

Dietary Management for Adolescents with Prader–Willi Syndrome

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Abstract: Prader–Willi syndrome (PWS) is a complex, multisystem neurodevelopmental disorder affecting approximately 1 in 25,000 live births. PWS is caused by absence of expression of paternally inherited imprinted genes on chromosome 15q11–q13. The syndrome typically occurs due to one of three genetic mechanisms: paternal deletion of involved genes, maternal uniparental disomy, or imprinting center defects. These genetic anomalies lead to well-described clinical phenotype that includes hypotonia, hypothalamic dysfunction, social and behavioral issues, life-threatening hyperphagia, and elevated probability of obesity. Adolescents with PWS are at the highest risk for development of life-threatening obesity due to increased access to food, decreased physical activity, and hyperphagia. Currently, the only treatment for the hyperphagia is environmental control, including locked kitchens and continuous supervision of the affected individual. Caloric intake must be restricted to prevent obesity, which subsequently increases the hunger drive even more. Research and clinical practice have demonstrated that increasing physical activity along with insuring a well-balanced, nutritionally dense diet can improve overall weight control in adolescents with PWS.

Keywords: Prader-Willi syndrome, diet, obesity, nutrition

Prader–Willi syndrome (PWS) is a neurobehavioral genetic disorder due to lack of paternally expressed genes on Chromosome 15q11–q13 that impacts virtually every aspect of the affected individual's life. Individuals with PWS have brain abnormalities, including dysfunction of the hypothalamus, which contributes to abnormal appetite and satiety control, atypical body temperature and pain regulation, self-mutilatory behaviors (eg, skin picking), and aberrant sleep cycle.¹ Additionally, affected individuals have an autism-like phenotype, including learning issues, anxiety, restrictive-repetitive (i.e. compulsive behaviors), and poor social skills.¹ Until recently, it was thought that there were two nutritional phases in PWS: Phase 1 – hypotonia and failure to thrive, and Phase 2 – obesity and hyperphagia. However, it is now recognized that there are several nutritional phases in this syndrome, beginning in utero, with weight and length restriction in affected babies (nutritional Phase 0). After birth, individuals with PWS have a decreased ability to suckle, as well as lack of desire to eat, which typically necessitates the use of a nasogastric or gastric tube to provide adequate nutrition to the infant (nutritional phase 1a).³ Between the ages of 3–12 months, the infant begins to exhibit more typical appetite and satiety signals and will eat normally (nutritional phase 1b).³ It is noteworthy that between 18 months – 3 years of age children with PWS can begin to exhibit excessive weight gain, even without a change in food intake or

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interest in food (nutritional phase 2a). Then, around age 4–5 years of age, food begins to have an increased significance for these children, and they begin to ask a lot of food-related questions (nutritional phase 2b). Interestingly, they are still able to express satiety in this phase, and will push away food they do not like or even leave some food on their plates.^{3,4} The onset of nutritional Phase 3, which is the classically described appetite phase associated with PWS (constant hunger and lack of satiety), typically occurs sometime after age 8 years.^{3,4} The abnormal brain development associated with the syndrome compound the appetite issues by conferring tendency for impulsive and compulsive behaviors around food, increased propensity for temper outbursts when denied access to food, and irregular sleep patterns, which afford the opportunity for food seeking while the remainder of the family is asleep. The underlying pathophysiology of the transition between the nutritional phases in PWS is unknown.

Currently, standard of care treatment for individuals with PWS includes growth hormone therapy during childhood.⁵ It is well established that growth hormone therapy improves metabolism in individuals with PWS, by changing body composition to increase lean muscle mass and decrease fat mass.^{6,7} It also can help contribute to improved weight control by improving muscle strength and motor development, thus increasing the ability of individuals with PWS to participate in physical exercise.⁸ Adolescents and young adults with PWS have to discontinue growth hormone treatment after completion of linear growth, unless they meet criteria for adult growth hormone deficiency.⁹ However, there is evidence that continuation of growth hormone therapy after cessation of linear growth does continue to have benefits in terms of body composition and metabolism, and that stopping growth hormone treatment in adolescents results in deterioration in body composition.^{10,11} Therefore, recommendations from experts in the care and treatment of individuals with PWS include continuation of growth hormone therapy to maintain healthier body composition.⁵ However, it has been noted that growth hormone therapy is not a substitute for dietary control in terms of managing obesity in individuals with PWS – optimal treatment is a combination of growth hormone therapy and dietary control.

At the current time, physicians are able to manage all of the problems associated with this syndrome, with the exception of the extreme, unrelenting hyperphagia. The meaning of the term “hyperphagia” is not well established, but is generally recognized as a relentless hunger with lack of satiety, even after consuming a significant

amount of calories.³ Therefore, without aggressive environmental food restriction and control, individuals with PWS develop severe obesity, with all of its well-known associated morbidities. Moreover, once hyperphagia begins, the focus on food becomes constant and almost impossible to redirect. As one could imagine, this has a profoundly negative impact on education, personal interactions and relationships, occupational performance, and quality of life.¹⁰ In nutritional phase 3, individuals with PWS display aggressive food seeking, and report that they are constantly looking for opportunities to obtain food. Parents report that their children with PWS will sometimes sneak food and hide or hoard it to eat at a later time, will eat non-edible items, steal food from stores or other people, or will steal money to buy food.^{3,4} One of the most dangerous behaviors that can occur in nutritional phase 3 is elopement from the home to get to food (convenience stores, fast-food restaurants, dumpsters, or neighbors’ homes). This often occurs at night when everyone else is asleep, and the individual is so driven to get to food that there seems to be complete oblivion regarding the dangers involved with this behavior.¹¹ In adolescence and adulthood, if they have access to food, individuals with PWS will consume unbelievably large quantities of food extremely quickly, even if it is spoiled, uncooked, or frozen.¹² This behavior leads to risk of death from choking or gastric necrosis, as they often do not chew the food well because they are stuffing as much as they possibly can get, as quickly as they can get it into their mouths, before getting caught.¹² Currently, individuals with PWS are unable to live independently, due to the need for constant food supervision and need for significant environmental restrictions to prevent access to food.

The prevalence of obesity in individuals with PWS varies by age groups, although it has been shown to have a prevalence of 40% in children and adolescents.⁸ As individuals with PWS enter adulthood, the prevalence of obesity increases to 82% - 98%, depending on the study group.¹³ It is well accepted that once excessive weight gain and hyperphagia begin, caloric intake must be significantly restricted to prevent obesity. However, experienced researchers and clinicians recognize that significant calorie restriction subsequently increases the hunger drive and behavioural problems even more. Thus, many research groups have sought to identify the optimal diet for individuals with PWS to maintain weight control, especially once the hyperphagia drive has developed.

It is well established that individuals with PWS have significant weight gain if they consume the Recommended Daily Allowance (RDA) of calories for their age, gender, and height.³ This weight gain propensity is due to the fact that those with PWS have significantly lower energy expenditure, including total energy expenditure (TEE), resting energy expenditure (REE), activity energy expenditure (AEE), sleeping energy expenditure (SEE), and diet-induced thermogenesis (DIT).¹⁴ Each of these various types of energy expenditure are significantly less in individuals with PWS compared to age/sex-matched controls or BMI-matched controls.¹⁴ This lower energy expenditure could be due to the abnormal body composition in individuals with PWS (lower lean mass, increased fat mass), the endocrine abnormalities in individuals with PWS (growth hormone deficiency, central hypothyroidism, leptin resistance), or inadequate fat oxidation.¹⁴ Perhaps most interesting is the development of leptin insensitivity that occurs as individuals progress through the various nutritional phases.¹⁵ Decreased central levels of leptin can lead to impaired release of α -melanocyte-stimulating hormone, which has the downstream effect of reducing energy expenditure.¹⁵ Thus, once the weight gain starts and leptin resistance begins to increase, the energy expenditure worsens even more, sedentary behaviour increases, and a vicious downhill cycle of weight gain spirals, often out of control. Individuals with PWS have been shown to be able to reach >200% of ideal body weight in late adolescence.^{14,15}

Not only do individuals with PWS have lower energy expenditure than controls but also have lower levels of spontaneous physical activity.¹⁶ Studies of exercise performance in individuals with PS have demonstrated impaired stamina and exercise tolerance, decreased cardiorespiratory (maximal oxygen consumption, heart rate recovery after exercise), and abnormally low hormonal responses to exercise.¹⁶ If caregivers are able to get individuals with PWS to engage in consistent aerobic exercise over several months, body composition and body mass index will improve, as will their physical performance. As with any consistent exercise intervention, these individuals experience biochemical (glucose homeostasis, lipid profile) and biomechanical (gait pattern) improvement.^{16,17} Including resistance training as part of the regular exercise routine increases muscle strength, thereby, hopefully increasing their energy expenditure over time.¹⁸ All of this information shows that the first tenant of weight control in adolescents with PWS has to be increasing physical exercise and movement.

A critical factor influencing adherence and maintenance of any activity for individuals with PWS (therapy, exercise, dietary changes) is the rapport between the coach/therapist/dietician/physician and the individual with PWS.¹⁹ Components of success for continuing participation in exercise include: clear communication with no ambiguity; provider willingness to adapt when necessary, so as to avoid a temper tantrum or task avoidance; and encouragement for continuation of the exercise routine by eliciting the individual's input into the types of exercise and goals of the exercise program.¹⁹ Anecdotally, our group recently had 389 individuals with PWS (children through adults) complete a month-long plank and push-up challenge when given a goal of 5 pushups and a 30-second plank after 30 days of practice. This experience emphasizes the fact that these patients can and will do regular exercise with the correct motivation and empowerment. Given current pharmacotherapy trials to aimed to decrease hyperphagia in individuals with PWS, improving confidence and fostering independence will have long-term benefits for success if these trials are effective for treatment of hyperphagia and more independent living becomes possible for individuals with PWS.

Currently, the most utilized/recommended dietary intervention to prevent worsening obesity in adolescents with PWS is calorie restriction.²⁰ Studies evaluating optimal calorie restriction in individuals with PWS have shown that a diet consisting of 8–11 kcal/cm height helps maintain body weight in a healthy range.²⁰ Around 2 years of age, when children with PWS enter nutritional phase 2a they can gain excessive weight, even without a change in appetite or intake.³ We demonstrated, in a long-term natural history study of individuals with PWS, that a well-balanced, energy-restricted diet (~30% fat, 45% carbohydrates, and 25% protein, and at least 20 g of fiber per day) limits weight gain and reduces excess fat mass.²¹ However, there are no long-term studies evaluating the efficacy of a calorie-restricted diet on appetite drive or mental health issues in this unique population.

An additional issue with calorie-restricted diet in adolescents with PWS is nutritional deficiencies that can occur when calories are restricted. Most low-calorie diets are relatively high in carbohydrates (65% carbohydrate, 15% fat, and 20% protein), and have a relatively high percentage of deficiencies in calcium, vitamin D, and iron.²² Because of these issues, some groups have studied the effects of a carbohydrate-restricted diet for weight control in adolescents with PWS (15% carbohydrates, 65% fat,

and 20% protein).²³ This diet, while effective, at least in the short term, for improved glycemic and weight control, is associated with deficiencies in vitamin D, calcium, and fiber. Elevations in C-reactive protein, as well as liver function tests (ALT, AST), have been shown in individuals with PWS following a low-carbohydrate diet.²³ Additionally, a low-carbohydrate diet can affect the gut microbiome, including bacteria taxa, richness and diversity.²⁴ Although a few studies have shown potential beneficial effects of a low-carbohydrate diet on the gut microbiome, most studies have reported that a low-carbohydrate diet has more significant negative effects on the gut microbiome, including lowered species diversity and increased pro-inflammatory bacteria.²⁴ Low-carbohydrate diets lead to significant impairment in growth if used long term, as well as negative alterations in lipid metabolism. Lastly, low-carbohydrate diets are extremely difficult to sustain in the long term.²⁵

Another area of controversy in recommended diet regimens for individuals with PWS is the consumption of non-nutritive sweeteners to replace natural sugars. Individuals with PWS do not like to drink plain water, and therefore are at risk for dehydration and worsened constipation.²⁶ They will drink sweetened or flavored beverages easily, so most families introduce sugar-substitutes in drinks in order to prevent dehydration in the child/adolescent. Although there have been no long-term studies done to investigate this issue in PWS, several studies in healthy individuals have demonstrated that non-nutritive sweeteners have a negative impact on the intestinal microbiome, as well as weight control. Low-calorie sweeteners disrupt the composition and function of the gut mucosa and microbiome.²⁷ Several large-scale prospective cohort studies found positive correlation between non-nutritive sweetener use and long-term weight gain.²⁷ Humans generally will seek to fulfill an innate craving for sweetness, even in the absence of hunger. This drive is compounded in individuals with PWS. Non-nutritive sweeteners activate hedonic response to sweetness and lead to increased appetite.²⁸ Non-nutritive sweeteners, precisely because they are sweet, encourage increased craving and dependence for sweet taste.²⁸ Repeated exposure trains flavor preference. There is a strong correlation between a person's customary intake of a flavor and preference for that flavor.²⁸ Because non-nutritive sweeteners are typically a staple component in any diet for individuals with PWS, they likely further increase hyperphagia and food seeking.

Upon review of all of the available evidence, it seems that the best diet for adolescents with PWS is most similar to the Mediterranean diet.²⁹ The nutritional profile of the Mediterranean diet is largely plant-based, rich in complex carbohydrates, vegetables, fruits, legumes and nuts, in addition to abundant fish intake (including oily fish). The Mediterranean diet encourages moderate consumption of animal-derived proteins, including eggs, poultry, and dairy products and low consumption of red meat, processed meats and sweets.²⁹ Moreover, the Mediterranean diet is a healthy diet for everyone, so if the whole family eats the same foods, there is improved adherence for the individual with PWS over the long term. Additionally, this diet is easier for families to adhere to long term compared to other hypocaloric diets used for weight management in PWS, mainly due to variety of foods and flavors, higher content of fiber and healthy fat to improve feelings of satiety, and liberal use of vegetables to provide more volume to meals.²⁹ Other aspects of this diet include reducing omega 3 to omega 6 fatty acids ratio (increase omega 3 while decreasing omega 6); avoiding simple carbohydrates; encouraging a large variety of foods, and avoidance of artificial sweeteners and processed foods.²⁹ Of note, vegetable bezoars have been seen in adolescents with PWS, which could be due to lower gastric motility or delayed gastric emptying, so it is generally recommended that the intake of raw vegetables be somewhat limited, with primarily cooked vegetables being given at meals (personal reports, unpublished).

Our recommendations are that parents introduce plain water early in childhood and never offer sweetened beverages as an option. Soups and fresh, homemade smoothies with fresh fruit and ice can augment fluid intake. Parents have to be cognizant that teens with PWS have an increased risk of developing severe hyponatraemia if exposed to psychiatric medications known to cause the syndrome of inappropriate antidiuretic hormone secretion (SIADH).³⁰ It is hypothesized that the abnormal water intake could be a result of a dysfunction of the hypothalamic nuclei engaged in antidiuretic hormone production.

A Mediterranean-type diet composition consisting of higher-fiber carbohydrates, dairy, healthy fats, and protein may limit the need for significant calorie restriction by providing the fodder for a more healthy gut microbiome, in addition to appropriate energy sources for growth and exercise and improvement of muscle mass.³¹ Reducing sweeteners in the diet may decrease the drive to obtain food, especially if implemented early in life. We have had

significant success with weight control in adolescents with PWS who are able to continue growth hormone therapy, follow a well-balanced Mediterranean diet, exercise regularly, and have adequate environmental restrictions on access to food. Other well-established experts in the care and treatment of individuals with PWS have noted similar success with maintenance of body mass index and decreased fat mass in adolescents utilizing this protocol.^{10,32} Studies evaluating the gut microbiome changes with various dietary interventions in PWS are currently ongoing, but there is no reason to believe that this diet, which is considered healthiest for the gut microbiome in the general population would be any different for the PWS population.³³

Portion sizes must be controlled based on the level of weight control and exercise for the individual. We typically recommend using the size of the individual's fist as a starting point for measurement of portion sizes for complex carbohydrates and protein, and advise limiting healthy fats and fruit portions to what will fit flat in the palm of the individual. We typically do not put a portion size limit on cooked, non-starchy vegetables, and advise that they should fill half of the plate, as is generally recommended with the Mediterranean diet. Basing the portions on the individual's own palm/fist allows for individualization of the amounts for each person as we are beginning this diet. We found that portion size recommendations based on standard measurements (eg, ½ cup, 1 tablespoon, etc.) led to patients overfilling the measurement cups/spoons in order to try to sneak in more food. Additionally, asking families to measure out foods often results in increased anxiety for the parents as well as an increased focus on food at mealtimes. Both of these issues are counterproductive when attempting to control the diet of an adolescent with PWS, as they lead to an increased interest and anxiety regarding food and portion sizes, which then can result in behavioral problems/meltdowns.³⁴

We advise that meal times be as low stress for the family as possible, in order to decrease behaviors centered around food for the individual with PWS. Therefore, we recommend that the whole family eat the same, well-balanced, healthy diet and drink plain water or milk with meals, as we ask our patients to do. We have found that following these recommendations results in improved weight control for the individual with PWS, as well as more peaceful meals for the family without arguments regarding differences in diet between various family members.

Disclosure

The authors report no conflicts of interest in this work.

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