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Review

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Polycystic ovary syndrome and non-alcoholic fatty liver disease: Matched pair or sporadic coexistence?

Zespół policystycznych jajników i niealkoholowa stłuszczeniowa choroba wątroby – dopasowana para czy sporadyczna koegzystencja?

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Summary

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in developed countries. This condition includes benign non-alcoholic fatty liver disease and non-alcoholic steatohepatitis with possible fibrosis leading to cirrhosis and hepatocellular carcinoma. Association of NAFLD and polycystic ovary syndrome (PCOS) has been widely discussed. Women with PCOS are prone to develop NAFLD more often. PCOS is one of the most common endocrine disorders among reproductive-age women, characterized by an excess of androgens, anovulation, and polycystic ovary on ultrasound. Obesity, dyslipidemia and insulin resistance (IR) are frequently observed in women with PCOS, being also important factors predisposing to the development of NAFLD. IR may stimulate theca cells to excessive production of androgens, inhibits the production of sex hormone-binding globulin in the liver, which contributes to the increase of the bioactive form of testosterone. Hyperandrogenemia also plays an important role in NAFLD pathogenesis and progression. Androgen excess promotes visceral fat accumulation, development of dyslipidemia, IR, and contributes to low-grade inflammation. The pathophysiological associations between PCOS and NAFLD are not fully understood although it seems reasonable to screen PCOS women for the presence of NAFLD.

Keywords: **polycystic ovary syndrome, non-alcoholic fatty liver disease, insulin resistance, hyperandrogenemia**

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Abbreviations: **DNL** – de novo lipogenesis, **ESHRE** – European Society of Human Reproduction and Embryology, **FFA** – free fatty acid, **HCC** – hepatocellular carcinoma, **HDL** – high-density lipoprotein, **IR** – insulin resistance, **LDL** – low-density lipoprotein, **MS** – metabolic syndrome, **NAFLD** – nonalcoholic fatty liver disease, **NASH** – non-alcoholic steatohepatitis, **NIH** – National Institutes of Health,

PCO – polycystic ovary, **PCOS** – polycystic ovary syndrome, **SHBG** – sex hormone-binding globulin, **TG** – triglycerides.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, with a prevalence of 6–20%, depending on the definition used [32, 47]. According to the criteria proposed by the members of European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine in 2003 (Rotterdam criteria), PCOS is recognized in women with at least two of the three characteristics: ovulatory dysfunction, polycystic ovary morphology (PCOM), and clinical or biochemical hyperandrogenism [4, 41]. Hyperandrogenism is expressed as hirsutism, alopecia and/or acne. Ovulatory dysfunction may occur as oligomenorrhea, secondary amenorrhea or abnormal uterine bleeding, although ovulatory dysfunction can also occur with regular cycles. Anovulation needs to be confirmed by serum progesterone measurement. PCOM is defined by a follicle number per ovary > 20 and/or an ovarian volume ≥ 10 ml in the absence of corpora lutea, cysts or dominant follicles [4, 41]. According to the Rotterdam criteria, PCOS is a heterogenous syndrome that also affects women with PCOM and clinical hyperandrogenism without ovulatory dysfunction as well as the most severe phenotype with biochemical hyperandrogenism, menstrual irregularities and PCOM. The 2006 Androgen Excess and PCOS Society (AE-PCOS) definition requires the presence of hyperandrogenism, PCOM, and ovulatory dysfunction, which represents the most severe PCOS phenotype [2, 6]. All of the currently used definitions require the exclusion of disorders associated with hyperandrogenism and/or anovulation, such as hypercortisolemia, congenital adrenal hyperplasia, thyroid dysfunction, and virilizing tumors. Women suffering from PCOS have not only an increased risk of infertility but also components of metabolic syndrome, such as insulin resistance (IR), type 2 diabetes (T2D), obesity, dyslipidemia which are also important cardiovascular diseases risk factors [5, 15, 33]. This association is much stronger in women with the most severe, hyperandrogenic phenotype of PCOS. There is also a considerable amount of data on the correlation between PCOS and non-alcoholic fatty liver disease (NAFLD) [2, 25, 35, 42]. NAFLD is one of the most common liver diseases, diagnosed in approximately 30% of the general population in developed countries with an even higher prevalence of 80–90% in a specific population – obese patients with T2D [7]. This condition ranges from benign non-alcoholic steatosis to non-alcoholic steatohepatitis (NASH) with possible fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) as a consequences [13]. Non-alcoholic steatosis is described as the presence of steatosis in more than 5% of hepatocytes. NASH in the histopathological examination is characterized by hepatic steatosis with varying degrees of hepatic inflammation (with hepatocyte ballooning degeneration and hepatic lobular inflammation) [37]. It is necessary to exclude secondary causes of intrahepatic fat accumulation (e.g. alcohol consumption higher than 30 g/day for men and 20 g/day for women, drugs, viral hepatitis and autoimmunity) [24]. Liver biopsy is the gold standard in the diagnosis of NAFLD, but it is an invasive method and is not recommended routinely. Imaging methods, such as abdominal ultrasound, computed tomography, or magnetic resonance techniques, are being used commonly, but cannot be used to establish the stage of the disease and fibrosis in the liver [22]. Patients with NAFLD are usually asymptomatic but share similar clinical traits, such as obesity, IR, dyslipidemia, T2D, cardiovascular diseases, chronic kidney disease, and endocrinopathies such as PCOS [1]. There is increasing evidence that the prevalence of NAFLD increases when the patient already has PCOS [9, 35, 45]. The aim of our review is to summarize the data about the coexistence of NAFLD and PCOS and to discuss the possible pathophysiological links between these two clinical entities.

REVIEW

There is much data about the link between PCOS and NAFLD. Primary studies as well as metaanalyses indicate higher prevalence of NAFLD in PCOS women, compared to the general population (34–70% vs. 13–34%, respectively) [27, 38, 42, 45]. Higher incidence of NAFLD in the PCOS group in comparison to women without PCOS (51% vs 34% respectively, p = 0.002) was observed, and this risk was increased even in women without metabolic comorbidities, which could indicate the possible role of hyperandrogenism in the etiology of NAFLD [27]. Cai et al. also demonstrated a higher prevalence of NAFLD in women with PCOS than in patients without this syndrome (56% vs 38%, respectively, p = 0.001), which was also confirmed by Zhang et al. (45% vs. 25%, p < 0.05) [9, 49]. In the meta-analysis of 17 studies published between 2007 and 2017, Rocha et al. as well as Wu et al. revealed that PCOS group had a 2.3- and 2.5-fold increased risk of developing NAFLD in comparison to healthy control groups [35, 45].

The pathogenesis of NAFLD and its association with PCOS are still not fully understood. Obesity and IR, which are the two major features associated with PCOS, are considered the main risk factors connecting PCOS and NAFLD [35]. Obesity increases the risk of developing NAFLD by 4.89-fold and hypertriglyceridemia by 1.56-fold [20]. In PCOS patients increased alanine transaminase activity (ALT) was associated with age, waist circumference and obesity [11, 12, 23, 39]. NAFLD incidence is much higher in patients with co-occurrence of PCOS and obesity [OR = 3.01, 95% CI = 1.88–4.82] than in women with PCOS without obesity [OR = 2.07, 95% CI = 1.12–3.85] [45, 49]. Weight loss was associated with the reduction of hepatic steatosis [25, 27]. However, a study conducted in lean PCOS women revealed higher NAFLD incidence in comparison to lean women without PCOS (6% vs. 2.8%, respectively), which might indicate that the association between PCOS and NAFLD is independent of the BMI [19]. Decreased insulin sensitivity may be a consequence of

obesity [12]. Patients with PCOS are more often obese and the accumulation of visceral fat correlates with IR [4, 26]. IR is a common entity among women suffering from PCOS [26]. The majority of studies indicate the prevalence of IR of 50–80% in patients with PCOS [28]. However, results are contradictory as Cassar et al. in comprehensive review of 28 articles, in which IR was measured by euglycaemic-hyperinsulinaemic clamp, reported lower incidence of IR in PCOS women (27%) [10].

Much data indicates that IR occurs more often not only in obese but also in normal-weight women with PCOS than in the healthy general population. It is suggested that the etiology of IR in PCOS may have a genetic basis or be caused by intrinsic disturbances, such as insulin receptor defects and impaired insulin signaling in the muscle cells [50]. IR plays a pivotal role in the etiopathology of PCOS. Insulin stimulates the ovarian CYP17α activity and leads to androgen overproduction, which can also increase the secretion of 17-hydroxyprogesterone and dehydroepiandrosterone sulfate from adrenal glands [14]. Additionally, hyperinsulinemia inhibits sex hormone-binding (SHBG) production, thus increasing the level of free androgens [14, 46]. IR is also an important factor in the pathogenesis of NAFLD, and NAFLD in turn can further aggravate hepatic and general IR [13]. IR causes excessive lipolysis in visceral adipose tissue thus augmenting the hepatic flow of free fatty acids (FFA) that can accumulate in the liver and further enhance the IR in liver and muscles [44]. IR also leads to the blockage of mitochondrial fatty acids oxidation, stimulates hepatic production of collagen and fibrinogen, which contributes to excessive hepatic fibrosis [16]. In turn, accumulation of lipids within hepatocytes aggravates hepatic IR. Hyperandrogenism is the most important component of PCOS. Approximately 87% of PCOS patients have functional ovarian hyperandrogenism. PCOS women usually have increased free androgen index (FAI), level of total testosterone and decreased SHBG [12]. Elevated androgen level supports NAFLD development in women with PCOS and it is currently known that women with hyperandrogenic phenotype of PCOS have a significantly higher risk of developing NAFLD in comparison to the normoandrogenic control group (OR = 3.31, 95% CI 2.58–4.24) [9, 28, 35, 45].

Increased androgens level is associated with obesity, IR and dyslipidemia, which are important factors for NAFLD [12]. Hyperandrogenic women are characterized by higher body mass index and waist circumference, increased TG, low-density lipoprotein (LDL), and decreased HDL levels [9]. Hyperandrogenemia can suppress the activity of adenosinomonophosphate-activated protein kinase, an inhibitor of lipogenesis in adipose tissue, which may lead to visceral fat accumulation [45]. It is unclear whether androgens play a direct role or act through the induction or stimulation of IR [28]. However, several studies showed that hyperandrogenemia, independently from obesity and other metabolic disturbances, influences the development of NAFLD [19, 45]. Hyperandrogenism is also associated with low-grade inflammation, as it stimulates tumor necrosis factor α secretion from mononuclear cells [28, 45]. Although there are no significant differences in circulating androgens, SHBG is usually lower and FAI is higher in PCOS women with NAFLD compared to PCOS women without NAFLD [40]. FAI and high sensitivity C-reactive protein better predicted NAFLD than the waist-to-hip ratio in both normal-weight PCOS women and controls [43]. Women with hyperandrogenic phenotype of PCOS were shown to have higher hepatic fat content compared with normoandrogenic PCOS women after adjustment for BMI and HOMA-IR [18]. Thus, it seems that hyperandrogenism could affect NAFLD independently of IR. Some data indicates that hyperandrogenism could have a direct effect on low-density lipoprotein receptor in the liver, thus leading to dyslipidemia and NAFLD in PCOS women [3]. Moreover, women with hyperandrogenic phenotype of PCOS have lower concentrations of serum adiponectin, which is also characteristic for NAFLD. Other adipokines, such as leptin and resistin, could also be involved in the pathogenesis of PCOS and NAFLD [34]. Data from animal studies demonstrated an association between hyperandrogenism and liver damage [29]. There are also studies indicating the potential role of SHBG in the pathogenesis of NAFLD [40]. SHBG plays an important role in the regulation of hepatic lipogenesis by reducing the concentration of acetyl-CoA-decarboxylase. PCOS is typically associated with reduced level of SHBG, which leads to hyperandrogenemia and promotes metabolic disturbances and cardiovascular diseases [40]. Factors leading to steatosis are the first hit in two-hits-hypothesis.

The second hit activates inflammatory cascades and fibrogenesis, causing NASH [8]. Progression of the disease may lead to cirrhosis and even HCC. Patients with NAFLD have increased risk of liver-related mortality. The fibrosis stage is the aggravating factor, which may lead to future liver-specific morbidity and mortality [17]. Genetic factors have also been considered to play an important role in in the pathogenesis and progression of NAFLD. Genetic variation in patatin-like phospholipase domain containing 3 (PNPLA3) increase susceptibility to fat accumulation in the liver and could be associated with severity of NAFLD and susceptibility to NASH [48]. It is also associated with fibrosis and even increased risk of HCC. The PNPLA3 variant (polymorphism rs738409) most likely impairs TG hydrolysis and stimulates capture of TG within hepatocytes and stellar cells [48].

There are several other candidate genes that could possibly be linked to the development of both NAFLD and PCOS, genes involved in androgen synthesis and availability, in the secretion and action of insulin and genes involved in the secretion and action of cytokines. Another factor that could contribute to the pathogenesis of both, PCOS and NAFLD, is ninein, a protein that participates in angiogenesis and neurogenesis. The mRNA on ninein is expressed 1.65 more times in patients with PCOS and NAFLD in comparison to women with PCOS without NAFLD, but this notion requires further investigation [3]. Some studies support the hypothesis of the role of ethnicity in the

association between PCOS and NAFLD, but overall the results are contradictory and may be dependent on the different PCOS diagnostic criteria used [31]. It seems that Caucasian women have milder PCOS phenotypes with higher BMI, Hispanic and Mediterranean have more severe hirsutism, Southeast Asians and indigenous Australians have higher metabolic risk. Many papers indicate that the hepatic steatosis prevalence is race and ethnicity-dependent, being more frequent in Hispanic patients and less prevalent in black individuals. These differences at least in part could be explained by the occurrence of the genetic variant of the PNPLA3 gene [31, 45].

CONCLUSIONS

The PCOS is a common condition affecting women in the childbearing age. The PCOS more than doubles the risk of developing NAFLD. IR and hyperandrogenemia are important features that contribute to the development and progression of NAFLD. IR leads to steatosis and obesity. It also stimulates excessive androgens production, decreases SHBG and leads to low-grade inflammation. An excess of androgens not only aggravates IR, but also is an independent factor that promotes NAFLD.

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