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Ketogenic diet for ovarian disorders - promising nutritional approach in polycystic ovarian syndrome and ovarian cancer

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Summary:

Introduction and purpose:

Polycystic ovary syndrome (PCOS) is the most common endocrine disease in the female reproductive age. As treatment guidelines include lifestyle changes, various diet types are being evaluated in terms of efficacy among them ketogenic diet (KD) which was also assessed in terms of its influence on another ovarian related disease - ovarian cancer. The aim of this paper is an analysis of the available scientific data in respect of the role of the KD as a part of the therapy of ovarian related disorders. The search was conducted using PubMed and Google Scholarship databases.

Brief description of the state of knowledge:

Ketogenic diet demonstrates favorable effects in the hormonal profile of PCOS-affected women. It was also noticed that its administration results in the reduction of BMI and the improvement in glycemic parameters. Most of the research was conducted by linking the ketogenic diet with the caloric restriction. In the matter of ovarian cancer the results are unclear; some of the research states the improvement of the quality of life of the participants, but there is some alarming data of the possible role of KD in enhancing the tumor growth.

Conclusions:

Ketogenic diet merits further research as a possible factor in the treatment of PCOS as foregoing results are pointing to its efficacy. Nevertheless, still more data is needed to determine its role as studies were conducted within a short period of time with relatively small research groups. There are also other limitations such as the lack of comparison with other dietary patterns with the caloric deficit which makes it difficult to deduce the main profitable factor. When it comes to ovarian cancer the results of the current data are also unclear and unambiguous with the possible negative effects.

Key words: Ketogenic diet; PCOS; ovarian cancer; obesity; hormones

1. Introduction

Some types of diets, such high-fat and high-glucose diets, are commonly known risk factors of many disorders including cardiovascular diseases or cancers. On the other hand, nutritional interventions are gaining attention as a potential adjuvant therapy for many disorders. So far the favorable effects of the ketogenic diet (KD) have been used mainly in neurological disorders, in particular in epilepsy treatment [1]. Recently, interest in the use of the KD as a complementary approach to the metabolic diseases and cancers therapy has grown. Thus, in this review we aim to assess the effects of the KD on clinical outcomes in women diagnosed with ovarian diseases such as polycystic ovarian syndrome (PCOS) or ovarian cancer.

The ketogenic diet is a high-fat/low-carbohydrate/adequate-protein diet, which places the body into a state of ketosis. Under these conditions ketone bodies, which are produced from fats, became the main source of energy for the body. That differs this form of nutrition from others, in which glucose remains the main source of energy. In the ketogenic diet about 70-80% (up to 90% for example in epilepsy treatment) of energy comes from fat. Proteins constitute about 20% of meals and carbohydrates supply do not exceed 50 g per day. The effects of this diet include strong anti-inflammatory properties, the elimination of simple sugars, the lower of total carbohydrates and the supply of a suitable amount of omega-3 fatty acids. The KD also revealed benefits in weight loss and has a favorable effect on blood pressure [2]. These multifaceted effects may be used in many disorders in which lifestyle correction by diet is the most important therapeutic option as it is for example in PCOS. The importance of finding appropriate and effective nutritional intervention is also crucial in ovarian cancer management, which is at high risk of malnutrition.

2. Effects of the ketogenic diet on polycystic ovarian syndrome

Polycystic ovary syndrome is the number one most common disorder that affects women in reproductive age. As statistics states it touches 1 in 5 women in their procreative years [3]. It

is characterized by hyperandrogenism, irregular menstrual cycles and the typical ovarian morphology that contains multiple cysts [3,4].

The diagnosis is based on the Rotterdam's criteria and at least two of the three following conditions needs to be fulfilled:

1. ovarian cysts in the ultrasound examination;
2. clinical hyperandrogenism with high circulating androgens levels;
3. oligo-amenorrhea with oligo-anovulation [5].

There are four phenotypes of this disorder depending on the spectrum of symptoms that women present. Phenotype A is the fully-developed type that manifests itself in all of the three previously mentioned conditions, while phenotype B does not contain polycystic ovaries. Phenotype C does not include menstrual dysfunction. Phenotype D is the one that appears without hyperandrogenism [6]. This endocrine dysfunction is associated with the various range of the other dysfunctions. It leads to infertility in about 40% of patients [7]. It is also linked with the hyperinsulinemia, insulin resistance, glucose intolerance, diabetes mellitus type 2.

PCOS-affected women tend to also have the higher risk of cardiovascular diseases and obesity [8]. It has also been evaluated as a risk factor for endometrial cancer [9]. Also, the higher frequency of mental disorders such as anxiety and depression in patients with PCOS has also been observed [10]. Currently, variable lifestyle approaches are being considered in the therapy of this disorder. Among the reduction of body weight in women with the incorrect body mass index and physical activity, various diet systems are also among the interests of scientists [11].

One of the possible beneficial strategies to obtain is the ketogenic diet. As in the previous years it has gained spotlight as possible treatment for various diseases and its possible beneficial effects on women with polycystic ovary syndrome has also been evaluated. In 2023 Khalid et al. conducted the first metaanalysis about this topic and observed the effects of the 45 days of following the ketogenic diet among 170 women. They noticed the advancement in the levels of reproductive hormones and serum sex hormone binding globulin. At the same time the LH/FSH ratio was lessened. The level of serum free testosterone was also decreased. It is worth

mentioning that dietary changes resulted also in the significant weight reduction. Authors stressed the shortage of the intervention and the unawareness of the effects of this strategy in an extended time [12]. In the same year as previously mentioned paper Calcaterra et al. evaluated the effects of the low calorie ketogenic diet in adolescents affected with PCOS. Their conclusion based on tha laboratory parameters stated that it is a profitable change that contributes to managing the right body weight, insulin resistance, glucose and also the hormonal profile of the participants. Authors also highlighted that it is yet to be known if this diet would also be profitable in the longer period of time. They also described the other limitation of the study: whether the achievable positive changes were due to the diet system or the loss of weight that was reached because of the caloric deficit [13]. Magagnini et al. in their study revealed that a very low calorie ketogenic diet also makes a positive impact on the hormonal profile of women with PCOS. Their study was based on 25 women that were on the ketogenic diet with caloric restriction for 12 weeks. After that time, their parameters significantly improved: there was a reduction in the level of the body mass index (BMI), waist circumference and the level of anti-Mullerian hormone. The HOMA index normalized in 24 out of 25 patients. Levels of progesterone and SHBG increased [14]. Those findings were also supported by the results of the pilot study conducted by Mavropoulos et al. They involved 11 women with PCOS and BMI >27 kg/m2. They were obliged to limit their carbohydrate intake to 20 grams per day for 24 weeks. Only 5 of the participants completed the study and their results showed an improvement in normalizing the body weight, reducing the level of free testosterone, LH/FSH ratio and fasting insulin [15].

The ketogenic diet is widely used in the treatment of obesity and has gained significant popularity in recent years. Due to its benefits in individuals with obesity and overweight, its favorable impact on patients with PCOS and obesity in consequences is postulated. Besides the potential benefits mentioned above, its positive impact may also reduce fat tissue, thereby decreasing the influence of hormones produced by it. Due to hormonal processes occurring in adipose tissue, such as androgen aromatization and estrogen production, its reduction may be crucial in alleviating symptoms resulting from their excessive effects, such as heavy uterine bleeding [16].

In a study conducted by Paoli et al. on a group of 14 overweight women diagnosed with PCOS, the authors focused on examining the effects of the KD on the body. After 12 weeks of the KD, an average body weight reduction of 9.43 kg and a decrease in BMI by 3.35 were observed. Additionally, a decrease in fat body mass and visceral adipose tissue was noted. Moreover, parameters related to glucose metabolism, cholesterol, and hormones improved. Free testosterone, LH, LH/FSH levels decreased, while FSH and estradiol levels increased [17]. Another study demonstrated the positive impact of the KD on a group of 17 obese women with PCOS. After 45 days of the diet, which had only 600 kcal, patients were reassessed, showing reductions in weight, BMI, and overall improvement in anthropometric characteristics. Blood and urine parameters, including triglycerides, cholesterol, LDL, HDL, glucose, insulin, and HOMA-IR, also improved. Furthermore the level of free testosterone, total testosterone, and SHBG decreased. It is important to note that this was a highly restrictive diet with low daily calorie intake, so the extent to which the KD contributed to the improvement of the parameters compared to the reduction in body weight from a low-calorie diet is unclear [18]. In another study, the impact of a very-low-calorie ketogenic diet (VLCKD) and a mediterranean diet (MD) on overweight women with PCOS who were candidates for IVF was compared. BMI and body weight decreased in women following the VLCKD compared to the MD [19]. Cincione et al. divided women with increased body weight and PCOS into equal groups and assigned them to either a KD or a MD. The authors showed that the KD had a better impact on anthropometric parameters, including BMI and weight [20]. PCOS often coexists with other organ disorders and diseases such as obesity or hypercholesterolemia, which may lead to fatty liver. Li et al. investigated how the KD in obese women with PCOS and liver dysfunction could affect health. After 12 weeks the markers of liver function reduced in the group of patients following the KD. Additionally, in 7 out of 8 patients following this diet, signs of fatty liver were not observed, indicating that the KD may have a beneficial impact on women with PCOS [21]. It is noteworthy that the reduction of fat tissue in women with PCOS is correlated with more regular menstrual cycles. Furthermore, in addition to the positive effects of the KD, physical activity has also shown a positive impact on weight [22]. The KD may also increase the levels of vitamin D in obese patients with PCOS. In studies conducted by Jian et al., after 4 weeks of the diet, vitamin D deficiency decreased, and there was also a reduction in body weight and improvement in glucose metabolism [23].

3. Effects of the ketogenic diet on ovarian cancer

The most common type of ovarian cancer is epithelial ovarian cancer. Although it can occur in any age, it is more probably in women older than 50 years [24]. While epithelial ovarian cancer is the leading cause of death amongst all gynecological cancers, treatment remains challenging. Almost 75% of women are diagnosed in advanced stages, which are associated with poor prognosis. They are subjected to first-line treatment consisting of aggressive cytoreduction and adjuvant treatment [25]. The response to this therapy is around 80-90%, but most women relapse and develop chemotherapy resistance. Thus, 5-year survival estimates less than 35% of patients diagnosed with ovarian cancer [26].

Lately, more and more research indicates that cancer is a metabolic disease and ketogenic diet is hypothesized to have an impact on tumor progression by altering its metabolism. This is suggested by the fact that cancer cells prefer to metabolize glucose for energy via glycolysis than use oxidative phosphorylation, which is observed in normal cells. Due to the fact that this process is relatively inefficient in terms of ATP, cancer cells need high amounts of glucose for proliferation. Thus, some researchers suggest that they might be vulnerable under conditions of glucose deprivation and reducing the amount of dietary carbohydrate may decrease the incidence or at least delay the emergency of cancer development [27]. Cancer cells are characterized by disproportionately populated insulin receptors. This hormone is responsible for regulating blood glucose concentration and the uptake of glucose both by normal and cancer cells. This mechanism probably allows cancer cells to supply sufficient glucose, even when glucose concentration is on the normal level [28]. Some research suggests that insulin and another hormone, which has sequence homology with insulin - insulin-like growth factor I (IGF-I), may take part in cancer cell proliferation via insulin receptor-mediated activation of MAPK and phosphatydalinositol-3 kinase [29]. Cancer cells depend on glucose for fuel, thus the KD using carbohydrate restriction and shifting to the production of the ketone bodies, which cannot be used by cancer cells, but may be an alternative energy source for healthy cells, seem to have a potential as the regimen for cancer therapy.

The glycolytic nature of cancer cells as the potent treatment target was investigated by Cohen et al. The trial was conducted on women diagnosed with ovarian or endometrial cancer, who

were randomly divided into the ketogenic diet group (70:25:5 energy from fat, protein and carbohydrate) and the American Cancer Society diet group (ACS; high-fiber, low-fat). In the KD group in comparison to the ACS group selective loss of fat mass and retention of lean mass were noticed. Researchers also observed reduction in visceral fat mass and fasting serum insulin, which may be associated with enhanced insulin sensitivity. Also serum β-hydroxybutyrate elevation was elevated, which influences a metabolic environment and makes it inhospitable to cancer proliferation [30]. The KD as a potential adjuvant therapy for cancer, may also influence the quality of life. The trial conducted on women diagnosed with ovarian or endometrial cancer receiving the KD or the ACS revealed that the KD-participants noticed improvement in physical function and increased energy. Those in the KD group, who have not gone chemotherapy, reported a significant between-group reduction in fatigue. Diminishing specific food cravings for starchy foods and fast food fats was also observed in the KD-group. No significant differences between both groups in mental function, hunger and appetite were observed [31]. The KD has been shown as beneficial and effective in tumor inhibition in previously mentioned human studies. However, AlHilli et al. revealed that KD administered in an unrestricted fashion in vivo may promote tumor growth and does not enhance the response to chemotherapy with cisplatin compared to other investigated diets. The impact of an unrestricted KD on epithelial ovarian cancer was assessed in a mouse model. In this trial the KD was associated with upregulation of fatty acid metabolism and regulation pathways including enrichment of fatty acid glutamine metabolites. Acceleration in tumor growth in the KD-fed mice allowed authors to conclude that unrestricted KD enhanced tumor progression in mouse model [32].

4. Conclusions

PCOS poses many therapeutic challenges, especially as it is the most common endocrine disorder in women of reproductive age. Due to the fact that the symptoms of the disease affect not only the reproductive system, a holistic approach is required in treatment. One of the non-pharmacological methods of treatment can be the implementation of an appropriate diet. The KD has proven beneficial effects in patients suffering from PCOS, not only those with obesity or overweight. The application of the KD helps reduce body weight, BMI, the level of free testosterone, LH/FSH ratio, and fasting insulin. However, it is still unknown how long the

beneficial effect will persist after the application of the diet and to what extent it is related to the KD versus the reduced calorie intake. The long-term effects of the KD in patients with PCOS are also still unknown.

In the treatment of ovarian tumors, there are hypotheses attempting to describe the potentially beneficial effects of the KD through the reduction of fat tissue and lowering insulin levels. However, these hypotheses have not found strong confirmation in studies. Results are ambiguous and some indicate potentially harmful effects of the KD. On the other hand, the KD has shown positive effects such as improvement in physical function and increased energy in some studies. Therefore, further research on the application of the KD is needed, especially considering its long-term impact on health.

Author Contributions:

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conceptualization,
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preparation of the publication
Sebastian Tomaszuk:
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Karolina Wąsik:
conceptualization,
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manuscript proofreading
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Conflicts of Interest

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