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# The impact of the Ketogenic Diet on the Metabolic Profile, Hormonal Balance and Fertility in Women with PCOS- A Literature Review

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**ABSTRACT**

**Introduction:** Polycystic ovary syndrome(PCOS) is the most common endocrine disorder among women of reproductive age. It is characterized by clinical symptom caused by high androgen level such as acne, hirsutism and irregular menstrual cycles. The cause of PCOS is unknown but both genetic and environmental factors are believed to play a role. The key elements in the patogenesis of this syndrome are insulin resistance, hyperinsulinemia and hyperandrogenism. PCOS increases the risk of metabolic and cardiovascular diseases. The aim of this review is to describe the efficiency, safety and potential benefits of the ketogenic diet on the metabolic profile, hormonal balance and fertility in women with PCOS.

**Materials and methods:** A literature review was conducted using the databases such as Pubmed and Google Scholar.

**Results:** The ketogenic diet focuses on reducing carbohydrate intake while proportionally increasing fat and protein consumption. This diet reduces insulin resistance and positively impacts Patients' metabolic profile and hormonal balance. This contributes to improve fertility in women, who often experience difficulty conceiving.

**Conclusion:** The results of the studies show that the ketogenic diet has a positive effect on metabolic profile and hormonal balance in Patients with PCOS. However, further research is

needed in larger groups of Patients and over longer periods of time to evaluate whether it can become an effective form of therapy for PCOS Patients.

**Keywords:** 'PCOS', 'ketogenic diet', 'insulin resistance', 'hyperandrogenism', 'fertility'.

## Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in the population of women of reproductive age. Its frequency depending on tested population and diagnostic method that was used ranges from 6% to 15% [1]. PCOS is characterized by the presence of increased levels of circulating androgens in the blood with clinical signs such as acne, hirsutism, as well as irregular menstrual cycles and fertility problems. One of the causes that leads to increased level of androgens it is hyperinsulinemia. The high level of insulin stimulates ovaries to producing androgens what causes symptoms of hyperandrogenism. Hyperinsulinemia is caused by insulin resistance which is the fundamental pathogenic element of the disease. The cause of PCOS progression has not been identified so far. Genetic, environmental, metabolic, and hormonal factors are being taken into account. Among the environmental factors, the key role is played by obesity. Studies show that obesity or overweight relates to 70-80% of the women who deal with PCOS [2]. The accumulation of visceral fat tissue is increased both in women with overweight/obesity but also in those with optimal body weight. The connection between central obesity and progression of insulin resistance has been well-established. PCOS - in according to the Rotterdam criteria - is being diagnosed when the person deals with at least two of the three following criteria: polycystic ovaries assessed in ultrasound examination; clinical signs of hyperandrogenism with elevated levels of circulating androgens; and oligo-amenorrhea with oligo-anovulation[3].

PCOS is associated with an increased risk of developing metabolic diseases, including type 2 diabetes, as well as endometrial cancer and cardiovascular diseases [4, 5, 6]. Studies show that women who deal with PCOS are more likely (about 3-7 higher risk) to get diabetes type 2 [3]. The risk gets higher during situations of decreased SHBG levels, which occur in PCOS[7].

According to the 2018 guidelines of the American Society for Reproductive Medicine (ASRM) the first line to treat PCOS it is changing lifestyle, controlling diet and body weight and regular physical activity[8]. It can be effective because the studies show, that the diet of women with PCOS is based on a significantly higher intake of high glycemic index foods compared to a group of healthy women, despite having the same energy value and intake of micro and macronutrients [9]. What is more, studies highlight that the diet of women with

PCOS compared to healthy women consists of reduced amount of the olive extra virgin, legumes, seafood, nuts, complex carbohydrates, fiber, monounsaturated fatty acids, and an increased amount of simple carbohydrates and saturated fatty acids[10]. It shows that a modification in lifestyle should be taken into account.

Obesity is a significant problem among Patients with PCOS. The American Association of Clinical Endocrinologists and the guidelines of the American Collage of Endocrinology recommend losing weight from 5 to 10% or even more for women with PCOS. However changing the eating habits is difficult so it requires professional help. This fact was confirmed by the meta-analysis conducted in 2020, which emphasized the role of professional dietary advice to all patients with PCOS, as diet can help with reducing insulin resistance and improving body composition [11]. It can also positively affect ovulation, regulate menstrual cycles, reduce hirsutism and insulin resistance. This studies and the recommendation of scientific societies show the importance of treating patients with changes in their diets. The main goal of the article is to evaluate the impact of the ketogenic diet on the metabolic profile, hormonal balance, and fertility in women with PCOS.

## Material and methods

The article was based on literature from PubMed and Google Scholar database, using keywords such as 'PCOS,' 'ketogenic diet', 'obesity,' 'insulin resistance,' 'hyperandrogenism,' an

## Results

### 1. Ketogenic diet

Ketogenic diet is characterized by limiting daily carbohydrate intake (<30g/day) and proportionally consuming protein and fat. At first, this kind of diet was focused on supporting the treatment of neurological disorders (mainly drug-resistant epilepsy), metabolic diseases (GLUT-1 deficiency, diabetes), cancers, and obesity. Currently, an increasing number of studies indicate its potential benefits in the treatment of PCOS.

Ketogenic diet modifies metabolic pathways of the human organism. Thanks to reduced intake of carbohydrates, the main source of energy become ketone bodies (instead of glucose). They are formed from fatty acids released from adipose tissue in the process of lipolysis. What is more, ketone bodies have one more function- they inhibit the secretion of ghrelin, the hunger hormone, thereby reducing appetite. The goal of ketogenic diet it is to

induct a state of ketosis in the body, in which the body is forced to use ketone bodies as an energy source[12]. Another factor which is important in PCOS patogenesis is oxidative stress and mitochondrial dysfunction. It causes a decrease in SHBG synthesis, increase in androgen synthesis, and have a negative impact on oocyte quality. Studies show that ketogenic diet has the ability to revert the normal function of mitochondria, independently of body weight reduction [13].

Moreover, it influences microorganism colonization of the gut by increasing the amount of Bacteroideted bacteria which is a major producer of short-chain fatty acids [14].

At the molecular level, the ketogenic diet activates AMPK (AMP-activated protein kinase) and SIRT-1 (sirtuin – a protein that suppresses so-called aging genes). That happens even if the amount of calories intake is not reduced. Activation of SIRT1 and AMPK positively affects glucose homeostasis and improves insulin sensitivity [15].

Currently, several ketogenic diet protocols are used: the classic ketogenic diet (CKD), low-calorie ketogenic diet (LCKD), very low-calorie ketogenic diet (VLCKD), and modified ketogenic diet (MKD) [16].

Apart from advantages, ketogenic diet can also bring unwanted effects such as feeling of tiredness, headaches, hypoglycemia and halitosis. These symptoms usually occur at the begining of the treatment and then resolve on their own. Deficiencies in micro and macronutrients can also occur, as well as constipation caused by reduced fiber intake. When the diet is used for a long time it can provide hypercalcemia, changes in lipid profile, gallstones, hair loss, and urinary stones [17]. However, as the newest study show, ketogenic diet has minor side effects which can be avoided and controlled due to properly following the indications and contraindications for this diet [18].

## 2. Ketogenic diet and metabolic profile

Studies show that a low-carbohydrate diet has more beneficial effects on hormonal balance, metabolic function, and fertility in women with PCOS than a standard low-calorie diet, due to its regulatory impact on insulin secretion. It makes using ketogenic diet as an important ‚tool' in therapy for women with PCOS. The biggest part of conducted studies relates to women with overweight or obesity. Several studies show that the use of a ketogenic diet influences laboratory test results and the severity of symptoms in patients with PCOS. One of the earliest studies about the influence of the ketogenic diet on the metabolic profile and hormonal balance in women with PCOS was conducted by Mavropoulos et al. There were

11 women with obesity in the reproductive age who took part in that study. For 24 days, they were following the diet with restriction only to 20g carbohydrates per day. Every two weeks the followed-up tests were conducted, and dietary recommendations were reinforced. Due to the fact that such a significant reduction in carbohydrate intake results in the production of ketone bodies, the presence of ketonuria served as an indirect indicator of patient adherence to the recommendations. The study observed a significant body weight reduction, reduction in the percentage of free testosterone, a decrease in the LH/FSH ratio, and fasting insulin levels. Based on the interpretation of the questionnaire completed by the patients before and after the study, an improvement in quality of life was also observed, particularly in the areas of hair, fertility, and menstruation. Two women became pregnant despite previous fertility issues [13].

Also the study conducted by Cincione et al, show positive influence of ketogenic diet on women with obesity and PCOS. In this study, 17 women of reproductive age, took part. The diet was tailored to the participants' personal preferences, with the condition of low carbohydrate intake (<30g/day), and its caloric value was 600 kcal. The body weight reduction was observed (around 9,4 kg), BMI decreased on average by 3.6 kg/m², waist circumference reduced by an average of 9.4 cm, and hip circumference by 8.1 cm. Fat mass decreased by an average of 7.9 kg. Fasting glucose levels dropped by an average of 10.07 mg/dL, and blood insulin levels by 12.9 mcU/mL. The HOMA insulin resistance index also decreased. Changes were also observed in lipid metabolism: the average triglyceride level dropped by 70 mg/dL, total cholesterol by 40 mg/dL, and LDL by 35 mg/dL. Hormonal parameters also improved: the LH level in plasma decreased on average by 4.6 mIU/mL, and the LH/FSH ratio decreased to 1.32. The levels of total and free testosterone also decreased. The levels of FSH and SHBG showed a statistically significant increase. In 5 of the women tested, there was a natural return of menstrual cycles after many years of absence, and in 12, regularity was restored - 5 women in this group became pregnant despite previous unsuccessful attempts [19].

Another study conducted by Paoli et al, had similar aim as the previous ones. The difference was connected with another kind of the ketogenic diet, which was the KEMEPHY diet. It is a ketogenic diet with the addition of fitoextracts, with a caloric value of 1600-1700 kcal/day. The results were measured after 12 weeks of the trial. Scientists observed that the average body weight reduction was approximately 9,5 kg. The significant reduction of BMI (3.35) was noticed, too. Furthermore, a significant decrease in fasting glucose and insulin levels, and consequently the HOMA index, was observed. The levels of triglycerides, total

cholesterol, and LDL fractions also decreased, while HDL levels increased. Hormonal tests showed a significant decrease in plasma LH levels, total and free cholesterol, and DHEAS, as well as a significant increase in SHBG. To conclude: nearly all anthropometric, biochemical, and hormonal indicators improved [20].

## 3. Hormonal balance and fertility

Infertility affects about 40% of women with PCOS [21]. It is the most common cause of the problems with ovulation (oligo/anowulation) in women of reproductive age. Insulin resistance in PCOS leads to a deterioration in oocyte quality and disrupts their growth, negatively impacting fertility. Hyperinsulinemia, a consequence of insulin resistance, stimulates the proliferation of theca cells in the ovary, which results in LH-dependent androgen secretion and increases the expression of receptors for LH and IGF-1[22]. Additionally, hyperinsulinemia reduces liver production of SHBG, leading to an increase in free testosterone levels [23]. Several studies showed the negative impact of diet rich in carbohydrates, saturated fats, and animal protein on women's fertility. This kind of diet leads to decrease in progesterone levels. Moreover, it causes reduction of the number of blastocysts despite a higher number of antral follicles [24]. A lot of studies confirm a significant effectiveness caused by ketogenic diet in the context of hormonal regulation and fertility. In a meta-analysis conducted by Khalid et al., 170 women with PCOS underwent a 45-day ketogenic diet cycle. A decrease in the LH/FSH ratio, a reduction in free testosterone levels, and an increase in SHBG were observed [25]. In another meta-analysis, insulin resistance markers were compared between women with recurrent miscarriages and healthy women. The study found that women with recurrent miscarriages had significantly higher fasting insulin levels, a higher HOMA index, and a lower glucose-to-insulin ratio compared to healthy women [26]. In a study conducted by Magagnini et al., the impact of a very low-calorie ketogenic diet on ovarian reserve and the luteal phase in women with PCOS was evaluated. The study was conducted on 25 obese women who followed a very low-calorie ketogenic diet for 12 weeks. After 12 weeks of the diet, a decrease in BMI, waist circumference, and HOMA index was observed. 19 out of 25 patients transitioned from obesity to overweight, and the HOMA index normalized in 24/25 patients. Furthermore, a significant decrease in serum AMH levels and an increase in SHBG and progesterone were observed, showing the beneficial effect of the ketogenic diet on ovarian reserve and luteal function in women with

PCOS [27]. Another study conducted by Tsushima et al., investigated the effect of the ketogenic diet on restoring menstrual cycle regularity and increasing pregnancy rates. Thirty women with PCOS followed a ketogenic diet for 3 months. All participants reported the restoration of regular menstrual cycles, and the overall pregnancy rate among women trying to conceive (n=18) was 55.6%. The study showed that 92% of women who had irregular cycles began menstruating regularly after 6 months, while the remaining 8% achieved regularity after 15 months. The results were compared between women taking metformin and those not using it. Regardless of metformin use, all women who had irregular cycles before the ketogenic diet achieved regular menstrual cycles after following the diet [28].

It was noticed that the use of ketogenic diet as a method for effective body weight reduction increases the chances of pregnancy in the in vitro fertilization procedures. Probably it is related to the reduction in insulin resistance, as well as fasting insulin and glucose levels, because high concentrations of these factors negatively affect the ovarian environment and IVF success. A meta-analysis conducted by Sermondade et al. in 2019 evaluated 682,532 cycles and found that obesity in women negatively impacts the live birth rate in women undergoing in vitro fertilization procedures [29]. The reduction of body weight in women with overweight or obesity increases fertility and the quality of fertilized egg cells in the in vitro fertilization (IVF) procedures. It also improves the quality of the transferred embryo [30]. In the study conducted by Palafox-Gomez et al. it was observed that using a ketogenic diet by women with PCOS trying to conceive increased endometrial thickness, the rate of successful embryo implantation, clinical pregnancy rates, and live birth rates in in vitro fertilization (IVF) procedures. The study involved overweight/obese women who had undergone one unsuccessful IVF cycle. After following the ketogenic diet, the patients underwent ovarian stimulation. Compared to the previous cycle, there were no differences in the number of oocytes, fertilization rate, or number of viable embryos. However, a significant improvement was observed in implantation rates (83.3% vs 8.3%), clinical pregnancy rates (66.7% vs 0%), and live birth rates (66.7% vs 0%) [31].

The mentioned studies prove the positive impact of a ketogenic diet on women's fertility as well as on improving the effectiveness of in vitro procedures.

## 4. Ketogenic diet vs other diets

There are no unequivocal guidelines that could give one, effective diet that is helpful in treatment for obesity in women with PCOS. There are several studies that compare the impact of different types of diets on the metabolic and hormonal profile of women with PCOS.

Deshmukh et al. assessed whether the positive effects of the ketogenic diet result from its composition or its caloric content. They compared a VLCD (very low-calorie diet) with a moderately calorie-restricted diet in obese women with PCOS. The impact on body weight, body composition, the free androgen index, and metabolic parameters was evaluated. The study lasted for 8 weeks. In both groups, a significant weight loss was observed, greater in the VLCD group (-10.9% vs. -3.9%), along with a reduction in the free androgen index (-32.3% vs. -7.7%). In the VLCD group, a significant increase in SHBG levels, reduction in fasting blood glucose, and WHR were observed compared to the second group. VLCD resulted in a significantly greater weight loss and was associated with more noticeable improvements in hyperandrogenism, body composition, and several metabolic parameters in obese women with PCOS compared to the moderately calorie-restricted diet [32].

One of the most popular diets is Mediterranean diet, which has anti-inflammatory effects (similarly to ketogenic diet). The Mediterranean diet is based on regular consumption of fiber, vitamins, antioxidants, as well as unsaturated fats, low-glycemic carbohydrates, and a moderate intake of animal protein [33]. In the study by Masooda et al., the effects of the ketogenic diet and the Mediterranean diet on the course of PCOS were compared. The study involved 80 women, who were divided into two groups. The first group followed a VLCKD (very low-carbohydrate ketogenic diet), and the second group followed a low-calorie Mediterranean diet for 45 days. The study observed a significant weight loss (-10.9 kg vs. -5.1 kg), a reduction in total cholesterol and its LDL fraction, a significant reduction of fasting glucose level in both groups. The values of C-peptide, LH, and FSH also showed greater improvement in the group following the ketogenic diet. Both the ketogenic and Mediterranean diet groups showed improvements in metabolic parameters, but the improvement was greater in the ketogenic diet group. [34] Similarly, Pandurevic et al. compared the effectiveness of a very low-calorie ketogenic diet (VLCKD) with a low-calorie Mediterranean diet in women of reproductive age suffering from obesity and polycystic ovary syndrome (PCOS) [35]. The study involved 30 women, who were divided into two groups. The first group- experimental (n=15)-followed VLCKD for 8 weeks, and then a low-calorie diet for the next 8 weeks. The second group-control (n=15)-followed the Mediterranean diet for 16 weeks. BMI decreased

significantly in both groups, with a greater reduction in the experimental group (-13.7% vs -5.1%). Significant differences between the experimental and control groups were also observed in waist circumference reduction (-11.4% vs -2.9%) and free testosterone (-30.4% vs -12.6%). The HOMA index significantly decreased only in the experimental group, but without significant differences compared to the control group (-23% vs -13.2%). At the start of the study, ovulation occurred in 38.5% of participants in the experimental group and 14.3% in the control group, and by the end of the study, this percentage increased to 84.6% and 35.7%, respectively. The researchers concluded that the 16-week VLCKD protocol with the Pronokal® method was more effective than the Mediterranean LCD therapy in reducing total and visceral fat, as well as in alleviating hyperandrogenism and ovulatory disorders in obese patients with PCOS [35]. In the short term, the ketogenic diet may be more effective for weight loss than the mediterranean diet. However, individual responses to diets can vary significantly, and the long-term sustainability of the diet is key when choosing it [36].

There are also studies which compare the ketogenic diet with DASH diet. The DASH diet is rich in carbohydrates and fiber, magnesium, potassium, and calcium (as well as other micronutrients), low in sodium (<2300mg) and fats (mainly saturated fats), with moderate protein content. It is mainly based on fruits, vegetables, whole grains, nuts, legumes, and low-fat dairy products, with reduced content of red and processed meats, refined grains, and sweets [37]. Its target group was initially patients with hypertension. The clinical trial is currently being conducted by Greenwell et al., which compares the effectiveness of a very low-carbohydrate diet with the DASH diet in improving glucose control and reducing PCOS symptoms. One of the studies is in progress. This study is being conducted on 184 women aged 21-45 years, with a BMI of 25-50kg/m², and its duration is set for 12 months. The hypothesis posed by the researchers is that there will be greater benefits (improved glycemic control, better PCOS symptoms, and greater weight loss) with the very low-carbohydrate diet compared to the DASH diet. Patient recruitment started in August 2022, with the expected completion date in December 2025 y [38].

Another randomized clinical trial, the results of which we are waiting for, is being conducted by Najafabadi et al. The aim is to compare the effectiveness of the ketogenic diet and PLCD—portfolio low-carbohydrate diet. PLCD is a plantbased diet where carbohydrates make up 40%, proteins 20%, and fats 40% of energy, combined with 5 cholesterol-lowering foods. The study included 46 overweight or obese women with a diagnosis of PCOS, aged 15-45 years, who were randomly divided into two

equal groups The results will be available soon [39].

The above studies, showed that the ketogenic diet was associated with a significant reduction in body weight, accompanied by improvements in body composition, glucose, and lipid parameters. Compared to other weight loss interventions, the ketogenic diet had a greater impact on reducing body weight and fat mass, waist circumference, total cholesterol, and triglycerides, as well as improving insulin sensitivity. The side effects were mild and transient. From the other hand, there is no consensus on the optimal dietary recommendations for women with PCOS. Some do not mention any specific diet [8], while others recommend the DASH diet [40], while others suggest a low-carbohydrate diet [41]. It is the reason why scientists are still searching in their clinical studies for a single effective diet that can be applied to patients with PCOS.

## 5. PCOS among adolescents

In the context of adolescents, the patogenesis is often discussed. It is believed that important role plays a theory called: a 'two hit' theory. According to this, the first hit is congenitally programmed predisposition, while the second is a provoking factor. Furthermore, studies conducted on young women proves that genetic factors play an important role in the patophysiology. It is estimated that 25% of adolescent girls with PCOS have mother suffering from PCOS. Compare to control group, higher androgen levels in the first years after menarche are found among girls, whose mothers had PCOS [42,43].

Diagnosing PCOS in this group is more challenging. Symptoms such as acne, seborrhea or irregular menstrual cycles are typical for adolescent girls and are related to the normal physiology of a maturing reproductive system. It results in the necessity to modify adults' criteria to avoid overdiagnosing. The latest guidelines by Pena in 2020[44] are presented below (Table 1).

Table 1. Recommendations for diagnosing PCOS in adolescents

| Criteria Definition | Pena et al. |
|---|---|
| Irregular menstrual cycles | >90 days for any cycle(>1 year post-menarche).<br>Cycles <21 or >45 days (>1 oto <3 years post-menarche).<br>Cycles <21 or >35 days (>3 years post-menarche).<br>Primary amenorrhea by age 15 or >3 years post-thelarche. |
| Huperandrogenism | Clinical:symptomes such as severe acne, |

| | |
|---|---|
| | hirsutism<br>Biochemical: hyperandrogenemia |
| Ovaries morfology on Ultrasound | Pelvic ultrasound is not recommended for diagnosis of PCOS within 8 years post menarche. |

Studies show that abnormal glucose metabolism is observed in 18.2% of young women with PCOS [45]. Moreover, it is estimated that 40-70% of adolescents with PCOS are obese or overweight [46]. It provides the evidence that there is a need to start lifestyle changes. Marzouk et al. in the study conducted on young women with BMI>30kg/m2 observed that losing weight is connected with the significant improvement in menstrual regularity, anthropometric parameters and reduction of hirsutism [47]. To conclude, the main target in the management of young women with PCOS is focused on improving metabolic and hormonal status, as well as quality of life. The first step in all cases are diet modification and physical activity. As ketogenic diet can help with reducing body weight and decrease insulin resistance, it can be taken into consideration in the future studies.

## 6. Animal research

The effects of the ketogenic diet have also been assessed in studies which based on animal models. One of them was presented by Liu et al.. In this study scientists used dehydroepiandrosterone(DHEA) to induce PCOS in mices. They were dived into three groups. The first one was a control group, the second one consisted of mices with PCOS and was fed with normal diet and the third one also suffered from PCOS however was fed with ketogenic diet. The results show that among PCOS-mices who ate ketogenic diet the level of ketone bodies was higher comparing to other two groups. However weight and blood glucose level significantly decreased. Scientists also paid attention to betahydroksybutyrat (kind of ketone bodies), which is produced during ketogenic diet consumption. It reduced inflammation and improved ovaries function.[48].

Unfortunately, during particular studies negative aspects were also observed. Lai et al. suggested that high-fat diet can caused metabolic alteration such as obesity, glucose intolerance, liver steatosis and dyslipidemia. But from the other hand, it has no influence on the reproductive phenotype [49].

## 7. Conclusion

The management of Polycystic ovary syndrome still remains a challenge for doctors and scientists. Many different methods are used however none of them is fully effective and safe. Nevertheless, it is believed that lifestyle modification is the first line of treating Patients. This research show that ketogenic diet can be a useful 'tool'. The observations from presented studies show that ketogenic diet has a positive influence on the metabolic prolife, hormonal balance and fertility in the women with PCOS. However, further research involving larger patient groups and longer durations are necessary to determine whether the ketogenic diet should be recommended for patients with PCOS, as well as to assess its safety and effectiveness.

**Disclosure**

**Authors' contribution**

Conceptualization: M.T.

Methodology: M.T., A.M., U.K., K.Z., A.W., K.S., K.W., M.B., N.H.,

Software: A.M., A.W., K.S., M.B., N.H.,

Check: M.T., A.M, U.K., A.C., K.Z., A.W., K.S., K.W., M.B., N.H.,

Formal analysis: M.T., A.M., U.K., A.C., K.Z., A.W., K.S., K.W., M.B., N.H.,

Investigation: M.T., A.M, U.K., A.C., K.Z., A.W., K.S., K.W., M.B., N.H.,

Resources: M.T., A.M., U.K., A.C., K.Z., A.W., K.S., K.W., M.B., N.H.,

Data curation: M.T., A.M., A.C., K.Z., A.W., M.B., N.H., U.K., K.S., K.W.,

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## Conflict of interest

The authors deny any conflict of interest.

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