The role of insulin and selected adipocytokines in patients with polycystic ovary syndrome (PCOS) – a literature review

Rola insuliny i wybranych adipocytokin u pacjentek z zespołem policystycznych jajników (PCOS)

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. It is manifested by hyperandrogenism, polycystic ovaries on ultrasound, oligomenorrhoea and anovulation. PCOS patients are more vulnerable to metabolic disorders: insulin resistance, obesity, endothelium dysfunction, atherosclerosis, and activation of proinflammatory factors. This association shows that PCOS might be an ovarian manifestation of a metabolic syndrome. Insulin resistance is also strongly correlated with reproductive failure. Approximately 100 factors, secreted in adipose tissue, are responsible for its regulation. Adipocytokines have been found to play an important role in regulating insulin sensitivity. Abnormal levels of adipokines are detected in patients with insulin resistance.

Studies indicate that these factors, and their different activity in PCOS women, may affect changes observed in their metabolism and, especially, may participate in the development of insulin resistance. There are several adipokines whose role has been thoroughly investigated and many that we still know very little about, for example apelin and visfatin.

Counseling PCOS patients about the possibility of developing metabolic syndrome, diabetes mellitus, and cardiovascular diseases should be a standard of care.

Key words: **metabolic syndrome** / **insulin resistance** / **polycystic ovary syndrome** /
/ **adipocytokines** /

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Streszczenie

Zespół policystycznych jajników (PCOS) jest najczęstszą endokrynopatią wśród kobiet w wieku rozrodczym. Manifestuje się hiperandrogenizmem, obrazem policystycznych jajników w ultrasonografii, zaburzeniami miesiączkowania o typie rzadkich miesiączek lub zaburzeniami owulacji. Pacjentki z PCOS są bardziej narażone na zaburzenia metaboliczne: insulinooporność, otyłość, nieprawidłowości endothelium, miażdżycę i aktywację czynników prozapalnych. Te zależności mogą świadczyć o tym, że PCOS może być jajnikową postacią zespołu metabolicznego. Insulinooporność silnie koreluje również z zaburzeniami rozrodu. Istnieje około 100 czynników produkowanych przez tkankę tłuszczową, odpowiedzialnych za funkcje regulacyjne. Adipocytokiny są ważnymi czynnikami regulującymi wrażliwość organizmu na insulinę. U pacjentek z insulinoopornością zauważalne są nieprawidłowe poziomy adipocytokin.

Badania pokazują, że te czynniki i ich odmienna aktywność u kobiet z PCOS, może mieć wpływ na zmiany w ich metabolizmie, a w szczególności w rozwoju insulinooporności. Istnieje wiele adipokin, których rola jest dobrze poznana, lecz nadal rola wielu z nich jest niedostatecznie zbadana: między innymi apeliny i wisfatyny.

Ocena czynników ryzyka zaburzeń metabolicznych, cukrzycy oraz choroby sercowo-naczyniowej powinna być standardem u kobiet z PCOS.

Słowa kluczowe: **zespół metaboliczny** / **adipocytokiny** / **zespół policystycznych jajników** / **insulinnooprność** /

Background

Polycystic ovary syndrome (PCOS) is a common endocrinopathy among women of reproductive age, with a prevalence varying from 3-15%, depending on the criteria used [1]. It is recognized in approximately 6-10% of women, according to the National Institute of Health criteria, but in up to 15% based on the Rotterdam Consensus [2]. PCOS is manifested by clinical or laboratory hyperandrogenism, polycystic ovaries on ultrasound, oligomenorrhea/amenorrhea and anovulation [2]. It is the most frequent cause of anovulatory infertility among women [3]. According to the 2003 Rotterdam Consensus, women with PCOS are not only at an increased risk for infertility, abnormal uterine bleeding, and cosmetic problems such as acne or hirsutism, but are also more vulnerable to a variety of metabolic disorders [3]. The patient, once diagnosed with PCOS, is at higher risk for insulin resistance, dyslipidemia, and overweight or obesity that may lead to diabetes, hypertension, atherosclerosis, and in consequence, to coronary heart disease [2, 4]. These different manifestations of PCOS result in the necessity to define whether each of the phenotypes is equal in terms of risk for metabolic syndrome and cardiovascular diseases.

Pcos and insulin resistance

Recently, hyperandrogenism, obesity and insulin resistance have been recognized to play a crucial role in the pathophysiology of PCOS [2]. The main feature which matches PCOS to metabolic syndrome is insulin resistance, occurring in 30% of lean and up to 80% of obese women with PCOS [5].

When obesity is present, severity of insulin resistance is higher than might be expected given both, age and body weight [6]. Hyperinsulinemia leads to abnormal ovarian androgen production and, consequently, to defective follicular development, causing irregular menstrual cycles [7]. Insulin resistance levels vary, depending on the severity of obesity and PCOS phenotype of the patient [6].

It is doubtful that hyperandrogenism is the primary cause of insulin resistance in PCOS patients because it occurs in women who have undergone either subtotal, or total, ovariectomy, or in those whose androgen production has been suppressed with the use of a long-acting gonadotropin-releasing hormone (GnRH) agonist [8].

Also, prepubertal women with acanthosis nigricans tend to be hyperinsulinemic, yet show no signs of elevated androgen levels until several years after the diagnosis of insulin resistance [9]. Finally, there is no tendency to insulin resistance in men, who have 10-30 fold higher concentrations of androgens. Elevated insulin levels may be the cause, and not the result, of the syndrome [10].

Insulin and ovaries

Insulin receptors are found in human ovaries, which suggests that they have a role in the regulation of ovarian function [10]. *In vitro* studies show that insulin directly stimulates androgen production by the ovarian stroma in women with PCOS [10], and that insulin as well as insulin-like growth factor I (IGF-I), intensify LH-stimulated androgen production in rat ovarian thecal cells [11]. LH pulse is increased in women with PCOS as compared to healthy, age- and weight-matched controls [11]. Insulin probably enhances ovarian androgen production in PCOS women through activation of a signal transduction system, different from that used to stimulate glucose transport [10, 11]. An inositol-phosphoglycan 'second-messenger' system serves as the signal transduction pathway for insulin-induced steroidogenesis in human placental cytotrophoblasts and in swine ovarian granulosa cells [12], and it may act completely normally under insulin-resistant conditions, although defects in the glucose transport and tyrosine kinase systems exist, so the action of insulin on steroidogenesis may be preserved despite glucose intolerance [10]. There is evidence to show that insulin stimulates ovarian androgen production in human ovarian granulosa cells directly through insulin receptors, and not by the IGF-I receptor [10, 11, 12]. Insulin also stimulates the inositolglycan system, serving as a signal transduction system to produce testosterone in human ovarian thecal cells [10, 11, 12].

Owing to high prevalence of insulin resistance, obesity, dyslipidemia and hypertension in PCOS patients, metabolic syndrome affects about 40% of subjects in this group and its risk increases even before the age of 30 [13]. Its prevalence is up two times higher than in weight-matched subjects without PCOS, and increases with patient weight [13].

Obesity

Although overweight (BMI> 25kg/m²) and obesity (BMI> 30kg/m²) are not in the diagnostic criteria for PCOS, they occur in 33-88% of the affected individuals [14]. Obesity is an independent risk factor for cardiovascular diseases and is associated with insulin resistance and dyslipidemia [14]. The risk of a heart attack in women with PCOS is seven times higher than in the general population [14].

Obesity and metabolic syndrome are the main factors contributing to diabetes mellitus [14,15]. Approximately 70% of patients with PCOS and insulin resistance will develop type 2 Diabetes Mellitus (T2DM) [15]. Even among women with PCOS, who have normal glucose tolerance, 25% will develop a carbohydrate metabolism disorder within 3 years [15]. Normal glucose tolerance does not exclude insulin resistance [15], which can be equally severe in women with, and without, diabetes. It may be more a precursor and a reason for metabolic changes in the body, rather than a separate disturbance [15].

Insulin resistance and cardiac damage

Studies in animal models have demonstrated insulin resistance to also cause destruction of heart muscle cells [16]. Data from human studies show a correlation between insulin resistance and cardiac muscle damage, including left ventricular hypertrophy [16, 17]. There is no single test to assess the cardiovascular risk in patients with PCOS. Measurement of glucose metabolism, including glucose tolerance tests, blood pressure, lipid concentrations and the thickness of the intima-media complex, may however, provide useful information [17].

Insulin and sex-hormones

Insulin is also one of the modulators of sex hormone binding-globulin (SHBG) [18]. An elevated level of insulin causes a reduction in SHBG production in the hepatic cells [18]. Low level of SHBG may be a marker of metabolic syndrome and cardiovascular risk among patients with PCOS [18]. An increase in SHBG level was reported among patients treated with insulin-sensitizing agents, such as metformin [18].

Insulin and reproduction

Insulin resistance is not only associated with metabolic disorders, but is also very strongly correlated with reproductive failure. Women with PCOS are at an increased risk for adverse pregnancy and neonatal complications [19]. Meta-analyses show that, during pregnancy, these patients are at a higher risk for developing gestational diabetes mellitus, pregnancy-induced hypertension, preeclampsia, premature delivery, an increased caesarean section rate, and the need for admission to neonatal intensive care units, as compared to controls. There is also a slight tendency to significantly lower birth weights in the PCOS group [19]. Although the structure of the endometrium appears to be unchanged in PCOS women, as compared to healthy subjects,

and the number of insulin receptors is comparable in both groups, there may be impaired activity and decreased binding capacity of insulin receptors, both of which can result in impaired embryo implantation [19]. To the best of our knowledge, there have been no studies evaluating whether the risk of the complications described above is the same in each, clinically distinct phenotype of PCOS patients. However, insulin resistance appears to be a common factor in all the above-mentioned cardiovascular and metabolic disorders, suggesting that early diagnosis of insulin secretion abnormalities enables timely implementation of appropriate treatment. It is therefore extremely important to search for new factors to identify this phenomenon in PCOS patients, before the appearance of the full-blown clinical picture of the metabolic syndrome and/or cardiovascular diseases.

The role of adipocytokines in insulin metabolism

There are about 100 factors secreted in adipose tissue that are responsible for its regulation i.a. appetite, metabolic functions, digestion and inflammatory reactions, and fat tissue is now regarded as a separate hormonal gland [20]. Adipokines (adiponectin, leptin) are only secreted by adipose tissue cells and adipocytokines, including tumor necrosis factor alpha-TNF alpha, resistin, interleukin-6 and interleukin-18, which are secreted by adipose stromal cells, are found to be important in regulating insulin sensitivity [20]. Abnormal levels of adipokines are detected in patients with insulin resistance and type 2 diabetes mellitus. A growing number of studies indicate that these factors, and their different activity in women with PCOS, may have an impact on the changes observed in their metabolism and may play an important role in the development of insulin resistance [21]. In this group of patients, the dysfunction of adipose tissue is manifested by the excess production of pro-inflammatory factors, such as TNF-alpha, and a lowered output of 'beneficial adipokines' such as adiponectin [21]. There are several adipokines whose role is well known, some new, and many that we still know very little about. They include the following:

Apelin

This protein, derived from the glandular epithelium of the stomach cells of an ox, was isolated in 1998. It turned out to be an endogenous ligand of a previously known Apelin receptor (also known as the APJ receptor) associated with G protein [22]. Depending on the length of the polypeptide chain, several isoforms of this protein are distinguished: endogenous apelin-13, apelin-16, apelin-17, apelin-36 and the exogenously synthesized apelin-12 [22]. Isoforms with shorter chains do not exhibit biological activity. Apelin-36 is a precursor protein with reduced biological activity, which, through post-translational modification, is converted to several active forms, mainly apelin-13 and apelin-17 [22,23]. Differences between isoforms arise not only from their construction, but also from their duration of action [23]. Longer activity was observed in apelin-36, and shorter in apelin-13 [22]. Both, the structure of apelin and its tissue expression resemble those of angiotensinogen [22,23]. The APJ receptor contains 30% amino acids and residues, which are the same as those in the AT-1 receptor for angiotensin II [22]. The presence of apelin mRNA was observed in the lungs, mammary gland, testicles and uterus, and much of the data on apelin is associated with the cardiovascular system [23,24]. Apelin mRNA

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and receptor have been identified in endocardium, endothelium and the smooth muscle cells of blood vessels of both, large and small caliber, including the aorta and the coronary arteries [24]. The similarity in the structure of apelin to the components of the renin-angiotensin-angiotensinogen (RAA) system may indicate its involvement in the regulation of the cardiovascular system [24]. Apart from its effect on this system, the influence of apelin on carbohydrate metabolism has to be highlighted [45,50]. It lowers blood glucose levels by increasing its absorption and utilization by adipose tissue and muscle cells thorough the activation of AMP-kinase [45,50]. During performance of oral glucose tolerance tests it was found that with the increase in insulin concentration, the apelin level also grew but it inhibited secretion of this protein during the fasting state [22,25]. Insulin directly influences apelin gene expression, by stimulating its formation and secretion into the bloodstream [25]. By contrast, increasing the concentration of apelin inhibits insulin secretion [25]. The concentration of apelin correlates positively with the fasting insulin level, the HOMA –IR index, and body weight. It is suspected that, in obesity and insulin resistance, apelin may increase glucose tolerance and help in its consumption [25]. It has also been observed that, in the initial stage of type 2 diabetes, apelin reduces insulin resistance. However, in more advanced stages of the disease, the rise of the phenomenon of insulin resistance is accompanied by an increase in the body's resistance to apelin [25]. This manifests itself i.a. in lowered glucose tolerance and reduced insulin effectiveness [25]. The modifying impact of apelin on insulin action may be compared to other cytokines, such as visfatin, adiponectin and resistin [45, 50]. It is believed that its overproduction in obesity may serve as a defense mechanism against the occurrence of complications of type 2 diabetes and cardiovascular diseases [25]. Studies in mice with an eradicated apelin gene, showed higher concentrations of insulin, reduced adiponectin production, higher levels of fasting and postprandial glucose, and impaired glucose and insulin concentrations after an oral glucose tolerance test [26]. Subcutaneous infusion of apelin significantly improved glucose and insulin tolerance in the examined group [26]. Studies show that intravenous infusion of apelin lowered plasma glucose levels, without changes in insulin levels, and improved glucose uptake in both adipose tissue and muscles [26]. These authors also observed that continuous infusion of apelin improved glucose tolerance in obese mice with insulin resistance [22, 23, 26]. In humans, apelin levels are higher when obesity is accompanied by hyperglycemia and hyperinsulinemia. It is observed that apelin mRNA expression correlates with the insulin level but not directly with the glucose level [27]. A decreased insulin level is associated with a significant reduction in the amount of apelin in adipose tissue [27]. So far, the relationship between apelin levels and metabolic disorders associated with polycystic ovary syndrome has been evaluated. However, it seems that studies into the participation of this protein in the pathogenesis of obesity, insulin resistance and diabetes, described above, may produce some interesting results and further understanding of the pathomechanism of PCOS.

Visfatin

Visfatin is a protein with a molecular weight of 52KDa and its gene encodes 491 aminoacids [28]. It is believed to be similar to pre-B cell colony- enhancing factor (PBEF), which has an effect on lymphocyte maturation and regulates the inflammatory reactions in the body [28]. At first, visfatin was thought to be produced in the visceral tissue and this was the origin of the name for this protein [28]. Now it is known that it is also produced in hepatocytes, muscles, leukocytes and adipose tissue [28]. A relationship between inflammation and the production of visfatin was observed [29]. It is released through macrophages infiltrating adipose tissue during inflammation and it may have endocrine, paracrine and autocrine action [28, 29]. There is some evidence to show that this protein may also have an effect on the regulation of insulin sensitivity [29]. An increased level of visfatin was found in patients with elevated levels of subcutaneous fat [29]. There is strong evidence to show that the visfatin level rises with the increase of body weight and its concentration normalizes 6 months after bariatric surgery, resulting in weight loss in morbidly obese patients [28]. A study of Fukuhara et al., showed that gaining weight by mice elevates their levels of visfatin [28]. Administration of visfatin reduced plasma glucose levels in both, insulin-resistant and insulin-deficient mice [28]. Their study also showed that visfatin can mimic the action of insulin by elevating glucose uptake in adipose tissue and muscles, suppressing the release of glucose in hepatocytes and increasing the synthesis and accumulation of triglycerides [28]. Although visfatin therefore mimics the action of insulin, their study proved that it has a different signaling method to that of insulin, and thus it does not compete with insulin receptors [30, 31]. Studies on a Chinese population showed a positive correlation between visfatin levels and the presence of type 2 DM [30]. Visfatin levels were higher in diabetic patients when compared to healthy controls [32]. However, studies where diabetic patients were compared to those with glucose intolerance showed similar levels of visfatin in both groups [32]. Also, the duration of diabetes influences the level of visfatin, with the levels of this protein being much higher in both, long-lasting types 1 and 2 diabetes, as compared to those in newly diagnosed diabetic patients [32].

Up to date, data show that visfatin may play an important role in the secretion of insulin, but there are still many controversies concerning a possible connection between this protein and the risk of diabetes [33]. It remains debatable whether it is a compensatory mechanism for the organism, or plays a role in the pathogenesis of glucose metabolism intolerance [33]. Visfatin may also play a role in cardiovascular complications. For example, it is elevated in patients with unstable coronary plaques [34]. Patients with ischemic symptoms and coronary complications have higher visfatin levels than asymptomatic controls [34]. An increase of visfatin was observed in patients with coronary artery disease (CAD) and those with acute coronary events [34]. There is a positive correlation between the level of visfatin and the thickness of the intima-media complex, independently of other risk factors, and this may suggest its role in the development of metabolic syndrome [34]. There are also studies that report a correlation between serum visfatin levels and patient BMI, or percentage of body fat [35]. Its level in the visceral and subcutaneous adipose tissue is inversely proportional to body weight [35]. In patients with normal BMI visfatin is produced in subcutaneous tissue but in obese patients this protein is mainly produced by macrophages in visceral adipocytes [30,31].

There are studies that show an increased concentration of visfatin in patients with PCOS and a correlation with the indi-

ces of insulin resistance and hyperandrogenism. However, these findings were mainly observed in lean PCOS patients [30, 31]. All in all, the activity and level of visfatin in obesity and diabetes, observed in many studies, suggest that visfatin may serve as a compensatory factor for impaired insulin production [30, 31]. Regardless, many publications continue to show conflicting information on the role of visfatin in regulating the action of insulin in humans [30,31].

Conclusions

Although the main problems that bring women with PCOS to seek health care are infertility, hirsutism and acne, there are many severe consequences of this disease that should be brought to attention. Counseling PCOS patients about the possible later development of metabolic syndrome, diabetes mellitus and cardiovascular disease should be a standard of care. Seeking new markers of insulin resistance and metabolic disturbances in PCOS may have clinical implications in finding and defining the group of patients at higher risk. Determining the risk factors and finding new indices of future metabolic disturbances, such as selected adipocytokines, different anthropometric parameters and their mutual correlation is crucial for the extension of better health prophylaxes in this group of patients.

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