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EDITORIAL

Nonalcoholic fatty liver disease risk in polycystic ovary syndrome patients

Polycystic ovary syndrome (PCOS) is the most prevalent female endocrinological disorder, affecting up to 20% of women, with negative consequences during the patient's entire life. The syndrome displays variable associations of oligomenorrhea, clinical or biochemical hyperandrogenism, insulin resistance, glucose and lipid metabolism alterations, and polycystic ovary morphology on ultrasonography. As occurs with other syndromes, PCOS includes heterogeneous populations with different evolutions and risks, being the metabolic syndrome (METS) and nonalcoholic fatty liver disease (NAFLD) manifestations of aggressive evolution of severe cases related to insulin resistance, obesity, and liver fat accumulation. This hepatic condition is a growing health problem, affecting almost a quarter of the world's population, and is globally recognized as the most common cause of chronic liver disease. The estimated global prevalence of NAFLD ranges from 6.3% to 33%, with a median of 20% [1]. In South America and the Middle East, the prevalence is around 30% [2], and among European adults, the prevalence exceeds 25%, being higher in those with METS component-related factors such as overweight and obesity, particularly in people from Mediterranean countries [3]. NAFLD is defined by the presence of more than 5% fat accumulation within the liver, either by imaging or by histology, in the absence of other identifiable causes of hepatic steatosis, particularly excessive alcohol consumption. The disease encompasses a spectrum of conditions ranging from simple liver steatosis to nonalcoholic steatohepatitis (NASH) to fibrosis, cirrhosis, and eventually hepatocellular carcinoma. In addition, the disease shares some common clinical characteristics with PCOS, including excessive body weight, insulin resistance, and METS.

In women with PCOS, the prevalence of NAFLD was reported in 39% in the lean group patients. Steatosis was associated with an increased body mass index (BMI). High homeostatic model assessment of insulin resistance (HOMA-IR) values, and a high prevalence of glucose intolerance and type 2 diabetes mellitus [4]. The Cerda et al. [5] prospective study reported in a population living in Chile that insulin resistance is a common finding in women with NAFLD or PCOS patients not consuming alcohol. Insulin resistance was present in 63.4% of PCOS patients and 41.5% of NAFLD patients, postulating that PCOS should be screened for the liver disease. On the other hand, the Cholongitas et al. [3] meta-analysis pointed out that in European countries the pooled prevalence of NAFLD was higher in women with METS or any of its components than in those without the syndrome. Therefore, PCOS patients have hepatic alterations that are not usually evaluated and may contribute to the increased risk of hepatic dysfunction and NAFLD [6,7].

PCOS patients frequently display hyperinsulinemia that may increase circulating androgen levels which in turn reduces the hepatic synthesis of sex hormone-binding globulin (SHBG), the principal plasma transporter of sex steroids [8]. Low SHBG is a frequent finding in PCOS patients and is considered an indirect marker of hyperandrogenism, insulin resistance, and the metabolic disorders of the syndrome [9]. The Deswal et al. [10] meta-analysis confirms that SHBG levels are significantly lower in PCOS patients than in women without the syndrome. Therefore, insulin levels may be involved in metabolic alterations of PCOS patients and might be useful as a biomarker of diagnosis and clinical evolution of this population. Vassilatou et al. [11] have reported that PCOS patients with menstrual function and not consuming alcohol show increased hepatic steatosis, age, BMI, waist circumference, HOMA-IR values, and free androgen index as compared to women without the syndrome and not consuming alcohol after age, BMI and waist circumference adjustments. Moreover, women with PCOS had a higher risk of insulin resistance than control women with similar BMI, and hyperandrogenism may be involved in the down-regulation of the low-density lipoprotein receptor, prolonging the half-lives of circulating very low-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol, inducing accumulation of fat in the liver and ultimately triggering NAFLD. In addition, women with hyperandrogenism have higher transaminase levels (predominantly alanine aminotransferase) compared to control subjects [11].

Different recent meta-analyses have pointed out significant differences and risks of PCOS patients as compared to women without the syndrome. The Shengir et al. [12] meta-analysis showed a substantial risk of NAFLD in overweight/obese PCOS patients as opposed to weight-matched controls, whereas no risk was noted in lean PCOS patients. Although normal BMI was not associated with an increased risk of NAFLD among PCOS patients, insulin resistance, and METS were more frequent than in non-PCOS cases. Overweight and obese women with PCOS have elevated liver enzymes that correlate with testosterone concentrations, and NAFLD has been associated with increased bioavailable testosterone [13]. Furthermore, NAFLD is more prevalent among postmenopausal women with a previous diagnosis of PCOS than premenopausal ones, suggesting that estrogen may have a protective role in the pathogenesis of NAFLD. The Manzano-Nuñez et al. [14] meta-analysis reported that BMI and waist circumference, metabolic abnormalities (HOMA-IR, alanine aminotransferase, and triglycerides), and PCOS-specific markers (hyperandrogenism and free androgen index) were identified as risk factors for NAFLD in PCOS patients. Meta-regression analysis showed metabolic features and PCOS-specific characteristics as potential effect modifiers, with rises in NAFLD prevalence mediated through increases in METS prevalence and higher levels of HOMA-IR, free androgen index, and total testosterone. Insulin resistance of PCOS in the skeletal system increases circulating glucose levels, leading to adipose tissue expansion and promoting obesity. In addition, insulin resistance can stimulate lipolysis and adipocyte inflammatory cytokine secretion, causing dyslipidemia, inflammation, and lipotoxicity [15]. These pathophysiological aspects fit well with the overall evidence that women with PCOS have an increased risk for NAFLD as those without the syndrome [16]. During the reproductive years, anti-Müllerian hormone (AMH) could be considered a marker of NAFLD in patients with PCOS, independent of chronologic aging. Low AMH levels are also associated with insulin resistance, obesity, cardiovascular

disease, and clinical severity of some inflammatory diseases such as multiple sclerosis and NAFLD [17]. Such findings most likely support the role of the hormone as an early biomarker of chronic inflammation, as opposed to its direct involvement in the pathogenesis of NASH. As a marker of ovarian aging, AMH may also allow for the early identification of young women at risk for NASH progression, cardiovascular disease, and other age-related conditions, when prevention and intervention may be most beneficial.

The *PCOS Evidence-Based Clinical Guidelines* recommend lifestyle management for the improvement of reproductive, metabolic, and psychological complications [18]. Overall, in women with PCOS and weight excess, lifestyle interventions that reduce weight by as little as 5% of total body weight have been shown to have health, metabolic, reproductive, and psychological benefits. A systematic review of lifestyle interventions in populations at risk of type 2 diabetes or cardiovascular disease, summarized key success factors in lifestyle interventions [19]. Behavioral change techniques in combination with diet and exercise interventions, increased weight loss over diet and/or physical activity alone. It can be concluded that NAFLD risk is notably increased in PCOS patients aside from excessive body weight and other metabolic alterations, displaying severe hepatic evolutions, advanced fibrosis, and cirrhosis. These severe forms may aggravate hepatic and general insulin resistance, releasing other products that at the same time may worsen the evolution of PCOS, creating a vicious hepato-ovarian circle, expressed by a higher prevalence of NAFLD in PCOS patients. Gynecologists should be aware of the hepatic risks of these women.

Author contributions

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Availability of data

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