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Review | Derleme

A GENETIC DISEASE BEHIND OBESITY AND ITS NUTRITIONAL TREATMENT; PRADER-WILLI SYNDROME

OBEZİTENİN ARKASINDAKİ GENETİK HASTALIK VE BESLENME TEDAVİSİ; PRADER-WİLLİ SENDROMU

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ABSTRACT

Obesity is a health problem that reduces quality of life and is associated with many chronic diseases. It has multiple causes, including physiological, socio-cultural, psychological, and genetic factors. Prader-Willi Syndrome (PWS) is the most common genetic disorder associated with obesity. It is characterized by severe anorexia in infancy and hyperphagia during childhood. The hyperphagia that begins in childhood is the main cause of obesity in PWS. Hyperphagia occurs because of an imbalance in the hunger-satiety metabolism. Due to elevated levels of the hormone ghrelin, a sense of satiety cannot be achieved. The aim of the treatments applied is to prevent obesity. Medical nutrition therapy is considered the most effective treatment method. To prevent obesity in individuals with PWS, lifelong adherence to nutritional therapy is required.

Keywords: Prader-Willi Syndrome, obesity, medical nutrition therapy

ÖZ

Obezite yaşam kalitesini azaltan, birçok kronik hastalıkla ilişkilendirilen bir sağlık sorunudur. Obezitenin fizyolojik, sosyo-kültürel, psikolojik, genetik birçok sebebi bulunmaktadır. Prader-Willi Sendromu (PWS) obezite ile ilişkilendirilen en yaygın genetik hastalıktır. Bebeklik döneminde şiddetli anoreksi, çocukluk döneminde hiperfaji ile karakterizedir. Çocukluk dönemi itibariyle başlayan hiperfaji PWS'de obezite oluşumunun temelidir. Hiperfaji açlık-tokluk metabolizmasındaki dengenin bozulması sonucu oluşmaktadır. Artan grelin hormonu seviyeleri sebebiyle tokluk hissi oluşamamaktadır. Uygulanan tedavilerin amacı obezitenin önlenmesine yöneliktir. En etkili tedavi yönteminin tıbbi beslenme tedavisi olduğu belirtilmektedir. PWS'de obezitenin önüne geçilebilmesi için yaşam boyu beslenme tedavisine devam edilmesi gerekmektedir.

Anahtar Kelimeler: Prader-willi sendromu, obezite, tıbbi beslenme tedavisi

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Introduction

Prader-Willi Syndrome (PWS) is a genetic disorder characterized by feeding difficulties and severe hypotonia in early infancy, followed by excessive eating and loss of control overeating behavior in in boys during childhood. The prevalence of the disease is reported to range between 1/10,000 and 1/30,000. Individuals with PWS exhibit delayed development of language and motor skills, along with mild cognitive impairment. Anger outbursts and manipulative behaviors are commonly observed phenotypic features accompanying these symptoms. Clinical manifestations include hypogonadism, genital hypoplasia, delayed pubertal development, and infertility affecting both sexes. Additionally, short stature due to growth hormone deficiency is commonly seen. The clinical features of PWS were first described first described in 1887 as increased adipose tissue. In 1956, Prader, Labhart, and Willi, who named the disease, made a definition that included clinical features such as cognitive impairment and hypogonadism along with obesity.[1,2] Prader-Willi Syndrome is associated with developmental disabilities and genetic abnormalities, such as lack of expression of genes inherited from the paternal chromosome 15q11-q13 region.[3] This lack of gene expression contributes to the unique clinical features of PWS, including hypotonia, short stature, and obesity.[4]

The excessive eating behavior that develops in conjunction with Prader-Willi syndrome leads to the formation of obesity. Consequently, comorbidities of obesity, such as insulin resistance, type II diabetes mellitus, and sleep disorders, are frequently observed in individuals with Prader-Willi syndrome.[5] Obesity formation in Prader-Willi syndrome is attributed to disruptions in hypothalamic control pathways and imbalance in hunger-satiety metabolism hormones. Despite research efforts investigating the genetic basis of obesity, there are relatively few studies exploring the relationship between Prader-Willi syndrome and obesity. This review aims to investigate the relationship between Prader-Willi syndrome—the most common genetic cause of obesity—and obesity itself.[6]

Clinical Findings in Prader-Willi Syndrome

Characteristic facial features such as almond-shaped eyes, low-set ears, and a small mouth are observed in individuals with PWS. In addition to these facial features, clinical findings include infantile central hypotonia, feeding difficulties in infancy, growth retardation, hypogonadism, hyperphagia (excessive eating), and rapid weight gain after infancy.[7] The age-dependent clinical findings in PWS are presented in Table 1.

Hypotonia: In PWS, signs of hypotonia can be detected as early as the fetal period. It is often associated with decreased fetal movements and an increased likelihood of cesarean delivery. In infancy, it results in reduced reflexes, lack of mobility, decreased response to spontaneous stimuli, feeding difficulties, and failure to achieve necessary weight gain. Mild to moderate hypotonia persists throughout the life of individuals with Prader-Willi syndrome.[8]

Table 1. Clinical Findings in Prader-Willi Syndrome.

Age Range (year)	Clinical Findings
0-2	• Inadequate sucking reflex • Hypotonia
2-6	• Inadequate sucking reflex • Hypotonia
6-12	• Hypotonia • Growth retardation • Obesity due to excessive eating
≥13	• Cognitive impairment • Uncontrolled eating behavior • Hypothalamic hypogonadism and/or typical behavioral issues

Hypogonadism: Congenital hypogonadism is a commonly encountered clinical manifestation in PWS. It results from inadequate secretion of gonadal steroids due to deficiency in pituitary gonadotropins, including Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH). Cryptorchidism is found in the majority of male children with Prader-Willi syndrome.[9,10]

Growth Retardation: Individuals with Prader-Willi syndrome (PWS) commonly experience developmental delays in motor skills. The prevalence of this delay is reported to range between 90-100%. In the majority of children with PWS, the acquisition of sitting, walking, and speaking skills occurs much later compared to their peers. When examining the IQ scores of PWS individuals, it is noted that the majority have a mild level of intellectual disability (IQ: 60-70). Regardless of IQ levels, children with PWS often struggle with learning difficulties, and their academic skills are generally weak.[11]

Diagnostic Criteria

Classic neonatal findings of PWS include central hypotonia and decreased deep tendon reflexes. Additional features are feeding difficulty, weak crying, decreased fetal movements, and characteristic facial features. Diagnostic criteria were developed by Holm et al. in 1993. Minor and major criteria are shown in Table 2. For diagnosing PWS, major criteria are assigned 1 point each, while minor criteria are assigned 0.5 points. Between the neonatal period and age 3, a total score of 5 or more, including at least four major criteria, is considered diagnostic. Between ages 3 and adolescence, a score above 8, including at least five major criteria, is diagnostic.[12]

Prader-Willi Syndrome and Obesity

Obesity is the most significant health issue in PWS. It is a risk factor for many diseases such as heart disease, atherosclerosis, and diabetes. Obesity develops in conjunction with excessive eating after anorexia experienced in infancy.[13] In Prader-Willi syndrome, individuals often exceed the ideal body weight

significantly, and if left untreated, obesity-related complications such as cardiopulmonary disorders, hypertension, and diabetes mellitus can result in significant morbidity and mortality. In PWS, the body fat percentage can reach 40–50%, markedly exceeding normal ranges.[13]

Table 2. Diagnostic Criteria for PWS.

Criteria	Score
Major Criteria • Infantile central hypotonia • Characteristic facial findings (dolichocephaly, narrow bifrontal diameter, almond eyes, downward-turned lips, small mouth) • Feeding difficulties in infancy • Developmental delay • Hypogonadism (hypoplasia of the scrotum, undescended testicle, small penis or testicle in boys; hypoplasia of the labia minora or clitoris in girls) • Hyperphagia • Rapid weight gain between the ages of 1-6	1-point for each
Minor Criteria • Decreased fetal movements and lethargy in the intrauterine period. • Esotropia, myopia • Small hands and feet • Short stature (compared to family members) • Hypopigmentation • Sleep disorder or apnea • Articulation defect • Viscous secretion • Behavior problems	0.5 point for each

In PWS, obesity arises due to hyperphagia, reduced satiety perception, and loss of appetite control. The combination of excessive caloric intake, reduced energy expenditure, and insufficient physical activity leads to morbid obesity. The use of appetite suppressant medications to control hyperphagia has not yet been proven effective in preventing obesity in PWS.[14] The physiological mechanisms involved in the formation of obesity include disturbances in limbic-hypothalamic pathways responsible for satiety control and changes in hormones regulating food intake.[15]

A persistent increase in plasma ghrelin is associated with an increase in appetite and food intake through central regulatory mechanisms in the hypothalamus. Decreased plasma Pancreatic Polypeptide (PP) and Peptide YY (PYY) play a role in the loss of satiety control. Growth hormone deficiency and hypogonadism lead to a decrease in muscle mass and an increase in body fat. Central hypothyroidism results in decreased energy expenditure.[16] Figure 1 illustrates the physiological mechanisms involved in the formation of obesity in PWS.

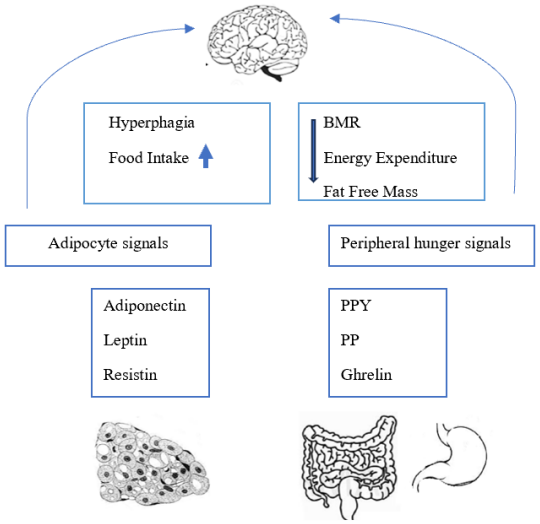

Figure 1. Physiological mechanisms of obesity in PWS.

Central Hormones and Peptides Playing a Key Role in Obesity Formation in Prader-Willi Syndrome

Ghrelin: Ghrelin, known as the hunger hormone, is secreted by the stomach. The release of ghrelin stimulates appetite and leads to food intake, after which blood ghrelin levels typically decrease. In Prader-Willi syndrome, it has been determined that ghrelin levels are above normal and show a continuous increase.[17-19] Additionally, A study evaluating ghrelin levels before and after food intake in individuals with PWS found no postprandial decrease in ghrelin levels.[20] Elevated ghrelin levels in PWS contribute to hyperphagia and are believed to play a fundamental role in the development of obesity.[19]

Pancreatic Polypeptide (PP) and Peptide YY (PYY): Pancreatic Polypeptide and Peptide YY are anorexigenic hormones released by the intestine that promote satiety and inhibit food intake.[21] In children with PWS, decreased levels of PP have been identified, indicating a lack of satiety.[22] Moreover, studies have found no difference in the brain expression patterns of ghrelin, PYY, or their receptors between individuals with and without PWS.[23]

Leptin: Leptin is a peptide produced by adipose tissue and plays a role in regulating appetite and fat storage. Released by adipocytes in response to signals of satiety, leptin inhibits neuropeptide Y neurons, reducing food intake and energy metabolism.[24] In a study by Goldstone et al, fasting leptin levels in individuals with PWS (n=42, aged 7 months to 5 years) were found to be significantly higher compared to age, gender, and body mass index-matched controls (n=9).[22] However, another study did not find a significant relationship between leptin levels and obesity in individuals with PWS or healthy controls.[25] The impact of leptin on appetite metabolism in PWS has not been conclusively established, and there are studies with varying results on this topic.

Adiponectin: Adiponectin is a peptide produced by adipose tissue and plays a role in regulating fat storage.

It has significant effects on increasing insulin sensitivity. In a study, serum adiponectin levels were found to be significantly lower in individuals with PWS who were obese compared to those who were lean.[26] It has been determined that adiponectin increases insulin sensitivity in Prader-Willi syndrome.[27] In another research, it was concluded that children with PWS have a lower likelihood of developing diabetes compared to a healthy control group with similar body mass index levels, attributed to the higher secretion of adiponectin in individuals with PWS.[28]

Nutritional Therapy in Prader-Willi Syndrome

Nutritional therapy for patients with PWS is typically structured as a standard two-stage process, based on the clinical course. The first stage (up to 18 months of age) addresses the period characterized by poor nutrition, often accompanied by hypotonia and growth retardation. In the second stage, the focus shifts to addressing obesity resulting from hyperphagia. During this stage, caloric intake is restricted to 60–80% of the Recommended Dietary Allowance (RDA) to prevent obesity caused by hyperphagia in children.[29]

The lack of satiety and hyperphagia is one of the most significant challenges affecting individuals with Prader-Willi Syndrome and their families. Individuals with PWS face numerous chronic diseases that pose a life-threatening risk due to the potential for obesity. Achieving and maintaining proper body weight is crucial in the treatment of Prader-Willi Syndrome. It is suggested that approximately 60% of the energy intake requirement is sufficient to achieve the necessary weight loss in these children.[13]

During adulthood, the recommended calorie intake to maintain weight varies among individuals but is generally advised to be between 1000-1200 kcal/day. For children, the recommended dietary treatment to achieve weight loss should be around 75-80% of their age-specific requirements. In cases of hyperphagia, energy intake needs to be restricted. The content of implemented diets should be balanced, including complex carbohydrates and being rich in fiber.[13] Without early, intensive nutritional therapy along with behavioral modification, PWS patients develop severe obesity associated with type 2 diabetes, obstructive sleep apnea, right-side heart failure, and other obesity-related metabolic complications.[30]

Dietary variety should be increased, with a particular emphasis on regular consumption of vegetable dishes and salads, while maintaining portion control with fruits. Increased water consumption is essential. Portion sizes should be reduced, and smaller plates should be used for serving to enhance visual appeal. The introduction of packaged products (biscuits, candies, etc.) to children with PWS should be delayed as much as possible. Food restrictions should not be used as a punitive measure, and no food item should be given as a reward to the child. PWS children should be encouraged to increase physical activity, including exercise, dance, and other calorie-burning activities. They should be kept away from stimuli that might encourage overeating. Establishing a daily routine that aids weight control is crucial, and its continuity should be ensured. Relatives and friends of individuals with PWS should be informed about the implemented diet plan, and they should be prevented from directing PWS individuals toward non-compliant eating habits. It should be communicated to the child with Prader-Willi Syndrome that giving them food "secretly" is not an expression of love; on the contrary, it negatively impacts the child's dietary regimen and health. While implementing dietary therapy, children should be educated in detail about what to consider in food choices, and if there is a deviation from the daily routine, the child should be informed in advance. Various activities should be organized to reduce repetitive food requests.[31]

The effectiveness of pharmacological treatments for Prader-Willi Syndrome has not been fully proven. Placebo-controlled studies of anorexigenic agents have shown no significant impact on hyperphagia. The effectiveness of endocannabinoid receptor agonists and various treatment approaches is still under investigation.[32,33]

Carbohydrate

Carbohydrates are organic compounds composed of carbon, oxygen, and hydrogen, serving as a primary source of energy for the body and being the most abundant nutrient in our diet. In a study focusing on carbohydrate intake ranging from 50% to 70%, with 12 grams or less of fiber, it was revealed that individuals with Prader-Willi Syndrome (PWS) could benefit from a well-balanced, energy-restricted diet with lower carbohydrate consumption and higher dietary fiber intake. It is known that individuals with PWS tend to prefer simple carbohydrates. However, excessive intake of simple carbohydrates, which are high in energy but low in nutrients, can lead to obesity. Therefore, while emphasizing the need to reduce energy intake in individuals with PWS, a healthy and balanced approach is recommended by providing complex carbohydrates. Considering the potential fluctuations in plasma glucose levels caused by simple carbohydrates, it is also suggested in the nutrition program to prefer carbohydrates with low glycemic index and load to avoid such fluctuations.[34]

In a study conducted by Irizarry et al., one group was given a low-carbohydrate diet (15% carb; 65% fat; 20% protein), while the other group received a low-fat diet (65% carb, 15% fat, 20% protein). In the study, subjects consuming the LF diet had lower postprandial insulin concentrations ($p<0.05$); and higher fasting GLP-1 ($p<0.05$).[35]

Dietary fiber is thought to be beneficial in body weight control due to its effect on the intestinal microbiota. Studies also emphasize dietary fiber intake in PWS.[36,37] In a study conducted by Zhang et al. on 38 obese children with PWS, they showed that a diet rich in indigestible carbohydrates had significant contributions to both weight loss and dysbiosis.[37]

Protein

Protein intake is crucial for individuals with Prader-Willi syndrome due to the unique challenges they face, such as obesity and altered energy metabolism. Adequate protein intake has an important role in increasing satiety. Proper protein intake is important in PWS patients with lean mass deficiencies.[38]

Butler et al.[32] conducted study that a comparison of two different obesity treatments for children with Prader-Willi syndrome. In this study, a group of 33 individuals followed a diet consisting of 45% of energy intake from carbohydrates (with a minimum of 20 grams of fiber per day), 25% from protein, and 30% from fats. The diet of another group of 30 individuals included 50%-70% carbohydrates (≤12 grams of fiber per day), 10%-23% fats, and 15%-20% proteins. Significant and higher losses in both body fat and body weight were observed in the first group of children.

The study, based on the premise that meals with high protein content increase energy expenditure, examined the postprandial energy expenditure of individuals with Prader-Willi syndrome consuming different meals. Isocaloric breakfasts were planned for 5 individuals with Prader-Willi syndrome aged between 10 and 25. One of these breakfasts contained 15% protein, while the other contained 50% protein. Upon examining the energy expenditure after consuming these two different meals, no significant difference was found.[39]

Fat

Fat intake, which is one of the essential nutrients for human life, ensures the intake of fat-soluble vitamins in the diet and the consumption of essential fatty acids that contribute to the structure of phospholipids in cell membranes. Different dietary models with varying levels of fat content are also being studied for Prader-Willi syndrome.[40]

Teke Kısa et al.[41] conducted a study investigating the impact of a ketogenic diet on weight management in children with Prader-Willi syndrome. In this study, 10 children followed a ketogenic diet for a minimum of 6 months. The diet was composed of 75%-85% of energy from fats, 15%-25% from protein, and carbohydrates. The median BMI SD score before diet intervention was 3.05 [−0.21–3.72], whereas it was 0.41 [−0.87–1.57] at the final evaluation ($p = 0.002$). While larger population studies are needed to determine the effectiveness of the ketogenic diet on body weight, it should be noted that it may have different side effects, such as hypercholesterolemia.

Bariatric surgery

The efficacy of restrictive bariatric procedures, such as gastric banding or bypass, on hyperphagia and long-term weight loss in individuals with PWS remains inconclusive.[42,43] While successful weight loss has been achieved with the use of biliopancreatic diversion, complications arising from intestinal absorption issues have been observed. Bariatric surgical procedures are generally recommended only in cases where excessive weight poses a life-threatening risk. Postoperative dietary control after bariatric surgery requires continuous and careful monitoring to ensure long-term success.[44]

New Approaches to Therapy in Prader-Willi Syndrome

Using belaronide to prevent hyperphagia

The PWS research community is highly interested in a medical agent that can decrease hyperphagia. Beloranib, an irreversible inhibitor of methionine aminopeptidase 2 (MetAP2), has garnered considerable attention as a potential treatment. MetAP2 inhibitors were previously utilized in cancer treatment due to their capability to slow endothelial cell growth and reduce angiogenesis. At lower doses, below those needed to inhibit angiogenesis and tumor growth, MetAP2 inhibitors have been shown to reduce food intake, body weight, and adipose tissue mass. Although the precise mechanism behind weight loss and reduced appetite are not fully understood, MetAP2 inhibitors lead to triglyceride lipolysis, fatty acid oxidation, ketogenesis, and suppression of food intake via alterations in the extracellular signal-related kinase stress kinase pathway.[45]

Using Co-enzyme Q10 (CoQ10) and Carnitine to increase energy expenditure

PWS is distinguished by infantile hypotonia, sarcopenia, and reduced resting energy expenditure. Some of these characteristics are shared with other conditions characterized by low levels of co-enzyme Q10 (CoQ10), an essential component of the mitochondrial respiratory chain and an electron carrier. Studies have indicated lower CoQ10 levels in both PWS and obese children compared to healthy non-obese controls. While CoQ10 is frequently used as a supplementary treatment in PWS without reported adverse effects, its effectiveness in enhancing motor development and metabolic function remains uncertain. Some reports suggest that CoQ10 supplementation may increase daytime alertness.[46]

Similar to CoQ10 deficiency, carnitine deficiency is linked to hypotonia, inadequate growth, and easy fatigability. Interestingly, unlike CoQ10, carnitine levels are higher in PWS individuals compared to healthy controls, indicating impaired carnitine utilization in PWS. Evidence regarding the beneficial effects of carnitine supplementation remains inconclusive. A recent study administered carnitine at a dosage of 25 mg/kg twice daily to twenty subjects; thirteen reported improved exercise tolerance and daytime alertness, while seven reported no benefits.[47]

Conclusions

Prader-Willi Syndrome is the most common genetic disorder underlying obesity, primarily due to impaired satiety signaling, which leads to hyperphagia. The increased rates of mortality and morbidity in PWS are attributed to coexisting diseases accompanying obesity. Therefore, preventing obesity is crucial for improving quality of life and preserving health in individuals with PWS. The most effective method used in the treatment

of obesity in PWS is nutritional therapy. Creating a balanced diet plan and ensuring its continuity are essential for controlling the disease.

Detecting endocrine disorders and applying replacement therapy for hormone deficiencies are crucial. Additionally, increasing physical activity significantly enhances the effectiveness of dietary interventions. A multidisciplinary treatment approach should be implemented for individuals with PWS, with dietary therapy supervised by a qualified dietitian. Caregivers, teachers, and family members should be thoroughly educated about PWS and the treatment strategies being implemented.

Conflicts of Interest

There is no conflict of interest between the authors.

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Author Contribution

GD, AB: Design, literature review and data collection, writing of the study; GD, AB: Analysis and interpretation, literature review, writing of the study.

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