Diabetes mellitus · Impaired glucose tolerance · Hyperglycemia

Introduction

Prader-Willi syndrome (PWS) is a rare and complex neurodevelopmental disorder, equally affecting both sexes, due to genetic abnormalities that result in the absence of expression of one or more of the paternally inherited genes at the locus q11-q13 of chromosome 15 [1••]. Approximately 60–65% of affected individuals have a deletion of the paternal chromosome 15q11-q13, while most of the remaining patients display a maternal uniparental disomy (UPD15) for chromosome 15 (about 25–30%). Only a small percentage of subjects (less than 5%) may have abnormalities of the imprinting center or a chromosomal translocation or rearrangements of the 15q11-q13 region [1••].

PWS is the most frequent cause of genetic obesity, occurring in about 1:10,000–1:30,000 live births and is usually due to sporadic cases [2, 3].

The clinical picture of PWS is typically characterized by neonatal hypotonia and poor sucking, dysmorphic features (characteristic facial appearance, small hands and feet and narrow hands with straight ulnar border), kyphoscoliosis, hypogonadism, short stature for genetic background, sleep-disordered breathing, early childhood-onset of hyperphagia with food-seeking behavior and progressive development of severe obesity, with its comorbidities, unless eating is not promptly restricted [4]. Cognitive impairments (usually mild intellectual disability), neuropsychomotor developmental delay, behavioral disturbances, as well as psychiatric disorders are also part of the syndrome [5].

A complex hypothalamic-pituitary dysregulation is currently thought to be partly responsible for the PWS phenotype including the lack of satiety, high pain threshold, temperature

This article is part of the Topical Collection on *Other Forms of Diabetes and Its Complications*

✉ Antonino Crinò
nino3381@gmail.com; a.crino@tiscali.it

Graziano Grugni
g.grugni@auxologico.it

[1] Reference Center for Prader-Willi Syndrome, Bambino Gesù Hospital, Research Institute, Via Torre di Palidoro, 00050 Palidoro, Rome, Italy

[2] Division of Auxology, S. Giuseppe Hospital, Research Institute, Italian Auxological Institute, Verbania, Italy

instability, decreased vomiting and various endocrine abnormalities [ie, hypogonadism, growth hormone deficiency (GHD), central hypothyroidism and central adrenal insufficiency] [1••, 6].

It has been noted that the clinical features of PWS differ significantly during lifespan, becoming more evident in adulthood. In this light, it is a major advantage if the diagnosis can be made in the neonatal period, in order to have the opportunity to modify the clinical course towards favorable outcomes [7•]. Methylation-specific multiplex ligation-dependent probe amplification analysis (methylation test) is able to detect all the main genetic subtypes (*deletion, UPD15 and imprinting center defect*), while a high-resolution karyotype is always required to detect translocations or other chromosomal rearrangements involving chromosome 15 [3].

Obesity in PWS

Hyperphagia is a constant feature of the syndrome and is associated with abnormal and extreme behaviors regarding food, including a constant obsession for food that sometimes leads to stealing money to acquire it [8•]. PWS patients characteristically have poor feeding and decreased appetite in infancy that develops into an uncontrolled hunger after the ages of two–three and progressively leads to weight gain [9, 10•]. They are almost always unable to satisfy their appetite even after eating a whole meal and, where there is no close supervision, many of these patients can develop severe obesity even in early childhood. In this respect, seven nutritional phases have been identified, starting from birth to adulthood, during which it is possible to observe the progressive transition from poor feeding and failure to thrive to normal eating with or without obesity, up to the increased interest in food, causing hyperphagia, weight gain and life-threatening severe obesity [11]. It is important to bear in mind that, in PWS, weight gain may begin before the child shows a specific interest in food and before the increase in food intake.

In later stages, incessant and never ending hunger leads the patients to behave badly in relation to food and they are never satisfied after having completed a meal. Most subjects are inclined to take in a large quantity of food, even if it is not edible for others.

It is noteworthy to observe, however, that during adulthood, some PWS patients can feel more satiety and thus reduce the search for food.

Altered brain structures, evaluated with imaging studies and documented by preclinical studies, have been demonstrated in PWS. They may be responsible for the excessive hyperphagia and constant hunger, suggesting a crucial role of several brain areas in the abnormal regulation of food intake in PWS [12–15].

In PWS subjects, obesity shows a distinct phenotype in comparison with simple obesity. Patients with PWS showed greater amount of fat mass than essential obesity, with the same degree of weight excess in all ages [16, 17]. Excessive adipose tissue in PWS is classically distributed at the level of the trunk and the proximal extremity of the limbs, with lower trunk-to-appendicular fat mass ratio [18]. Differently to what occurs in non-syndromic obesity, PWS subjects showed less visceral adipose tissue and more subcutaneous fat tissue than Body Mass Index (BMI)-matched controls [16, 19]. In addition, lean body mass is significantly lower than the reference age- and BMI-matched population.

Current evidence suggests that PWS have a reduction in resting energy expenditure (REE), which may be explained by less skeletal muscle mass. In fact, once fat-free mass is considered, these differences between PWS and controls disappear [20, 21]. Data about body composition in PWS, however, are not homogeneous. Other authors have observed a similar proportion of abdominal subcutaneous and visceral fat in PWS subjects with severe obesity in comparison to non-syndromic obesity [22, 23].

In conclusion, hyperphagia, abnormal body composition and low resting expenditure seem to be the main determinants of the development of severe obesity in PWS.

Complications and Comorbidities of Obesity in PWS

Morbid obesity and its complications significantly worsen the long-term prognosis and are the major causes of premature morbidity and mortality in PWS [24]. Mortality is high among patients with PWS (3% annual death rate across all ages), and, without supervision, these patients may suddenly die as a result of choking (above all during bouts of heavy eating) [25] or stomach rupture and necrosis [26].

The main comorbidities associated with severe obesity in PWS include obstructive sleep apnea and other respiratory disorders (including pulmonary embolism, respiratory failure and pulmonary hypertension), cardiovascular diseases (right heart dysfunction, myocardial infarction and arterial hypertension), alteration of the digestive system (hepatic steatosis and gallstones), venous thromboembolism and chronic leg edema [24, 27–29]. In this regard, it has been reported that 38% and 16% of deaths in these subjects are due to respiratory and cardiac diseases, respectively [30].

Taking into account the metabolic profile, hyperlipidaemia is reported in about one third of PWS subjects [31]. Furthermore, severe obesity is a strong risk factor for the development of altered glucose metabolism in PWS, particularly for diabetes mellitus.

Type 2 Diabetes Mellitus in PWS

The majority of cases of diabetes in PWS have the phenotype of type 2 diabetes (T2DM) [32•], while both type 1 diabetes mellitus (T1DM) [17, 33–35] and monogenic diabetes [36] are extremely rare. In this context, there have been occasional reports of islet autoantibodies in PWS subjects with phenotypic T2DM [37]. In a group of 23 PWS patients with diabetes onset at age < 20 years (13.4 ± 3.9 years), β-cell antibodies were found positive in 4 out of 10 tested for antibodies [38]. Thus so far, however, the anti-islet cell antibodies and other markers of autoimmune islet cell destruction in PWS have not been extensively studied.

It has been assumed that, in PWS, abnormal glucose metabolism develops as a consequence of morbid obesity and concomitant insulin resistance. The relationship between the obese condition and the development of diabetes, however, is not clear and seems to be different than that seen in individuals with simple obesity.

T2DM has been found in 7–24% of adults with PWS [39–41] and affects 50% of patients after the 5th decade. [42]. In a cohort of 66 adults with PWS, the mean age of diagnosis of impaired glucose tolerance (IGT)/T2DM was 20 ± 8.2 years [43] (Table 1). Its prevalence exceeds greatly the prevalence in the general population (5–7%) [43] and is less frequent in prepubertal children with PWS. T2DM in fact was detected in 1/50 (2%) PWS patients under 18 years of age, while IGT is reported with a prevalence of 4.3–17% [44, 45].

A study performed in a large French cohort with PWS (ages 2–18.8 years) showed the presence of IGT only in 4% of patients but none had T2DM [41]. On the other hand, an earlier onset of T2DM was observed in Japanese PWS patients, even if this occurrence may be due to the higher rate of T2DM in Asian children than in Caucasians [46] (Table 1).

Nevertheless, an early onset of T2DM in PWS may be related to the duration of the weight excess, as in non-PWS populations. In this light, non-obese PWS children showed lower frequency of glucose homeostasis alterations in comparison to obese PWS subjects [47]. It should be noted that, since the 1990s, early diagnosis followed by preventive interventions, including GH therapy, has been shown to prevent obesity in a significant percentage of PWS [39]. The metabolic syndrome (MS) has been shown to be associated with both T2DM and coronary heart disease. As a result, the MS could be involved in determining the excessive mortality observed in PWS. To date, obesity is believed to play a crucial role on the development of MS in PWS, both in children [47] and in adult subjects [48].

Although many individuals with PWS are able to maintain healthier BMI with early diagnosis and appropriate care, T2DM and IGT are still common in PWS in adult age. In a multicenter study based on 274 PWS patients, altered glucose metabolism was detected in 24.4% of the patients and was significantly correlated to age, BMI and homeostasis model assessment insulin resistance index (HOMA-IR). This study shows a strong correlation between development of altered glucose metabolism, obesity and aging [49••] (Table 1).

In conclusion, the differences in the frequency of T2DM could result from various sizes of the PWS population included in the study, as well as from the wide range of the age and body weight between the study groups, the study period and different genetic predisposition in the various study groups.

Carbohydrate and Insulin Metabolism in PWS

It has been widely demonstrated that PWS subjects exhibited a state of relative hypoinsulinemia despite their severe obesity. According to early reports, the insulin response to both a mixed meal and an oral glucose load was found significantly lower in obese children with PWS in contrast with BMI-matched controls [50, 51]. Another study has demonstrated that nondiabetic PWS adult subjects show a reduced first- and second-phase insulin and C-peptide secretion response to intravenous glucose administration (IVGTT), as well as a significantly increased hepatic insulin extraction compared with obese subjects [52].

More recently, lower fasting insulin levels and reduced insulin resistance (measured by HOMA-IR) have been reported at all ages in obese patients with PWS, when compared with non-syndromic obesity [53–55].

Furthermore, non-obese PWS showed lower insulin and glucose values in respect to obese PWS, both in children and in adults [47, 48].

Moreover, HOMA-IR in PWS are comparable with those in BMI-age-matched controls before 5 years of age [56] and are significantly lower by age 11 [22], but lower HOMA-IR is seen also in adult PWS [55].

In addition, PWS with normal BMI showed no difference in HOMA-IR compared with lean controls, while insulin sensitivity (assessed by QUICKI) was slightly but significantly increased in lean PWS compared with controls [57•].

It seems that the reasons for high insulin sensitivity in PWS include a selective reduction of visceral fat in PWS after adjustment for total adiposity [16, 55], an elevated ghrelin concentration for the degree of obesity [8•, 10•, 58] and an impaired GH secretion [59]. Acylated ghrelin is an orexigenic hormone that has been implied as a potential cause of hyperphagia and weight gain inducing a positive energy balance and could be involved in the development of diabetes in PWS [60]. Additionally, the explanation for beta cell dysfunction in PWS is an impaired vagal parasympathetic efferent tone to the pancreas, as demonstrated by the blunted pancreatic polypeptide secretion in PWS children [56].

Furthermore, the increased insulin sensitivity of PWS subjects has been related to the presence of high levels of

Table 1 Main clinical data on diabetes mellitus and glucose metabolism alterations in PWS (shown according to the year of the study)

Authors (nationality)	Year	PWS pts studied (n°)	Age years (range)	IFG/IGT/T2DM n° (%)	Mean age at diagnosis of IGT/T2DM (years) (range)	Therapy
Lutski M (Israel)	2019	40	< 19	T2DM n.1 *(2.5%)*	< 17 years	GHT
Yang A (South Korea)	2017	84	17.4 ± 5.1 *(10.3–3.8)*	T2DM n.29 *(34.5%)*	15.9 ± 3.6 years *(10,1–27)*	GHT: n. 21/29 *(72.4%)*
Hedgeman E (Denmark)	2017	155	18 ± 17	T2DM n.14 *(9%)*	NA	NA
Fintini D (Italy)	2016	274	20.3 ± 10.4 *(8.1–50.1)*	IFG: n. 2 *(0.7%)* IGT: n.28 *(10.2%)* T2DM:n.37 *(13.5%)*	17.9 ± 3.9 years *(5–45,8)*	GHT: n. 13/110 *(11.8%)*
Laurier V (France)	2014	154	28.4 ± 7.7 *(16–54)*	T2DM n.39 *(25.3%)*	≤ 27 years = n.14 > 27 years = n.25	Oral antidiabetic agents: *24.7%* Injectable antidiabetic agents (GLP-1): *5.2%* Insulin: *9.1%*; GHT: *13.6%*
Hauber M (Germany)	2013	155	18 ± 17	T2DM n.14 *(9.9%)*	NA	NA
Sinnema M (The Netherlands)	2011	102	18–66	T2DM n.17 *(17%)*	< 25 years: *n.1*; 25–34 years: *n.4;* 35–44 years: *n.3;* 45+ years: *n.9*	NA
Tsuchiya T (Japan)	2011	65	10–53	T2DM n.17 *(26,2%)*	10–29 years (median:15 years)	Alpha-glucosidase inhibitors: *58.8%* Insulin: *64.7%*
Diene G (France)	2010	74	10.2 *(2–18.8)*	IGT: n. 3 *(4%)* T2DM: *0*	15.5–8.6–12.8 years *(patients with IGT)*	GHT
Sode-Carlsen R (Denmark)	2010	46	28 *(16–41)*	IGT: n.10 *(22%)* T2DM: n.6 *(13%)* T1DM: 1 *(2%)*	NA	NA
Crinò A (Italy)	2007	24	5.8 ± 2.8 *(1.4-9.8)*	IGT: n. 2 *(8.3%)* T2DM: *0*	10.6–12.8 years *(patients with IGT)*	GHT
Krochik AG (Argentina)	2006	75	8.4 ± 3.6 *(3.4-17.2)*	IGT: n. 7 *(9.3%)* T2DM: *0*	NA	NA
Vogels A (Belgium)	2004	54	29 *(≥18 years)*	T2DM: n.2/29 *(7%)*	NA	NA
Butler JV (UK)	2002	66	19 ± 12.9 *(< 46 years)*	T2DM: n.8/32 (> 17 years) *(25%)*	20.5 ± 8.2 years	Oral agents; Insulin: n. 4

PWS Prader-Willi syndrome, *T2DM* type 2 diabetes, *T1DM* type 1 diabetes, *IGT* impaired glucose tolerance, *IFG* impaired fasting glucose, *GHT* growth hormone therapy, *NA* data not available

adiponectin, a protein secreted by adipocytes that has beneficial effects in the development of inflammatory and atherosclerotic disease and exerts a dominant role in modulation of insulin sensitivity [54].

Another possible reason for hypoinsulinemia in PWS is the impaired processing of proinsulin to insulin, due to deficiency in prohormone convertase PC1 [61].

Data about the differences in insulin secretion in PWS, however, are still under debate. Other authors failed to find a significant difference in plasma insulin levels and insulin resistance between obese PWS and BMI-matched controls, both in pediatric age [47, 56] and in adult patients [48, 62]. Moreover, a clear relationship between obesity status and insulin levels is still detectable in PWS children, as obese subjects showed higher insulin levels and HOMA-IR than non-obese patients [47]. In this context, insulin resistance in PWS individuals had significant positive correlations with age with a peak in adolescents [49••], similarly to what observed in normal-weight and obese subjects [63].

These discrepancies may depend on the different clinical characteristics of the study groups, including age, degree of weight excess, body composition parameters and different percentage of patients undergoing GH and/or sex steroids therapy. Finally, a familial component in insulin resistance, as in general population, could also contribute in PWS subjects. On the other hand, the different genotypes (deletion or UPD15) do not appear to influence the development of altered glucose homeostasis in PWS [49••].

In conclusion, the exact mechanism of glucose metabolism alterations and, in particular, of T2DM remains to be clarified and further research is needed.

Effects of GH Therapy on Glucose Metabolism in PWS

Multiple studies demonstrate the presence of quantitative and qualitative defects of the GH/IGF-I axis in the great majority of children and in a significant percentage (8–38%) of adults with PWS [2]. Apart from the positive effects on linear growth in pediatric age, published data support benefits of GH therapy (GHT) both in children and during adulthood, with beneficial effects on body composition, muscle strength, exercise tolerance, lipid profile, cognition and quality of life [59].

The potential causal relationship between GHT and the occurrence of T2DM in PWS has been a controversial question for a long time.

Because of the counterregulatory effects of GH on insulin action, alteration in glucose metabolism is a side effect to be considered in patients with PWS during GHT. For this reason, it has been established by consensus of experts to include a diabetes risk assessment in PWS patients receiving GHT, mainly those who are obese and/or are older than 12 years or who have a positive family history of diabetes or concomitant therapy with antipsychotics [64]. In this context, it has been reported that GHT could contribute to decrease insulin sensitivity and to impair glucose homeostasis both in PWS children, especially in obese subjects [65], and in adult patients [66]. In a meta-analysis, a slight increase in glucose levels and insulin resistance during GHT has been observed [67]. Consequently, doubts have arisen on whether GH administration can impair glucose homeostasis in subjects prone to develop diabetes.

However, the evidence of the degree to which GHT worsens insulin and glucose metabolism in PWS is not unequivocal. Other reports have demonstrated that long-term GHT did not adversely affect glucose homeostasis in all ages [35, 68]. In this context, fasting insulin levels during GHT might be slightly elevated in children with PWS, but this is transient and does not progress to diabetes [35, 68, 69].

Furthermore, it is interesting to note that adults with PWS who underwent GHT during childhood had lower mean hemoglobin A1c (HbA1c) and lower mean insulin resistance index compared with those who were not treated [70].

The relevance of altered glucose metabolism during GHT has been investigated in a large cohort of PWS subjects, resulting in a negative correlation between GH administration and impaired glucose homeostasis [49••]. Altogether, it seems that altered glucose metabolism during GHT in PWS could mainly result from weight gain rather than GHT [49••, 68]. In this light, an evaluation of diabetes risk is recommended prior to initiation of GHT and a careful periodic surveillance of glucose homeostasis is required for all PWS subjects treated with GH. Finally, the presence of severe obesity and/or uncontrolled diabetes mellitus should be an exclusion criterion for the use of GH [64].

Clinical Characteristics and Management of PWS with Altered Glucose Metabolism

The clinical impact of T2DM is quite variable, and most PWS subjects are asymptomatic. In some cases, however, T2DM may be present with the classic symptoms, including polyuria, polydipsia and, in rare cases, unexpected weight loss despite hyperphagia [34, 71]. Consequently, the recommendations for screening of T2DM or IGT in PWS subjects, mainly in obese individuals, are similar to the guidelines for the general population.

Starting from childhood, patients with PWS should have as an initial surveillance a periodic and regular evaluation of glucose levels, HbA1c, fasting lipid profile, transaminases and blood pressure, with yearly screening thereafter, especially in patients that are obese. A standard oral glucose tolerance test *(OGTT)* should be performed after 9–10 years of age and in all obese PWS patients. For definition of impaired fasting

Table 2 Drugs used for treatment of type 2 diabetes mellitus and glucose metabolism alterations in PWS

Type of drugs	Generic name	Mechanism of action	Positive effects	Method of administration	Cost	Side effects
Biguanide	Metformin	Insulin sensitizer; might allow insulin to stimulate satiety in the hypothalamus	Improves sense of satiety and decreases anxiety about food	orally	Low	Gastrointestinal problems; lactic acidosis; vitamin B12 deficiency
Thiazolidinediones (TZDs)	Pioglitazone/Troglitazone Rosiglitazone *(withdrawn)*	Insulin sensitizer; improve insulin resistance	Decrease blood sugar	orally	Low	Weight gain; peripheral edema; bone loss
Sulfonylureas	Glimepiride Glipizide Glyburide/Glibenclamide	Stimulate the pancreas to produce more insulin	Improve glycemic control	orally	Low	Weight gain; hypoglycemia
Alpha-Glucosidase Inhibitors	Acarbose	Slows the absorption of starches in small bowel	Reduction of body weight and basal/peak glycemic values	orally	Moderate	Gastrointestinal symptoms *(flatulence, meteorism, abdominal pain)* often transient
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin	Increase incretin levels *(GLP-1 and GIP)*, which inhibit glucagon release, and stimulate insulin secretion	Lowering blood glucose, additive effect with metformin	orally	High	Joint pain; risk of heart failure; inflammatory bowel disease and acute pancreatitis; upper respiratory symptoms
Gliflozins (SGLT2 inhibitors)	Canagliflozin Dapagliflozin Empagliflozin	Inhibiting sodium-glucose transport protein 2 (SGLT2), inhibit kidney glucose reabsorption	Lower blood sugar, reduce body weight and blood pressure, cardiovascular benefit	orally	High	Mycotic infections; urinary tract infections and osmotic diuresis; decreased bone mineral density
Meglitinides	Repaglinide Nateglinide	Stimulate pancreatic β-cells to release insulin after meals	Shorter action better than sulfonylureas. Improve post meals glucose	orally	Moderate	Weight gain and hypoglycemia (mild)
Insulin	Short-acting insulin *(Aspart, Glulisine, Lispro)* - Long-acting insulin *(Glargine, Degludec, Detemir)* - *(Glargine U-300)*	Increases the passage of glucose from the bloodstream into the cells and decreases the production of glucose by the liver	Lower blood glucose levels	subcutaneously	Low	Hypoglycemia; local lipodystrophy
Glucagon-like polypeptide-1 (GLP-1) receptor agonists	Exenatide Exenatide LAR* Liraglutide Dulaglutide Lixisenatide	Increase insulin secretion when blood glucose is high and lower the amount of glucose produced by the liver	Improve glycemic control, increase satiety, and reduce body weight	subcutaneously	High	Nausea; delayed gastric emptying; increase in heart rate

**Exenatide LAR* exenatide long-acting release

glucose, IGT or T2DM, the classical criteria of American Diabetes Association are used [72]. Special attention must be given to those children and adults on GH treatment. Periodic fasting glucose and insulin levels are recommended before and after initiation of GH administration. All PWS patients on GHT, even if non-obese, should have annual glucose metabolism screening. In these cases an OGTT should be periodically carried out especially in presence of obesity and/or diabetes or obesity in the family.

There have been surprisingly few reports of diabetes-related complications in PWS [32•, 34, 73, 74]. However, at least annually, PWS individuals with T2DM should be routinely monitored for evidence of microvascular complications (eye examination by an ophthalmologist, 24-h urine collection with creatinine and microalbumin and screening for autonomic neuropathy) as well as for hypertension and cardiovascular diseases, together with the appropriate therapy needed for general standard-of-care practice guidelines.

No definitive treatment strategy for glucose metabolism alterations with PWS has yet been established. The prevention of obesity remains the most important goal of the therapeutic strategy in all PWS patients since severe excess weight certainly promotes the development of T2DM. Continuous lifelong supervision, strict control over access to food, dietary restriction and regular exercise are still the only available options [75]. This is because there are to date no effective pharmacological treatment options for hyperphagia and excessive eating behavior in PWS. At the beginning, the majority of patients achieve normal glycemic control without drugs when exercise and diet are appropriately carried out. In milder cases weight loss may lead to complete resolution of glucose alteration.

Pharmacological treatment for T2DM in PWS should follow routine guidelines as for the general population [76].

T2DM in PWS needs similar pharmacological agents as with non-syndromic obesity-related diabetes, e.g. insulin-sensitizing agents, such as metformin or thiazolidinediones, with the introduction of insulin if required [77] (Table 2)

Since increased insulin resistance is observed in some PWS patients [78], metformin should be considered as a first-line medication, especially if T2DM and obesity are present [79]. It has been reported that metformin is able to improve both the sense of satiety and the anxiety towards the food in children and adolescents with PWS, probably through its positive action on insulin sensitivity [80]. However, metformin can frequently cause gastrointestinal disorders and in some cases a vitamin B12 deficiency (Table 2).

Administration of thiazolidinediones as well as sulfonylureas can cause an increase of body weight and may not always be appropriate for T2DM in obese subjects with PWS. Troglitazone was used in PWS patients complicated by diabetes mellitus with beneficial effects on glycemic control by improving insulin sensitivity [81].

However, the efficacy of these drugs in subjects with PWS and T2DM has not been thoroughly evaluated.

Among oral hypoglycemic agents, alpha-glucosidase inhibitors (Acarbose) have been reported as the ones most used in Japanese PWS population [46]. This drug can significantly reduce body weight and postprandial blood glucose levels and improves the symptoms associated with nocturnal hypoglycaemia reducing the daily insulin dosage.

Several case reports suggest favorable outcomes of T2DM in PWS using glucagon-like peptide-1 (GLP-1) receptor agonist *(exenatide)* and analog *(liraglutide)* with regard to reduction of ghrelin secretion, control of glucose and appetite, weight loss and pre-prandial insulin secretion [9, 82–86]. In our experience the use of GLP-1 agonists/analogs seems to induce a true improvement/stabilization of altered glucose metabolism [87]. However, caution must be taken due to potential side effects of delayed gastric emptying and pre-existing risk for gastric rupture in the population [88]. Therefore, the role of GLP-1 agonist therapy in PWS is promising, but has not yet been fully elucidated as a long-term therapy (Table 2).

Dipeptidyl peptidase-4 (DPP4) inhibitors have been successfully used in these patients with regard to weight management and HbA1c control to avoid or replace insulin therapy [89].

Glucose-lowering SGLT2 inhibitor (canagliflozin, dapaglifozin and empagliflozin) could be another good option for treating PWS with T2DM. An improvement in both HbA1c and body weight has been observed with canaglifozin in a 40-year-old woman with PWS [90].

Insulin therapy is required when the patient is no longer controlled by other types of drugs, and there is evidence of insulin deficiency (ketoacidosis and unexplained weight loss). Insulin is not recommended in all other cases since it may increase body weight. However, PWS patients do not always accept self-monitoring of blood glucose and insulin injections. PWS is often associated with stubbornness, persistence and obsessive-compulsive symptoms which make the management of diabetes more difficult. In addition, the risk of severe hypoglycemia during insulin therapy should be taken into consideration, particularly when their access to food is suddenly interrupted by hospitalization or other interventions.

Bariatric surgery has recently found increasing success in the treatment of morbid obesity in PWS. This procedure causes weight loss through either a diminished capacity for food intake and/or a reduced digestional absorption of food. In particular, laparoscopic sleeve gastrectomy and mini-gastric by-pass can induce a better control of hyperphagia and food seeking behaviors postoperatively [91, 92]. In addition to weight loss, favorable metabolic changes are obtained (reduction in ghrelin and increase in GLP-1) with improvement or healing of glucose metabolism alterations. No major perioperative complications or mortality occurred, and the follow-up of the patients seems to be satisfactory with minimal nutrient malabsorption. Other authors reported a

successful weight loss after bilio-pancreatic diversion but with some complications due to intestinal malabsorption [93]. Unfortunately, there is not always a positive effect of bariatric surgery on hyperphagia in PWS [94]. In all cases, however, dietary intervention and careful monitoring are always recommended. Over the long-term, weight gain may recur after the patient develops compensatory dietary strategies. In this light, long-term results for up to 10 years have recently demonstrated that bariatric surgery is unable to produce sustainable long-term weight loss or comorbidity resolution in PWS [95]. Since the best outcomes for bariatric surgery in the general population are found in those subjects who are the most insulin resistant [96], it should be argued that poor effectiveness of surgery in PWS may be related, at least in part, to the state of relative hypoinsulinemia. However, other experiences with bariatric surgery in PWS have been encouraging, and a relatively long-term success has been reported in selected patients [97, 98].

Consequently, bariatric surgery should be considered in only those severe cases in which serious obesity-related morbidities (i.e T2DM) are present and where a rapid weight loss is potentially beneficial. Bariatric surgery can be considered an option in selected and well-disciplined PWS patients, with cooperating families, particularly when other classical approaches have failed and if no other effective alternative therapies are available.

Conclusions

Glucose metabolism alterations and T2DM can occur with variable prevalence in patients with PWS, particularly in obese individuals and in adults. Since obesity has a main role in the individual metabolic risk clustering in PWS, T2DM is less frequent in normal weight or overweight patients with PWS. Therefore, weight control can prevent glucose metabolism alterations and subsequent related morbidity and remains the most important goal for any treatment program in these patients. Physical inactivity and early onset obesity should be prevented with appropriate interventions. However, PWS patients are prone to avoid physical exercise and behavior disturbances make dietary intervention hard for families.

Clinically, cases of T2DM in PWS are indistinguishable from obesity-related T2DM, although it seems that diabetes-related complications are less frequent than in BMI-matched controls. Nevertheless, a screening for associated glucose metabolism alterations should be a routine element of care and treatment for all subjects with PWS, particularly obese and/or adults, as well as in patients receiving GH treatment, even if GHT does not seem to influence the development of altered glucose metabolism.

An early identification and treatment of cases with T2DM could be useful to improve morbidity and prevent mortality in these patients. Unfortunately, systematic studies regarding T2DM in PWS are not available. Therefore, recommendations and treatment guidelines are mostly extrapolated from studies in the general population.

In fact, the pharmacological approach in PWS is similar to that of non-syndromic T2DM. On the other hand, bariatric surgery seems to be less effective than in simple obesity, partly because PWS subjects have a tendency towards hypoinsulinemia.

However, more research is needed to evaluate the effectiveness and safety of long-term therapies in PWS with T2DM.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Butler MG, Miller JL, Forster JL. Prader-Willi syndrome - clinical genetics, diagnosis and treatment approaches: an update. Curr Pediatr Rev. 2019;15 (4):207-44. https://doi.org/10.2174/1573396315666190716120925. **A very recent and complete update on appropriate medical management, and best practice treatment approaches of Prader-Willi syndrome**.

2. Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. J Endocrinol Investig. 2015;38(12):1249–63. https://doi.org/10.1007/s40618-015-0312-9.

3. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med. 2012;14:10–26.

4. Crinò A, Di Giorgio G, Livieri C, et al. A survey on Prader-Willi syndrome in the Italian population: prevalence of historical and clinical signs. J Pediatr Endocrinol Metab. 2009;22(10):883–93.

5. Jauregi J, Laurier V, Copet P, Tauber M, Thuilleaux D. Behavioral profile of adults with Prader-Willi syndrome: correlations with individual and environmental variables. J Neurodev Disord. 2013 Aug 6;5(1):18. https://doi.org/10.1186/1866-1955-5-18.

6. Muscogiuri G, Formoso G, Pugliese G, Ruggeri RM, Scarano E. Colao a; RESTARE. Prader- Willi syndrome: an uptodate on endocrine and metabolic complications. Rev Endocr Metab Disord. 2019;20(2):239–50. https://doi.org/10.1007/s11154-019-09502-2.

7.• Duis J, van Wattum PJ, Scheimann A, Salehi P, Brokamp E, Fairbrother L, et al. A multidisciplinary approach to the clinical management of Prader-Willi syndrome. Mol Genet Genomic Med. 2019;7(3):e514. https://doi.org/10.1002/mgg3.514. **This article takes into consideration the multidisciplinary care model for an optimal clinical management of PWS patients and emphasize the development of a "Center of Excellence" for these patients**.

8.• Irizarry KA, Miller M, Freemark M, Haqq AM. Prader Willi syndrome: genetics, metabolomics, hormonal function, and new approaches to therapy. Adv Pediatr Infect Dis. 2016;63(1):47–77. **This paper reports an overview on metabolic studies and glucose omeostasis in PWS and takes into consideration the current standard therapies and new therapeutic approaches in PWS**.

9. Crinò A, Fintini D, Bocchini S, Grugni G. Obesity management in Prader-Willi syndrome: current perspectives. Diabetes Metab Syndr Obes. 2018;11:579–93.

10.• Tauber M, Coupaye M, Diene G, Molinas C, Valette M, Beauloye V. Prader-Willi syndrome: A model for understanding the ghrelin system. J Neuroendocrinol. 2019;31(7):e12728. https://doi.org/10.1111/jne.12728. **Findings from this review provide recent data on the ghrelin dysfunction in PWS and discuss therapeutic perspectives targeting the ghrelin system in PWS**.

11. Miller JL, Lynn CH, Driscoll DC, Goldstone AP, Gold JA, Kimonis V, et al. Nutritional phases in Prader-Willi syndrome. Am J Med Genet A. 2011;155A:1040–9.

12. Dimitropoulos A, Schultz RT. Food-related neural circuitry in Prader-Willi syndrome: response to high- versus low-calorie foods. J Autism Dev Disord. 2008;38(9):1642–53. https://doi.org/10.1007/s10803-008-0546-x.

13. Zhang Y, Zhao H, Qiu S, Tian J, Wen X, Miller JL, et al. Altered functional brain networks in Prader-Willi syndrome. NMR Biomed. 2013 Jun;26(6):622–9. https://doi.org/10.1002/nbm.2900.

14. Pujol J, Blanco-Hinojo L, Esteba-Castillo S, Caixàs A, Harrison BJ, Bueno M, et al. Anomalous basal ganglia connectivity and obsessive-compulsive behaviour in patients with Prader-Willi syndrome. J Psychiatry Neurosci. 2016 Jun;41(4):261–71.

15. Xu M, Zhang Y, von Deneen KM, Zhu H, Gao JH. Brain structural alterations in obese children with and without Prader-Willi syndrome. Hum Brain Mapp. 2017 Aug;38(8):4228–38. https://doi.org/10.1002/hbm.23660.

16. Goldstone AP, Thomas EL, Brynes AE, Bell JD, Frost G, Saeed N, et al. Visceral adipose tissue and metabolic complications of obesity are reduced in Prader-Willi syndrome female adults: evidence for novel influences on body fat distribution. J Clin Endocrinol Metab. 2001;86:4330–8.

17. Sode-Carlsen R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, et al. Body composition, endocrine and metabolic profiles in adults with Prader-Willi syndrome. Growth Hormon IGF Res. 2010 Jun;20(3):179–84. https://doi.org/10.1016/j.ghir.2009.12.004.

18. Bedogni G, Grugni G, Tringali G, Marazzi N, Sartorio A. Does segmental body composition differ in women with Prader-Willi syndrome compared to women with essential obesity? J Endocrinol Investig. 2015 Sep;38(9):957–61. https://doi.org/10.1007/s40618-015-0266-y.

19. Tanaka Y, Abe Y, Oto Y, Itabashi H, Shiraishi M, Yoshino A, et al. Characterization of fat distribution in Prader-Willi syndrome: relationships with adipocytokines and influence of growth hormone treatment. Am J Med Genet A. 2013 Jan;161A(1):27–33. https://doi.org/10.1002/ajmg.a.35653.

20. Alsaif M, Elliot SA, MacKenzie ML, Prado CM, Field CJ, Haqq AM. Energy metabolism profile in individuals with Prader-Willi syndrome and implications for clinical management: a systematic review. Adv Nutr. 2017 Nov 15;8(6):905–15. https://doi.org/10.3945/an.117.016253.

21. Butler MG, Theodoro MF, Bittel DC, Donnelly JE. Energy expenditure and physical activity in Prader-Willi syndrome: comparison with obese subjects. Am J Med Genet A. 2007 Mar 1;143A(5):449–59.

22. Talebizadeh Z, Butler MG. Insulin resistance and obesity-related factors in Prader-Willi syndrome: comparison with obese subjects. Clin Genet. 2005;67:230–9.

23. Marzullo P, Marcassa C, Minocci A, Campini R, Eleuteri E, Alessandro Gondoni L, et al. Long-term echocardiographic and cardioscintigraphic effects of growth hormone treatment in adults with Prader-Willi syndrome. J Clin Endocrinol Metab. 2015 May;100(5):2106–14. https://doi.org/10.1210/jc.2015-1063.

24. Hedgeman E, Ulrichsen SP, Carter S, Kreher NC, Malobisky KP, Braun MM, et al. Long-term health outcomes in patients with Prader-Willi Syndrome: a nationwide cohort study in Denmark. Int J Obes. 2017 Oct;41(10):1531–8. https://doi.org/10.1038/ijo.2017.139.

25. Stevenson DA, Heinemann J, Angulo M, Butler MG, Loker J, Rupe N, et al. Deaths due to choking in Prader-Willi syndrome. Am J Med Genet A. 2007 Mar 1;143A(5):484–7.

26. Stevenson DA, Heinemann J, Angulo M, Butler MG, Loker J, Rupe N, et al. Gastric rupture and necrosis in Prader-Willi syndrome. J Pediatr Gastroenterol Nutr. 2007;45(2):272–4.

27. Einfeld SL, Kavanagh SJ, Smith A, Evans EJ, Tonge BJ, Taffe J. Mortality in Prader-Willi syndrome. Am J Ment Retard. 2006 May;111(3):193–8.

28. Grugni G, Crinò A, Bosio L, et al. The Italian National Survey for Prader-Willi syndrome: an epidemiologic study. Am J Med Genet A. 2008;146:861–72.

29. Manzardo AM, Loker J, Heinemann J, Loker C, Butler MG. Survival trends from the Prader-Willi Syndrome Association (USA) 40-year mortality survey. Genet Med. 2018 Jan;20(1):24–30. https://doi.org/10.1038/gim.2017.92.

30. Butler MG, Manzardo AM, Heinemann J, Loker C, Loker J. Causes of death in Prader-Willi syndrome: Prader-Willi Syndrome Association (USA) 40-year mortality survey. Genet Med. 2017 Jun;19(6):635–42. https://doi.org/10.1038/gim.2016.178.

31. Laurier V, Lapeyrade A, Copet P, Demeer G, Silvie M, Bieth E, et al. Medical, psychological and social features in a large cohort of adults with Prader-Willi syndrome: experience from a dedicated centre in France. J Intellect Disabil Res. 2015;59(5):411–21.

32.• Yang A, Kim J, Cho SY, Jin DK. Prevalence and risk factors for type 2 diabetes mellitus with Prader-Willi syndrome: a single center experience. Orphanet J Rare Dis. 2017;12(1):146. https://doi.org/10.1186/s13023-017-0702-5. **This is the first study that identifies a high frequency of microvascular complications (24% of cases) in PWS patients with T2DM, which appear to be positively correlated with HOMA-IR and advanced age**.

33. Anhalt H, Eckert KH, Hintz RL, Neely EK. Type I diabetes mellitus, ketoacidosis and thromboembolism in an adolescent with Prader-Willi syndrome. Acta Paediatr. 1996;85:516.

34. Bassali R, Hoffman WH, Chen H, Tuck-Muller CM. Hyperlipidemia, insulin-dependent diabetes mellitus, and rapidly progressive diabetic retinopathy and nephropathy in Prader-Willi syndrome with del(15)(q11.2q13). Am J Med Genet. 1997;71(3):267–70.

35. Bakker NE, Kuppens RJ, Siemensma EP, Tummers-de Lind van Wijngaarden RF, Festen DA, Bindels-de Heus GC, et al. Eight years of growth hormone treatment in children with Prader-Willi syndrome: maintaining the positive effects. J Clin Endocrinol Metab. 2013;98:4013–22.

36. Mariani B, Cammarata B, Grechi E, Di Candia S, Chiumello G. Maturity onset diabetes of the young in a child with Prader-Willi syndrome. Horm Res. 2012;78(suppl 1):162.

37. Bogova E, Shiryaeva T, Nagaeva E, Volevodz N, Peterkova V, Bezlepkina O. The "double diabetes" in adolescent with Prader-Willi syndrome. ESPE Abstracts. 2019;92:P1–356.

38. Schmidt F, Kapellen TM, Wiegand S, Herbst A, Wolf J, Fröhlich-Reiterer EE, et al. Holl RW; DPV-Wiss study group; BMBF competence network diabetes. Diabetes mellitus in children and adolescents with genetic syndromes. Exp Clin Endocrinol Diabetes. 2012;120(10):579–85.

39. Vogels A, Fryns JP. Age at diagnosis, body mass index and physical morbidity in children and adults with the Prader-Willi syndrome. Genet Couns. 2004;15(4):397–404.
40. Diene G, Mimoun E, Feigerlova E, Caula S, Molinas C, Grandjean H, et al. Endocrine disorders in children with Prader-Willi syndrome - data from 142 children of the French database. Horm Res Paediatr. 2010;74(2):121–8.
41. Sinnema M, Maaskant MA, van Schrojenstein Lantman-de Valk HM, van Nieuwpoort IC, Drent ML, Curfs LMG, et al. Physical health problems in adults with Prader–Willi syndrome. Am J Med Genet A. 2011;155:2112–24.
42. Sinnema M, Schrander-Stumpel CT, Maaskant MA, Boer H, Curfs LM. Aging in Prader-Willi syndrome: twelve persons over the age of 50 years. Am J Med Genet A. 2012;158A:1326–36.
43. Butler JV, Whittington JE, Holland AJ, Boer H, Clarke D, Webb T. Prevalence of, and risk factors for, physical ill-health in people with Prader-Willi syndrome: a population-based study. Dev Med Child Neurol. 2002;44:248–55.
44. Krochik AG, Ozuna B, Torrado M, Chertkoff L, Mazza C. Characterization of alterations in carbohydrate metabolism in children with Prader-Willi syndrome. J Pediatr Endocrinol Metab. 2006;19(7):911–8.
45. Lutski M, Zucker I, Zadik Z, Libruder C, Blumenfeld O, Shohat T, et al. Prevalence of diabetes among children treated with growth hormone in Israel. Diabet Med. 2019. https://doi.org/10.1111/dme.13910.
46. Tsuchiya T, Oto Y, Ayabe T, Obata K, Murakami N, Nagai T. Characterization of diabetes mellitus in Japanese Prader-Willi syndrome. Clin Pediatr Endocrinol. 2011;20:33–8.
47. Brambilla P, Crinò A, Bedogni G, Bosio L, Cappa M, Corrias A, et al. Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED). Metabolic syndrome in children with Prader-Willi syndrome: the effect of obesity. Nutr Metab Cardiovasc Dis. 2011;21:269–76.
48. Grugni G, Crinò A, Bedogni G, Cappa M, Sartorio A, Corrias A, et al. Metabolic syndrome in adult patients with Prader-Willi syndrome. Nutr Metab Cardiovasc Dis. 2013;23(11):1134–40.
49.•• Fintini D, Grugni G, Bocchini S, Brufani C, Di Candia S, Corrias A, et al. Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED). Disorders of glucose metabolism in Prader-Willi syndrome: Results of a multicenter Italian cohort study. Nutr Metab Cardiovasc Dis. 2016;26(9):842–7. **The results of this study show a high prevalence of glucose metabolism alterations in a large cohort of PWS patients, which appear to be more common in obese and adults subjects. The authors reported that impaired glucose metabolism during GH therapy in PWS could be mainly due to weight gain rather than to GH administration**.
50. Zipf WB, Odorisio TM, Cataland S, Dixon K. Pancreatic polypeptide responses to protein meal challenges in obese but otherwise normal children and obese children with Prader-Willi syndrome. J Clin Endocrinol Metab. 1983;57:1074–80.
51. Gumus Balikcioglu P, Balikcioglu M, Muehlbauer MJ, Purnell JQ, Broadhurst D, Freemark M, et al. Macronutrient Regulation of Ghrelin and Peptide YY in Pediatric Obesity and Prader-Willi Syndrome. J Clin Endocrinol Metab. 2015 Oct;100(10):3822–31. https://doi.org/10.1210/jc.2015-2503.
52. Schuster D, Osei K, Zipf WB. Characterization of alterations in glucose and insulin metabolism in Prader-Willi subjects. Metabolism. 1996;45(12):1514–20.
53. Haqq AM, Muelhlbauer M, Newgard CB, Grambow SC, Freemark MS. The metabolic phenotype of Prader-Willi syndrome (PWS) in childhood: heightened insulin sensitivity relative to body mass index. J Clin Endocrinol Metab. 2011;96:E225–32.
54. Lacroix D, Moutel S, Coupaye M, Huvenne H, Faucher P, Pelloux V, et al. Metabolic and adipose tissue signatures in adults with Prader-Willi syndrome: a model of extreme adiposity. J Clin Endocrinol Metab. 2015;100(3):850–9.
55. Hoybye C, Hilding A, Jacobsson H, Thoren M. Metabolic profile and body composition in adults with Prader-Willi syndrome. J Clin Endocrinol Metab. 2002;87:3590–7.
56. Goldstone AP, Holland AJ, Butler JV, Whittington JE. Appetite hormones and the transition to hyperphagia in children with Prader-Willi syndrome. Int J Obes. 2012;36(12):1564–70.
57.• Hirsch HJ, Gross I, Pollak Y, Eldar-Geva T, Gross-Tsur V. Irisin and the metabolic phenotype of adults with Prader-Willi syndrome. PLoS One. 2015;10(9):e0136864. https://doi.org/10.1371/journal.pone.0136864. **This study highlights the peculiar metabolic phenotype of PWS compared to subjects with simple obesity and hypothesize that abnormal secretion or regulation of irisin activity may contribute to some of the metabolic features of PWS, including glucose metabolism**.
58. Emerick JE, Vogt KS. Endocrine manifestations and management of Prader-Willi syndrome. Int J Pediatr Endocrinol. 2013;21:14.
59. Grugni G, Marzullo P. Diagnosis and treatment of GH deficiency in Prader-Willi syndrome. Best Pract Res Clin Endocrinol Metab. 2016;30(6):785–94.
60. Kuppens RJ, Diène G, Bakker NE, Molinas C, Faye S, Nicolino M, et al. Elevated ratio of acylated to unacylated ghrelin in children and young adults with Prader-Willi syndrome. Endocrine. 2015 Dec;50(3):633–42. https://doi.org/10.1007/s12020-015-0614-x.
61. Burnett LC, LeDuc CA, Sulsona CR, Paull D, Rausch R, Eddiry S, et al. Deficiency in prohormone convertase PC1 impairs prohormone processing in Prader-Willi syndrome. J Clin Invest. 2017;127(1):293–305.
62. Purtell S, Sze L, Loughnan G, Smith E, Herzog H, Sainsbury A, et al. In adults with Prader-Willi syndrome, elevated ghrelin levels are more consistent with hyperphagia than high PYY and GLP-1 levels. Neuropeptides. 2011;45:301–7.
63. Shashaj B, Luciano R, Contoli B, Morino GS, Spreghini MR, Rustico C, et al. Reference ranges of HOMA-IR in normal-weight and obese young Caucasians. Acta Diabetol. 2016;53(2):251–60.
64. Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS; 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants, GrowthHormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. 2013; 98:E1072–1087.
65. Crinò A, Di Giorgio G, Manco M, Grugni G, Maggioni A. Effects of growth hormone therapy on glucose metabolism and insulin sensitivity indices in prepubertal children with Prader-Willi syndrome. Horm Res. 2007;68:83–90.
66. Jørgensen AP, Ueland T, Sode-Carlsen R, Schreiner T, Rabben KF, Farholt S, et al. Glucose homeostasis in adults with Prader-Willi syndrome during treatment with growth hormone: results from a 12-month prospective study. Growth Hormon IGF Res. 2014;24(1):16–21.
67. Sanchez-Ortiga R, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy in adults with Prader-Willi syndrome: a meta-analysis. Clin Endocrinol. 2012;77:86–93.
68. Höybye C. Growth hormone treatment of Prader-Willi syndrome has long-term, positive effects on body composition. Acta Paediatr. 2015;104(4):422–7.
69. L'Allemand D, Eiholzer U, Schlumpf M, Torresani T, Girard J. Carbohydrate metabolism is not impaired after 3 years of growth hormone therapy in children with Prader-Willi syndrome. Horm Res. 2003;59(5):239–48.
70. Coupaye M, Tauber M, Cuisset L, Laurier V, Bieth E, Lacorte JM, et al. Effect of genotype and previous GH treatment on adiposity in adults with Prader-Willi syndrome. J Clin Endocrinol Metab. 2016;101(12):4895–903.

71. Basheer R, Jalal MJ, Gomez R. An unusual case of adolescent type 2 diabetes mellitus: Prader-Willi syndrome. J Family Med Prim Care. 2016;5(1):181–3.
72. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2019;42 (Suppl.1):S13-S28
73. Yigit S, Estrada E, Bucci K, Hyams J, Rosengren S. Diabetic ketoacidosis secondary to growth hormone treatment in a boy with Prader-Willi syndrome and steatohepatitis. J Pediatr Endocrinol Metab. 2004;17(3):361–4.
74. Hori H, Sato Y, Nakashima M. Prader-Willi syndrome case with proliferative diabetic retinopathy in both eyes treated by early vitrectomy under local anesthesia. Nippon Ganka Gakkai Zasshi. 2012 Feb;116(2):114–8.
75. McCandless SE. Committee on genetics. Clinical report-health supervision for children with Prader-Willi syndrome. Pediatrics. 2011 Jan;127(1):195–204. https://doi.org/10.1542/peds.2010-2820.
76. Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M. Speakers contributors at the second expert meeting of the comprehensive care of patients with PWS: recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab. 2008;93:4183–97.
77. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018;61(12):2461–98. https://doi.org/10.1007/s00125-018-4729-5 Erratum in: Diabetologia. 2019 May;62(5):873.
78. Kousholt AM, Beck-Nielsen H, Lund HT. A reduced number of insulin receptors in patients with Prader-Willi syndrome. Acta Endocrinol. 1983;104(3):345–51.
79. Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. Drugs. 2003;63(18):1879–94.
80. Miller JL, Linville TD, Dykens EM. Effects of metformin in children and adolescents with Prader-Willi syndrome and early-onset morbid obesity: a pilot study. J Pediatr Endocrinol Metab. 2014;27(1–2):23–9.
81. Yamakita T, Ishii T, Mori T, Yoshioka K, Sato T, Tanaka S, et al. Troglitazone ameliorates insulin resistance in a diabetic patient with Prader-Willi syndrome. Diabetes Res Clin Pract. 1998;42(3):205–8.
82. Seetho IW, Jones G, Thomson GA, Fernando DJ. Treating diabetes mellitus in Prader-Willi syndrome with Exenatide. Diabetes Res Clin Pract. 2011 Apr;92(1):e1–2. https://doi.org/10.1016/j.diabres.2010.12.009.
83. Cyganek K, Koblik T, Kozek E, Wojcik M, Starzyk J, Malecki MT. Liraglutide therapy in Prader-Willi syndrome. Diabet Med. 2011;28(6):755–6.
84. Sze L, Purtell L, Jenkins A, Loughnan G, Smith E, Herzog H, et al. Effects of a single dose of exenatide on appetite, gut hormones, and glucose homeostasis in adults with Prader-Willi syndrome. J Clin Endocrinol Metab. 2011;96(8):E1314–9. https://doi.org/10.1210/jc.2011-0038.
85. Senda M, Ogawa S, Nako K, Okamura M, Sakamoto T, Ito S. The glucagon-like peptide-1 analog liraglutide suppresses ghrelin and controls diabetes in a patient with Prader-Willi syndrome. Endocr J. 2012;59(10):889–94.
86. Cadena-Obando DA, Molina-Ayala MA, Ferreira-Hermosillo A. Obesity treatment with liraglutide in a patient with Prader-Willi syndrome: a case report. Nutr Hosp. 2018;35(3):743–6. https://doi.org/10.20960/nh.1525.
87. Fintini D, Grugni G, Brufani C, Bocchini S, Cappa M, Crinò A. Use of GLP-1 receptor agonists in Prader-Willi syndrome: report of six cases. Diabetes Care. 2014;37:e76–7. https://doi.org/10.2337/dc13-2575.
88. Arenz T, Schwarzer A, Pfluger T, Koletzko S, Schmidt H. Delayed gastric emptying in patients with PraderWilli syndrome. J Pediatr Endocrinol Metab. 2010;23(9):867–71.
89. Hauber M, Stratmann B, Hoedebeck-Stuntebeck N, Tschoepe D. Medical management for adults with Prader-Willi syndrome. Metab Syndr Relat Disord. 2013;11(6):392–6.
90. Kato E, Kimura M, Okuda T, Toyoda M, Fukagawa M. Behavior modification maintenance with long-term blood glucose and weight management in Prader-Willi syndrome complicated with diabetes: team management approach combined with pharmacological treatment. Case Rep Med. 2019;19:1–7. https://doi.org/10.1155/2019/6129019.
91. Fong AK, Wong SK, Lam CC, Ng EK. Ghrelin level and weight loss after laparoscopic sleeve gastrectomy and gastric mini-bypass for Prader-Willi syndrome in Chinese. Obes Surg. 2012;22(11):1742–5.
92. Alqahtani AR, Elahmedi MO, Al Qahtani AR, Lee J, Butler MG. Laparoscopic sleeve gastrectomy in children and adolescents with Prader-Willi syndrome: a matched-control study. Surg Obes Relat Dis. 2016 Jan;12(1):100–10. https://doi.org/10.1016/j.soard.2015.07.014.
93. Papavramidis ST, Kotidis EV, Gamvros O. Prader-Willi syndrome-associated obesity treated by biliopancreatic diversion with duodenal switch. Case report and literature review. J Pediatr Surg. 2006 Jun;41(6):1153–8.
94. Scheimann AO, Butler MG, Gourash L, Cuffari C, Klish W. Critical analysis of bariatric procedures in Prader-Willi syndrome. J Pediatr Gastroenterol Nutr. 2008;46(1):80–3.
95. Liu SY, Wong SK, Lam CC, Ng EK. Bariatric surgery for Prader-Willi syndrome was ineffective in producing sustainable weight loss: long term results for up to 10 years. Pediatr Obes. 2020;15(1):e12575 https://doi.org/10.1111/ijpo.12575.
96. Azim S, Kashyap SR. Bariatric surgery: pathophysiology and outcomes. Endocrinol Metab Clin N Am. 2016 Dec;45(4):905–21. https://doi.org/10.1016/j.ecl.2016.06.011.
97. Yu H, Di J, Jia W. Laparoscopic sleeve gastrectomy in Chinese female patient with Prader-Willi syndrome and diabetes. Surg Obes Relat Dis. 2013;9(2):e25–7. https://doi.org/10.1016/j.soard.2012.07.009.
98. Cazzo E, Gestic MA, Utrini MP, Chaim FDM, Cândido EC, Jarolavsky LBDS, et al. Bariatric surgery in individuals with severe cognitive impairment: report of two cases. Sao Paulo Med J. 2018;6(1):84–8. https://doi.org/10.1590/1516-3180.2016.0299071216.