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Management of obesity in prader-willi syndrome

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ABSTRACT

Introduction: Obesity is a significant health concern in individuals with Prader-Willi Syndrome (PWS), a rare genetic condition characterized by insatiable appetite. This study aims to address obesity in PWS, understanding the management strategies and their impact on the health of these patients. Objectives: The objective of this research is to evaluate therapeutic approaches and their outcomes in the treatment of obesity in individuals with Prader-Willi Syndrome. Additionally, we seek to understand how these interventions affect the overall quality of life and health of the patients. Methodology: A comprehensive review of medical literature related to obesity in Prader-Willi Syndrome was conducted. Clinical studies, systematic reviews, and case reports describing dietary, behavioral, and medical interventions used in the treatment of obesity in PWS patients were analyzed. Results: The results underscore the importance of a multidisciplinary approach in the treatment of obesity in Prader-Willi Syndrome. Restrictive dietary interventions, regular medical monitoring and adapted physical activity have proven effective in weight management. Furthermore, early intervention plays a crucial role in the successful management of obesity. Conclusion: Obesity in Prader-Willi Syndrome presents a complex challenge, but with the right approach, positive outcomes are achievable. Personalized treatment, taking into consideration the individual needs of each patient, is essential. Managing obesity in PWS not only improves physical health but also contributes to enhancing the quality of life for these individuals and their families.

Keywords: Prader-Willi Syndrome, Obesity, Management.

1 INTRODUCTION

Prader-Willi Syndrome is a rare genetic pathology that affects several systems of the body. It is caused, in approximately 60% of cases, by the loss of gene expression of the paternal chromosome 15q11-q13. In even rarer cases, approximately 35% of cases, it may be caused by a maternal

uniparental disomy of chromosome 15. The prevalence of the syndrome is 1/15,000 live births, affecting boys and girls equally, and with no predilection for ethnicity or groups. (Aguiar *et al.*, 2022; Goulart *et al.*, 2021)

The clinical picture is characterized by two distinct clinical phases. In the first phase, the child presents neonatal hypotonia, lethargy, difficulty sucking, weak crying, and hyporeflexia in the neonatal period. After the first 6 months of age, hypotonia improves and the child begins to present dyspnea and apnea during sleep, leading to significant sleepiness, moderate to severe mental retardation associated with learning disorders, short stature due to growth hormone deficiency, hypogonadism that predisposes to a deficiency in sexual development and increased appetite leading to obesity. Hyperphagia is the most pronounced symptom of the syndrome. Associated with the improperly reduced use of ingested calories, the voluminous intake of food contributes to intense sleepiness, increasing the chances of the child developing severe obesity. (Junior *et al,* 2005; Holm *et al.* 1993)

Obesity is a chronic metabolic condition that develops due to the excessive accumulation of adipose tissue in the body, caused by the combination of exogenous factors, such as hypercaloric diets associated with a sedentary lifestyle, and endogenous factors, such as alterations in specific genes (Zubrzycki *et al.*, 2018). It is an important factor in the development of type 2 diabetes mellitus (DM2) and carries additional health risks, since the high body mass index is related to increased cardiovascular risk and, consequently, morbidity and mortality (Borgundvaag; Mak; Kramer, 2020).

The cause of obesity in PWS is intrinsically linked to dysregulated appetite, a central feature of the syndrome. Affected individuals experience a constant feeling of hunger, which leads to an excessive consumption of food and, consequently, weight gain. In addition, reduced metabolic rate in people with PWS contributes to the tendency toward obesity. These factors combined make obesity one of the main morbidities in this syndrome, increasing the risk of serious health problems such as diabetes, heart problems, and sleep apnea. (Bellis *et al.*, 2022)

Effective management of obesity in PWS is of critical importance, since obesity can further aggravate already present health complications. Intervention should be started early, ideally in childhood, to maximize benefits and minimize risks associated with obesity. The health care team that deals with patients with PWS should consist of professionals from a variety of specialties, including physicians, nutritionists, psychologists, occupational therapists, and physical therapists. The approach should be tailored to the individual needs of each patient, taking into account factors such as age, severity of obesity, associated medical conditions, and medical history. (Muscogiuri *et al.*, 2019)

A key part of obesity management in PWS is a restricted and controlled diet. Calories ingested should be strictly monitored and controlled to prevent excessive weight gain. However, this dietary restriction should not be excessive, since it can lead to obsessive behaviors towards food. Therefore,

careful supervision by a dietitian is crucial to balance calorie restriction with basic nutritional need. (Mackenzie *et al.*, 2018)

In addition to diet, behavioral therapy plays an essential role in the management of obesity in PWS. Patients and their families must learn strategies to cope with insatiable appetite and food urges. This includes developing self-regulation and control skills, as well as identifying triggers that trigger excessive food consumption. (Tan *et al*., 2020)

Adapted physical activity is another key component in the management of obesity in patients with PWS. Due to the hypotonia characteristic of the syndrome, physical activity should be adapted to individual capacities, with a focus on improving muscle strength and promoting mobility. Targeted and supervised exercise programs can be beneficial for avoiding a sedentary lifestyle and contributing to weight management. (Bellicha *et al.*, 2021)

2 OBJECTIVE

This study aims to address the management of obesity in people with Prader-Willi Syndrome and its nuances, since it is a condition characterized by significant hyperphagia and metabolic dysfunctions.

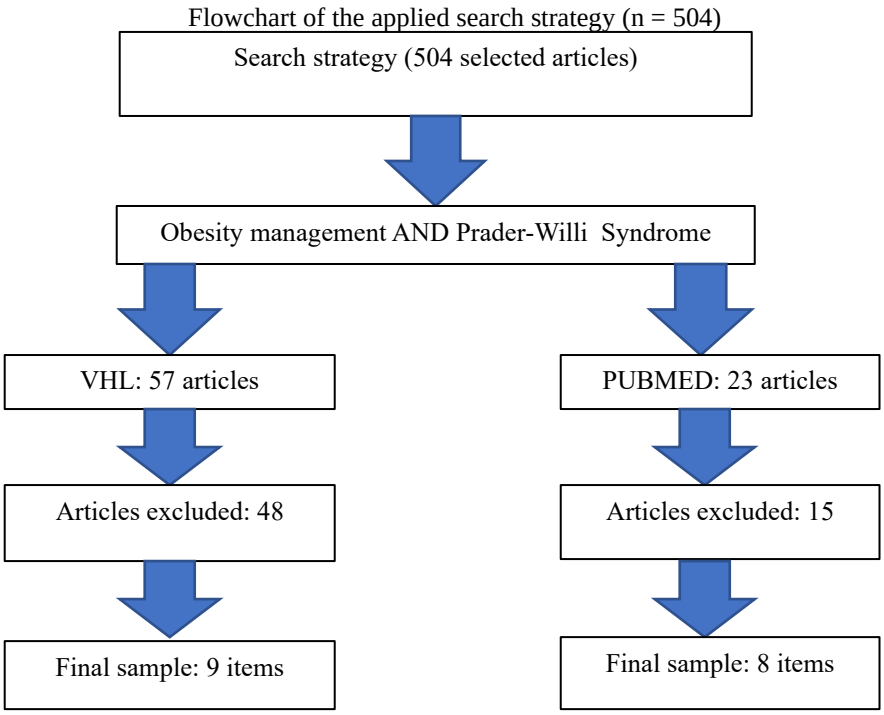
3 MATERIALS AND METHODS

The present study is an integrative literature review that enables the search, critical evaluation and synthesis of available evidence on the investigated topic. In the first stage, the following guiding question was asked: "How to manage obesity in patients with Prader-Willi Syndrome?".

Then, in the second stage, in October 2023, the scientific search was carried out through the PubMed and VHL platforms, using the following descriptors indexed in the Health Sciences Descriptors (DeCS): "*obesity management" and "*Prader-Willi syndrome"*, which were gathered using the Boolean descriptor AND.*

Regarding the inclusion criteria for the selection of articles, the following were established: articles published in the last five years, available as full text and in English or Portuguese.

Initially, 504 studies were found based on the use of the descriptors in the databases, 33 in PubMed, 445 in Medline, 11 in the Latin American and Caribbean Health Sciences Literature (LILACS), 11 in the Index Medicus for the Western Pacific (WPRIM) and 4 in the Bibliographic Index Español en Ciencias de la Salud (IBECS). After applying the inclusion and exclusion criteria, 80 studies were selected; these were screened considering the reading of the title and keywords, and 28 studies were considered in the next stage of selection. Then, 4 were excluded due to duplicity, leaving 24 papers to be read and, of these, 22 underwent a full analysis and 17 investigations made up the final sample.



Finally, a data collection form was used for the critical analysis of the studies, consisting of the following information: title, authors, year, place of execution of the study, sample, objective, design, and main results (Pinheiro *et al.*, 2021). The selection of articles was carried out independently by three authors and there was no disagreement regarding the selected works.

4 RESULTS

The studies analyzed were published between 2018 and 2023 and conducted in Brazil, France, Italy, Canada, the United States, China, and Australia. Regarding the methodological approach, the studies were literature review (n=12, 70%); double-blind randomized clinical trial (n=1; 6%); non-randomized clinical trial (n=3; 18%) and retrospective cohort (n=1; 6%). Adults and children participated in the study, either by undergoing interventions or by composing, quantitatively, the results in the literature reviews. (Chart 1).

Table 1 – Characteristics of the selected studies. (n=17).

Author and year	Outline	Objective	Sample & Scenario	Main results
Alves; Franco, 2020	Literature review	To update on the endocrinological aspects of PWS considering diagnosis and treatment.	Not applicable	Not applicable
Diene *et al.*, 2022	Double-blind randomized clinical trial	To determine whether pharmacological treatment with liraglutide is superior or not to	52-week clinical trial with a 16-week double-blind period. The sample consisted of 31 adolescents between	There were no significant differences in BMI between the adolescent group and the adult group.

		placebo in paediatric patients with PWS.	12 and 17 years old and 24 children between 6 and 11 years old with PWS and obesity. Liraglutide was administered 3mg in one group and placebo in the other group.	
Crinò *et al.*, 2018	Literature review	To analyze therapeutic options for PWS, including pharmacological and surgical interventions.	Not applicable.	Not applicable
Miller; Tan, 2020	Literature review	Address the main forms of non-pharmacological management of PWS	Not applicable.	Not applicable.
Barrea *et al.*, 2022	Literature review	Update on the main forms of pharmacological and non-pharmacological management of PWS	Not applicable.	Not applicable.
Calcaterra *et al*., 2023	Literature review	Dissertation on the main ways to prevent hyperphagia and obesity in PWS.	Not applicable.	Not applicable.
Wolfe *et al.*, 2023	Literature review	To define the change in BMI resulting from the main bariatric surgeries: Laparoscopic sleeve gastrectomy, gastric bypass, and biliopancreatic diversion.	Not applicable.	Not applicable.

Bellicha *et al.*, 2021	Literature review	To describe sedentary behavior and level of physical activity in children and adults with PWS; Analyze their relationships with their health levels and physical compositions.	Not applicable.	Not applicable.
Éva erhardt; Dénes molnár, 2022	Literature review	To summarize the current knowledge about the dietary management and treatment of PWS for the prevention of excessive weight gain.	Not applicable.	Not applicable.
Nolan; Proietto; Sumithran, 2022	Retrospective cohort	To examine the efficacy, safety, and tolerability of interventions that cause sudden weight loss in PWS patients.	18 individuals with PWS (13 with obesity). Average weight of 97kg and average BMI of 41kg/m2. The work took place at Austin Hospital in Melbourne, Australia.	There was significant weight loss and BMI improvement in all participants.
BELLIS *et al.*, 2022	Literature review	To quantify the type and severity of hyperphagia-related morbidity and mortality in PWS patients.	Not applicable.	Not applicable.
Li et al., 2021	Non-randomized clinical trial	OBJECTIVE: To analyze the relationship between diets with high dietary fiber content and improved quality of life standards in PWS patients.	Children with nonsyndromic obesity (n=19) and children with PWS (n=17) underwent dietary protocols at a children's hospital in Guangdong for 30-90 days.	The dietary intervention caused important positive changes in the gut microbiota of both groups.

Muscogiuri *et al.*, 2019	Literature review	Provide an up-to-date overview of the endocrine and metabolic complications of PWS.	Not applicable.	Not applicable.
Tan *et al.*, 2020	Literature review	To provide an evidence-based update on treatment options for hyperphagia and obesity in PWS patients.	Not applicable.	Not applicable.
Rubin *et al.*, 2018	Non-randomized clinical trial	To determine whether participation in 24 weeks of physical activity causes positive cardiometabolic changes in children with PWS and non-PWS.	18 children with PWS (aged between 9.8 and 11.2 years), perceived fat between 42.6% and 46.6% and 30 children with non-syndromic obesity (between 9.5 and 9.9 years of age). They underwent a 24-week physical activity program.	All children in the study showed a reduction in inflammatory markers, improvement in HOMA-IR parameters, and improvement in HDL levels.
Mackenzie *et al.*, 2018	Non-randomized clinical trial	OBJECTIVE: To estimate the intake of essential nutrients and the dietary quality of young people with PWS in relation to young people who do not have the syndrome.	23 young people with PWS and 23 young people who do not have PWS. Food intake was controlled.	The two groups had similar results, with substantial improvement in body composition.
Muscogiuri *et al.*, 2021	Literature review.	To provide an up-to-date perspective on obesity in PWS, from a pathophysiological point of view to the complications resulting from obesity and conservative management.	Not applicable.	Not applicable.

Due to the limited volume of randomized and non-randomized clinical trials and adequate prospective and retrospective cohort studies in the main databases evaluated, literature reviews were included in the study sample. This is mainly due to the promotion of counterpoints and discussion of biases that will be addressed in the discussion of the work.

5 DISCUSSION

Obesity in individuals with Prader-Willi Syndrome has characteristics that are not common to simple obesity. In fact, lean mass is lower in individuals with PWS than in normal-weight people and even lower than in obese individuals. The decrease in muscle mass is responsible for the reduction in resting energy expenditure (REE), but a normal ratio of fat-free mass to REE is maintained in individuals with PWS. That is, adults and children with PWS accumulate more adipose tissue due to the low amount of musculoskeletal mass. Typically, obesity in PWS affects the trunk and proximal extremities of the limbs. Differently from what occurs in non-syndromic obesity, individuals with PWS have a lower ratio between trunk and limb fat mass, as well as lower visceral adiposity. In addition, patients with PWS have a higher insulin sensitivity compared to obese patients who do not have the syndrome. (Crinó *et al.*, 2018)

Obesity in Prader-Willi Syndrome presents nuances that make the management of the condition more complex compared to obese patients who do not have the clinical condition. Hypogonadism and growth hormone (GH) deficiency are the most prominent problems involved (Muscogiuri *et al.*, 2019). Girls with PWS may have hypoplasia of the labia minora and clitoris. They are usually fertile and, therefore, contraceptive methods should be indicated. Boys usually have cryptochidisa, hypoplastic scrotum, micropenis, and are often infertile. For boys, the use of human chorionic gonadotropin (hCG) may be an option while still a child. From the age of 14, the use of testosterone as a form of hormone replacement therapy (HRT) is a viable option. For cryptokyrdia, orchidopexy in the first years of life. For girls, the use of combined oral or transdermal contraception is indicated. (Alves; Franco, 2020)

Short stature is common in Prader-Willi syndrome, and without growth hormone replacement, the final average height is 155-160 cm for men and 145-150 cm for women. Younger children may have a normal reserve of growth hormone in the pituitary gland, but are deficient in hypothalamic secretion of GH-releasing hormone. As these children grow, they can deplete this GH reserve and become disabled. Growth hormone (GH) replacement therapy results in less decline in IQ scores with age. Despite the recommendation to start rhGH replacement in PWS in an average of 7 years, rhGH treatment has been indicated earlier. The benefits of rhGH treatment starting at 4-6 months of age have already been demonstrated. Recent studies have shown positive effects on neurocognitive and behavioral development when rhGH treatment is started before 2 years of age. (Alves; Franco, 2020; Muscogiuri *et al.*, 2019)

During early childhood, individuals with Prader-Willi Syndrome (PWS) experience hypotonia, feeding difficulties, and a drastically decreased appetite. It is often necessary to monitor feeding in the first months of life due to failure to gain weight. From 9 to 25 months of age, appetite improves, and these babies grow steadily along the growth curve with a normal diet. In early childhood, they experience rapid weight gain with no change in appetite (still age-appropriate). However, in the next phase, excessive weight gain continues and appetite increases; Obesity usually develops if eating is not controlled externally. From the age of 8, individuals with PWS often develop an insatiable and uncontrollable desire to consume food, called hyperphagia, accompanied by an absence of satiety. Individuals with PWS require supervision to prevent choking and binge eating, which can lead to stomach rupture, gastric necrosis, and death. Overeating can result in severe obesity. (Tan *et al.*, 2020; Bellis *et al.*, 2022)

Regarding the dietary management of obesity in Prader-Willi Syndrome, several approaches have been studied and analyzed for their efficacy in reducing morbidity and mortality associated with the condition. In this vein, the studies by Hui *et al*. (2021) and Calcaterra *et al.* (2023) drew contrasting conclusions. Hui *et al*. (2021) described that a high-fiber dietary intervention can suppress inflammation in obese children, which can be attributed to modulating the structure of the gut microbiota. The investigation of virulence genes (VF) carried out in the current study suggests that the intervention decreased the inflammatory state in obese children with PWS and obese children without the condition. Calcaterra *et al.* (2023), on the other hand, described that the best nutritional strategy for these patients is a well-balanced, low-calorie diet, as there are currently no specific recommendations that suggest accurate carbohydrate, protein, or fiber intake for children with PWS. The paper written by Hui *et al*. (2021) presents a higher level of evidence, but has a small sample and short follow-up time, thus making it difficult to interpret the facts.

A Mediterranean-type dietary composition, which includes fiber-rich carbohydrates, dairy, healthy fats, and protein, can limit the need for significant calorie restriction while providing adequate sources of energy for growth, exercise, and improved muscle mass. Thus, currently, the best nutritional strategy in individuals with PWS seems to be a balanced, low-calorie diet. Supplements may be necessary to meet micronutrient recommendations in young people who are unable to achieve them through food and beverage intake alone. (Mackenzie *et al.,* 2018; Miller; Tan, 2020; Muscogiuri *et al.*, 2021)

Obese children and adults with PWS have a lower level of physical activity when compared to obese individuals who do not have the condition. Ideally, due to the smaller amount of musculoskeletal mass, patients with the syndrome should perform combined aerobic and anaerobic activities (Bellicha *et al.*, 2021). On the other hand, participation in a 24-week physical activity routine did not increase levels of moderate-to-vigorous physical activity (MVPA), which is primarily associated with

improvement in metabolic factors or a reduction in body fat. To elucidate whether the changes observed in the results were related to body fat, analyses were performed on a subsample of children who had body fat gain equal to or less than zero percent. Participants showed significant small to moderate improvements in some cardiometabolic and inflammatory factors (HDL, HOMA-IR, and IL8), with some improvements becoming statistically significant when children showed body fat gain equal to or less than zero percent (HOMA-IR and HDL). (Rubin *et al.*, 2018)

As pharmacological interventions, several options are feasible for weight gain control and obesity management. The main drugs for this purpose are: topiramate, metformin, naltrexone + bupropion and GLP-1 agonists, each medication with its own particularity and contraindication. Topiramate is an antiepileptic drug with off-label use for weight reduction. Its mechanism is not fully understood, but it appears to block sodium and calcium channels, enhancing the suppression effects of GABA. An open-label study of seven patients with PWS demonstrated weight reduction or decreased weight gain and improved mood. Metformin is a classic oral medication for the treatment of type 2 diabetes by improving hyperglycemia and is also used off-label to treat obesity and prediabetes. Naltrexone-bupropion is a combination drug used to treat obesity and impulsive behavior. Naltrexone is an opioid receptor antagonist, and bupropion is a dopamine/norepinephrine reuptake inhibitor. The glucagon-like peptide-1 receptor (GLP-1) agonist stimulates insulin release, inhibits glucagon secretion, and decreases plasma ghrelin levels. Studies indicate increased satiety after meals in patients with PWS. (Barrea *et al.*, 2022; Éva Erhardt; Dénes Molnár, 2022; Nolan; Proietto; Sumithran, 2022)

Liraglutide (GLP-1 analogue) has been shown to reduce BMI in children and adolescents with PWS and obesity. However, there were no significant differences between the children and adolescents who received liraglutide and those who received placebo or no treatment. This was probably due to a hypothalamic dysfunction characteristic of the syndrome, but which still needs further studies to be elucidated. (Diene *et al.*, 2022)

Surgical interventions offer important control of hyperphagia, significant short- and long-term weight loss, minimal rates of surgical complications, and low but manageable nutritional risks. Laparoscopic Sleeve Gastrectomy (LSG) seems to address several of these aspects, however, a significant decrease in BMI, due to surgery, may not be sustained after 3 years. Therefore, Biliopancreatic Shunt (BPD) or Biliopancreatic Shunt with Duodenal Shunt (BPD-DS) surgery can maintain a significant reduction in BMI for up to 10 years, but requires greater adherence to nutritional supplementation. (Wolfe *et al.*, 2023)

6 CONCLUSION

The management of obesity in Prader-Willi Syndrome (PWS) is a complex and challenging task that requires a multidisciplinary and personalized approach. Obesity is a prevalent concern for

individuals affected by PWS, due to the insatiable appetite that characterizes this genetic condition. As demonstrated throughout this study, several interventions are possible and feasible for the prevention and treatment of obesity in individuals with the syndrome.

The controlled diet, although challenging, is one of the pillars of treatment, maintaining the balance between the necessary calorie restriction and the promotion of a healthy relationship with food. Behavioral therapy plays an equally crucial role in empowering patients and their families to cope with insatiable appetite and food urges.

In addition, adapted physical activity, designed to meet the specific capabilities of each patient, contributes to the improvement of muscle strength and mobility, avoiding a sedentary lifestyle and helping to control weight.

REFERENCES

ALVES, C.; FRANCO, R. R. Prader-Willi syndrome: endocrine manifestations and management. Archives of Endocrinology and Metabolism, v. 64, n. 3, p. 223–234, 2020.

BARREA, L. et al. Prader–Willi Syndrome in Adults: An Update On Nutritional Treatment and Pharmacological Approach. Current Obesity Reports, v. 11, n. 4, p. 263–276, 5 set. 2022.

BELLICHA, A. et al. Physical Activity in Patients with Prader-Willi Syndrome—A Systematic Review of Observational and Interventional Studies. Journal of Clinical Medicine, v. 10, n. 11, p. 2528, 7 jun. 2021.

BELLIS, S. A. et al. The consequences of hyperphagia in people with Prader-Willi Syndrome: A systematic review of studies of morbidity and mortality. European Journal of Medical Genetics, v. 65, n. 1, p. 104379, 1 jan. 2022.

BORGUNDVAAG, E.; MAK, J.; KRAMER, C. K. Metabolic Impact of Intermittent Fasting in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis of Interventional Studies. The Journal of Clinical Endocrinology & Metabolism, v. 106, n. 3, 15 dez. 2020.

CALCATERRA, V. et al. Prader–Willi Syndrome and Weight Gain Control: From Prevention to Surgery—A Narrative Review. Children, v. 10, n. 3, p. 564, 1 mar. 2023.

CRINÒ, A. et al. Obesity management in Prader–Willi syndrome: current perspectives. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, v. 11, n. 2018, p. 579–593, 4 out. 2018.

DE FRANÇA, A. et al. SÍNDROME DE PRADER WILLI: RELATO DE CASO Prader-Willi Syndrome: a Case Report. [s.l: s.n.]. Disponível em: <https://www.revistacirurgiabmf.com/2006/v6n1/pdf%20v6n1/5.pdf>.

DIENE, G. et al. Liraglutide for Weight Management in Children and Adolescents With Prader–Willi Syndrome and Obesity. The Journal of Clinical Endocrinology & Metabolism, v. 108, n. 1, 1 out. 2022.

ÉVA ERHARDT; DÉNES MOLNÁR. Prader–Willi Syndrome: Possibilities of Weight Gain Prevention and Treatment. Nutrients, v. 14, n. 1950, p. 1950–1950, 1 maio 2022.

GOULART, K. C. F. et al. Síndrome de Prader-Willi/ Prader-Willi syndrome. Brazilian Journal of Health Review, v. 4, n. 5, p. 21636–21643, 13 out. 2021.

HOLM, V. A. et al. Prader-Willi Syndrome: Consensus Diagnostic Criteria. Pediatrics, v. 91, n. 2, p. 398–402, 1 fev. 1993.

LEMES AGUIAR, D. et al. CARACTERIZAÇÃO DAS MANIFESTAÇÕES CLÍNICAS DA SÍNDROME DE PRADER-WILLI E TRATAMENTOS: UMA REVISÃO INTEGRATIVA DE LITERATURA. RECIMA21 - Revista Científica Multidisciplinar - ISSN 2675-6218, v. 3, n. 3, p. e331199, 2 mar. 2022.

LI, H. et al. Suppressed inflammation in obese children induced by a high-fiber diet is associated with the attenuation of gut microbial virulence factor genes. Virulence, v. 12, n. 1, p. 1754–1770, 8 jul. 2021.

MACKENZIE, M. L. et al. Dietary intake in youth with prader-willi syndrome. American Journal of Medical Genetics. Part A, v. 176, n. 11, p. 2309–2317, 1 nov. 2018.

MILLER, J. L.; TAN, M. Dietary Management for Adolescents with Prader–Willi Syndrome. Adolescent Health, Medicine and Therapeutics, v. Volume 11, p. 113–118, ago. 2020.

MUSCOGIURI, G. et al. Prader- Willi syndrome: An uptodate on endocrine and metabolic complications. Reviews in Endocrine and Metabolic Disorders, v. 20, n. 2, p. 239–250, 7 maio 2019.

MUSCOGIURI, G. et al. Obesity in Prader–Willi syndrome: physiopathological mechanisms, nutritional and pharmacological approaches. Journal of Endocrinological Investigation, v. 44, n. 10, p. 2057–2070, 2021.

NOLAN, B. J.; PROIETTO, J.; SUMITHRAN, P. Intensive management of obesity in people with Prader-Willi syndrome. Endocrine, v. 77, n. 1, p. 57–62, 7 maio 2022.

PINHEIRO, M. L. A. *et al*. A evolução dos métodos de ensino da anatomia humana –uma revisão sistemática integrativa da literatura. Revista Bionorte, Montes Claros, v. 10, n. 2, p. 168-181, jul./dez. 2021. Disponível em: https://doi.org/10.47822/bionorte.v10i2.279.

RUBIN, D. A. et al. Changes in cardiometabolic markers in children with Prader-Willi syndrome and nonsyndromic obesity following participation in a home-based physical activity intervention. Pediatric Obesity, v. 13, n. 11, p. 734–743, 17 set. 2018.

TAN, Q. et al. Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: A narrative review. Obesity Reviews, v. 21, n. 5, maio 2020.

WOLFE, G. et al. Metabolic and bariatric surgery for obesity in Prader Willi syndrome: systematic review and meta-analysis. Surgery for Obesity and Related Diseases, v. 19, n. 8, p. 907–915, 1 ago. 2023.

ZUBRZYCKI, A. et al. The role of low-calorie diets and intermittent fasting in the treatment of obesity and type-2 diabetes. Journal of Physiology and Pharmacology: An Official Journal of the Polish Physiological Society, v. 69, n. 5, 1 out. 2018.