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Polycystic ovary syndrome and type 1 diabetes — the current state of knowledge

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Abstract

Type 1 diabetes mellitus (T1DM) is characterized by an increased prevalence of polycystic ovary syndrome (PCOS) with its negative metabolic consequences, including increased cardiovascular risk. Both diseases affect patients, significantly deteriorating the quality of life.
During the treatment of patients with T1DM and PCOS, lifestyle modification and increased physical activity resulting in weight reduction should always be recommended. Pharmacological treatment should be applied in accordance with the current standards. In most of these patients metformin alone or with combined oral contraceptive pills could be considered for cycle regulation. In obese patients with T1DM and PCOS glucagon-like peptide-1 receptor agonists (GLP-1 Ras) (liraglutide, semaglutide) and dual glucose-dependent insulinotropic polypeptides (GIP)/GLP-1 RAs (tirzepatide) are regarded as a safe approach. Anti-androgens could also be considered especially to treat hirsutism and hyperandrogenism in women with PCOS. There are relatively limited evidence on anti-androgens in PCOS and we should consider use them in only selected cases. Some other substances may have a positive effect on patients with T1DM and PCOS include inositol, alpha-lipoic acid, folic acid, vitamins (B1, B6, B12, D, K, E, A), chromium and selenium compounds, as well as omega-3 fatty acids. The gut microbiome is also considered as a critical modulator of the predisposition to PCOS and T1DM and may be the future goal of the treatment.
The proper treatment of PCOS will translate into a reduction in the severity of typical symptoms and also into the improvement in the metabolic control of diabetes and the patients' quality of life. **(Endokrynol Pol 2024; 75 (5): 479–485)**

Key words: *PCOS; type 1 diabetes; adjuvant therapy*

Introduction

Polycystic ovary syndrome (PCOS) is considered the most common endocrinopathy in women of reproductive age. It occurs in about 6–13% of women of reproductive age and is the leading cause of infertility of endocrine origin [1]. The clinical picture of PCOS consists of menstrual and ovulation disorders, clinical or biochemical hyperandrogenism, polycystic ovarian morphology (PCOM) and elevated levels of anti-Mullerian hormone (AMH) in adult women [European Society of Human Reproduction and Embryology (ESHRE) 2023] [2]. According to the definition, PCOS is a disease of women of reproductive age. However, it can be a life-long disorder with its onset as early as in the prenatal period. The pathophysiology of PCOS is complex and not fully understood. Both genetic and environmental factors are involved. The underlying causes include abnormal ovarian steroidogenesis, impaired insulin signaling and excessive oxidative stress resulting in increased insulin resistance of peripheral tissues. Decreased insulin sensitivity is an inherent component of PCOS, regardless of the presence of obesity [3]. The insulin receptors were found in the ovaries, insulin resistance and compensating hyperinsulinemia in PCOS directly stimulate the ovaries to produce androgens along with reduced production of sex hormone binding globulin (SHBG) in the liver, which consequently leads to hyperandrogenism [3]. More recent studies have emphasized the significance of the dysfunction of the hypothalamic-pituitary-ovarian axis [3, 4]. Neurotransmitters, such as kisspeptin and gamma-aminobutyric acid (GABA), which regulate the secretion of gonadotropin-releasing hormone (GnRH), may also be responsible for the development of PCOS. Additionally, the stimulating effect of androgens and AMH is also crucial. Increased androgen concentrations predispose to male-pattern obesity associated with greater deposition of visceral fat regardless of the body mass index (BMI). They also adversely affect the lipid profile by lowering the serum concentration of high-density lipoprotein (HDL) cholesterol through direct modulation of lipoprotein lipase and lipolysis. Concomitant metabolic disorders, including insulin and leptin resistance, also contribute to the abnormal secretion of GnRH. Accumulating evidence indicates

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the importance of the gut microbiota, whose metabolites such as short-chain fatty acids (SCFAs) and bile acids also regulate the action of gonadotropins [3].

Polycystic ovary syndrome is associated with an increased risk of type 2 diabetes mellitus (T2DM), cardiovascular diseases, obstetric complications, endometrial cancer and sleep apnea. In addition, patients with PCOS have a higher prevalence of depressive and anxiety disorders. The disorder translates into a significant reduction in the quality of life [5]. While the link between PCOS and T2DM seems obvious, the increased prevalence of PCOS in patients with T1DM is a surprising phenomenon, which is conditioned by absolute insulin deficiency rather than insulin resistance.

The estimated prevalence of PCOS in patients with type 1 diabetes mellitus (T1DM) may range from 12–41% [3, 5], depending on the criteria (the highest prevalence is reported when the Rotterdam definition is applied). Several theories explain such a high prevalence of the co-occurrence of PCOS and T1DM. According to one of them, the need for subcutaneous insulin therapy in the prepubertal period is associated with the development of PCOS in patients with T1DM. During childhood, insulin stimulates the non-cyclic recruitment of primordial follicles in the ovaries and prompts them to increase androgen secretion. When puberty begins, this action is enhanced by gonadotropins. Exogenous insulin administered at doses higher than the physiological secretion bypasses the hepatic circulation, leads to hyperinsulinemia and is responsible for higher androgen secretion [6, 7]. Insulin doses, duration of insulin therapy and glycemic control may be possible contributing factors to the pathogenesis of PCOS in T1DM regardless of insulin therapy (multiple dose injections or continuous subcutaneous insulin infusion) [6, 7].

In their study, Łebkowska et al. (2021) published the results of a Polish study that assessed the risk of developing PCOS in patients with T1DM in relation to the age of onset – before or after puberty [8]. Their study showed a higher incidence of PCOS in women with T1DM compared to previous reports that used the Rotterdam criteria. It was found that earlier menarche could have a positive effect on the diagnosis of PCOS in women with T1DM, and the insulin dose was positively associated with the testosterone level. Earlier onset of T1DM and a longer duration of ovarian exposure to high insulin doses resulted in a higher number of ovarian follicles. Their study also showed that glycated hemoglobin (HbA_{1c}) concentration was lower in patients with PCOS than in controls [8].

According to another theory, a more frequent co-occurrence of PCOS and T1DM is associated with an increased prevalence of obesity in children and adults. Obesity is a growing health and socio-economic problem. It is estimated that by 2035, 14% of girls (< 19 years of age) and 21% of boys (< 19 years of age) will be diagnosed with obesity. Among the adult population, 35% of women and 39% of men will be affected (World Obesity Report 2023) [9]. The prevalence of overweight and obesity among young patients with T1DM is also increasing. It is estimated that up to 35% of young patients with T1DM are overweight or obese. Obesity is a risk factor for autoimmune diabetes and is associated with earlier onset in predisposed patients. The prevalence of obesity in patients with T1DM increases significantly during puberty (more frequently in girls). It has a negative effect on metabolic control, glycemic variability and insulin demand [10]. A study published in 2020 on the prevalence of PCOS, obesity, and menstrual disorders in young patients with T1DM aged 18-23 years found that obesity in patients with T1DM increased the risk of developing PCOS four-fold compared to the healthy population. At baseline, 54.4% of women with T1DM were overweight or obese, while the prevalence of abnormal weight was 32.9% in the control group (without diabetes). During a 2-year follow-up, women with T1DM and PCOS gained 4 kg in weight compared to 2 kg in the controls despite a similar level of physical activity. Higher prevalence of obesity may be an anabolic effect of insulin which was used in T1DM group [7].

The presence of many risk factors for cardiovascular diseases (CVD), including hypertension, insulin resistance, metabolic syndrome, elevated BMI and dyslipidemia in women with T1DM and PCOS as well as in those with T2DM contributes to a significantly higher risk of CVD events [10–12].

Non-pharmacological management of T1DM and PCOS

All women with T1DM and PCOS should be recommended to make lifestyle changes characterized by healthy eating and regular physical activity. The aim of dietary treatment is to achieve and maintain normoglycemia, normal serum lipid levels, optimal blood pressure and the desired body weight. Currently, the gold standard is associated with following the principles of proper nutrition and controlling portion size and carbohydrate intake, considering the glycemic index (GI) and glycemic load (GL) of food and the limitation of easily digestible carbohydrates. Various nutritional strategies can be used in treatment, e.g. the Mediterranean diet, the DASH diet (Dietary Approaches to Stop Hypertension), the flexitarian diet, or plant-based diets that consider a significant proportion of non-starchy vegetables and an increase in the proportion of mini-

mally processed foods. The general principles of a properly balanced diet should be followed [13].

The increasingly popular ketogenic diet (KD) does not have a clear beneficial effect on patients with T1DM and PCOS. However, there are some data from relatively small studies that showed a beneficial effect of short-term dietary carbohydrate restriction on the improvement of hormonal disorders in patients with PCOS [14]. Importantly, the ketogenic diet leads to ketosis, which in patients with T1DM may translate into an increased risk of ketoacidosis. Moreover, there is no consensus on the acceptable level of ketosis in patients with T1DM on this diet. According to the latest recommendations of Diabetes Poland and the standards of medical care of the American Diabetes Association, ketogenic and low-carbohydrate diets are not included in the recommendations for nutritional treatment of T1DM. However, they are very popular among patients [13, 15].

Vitamins, dietary supplements and nutrients in the treatment of T1DM and PCOS

Over the past few years, there have been reports showing that some vitamins, dietary supplements, and nutrients may provide a promising and safe therapeutic strategy for women with PCOS.

Inositol (vitamin B8)

Inositol is one of the most promising substances, particularly its isomers (Myo-inositol and D-chiro-inositol). Myo-inositol (MI) is involved in modulating glucose uptake and FSH signaling, while D-chiro-inositol (DI) controls glycogen synthesis and insulin-induced androgen synthesis. Inositol metabolism is often impaired in women with PCOS. Both MI and DI isomers are second messengers of insulin, either through the expression of glucose transporters and cellular glucose uptake or glycogen synthesis and storage, respectively. A meta-analysis on the effects of MI in women with PCOS found that supplementation of MI decreased fasting insulin levels and increased SHBG levels. Other studies showed improvement in ovulation rates and regulation of the menstrual cycle with MI supplementation [16].

Alpha-lipoic acid

Another promising molecule is alpha-lipoic acid (ALA), commonly used to treat diabetic neuropathy. It is a potent scavenger of free radicals and it has an insulin-sensitizing effect. It stimulates the translocation of glucose transport proteins (GLUT-4 and GLUT-1) into the cell membrane of adipocytes, mimicking the action of insulin, thereby increasing insulin sensitivity. ALA and dihydrolipoic acid (DHLA) in its reduced form are potent antioxidant molecules. They inhibit the NF- B-mediated inflammatory pathway, blocking its translocation to the nucleus and reducing the release of pro-inflammatory cytokines. Research suggests that ALA regulates body weight due to its potential to reduce food intake and increase energy expenditure by suppressing hypothalamic AMP-activated protein kinase (AMPK) activity. Long-term use of ALA (16 weeks) in PCOS patients was associated with decreased insulin resistance and improved lipid profile [17]. Various studies investigated the role of ALA in the reproductive function and its influence on the hormonal profile in women affected by PCOS. The studies showed a significant reduction of testosterone [18], luteinizing hormone (LH) [19] and dehydroepiandrosterone sulphate (DHEAS) levels [20] and a significant improvement in estradiol. This study suggested that ALA could improve ovarian function and oocyte quality by reducing LH and increasing estradiol levels and may also reduce hyperandrogenism, decreasing testosterone and DHEAS levels [18–20].

Other substances that may have a positive effect on patients with T1DM and PCOS include folic acid, vitamins (B1, B6, B12, D, K, E, A), chromium and selenium compounds, as well as omega-3 fatty acids [17].

Gut microbiota in T1DM and PCOS

Microbiota and PCOS

Differences in the gut microbiota between patients with PCOS and controls may be one of the reasons for their susceptibility to many diseases. Changes in the ratio of *Bacteroidetes to Firmicutes* and *Lactobacilli* to *Bifidobacterium* lead to altered production of short-chain fatty acids (SCFAs), which in turn affects the integrity of the intestinal barrier, increases nutrient absorption and alters immunity and metabolism [21]. In PCOS, an increased abundance of *Bacteroides vulgatus was also found* with decreased concentrations of glycodeoxycholic and tauroursodeoxycholic acids, which resulted in changes in the concentration of interleukin 22 (IL-22) [21]. Lower IL-22 levels in patients with PCOS are associated with infertility and deterioration of ovarian function. Changes were also related to *Prevotella species* — their abundance increased intestinal inflammation. The intestinal flora also changes the concentrations of peptide YY (PYY) and ghrelin, increasing insulin resistance.

Probiotics and symbiotics have been shown to improve hormonal [SHBG and free androgen index (FAI)] and inflammatory indices in women with PCOS. In these patients, probiotic supplementation lowered fasting glucose, low-density lipoprotein (LDL) cholesterol and triglycerides. Significant reductions in body

weight and BMI were also observed in patients with PCOS who were treated with probiotic supplementation (*L. casei*, *L. acidophilus* and *B. bifidum*). Eight weeks of supplementation with *L. casei*, *L. acidophilus*, *L. rhamnosus*, *L. bulgaricus*, *B. breve*, *B. longum* and *Streptococcus thermophilus* led to a significant decrease in serum glucose and insulin levels [21].

Microbiota and T1DM

The gut microbiome is considered an important modulator of susceptibility to T1DM. The composition of the gut microbiota is altered before the onset of T1DM, including reduced microbial diversity and an increased abundance of *Bacteroidetes.* In particular, the abundance of *B. dorei* within *Bacteroidetes* may be a useful predictor of T1DM [22]. A higher ratio of Bacteroidetes to Firmicutes was observed in people with anti-islet autoantibodies. *An increase in Bacteroides dorei* and *vulgatus* and a decrease in *Lactobacillus and Bifidobacterium* occurred in children at high risk of T1DM. Evidence shows that gut microbiome dysbiosis increases a predisposition to T1DM. Lower diversity of the gut microbiome occurs before disease onset and remains after the diagnosis of T1DM. Once the balance of the intestinal microbiota is disrupted, the permeability of the intestinal mucosa is impaired, which can lead to the penetration of external or bacterial antigens, stimulating an excessive immune response or activating autoreactive T cells by molecular mimicry [22].

There have been no studies evaluating the impact of the microbiome on the risk of PCOS in patients with T1DM. However, in light of the available literature data, it can be assumed that the gut microbiome may be a critical modulator of the predisposition and pathogenesis of T1DM and PCOS. More research is warranted to better understand the role and mechanism of the gut microbiome in this group of patients.

Pharmacotherapy of PCOS in patients with T1DM

Next to dietary treatment and aiming for a normal glucose level, pharmacological treatment of patients with PCOS and T1DM is focused on restoring ovulation cycles, reducing androgenization and hirsutism and improving insulin sensitivity.

Hormonal contraception

Combined oral contraceptives (COCPs) are the first-line treatment option for cycle regulation and hirsutism. The estrogenic component increases SHBG, which decreases the amount of free testosterone. Both the estrogen and progestogen components affect the negative feedback mechanism and the production of LH by the pituitary gland and reduce the production of LH-induced ovarian androgens. Better effects of therapy were not demonstrated with a higher dose of ethinylestradiol (i.e. > 30 μg/tablet compared to 20 μg) [2]. According to the latest recommendations of Polish Diabetes Society (2024), T1DM is not a contraindication to hormonal contraception. However, in patients with at least a 20-year history of diabetes or with microvascular complications, the use of intrauterine devices or gestagen preparations is recommended. When choosing estrogen-progestogen preparations, the amount of ethinyl estradiol should be considered. The preparations containing less than 35 μg (preferably 15 and 20 μg) should be selected due to their minor effect on carbohydrate and lipid metabolism. Levonorgestrel and norethisterone are the preferred progestogen components due to their lower prothrombotic potential [13].

Antiandrogens

According to the current recommendations, drugs from this group should be used in combination with effective contraception due to their teratogenic potential. Anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of six months of COCPs and/or cosmetic therapy and when there are contraindications for COCPs or when COCPs are poorly tolerated [2].

There are relatively limited evidence on anti-androgens in PCOS and we should consider use them in selected cases.

Flutamide (FLU), which acts at the peripheral level, is an androgen receptor antagonist. It blocks cytoplasmic and nuclear binding of androgens. However, its use is restricted due to the risk of significant hepatotoxicity and teratogenicity. Administration of FLU alone or in combination with metformin significantly improved indices of insulin resistance and the distribution of visceral fat [23].

Spironolactone (SPA) is one of the most common antiandrogens. Its direct antiandrogenic effect results from blocking the activity of 5 -reductase. It competes with androgens for binding to SHBG. It also blocks the conversion of testosterone to dihydrotestosterone (DHT) in dermal papilla cells and antagonizes the androgenic effects of DHT on the hair follicle. It decreases the concentrations of GnRH and LH, thus lowering the secretion of androgens stimulated by LH [23]. When healthcare professionals use anti-androgens they should consider that spironolactone at small dose (25–100 mg/day) appears to have lower risks of adverse effects [2].

Oral contraceptives containing cyproterone acetate (CPA) are commonly recommended for the treatment of hyperandrogenism. CPA has high antiandro-

genic activity. However, it can adversely affect carbohydrate metabolism and the lipid profile. It can be combined with metformin to improve the metabolic profile [17]. The ESHRE recommends a maximum of 10 mg of CPA due to the increased risk of meningioma with higher doses [2].

Metformin

Metformin, which increases insulin sensitivity, should be considered if oral contraceptives are not tolerated or are contraindicated in adult patients with T1DM, PCOS and BMI > 25 kg/m^2 and in adolescents. Metformin in patients with T1DM promotes a moderate weight reduction and decreases insulin level, which translates into improved cycle regularity and reduced hyperandrogenism. Additionally, metformin has a beneficial effect on the lipid profile, leading to a decrease in total cholesterol, triglycerides and LDL-cholesterol, which is particularly important for reducing cardiovascular risk in patients with diabetes [24]. Compared to metformin, hormone therapy has a better effect on menstrual regularity, but it does not have a beneficial effect on metabolic disorders (weight reduction, better lipid profile and dysglycemia) [24–26]. Metformin increases estrogen secretion, decreases the production of androgens in the ovary and adrenal glands and increases the concentration of SHBG. As a result, the serum concentration of androgens is decreased, but with no impact on hirsutism or acne. Therefore, it is used as a second-line drug in patients with severe clinical symptoms of hyperandrogenism in combination with low-dose hormonal contraception. Metformin increases menstrual cycles, but it is not the first-line treatment for oligoovulation or infertility in women with PCOS [26].

Metformin has been studied for many years in terms of improving glycemic control in patients with T1DM, normalizing body weight and influencing insulin demand. Although inconclusive, study findings show the benefits of including metformin adjuvant therapy in insulin therapy in patients with obesity or high insulin demand [25–27]. Adding metformin does not significantly increase the risk of hypoglycemia, diabetic ketoacidosis, or lactic acidosis [25, 27–28]. It may require insulin dose reduction. Based on our experience, we believe that metformin is a safe, effective and well-tolerated therapeutic option for patients with metabolic syndrome, as well as with high insulin demand in the course of endocrinopathy, such as PCOS.

Metformin significantly helps reduce and maintain lower body weight, motivating patients to pursue a healthy lifestyle. It reduces visceral fat accumulation and positively affects the liver in people with metabolic dysfunction-associated steatotic liver disease (MASLD).

Importantly, patients with PCOS are often in reproductive age and plan pregnancy. Although metformin does not have a teratogenic effect on the developing fetus, it is not recommended for the treatment of pregnant women due to the lack of data on the long-term effects on fetal development (current guidelines of Polish Diabetes Society; 2024). Patients with PCOS and obesity who have previously used it are recommended to discontinue metformin until the end of the first trimester of pregnancy [13]. Metformin is a safe drug during lactation - it passes into breast milk in small amounts (< 1% of maternal concentration). No sequelae have been observed in newborns of mothers using it during lactation [13].

Glucagon-like peptide-1 receptor agonists

The documented effectiveness of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in reducing body weight has contributed to their established position in the treatment of T2DM and obesity. Their metabolic effects include a meal-related increase in insulin production, decreased glucagon synthesis, decreased food intake and a change in energy expenditure. In addition, GLP-1 RAs affect the activity of hypothalamic neurons responsible for the production of GnRH. Although inconsistent in terms of methodology and based on a small number of patients, medical reports have shown that the inclusion of GLP-1 RAs or the addition of the drug to metformin therapy in patients with PCOS promoted weight reduction, a decrease in the Homeostatic Model Assesment — Insulin Resistance (HOMA-IR) index and increased the likelihood of conception. According to the 2023 International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome [2], the use of GLP-1 RAs (liraglutide, semaglutide) may be considered in the treatment of obesity or overweight since they are registered for the treatment of obesity. The use of such agents can be an adjunct to lifestyle modification in adults with PCOS. Patients undergoing such therapy should be provided with effective contraception due to the lack of data on the safety of these drugs during pregnancy. The authors of the recommendations emphasize the lack of long-term data on the safety of GLP-1 RAs and the high risk of regaining body weight after discontinuation of therapy [2]. Despite the effect of GLP-1 analogs on insulin resistance and hyperandrogenism, they should not be used for the treatment of non-obese patients with PCOS. There are also some data on the use of GLP-1 RAs as adjuvant therapy in T1DM [26]. A meta-analysis of 11 randomized clinical trials published in 2023 showed that the combination of GLP-1 RAs and insulin resulted in moderate improvement in metabolic profile, including a reduction in HbA1c, weight loss, reduced

insulin requirements and lower blood pressure in patients with T1DM [29]. Moreover, GLP-1 RAs did not increase the prevalence of severe hypoglycemia, diabetic ketoacidosis, or serious adverse events. However, an increased incidence of gastrointestinal disorders was reported [30]. In one study, adding exenatide to insulin therapy in patients with T1DM for 18 months significantly reduced the total daily insulin dose [31]. According to the current data, liraglutide, semaglutide and tirzepatide [a dual glucose-dependent insulinotropic polypeptides (GIP)/GLP-1 RA] are registered for the treatment of obesity. It seems that they can be used in obese patients with T1DM and PCOS [32–34]. It is worth emphasizing that GLP-1 RAs and double GIP/GLP-1 RAs should be discontinued three months before the planned pregnancy [13].

Conclusions

Type 1 diabetes mellitus is characterized by an increased prevalence of PCOS with its negative metabolic consequences, including increased cardiovascular risk. Both diseases affect patients, significantly deteriorating the quality of life. Difficulties in maintaining proper glycemic control may be caused by hormonal disorders and increased insulin resistance and may not be due to non-compliance with dietary or insulin therapy.

During the treatment of patients with T1DM and PCOS, lifestyle modification and increased physical activity resulting in weight reduction should always be recommended. Pharmacological treatment should be applied in accordance with the current standards. In most of these patients, metformin alone or with combined oral contraceptive pills could be considered for cycle regulation. In obese patients with T1DM and PCOS GLP-1 RAs (liraglutide, semaglutide) and dual GIP/GLP-1 RAs (tirzepatide) are regarded as a safe approach.

The above will translate into a reduction in the severity of symptoms typical of specific components of PCOS and also into the improvement in the metabolic control of diabetes and the patients' quality of life. Despite recommendations for screening for PCOS in women with T2DM, such guidelines do not apply to women with T1DM. PCOS is a significant problem in patients with T1DM, especially young people of reproductive age, as indicated in this paper.

Author contributions

E.C., A.M.-P., J.G. devised the idea. All authors discussed the idea and contributed to the final manuscript. E.C. wrote the final version of the manuscript. All authors reviewed the manuscript.

Conflict of interest

The authors report no conflict of interest.

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