The treatment of hyperphagia and obesity in Prader-Willi Syndrome

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Abstract

Introduction: Prader-Willi Syndrome (PWS) is a genetic neurodevelopmental disorder, in which the central clinical characteristics are hyperphagia and obesity. Obesity leads to higher mortality rates in PWS patients and thus, effective and safe treatment of hyperphagia and obesity in PWS individuals is an important aspect of PWS therapy.

Aim of the study: The aim of the study was to research both the new and the more standard treatment options of hyperphagia and obesity in PWS patients.

Methods and Materials: An extensive literature search was conducted using PubMed database. Only articles from the past 5 years were taken into consideration. The keywords used during the search were: prader willi syndrome, obesity, treatment.

Results: Our research showed that in the treatment of hyperphagia and obesity in PWS patients, health professionals may consider the use of pharmacological treatment options, surgery and neuromodulatory options. Moreover, physical activity and environmental control are beneficial in limiting caloric intake and improving body mass index. Furthermore, early diagnosis and thus starting treatment in early childhood are beneficial in preventing the progression of obesity. However, more research is needed to determine which treatment options are best suited for specific patients.

Keywords: prader willi syndrome, obesity, treatment
Introduction

Prader-Willi Syndrome (PWS) is a rare multi-system genetic neurodevelopmental disorder. Its birth incidence is estimated to be of 1:1 500 to 1:20 000. PWS is caused by the absence of expression of the paternally inherited genes localized on chromosome 15q11.2-q13 (Barrea et al., n.d.). The lack of expression is usually explained by paternal deletion of the 15q11.2-q13 region (61% of cases), maternal uniparental disomy 15 (36% of cases) or an imprinting defect (3% of cases) (V. E. Kimonis et al., 2019). Typically, in healthy population, the paternal gene copies of the 15q11.2-q13 region are expressed, while the maternal copies are silenced (Alves & Franco, 2020). The mechanisms responsible for the inactivation of the maternal genes involve DNA methylation and other epigenetic factors throughout gametogenesis. Thus, the method of choice for confirming the Prader-Willi Syndrome diagnosis is a DNA methylation test, which can detect almost all (99%) of individuals with PWS (Drabik et al., 2022; V. E. Kimonis et al., 2019). Patients diagnosed with Prader-Willi Syndrome present different clinical characteristics throughout their life. In the infancy, main symptoms include severe hypotonia, feeding disorders (impaired sucking/ failure to thrive) and growth difficulties (Couto-Rosende et al., 2023). In the second stage of the disorder, at a median age of 8 years old, patients show signs of hyperphagia, characterized by food obsession, lack of satiety and food seeking, which, if left unattended, may lead to severe obesity (Strong et al., 2024). Hypothalamic dysfunction may lead to other abnormalities, such as hypogonadism, hypothyroidism, growth hormone deficiency (GHD) and central adrenal insufficiency (Ben-Cnaan et al., 2022; Erhardt & Molnár, 2022). It is important to note the significance of hypothalamic dysfunction in PWS patients, which is considered to be the reason for the lack of satiety and the following pathological weight gain (Hu & Lei, 2024). Other clinical traits of PWS include low muscle mass, intellectual disability, short stature, distinctive facial features, behavioral problems (for example compulsion, tantrums, self-harming) (Couto-Rosende et al., 2023; Strong et al., 2024). However, the central clinical feature of the PWS patients remains abnormal weight, with reports of 82-98% of patients diagnosed with PWS to be overweight or obese. It is important to note that PWS is considered to be the most common genetic cause for morbid obesity (Bellis et al., 2022). Severe obesity in PWS patients can lead to significant health consequences, such as endocrine, cardiologic, metabolic, orthopedic and respiratory complications. In addition, obesity increases the risk of aspiration, gastrointestinal perforation,
choking and reduces gastrointestinal motility. In understanding the significance of obesity in PWS patients, and the health risk it poses, it is crucial to remember that the morbidity and mortality (about 1.5% per year) is substantially linked to the complications caused by severe obesity (Calcaterra et al., 2023). Therefore, effective management of hyperphagia and the following obesity is pivotal in reducing morbidity and mortality.

Materials, Methods and Purpose:
The purpose of this article was to research the treatment options for managing hyperphagia and obesity in PWS patients. The search was conducted using PubMed database and the following keywords: prader willi syndrome, obesity, treatment. Only full-length articles from the last 5 years were taken into consideration.

Treatment options
Extreme hyperphagia is the problem which physicians find the most difficult to treat in PWS. At present, patients diagnosed with PWS and their families are advised to insert environmental control to manage the calorie intake. It includes locked kitchen and constant supervision of the patient. Nowadays, the standard treatment for individuals diagnosed with PWS involves administration of growth hormone during childhood, with the GH replacement therapy for PWS approved by the Federal Drug Agency (FDA) (Miller & Tan, 2020). In addition, there are new therapeutic agents and more invasive, surgical methods, which may be effective in managing hyperphagia and obesity (Alves & Franco, 2020; Wolfe et al., 2023). Moreover, it is important to note the significance of inserting physical activity in everyday lives of PWS patients (Miller et al., 2022).

Growth Hormone
According to different studies, about 40-100% of PWS patients may have growth hormone deficiency (Erhardt & Molnár, 2022). However, it was reported that GH may improve the physical health in children with or without the GH deficiency (Rosenberg et al., 2021). In the systematic review and meta-analysis, conducted by Caroline de Gouveia Buff Passone and her co-authors, the impact of the recombinant human GH (rhGH) therapy on PWS patients was evaluated. It was concluded, that rhGH treatment is advantageous in improving the stature, body mass index and body composition. Moreover, it modifies the natural history of the disease. Furthermore, rhGH therapy may also improve motor development and cognition in children diagnosed with PWS. It should also be noted, that in the research there was indication of few reported adverse events (Passone et al., 2020). Nowadays, the advantages of growth hormone therapy in children with PWS are already well established (Damen et al., 2020). However, growth hormone treatment in adults is not a standard therapy. In a letter to
the editor, written by Charlotte Höybye and associates, and published in Orphanet Journal of Rare Diseases, the authors advocated for the use of GH in adults with PWS to be internationally improved. Höybye and her colleagues recommended GH therapy for adults with PWS, based solely on the genetic diagnosis and regardless of the GH secretory status. The authors of the letter, on behalf of The Clinical and Scientific Advisory Board of The International Prader-Willi Syndrome Organisation, attempted to draw attention to the benefits of GH treatment in PWS adults, such as maintaining normal metabolism and body structure, positive effects on physical fitness, body composition, cardiovascular risk markers, quality of life and behavior. Thus, the authors attempted to display the advantages of growth hormone therapy not only in the children diagnosed with PWS, but also in the adult population (Höybye et al., 2021). The effects of growth hormone treatment on adults with PWS were also the focal point of the research conducted by Layla Damen and her co-authors. In the open-label prospective study, the authors attempted to investigate the longer-term effects of the GH therapy on body composition in adult patients. 43 patients participated in the study, with a median age of 19 years old. The participants took part in GH therapy for 3 years, receiving a dose of 0.33mg/m²/day. In the research it was noted, that fat mass percentage SDS decreased during the treatment, and at the same time lean body mass SDS remained stable. There were no significant changes in the insulin and fasting glucose levels and there were no GH-related adverse reactions observed. Thus, it was concluded, that three years of GH therapy in young adults diagnosed with PWS aids in maintaining the positive results on body composition acquired during childhood. Therefore, longer term GH treatment benefits adults with Prader-Willi syndrome (Damen et al., 2020). The advantages of growth hormone treatment in adult patients with PWS were also reported in the meta-analysis conducted by Anna G. W. Rosenberg and her co-authors. In the research, the authors concluded, that not only GH therapy improves body composition of the adults diagnosed with PWS, but it also might decrease the risk of cardiovascular complications. The authors determined this conclusion, by taking note of the significant connection between poor body composition and reported high incidence rate of cardiovascular morbidity in adult patients diagnosed with PWS (Rosenberg et al., 2021). In a study conducted by Graziano Grugni and his associates, the long-term effects of growth hormone therapy in adults with PWS were also researched. In the longitudinal study, twelve obese patients with PWS, with a median age of 27,1 years, were treated with a median growth hormone dose of 0,35mg a day. The median time of the therapy was 17 years. In the study, body composition, anthropometric, biochemical, blood pressure and hormonal variables were evaluated in the participants. In the paper, the authors
determined that long-term growth hormone therapy had beneficial effects on body fat distribution and body composition in adult obese patients with PWS. Notwithstanding, it was also reported, that during GH treatment, the patients may experience the increase in glucose levels and thus regular surveillance of glucose values should be mandatory throughout long-term growth hormone therapy (Grugni et al., 2023). Another point of view on the growth hormone treatment in adult PWS patients was presented in the letter to the editor written by Harry J. Hirsch and Varda Gross-Tsur and published in Orphanet Journal of Rare Diseases. In the letter, the authors questioned if the benefits of GH therapy in PWS adults, especially improvement of body composition, were remarkable enough to warrant the possible, not yet known, consequences of long-term therapy in adult PWS patients. The authors called attention to increase in insulin-like factor 1, which may be the result of several decades of GH therapy in adults diagnosed with PWS. The authors cautioned, that this increase in the factor may increase the risk of cancer and furthermore they put into question the patients’ possible compliance with the necessary daily injections (Hirsch & Gross-Tsur, 2021).

**Topiramate**

Topiramate is an antiepileptic medication, which modulates Na+ channels, AMPA/kainite receptors and GABA (Muscogiuri et al., 2021). Topiramate is most well known for its use in the treatment of seizures and migraines. Off-label, the drug is also used to treat essential tremor, binge eating disorder, stabilize mood and help in weight loss. However, the mechanism behind the weight loss is not well understood and topiramate is not FDA-approved in the treatment of obesity (Goldman et al., 2021). Moreover, it is important to point out, that other research papers negate the possible influence of topiramate on weight lose and report solely its positive influence in decreasing hyperphagia (Barrea et al., n.d.; Muscogiuri et al., 2021). In a double-blind randomized placebo-controlled trial conducted by Angèle Consoli and her colleagues, the authors aimed to study the tolerance and efficacy of topiramate on behavioral problems in patients diagnosed with PWS. All participants in the study had PWS and severe impulsivity/irritability, obesity and/or eating disorders and skin picking. 62 participants took part in the study, with 30 patients receiving topiramate (50-200mg a day) for 8 weeks, and the rest of the participants being placed in a placebo group. At the end of the study it was confirmed, that patients receiving topiramate displayed less severe hyperphagia vs. patients in the placebo group (which was measured by the scores on the Dykens Hyperphagia Questionnaire - DHK). However, the DHK scores were also linked with hospitalization status and genetic subtype. During the study it was discovered, that topiramate had a dose-effect relationship associated with influence on eating disorders. Taking into
consideration the significant effect of topiramate on the severity of hyperphagia, the drug may become extremely helpful in the treatment of obesity in the patients diagnosed with PWS (Consoli et al., 2019).

**GLP-1 agonists**

GLP-1 agonists are believed to be one of the most promising molecules to be used in the treatment of monogenic obesity (Faccioli et al., 2023). They stimulate insulin release, slow gastric emptying, inhibit glucagon secretion and increase satiety after eating (Goldman et al., 2021). Three GLP-1 analogs have been approved by FDA to treat obesity: liraglutide, semaglutide, and most recently – tirzepatide (Kalinderi et al., 2024). In a multicenter, placebo-controlled trial, Gwenaelle Diene and her co-workers attempted to determine if liraglutide in the management of weight was superior to no/treatment placebo in children/adolescents with PWS. 55 pediatric individuals with PWS took part in the study. Patients were either given liraglutide (at 3.0 mg a dose or maximum-tolerated) or placebo, for about 16 weeks. After this time placebo was stopped, and liraglutide was prolonged for 52 weeks. During the trial the patients were advised to follow a structured diet and an exercise program. After the study, it was revealed that there were no significant changes in BMI between participants from different treatment groups. However, there was improvement in the severity of hyperphagia in the group of adolescents who were treated with liraglutide versus those with no treatment (Diene et al., 2023). In a retrospective audit conducted by Brendan J. Nolan and his colleagues, 7 patients with PWS were treated with liraglutide. Although the median weight loss in patients treated with liraglutide (median 9kg over 96 weeks) was smaller than in the group of PWS patients following very-low-energy diets, it was important to note, that the patients prescribed with liraglutide experienced no significant adverse effects (Nolan et al., 2022). There are also case reports of successful, rapid weight loss in patients diagnosed with PWS (Ahmed et al., 2023; Y. M. Kim et al., 2020).

**Diazoxide Choline**

Diazoxide choline is a benzothiadiazine, which stimulates an ion flux into ATP-sensitive potassium channels. It is used in the treatment of hyperinsulinemia hypoglycemia in pediatric and adult population. More recently, diazoxide choline controlled-release (DCCR) has become the subject of clinical trials focused on researching its efficacy on treating hyperphagia in PWS patients (Mahmoud et al., 2023). In a study conducted by Theresa V. Strong and her colleagues, the authors aimed to research the longer-term effect of DCCR. Thus, they compared the hyperphagia in the cohort from a natural history study (PATH for PWS) with the DCCR-treated cohort. The results showed, that DCCR treatment caused an
improvement of the severity of hyperphagia in the PWS patients, and thus, could lessen the burden of the disorder on the patients and their families (Strong et al., 2024). In another study, conducted by Virginia Kimonis and her co-authors, the authors attempted to evaluate the efficacy and safety of orally administered DCCR in patients with PWS. 13 obese or overweight participants, all diagnosed with PWS, took part in this single-center, phase II study, with an average age of 15.5 years. During the study, the patients were dose escalated for the first 10 weeks, and later, the subjects experienced 4 weeks of double-blind, placebo-controlled treatment period. Diazoxide choline controlled-release treatment resulted in significant amelioration in hyperphagia. Moreover, less patients displayed aggressive behavior. It is important to add, that there were reported increases in lean body mass, reductions in fat mass and waist circumference. During the study, the most commonly observed adverse effects were transient increases in the levels of glucose and peripheral edema (V. Kimonis et al., 2019).

Oxytocin

PWS patients are reported to have lower plasma levels of oxytocin, which is believed to be connected to hyperphagia, obsessive-compulsive disorder, autistic characteristics and anxiety. Thus, there are studies focused on oxytocin treatment and its possible positive effect on PWS patients (Alves & Franco, 2020). In a study conducted by Elizabeth Roof and her colleagues, the researchers attempted to evaluate the efficacy and safety of an oxytocin analog – intranasal carbetocin – in PWS patients. 130 patients (at age 7-18 years old) took part in this randomized, placebo-controlled, double-blind phase 3 trial. However, the COVID-19 pandemic stopped the enrollment prematurely. Nevertheless, carbetocin was reported to be well tolerated. Moreover, its dose at 3.2mg showed significant improvements in hyperphagia, distress behaviors and anxiousness in patients with PWS (Roof et al., 2023). In another study, conducted by Layla Damon and her co-authors, the researchers evaluated the effects of intranasal oxytocin 3 months therapy on the severity of hyperphagia and behavior in PWS children. The effects were compared to placebo, and the participants received the drug twice a day. 26 children took part in the study, with varying results depending on their sex. In the total group, the effects of oxytocin on hyperphagia or social behavior were not significant. However, in boys with PWS, oxytocin had positive results in both eating and social behavior (Damen et al., 2021).

Setmelanotide

Setmelanotide, also known as RM-493, is an agonist of melanocortin-4 receptor (MC4R). Its adverse effects include skin darkening, arthralgia or headache (S. J. Kim et al., 2021).
Setmelanotide, through the activation of MC4R, is believed to inhibit food intake (Qaddra et al., 2023). However, the results of a phase 2 trial, in which obese patients with PWS took part, were not promising, showing not-statistically-significant improvement in the hyperphagia, mean weight and body composition (Mahmoud et al., 2023).

**Orlistat**

Orlistat (a pancreatic lipase inhibitor) limits fat absorption to about 30% of ingested fat (Muscogiuri et al., 2021). The medication is approved by FDA to treat obesity in patients, who are at least 12 years old (Goldman et al., 2021). However, its efficacy in PWS patients has been demonstrated to be modest. The poor success ratio of the drug in PWS patients has been believed to be due to gastrointestinal adverse effects leading to poor compliance (Barrea et al., n.d.). Orlistat was the focus of three studies, in which its efficacy in lowering BMI scores in pediatric populations was reported (Goldman et al., 2021). Nevertheless, more studies evaluating the safety and efficacy in patients with PWS is needed.

**Beloranib**

Beloranib is a methionine aminopeptidase 2 (MetAP2) inhibitor, which stimulates the metabolism of stored fat, while reducing hunger (Qaddra et al., 2023). In a study conducted by Zafgen, its efficacy in improving hyperphagia and weight reduction was demonstrated. However, during the study multiple thromboembolic events have been reported, with two patients dying. Thus, the trial was terminated early (V. Kimonis et al., 2019).

**Livoleotide**

Livoleotide, also known as AZP-531, is an unacylated ghrelin analog. Ghrelin stimulates appetite, and livoleotide is believed to decrease this effect (Qaddra et al., 2023). The efficacy of livoleotide in PWS patients was evaluated in a multi-center, randomized placebo-controlled study. 47 patients took part in the study, and no significant adverse effects were reported. In the study there were reports of improvement in hyperphagia, fat mass and waist circumference, however, 3 months after the livoleotide treatment, none of the positive results were maintained (Barrea et al., n.d.). In another study, 158 patients diagnosed with PWS were treated with livoleotide. The drug was once again well tolerated, but the hyperphagia in patients was not improved (Mahmoud et al., 2023).

**Metformin**

Metformin is a well-known oral hypoglycemic medication, approved for treatment in type 2 diabetes mellitus patients. The drug not only sensitizes muscle and liver to insulin, but also seems to carry an anorectic effect. The mechanism behind the anorectic effect is not fully known, though the influence on the increase of GLP-1 in the intestine and the impact on the
central hypothalamic-pituitary circuits are believed to play part in the mechanism (Muscogiuri et al., 2021). Metformin supplementation was the focus of a pilot study, and 21 pediatric patients diagnosed with PWS took part in it. In the study, an improvement in hyperphagia was reported, however, there was no significant change in body weight of the participants (Barrea et al., n.d.).

**Naltrexone-bupropion**

Naltrexone-Bupropion is a combination of drugs, which have already been tested for many years in monotherapy: naltrexone (useful in treatment of opioid and alcohol addiction) and bupropion (known for its efficacy in the treatment of depression). Together, this combination has a hypothalamic synergistic effect in appetite suppression and reducing body weight (Muscogiuri et al., 2021). This combined drug has been FDA-approved in the obesity treatment (Erhardt & Molnár, 2022). In a case report of a 13 years old adolescent with PWS and difficulties in impulse control, the medication helped to decrease BMI and improve aggression (Goldman et al., 2021). In another study, in which efficacy of pharmacotherapy in patients with PWS was evaluated, 4 individuals were treated with naltrexone-bupropion. 2 out of the 4 patients have exhibited weight loss (Nolan et al., 2022).

**Bariatric surgery**

Another therapeutic approach worth consideration in treating obesity in PWS patients is bariatric surgery. Taking into account both the efficacy in achieving and maintaining weight loss, mini gastric bypass (MGB) and sleeve gastrectomy appear to be the most appropriate surgical choices for PWS patients (Barrea et al., n.d.). At the same time, in a systematic review, laparoscopic sleeve gastrectomy (LSG) has been proven to be efficient in reducing hyperphagia in patients diagnosed with PWS. This effect was explained by reduction of the ghrelin levels, which is maintained even 3 years after LSG (Wolfé et al., 2023). Other studies also showcase the possible superiority of LSG over Roux-en-Y gastric bypass (RYGB), citing fewer nutritional risks. Moreover, thanks to the nature of the procedure, LSG eludes the potential complications related to the presence of a foreign body (Calceterra et al., 2023). However, the surgical intervention in PWS patients is still believed to be controversial, mainly because of few studies of high quality and credibility regarding the topic – most of the available studies are case reports (Barrea et al., n.d.). In addition to it, the available reports are at times inconsistent, with some authors reporting reduction in food seeking and body weight, and other authors describing bariatric surgery as ineffective in providing sustainable weight loss (Mahmoud et al., 2023). Moreover, the compliance of PWS patients after bariatric
surgery was most often disappointing (Muscogiuri et al., 2021). Furthermore, PWS patients demonstrate delayed gastric emptying, which increases the risk of gastric necrosis/rupture, and is another reason for the low frequency of bariatric surgeries performed in PWS patients (S. J. Kim et al., 2021). Thus, bariatric treatment is regarded with caution, especially as its long-term outcomes are still questionable (Kalinderi et al., 2024).

Neuromodulatory therapies

Deep Brain Stimulation (DBS) is an example of neurosurgical approach considered in the therapy of PWS associated obesity. In this treatment, the stimulation is usually focused on either reward circuitry nuclei or a specific hypothalamic area (Contreras López et al., 2022). The procedure involves the implantation of electrodes in specific brain areas, placed to modify neural activity. However, there are few reports of the DBS therapy in PWS treatment. In a case series of 4 patients with PWS, there were not reported any significant changes in the calorimetric and anthropometric parameters in the 6 month after the treatment (Qiu et al., 2024). Another example of a neuromodulation method is transcranial direct current stimulation, also known as tDCS. The treatment consists of delivering a weak electrical current to the brain parenchyma and scalp, which leads to modulation of the cortical activity (Poje et al., 2021). Other neuromodulatory treatments, which may be used in the treatment of PWS, are vagus nerve stimulation and repetitive transcranial magnetic stimulation. However, more research is needed to fully understand the effects those methods may have on hyperphagia and their possible involvement in the treatment of PWS patients (Qiu et al., 2024).

Lifestyle intervention

A crucial part of clinical management of the obesity in PWS patients is lifestyle modification, which should be started as early as possible. Health professionals play an important part in managing the symptoms of PWS individuals, by assisting and providing information in the subjects of appropriate behavioral, nutritional and exercise intervention. The most important aspect of diet in PWS patients is preventing uncontrolled food intake. Environment control of food intake has been reported to bring positive results to PWS individuals through slowing the advancement of obesity (Faccioli et al., 2023). Moreover, PWS patients demonstrate lower energy expenditure than their peers, and are less likely to engage in spontaneous physical activity. In studies, PWS individuals show impaired exercise tolerance and stamina and low hormonal responses to physical activity. However, engaging PWS individuals in training, such as regular aerobic exercise, for several months would bring positive results for the patients: their BMI, body composition and physical performance would improve. If they were
to also participate in resistance training, the PWS patients would demonstrate over time increase in muscle strength and energy expenditure. Thus, increasing physical exercise in PWS individuals is a crucial part of weight management (Miller & Tan, 2020).

Summary
One of the most characteristic clinical symptoms of Prader-Willi syndrome is hyperphagic obesity, which has been associated with reduced quality of life, elevated morbidity and mortality (Cowen & Bhatnagar, 2020). In a study focused on mortality in PWS patients, the results demonstrated the significance of obesity in the patients. Most of the patients in the study died prematurely because of respiratory causes, and in those patients with information available on their obesity state, 98% of them were obese (Alfaro et al., 2019). Moreover, in a 2014 survey, PWS patients’ caregivers stated, that improving food-related habits and reducing hunger were the most significant unmet needs in individuals with PWS. Thus, the development of an effective therapeutic agent in the treatment of hyperphagia and obesity in PWS patients is of utmost importance (Mahmoud et al., 2023). Nowadays, the most standard medication for PWS patients is administration of growth hormone in childhood. However, the emergence of new therapeutic options brings hope for better management of hyperphagia and the following obesity in patients (Miller & Tan, 2020). Notwithstanding the role of the pharmacological treatment options in managing hyperphagic obesity in PWS individuals, it is vital to remember the major role of physical activity and control of the calorie intake. In addition, the patients benefit from the help of not only health professionals, but also their caregivers/parents, who may insert strict environmental controls to limit calorie intake (Felix et al., 2020). In some cases, more invasive treatment options, such as a bariatric surgery, may be worth consideration, especially in patients, in which less invasive therapies have proven to be ineffective (Wolfe et al., 2023). Furthermore, neuromodulatory approaches may become in future a novel, safe treatment option for PWS (Qiu et al., 2024). However, it is important to note, that treatment of PWS patients needs to be personalized to their individual needs and the patients may benefit from more research focused on new therapeutic options for hyperphagic obesity.

Conceptualization, Ilona Jastrzębska, and Paulina Cuper; methodology, Patrycja Nowoświat; software, Krzysztof Bilecki; check, Michał Andrzej Kozicz, Hubert Gugulski; formal analysis, Michał Bado; investigation, Ilona Jastrzębska; resources, Krzysztof Bilecki; data curation, Patrycja Nowoświat; writing - rough preparation, Paulina Cuper; writing - review and editing, Ilona Jastrzębska; visualization, Hubert Gugulski; supervision, Michał Bado; project
administration, Michał Andrzej Kozicz; receiving funding, Patrycja Nowoświat
All authors have read and agreed with the published version of the manuscript.

Funding statement
The study did not receive special funding.

Informed Consent Statement
Not applicable

Acknowledgments
Not applicable

Conflict of Interest Statement
The authors report no conflict of interest

Bibliography:


