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REVIEW

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Nonalcoholic fatty liver disease in women with polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) affects 6–15% of women of reproductive age. Nonalcoholic fatty liver disease (NAFLD) affects 25–30% of the general population and its prevalence increases in parallel with the epidemics of obesity and type 2 diabetes mellitus. A growing body of evidence suggests that NAFLD and PCOS quite often co-exist. The aim of this article is to summarize and critically appraise the literature regarding: (1) the rates of co-existence of the two entities, (2) the possible pathophysiological links, (3) the proper diagnostic assessment and (4) the appropriate management of women with NAFLD and PCOS. Data from clinical studies and meta-analyses indicate a higher prevalence of NAFLD in women with PCOS ranging from 34% to 70% compared with 14% to 34% in healthy women. Inversely, women with NAFLD are more often diagnosed with PCOS. Insulin resistance (IR) and hyperandrogenism are two main potential pathophysiological links between the two entities. In this regard, IR seems to interplay with obesity and hyperandrogenism, thus affecting NAFLD and PCOS and being affected by them. Women with PCOS, particularly those with IR and/or hyperandrogenism, are suggested to be screened for NAFLD, while premenopausal women with NAFLD is suggested to be screened for PCOS. Lifestyle recommendations with a change in dietary habits, weight loss and exercise, constitute currently the cornerstone of the management of both NAFLD and PCOS. Insulin sensitizers maybe used for the treatment of these women, while there are limited promising data for the use of liraglutide.

Keywords Nonalcoholic fatty liver disease · Nonalcoholic steatohepatitis · Polycystic ovary syndrome · Ovaries, Hyperandrogenism, Insulin resistance, Metabolic syndrome

Introduction

Polycystic ovary syndrome (PCOS) represents the most common endocrine disorder in women of reproductive age, with a prevalence of 6–15% [1], varying according to the applied criteria [2–4]. The syndrome is characterized by chronic anovulation and hyperandrogenism, with women often presenting menstrual cycle disturbances and hirsutism or acne [1]. From a metabolic point of view, insulin resistance (IR) is a cardinal feature of PCOS. In this regard, many women with PCOS develop features of the IR or metabolic syndrome (MetS), such as obesity, dyslipidemia, hypertension, and glycemic dysregulation [1, 5, 6].

Nonalcoholic fatty liver disease (NAFLD) affects 25–30% of the general population, which may increase to 80–90% in specific populations, such as obese patients with type 2 diabetes mellitus (T2DM) [7]. NAFLD is diagnosed after the exclusion of secondary causes of fatty liver, including viral or autoimmune hepatitis, Wilson's disease,

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α1 anti-trypsin deficiency, hemochromatosis, treatment with hepatotoxic medications and significant alcohol consumption [8, 9]. Histologically, it ranges from simple steatosis (SS), characterized by intrahepatic fat accumulation, to nonalcoholic steatohepatitis (NASH); the latter is characterized by hepatic inflammation and may progress to fibrosis, cirrhosis and hepatocellular carcinoma. The gold standard for the diagnosis and staging of NAFLD is a liver biopsy. However, as it is not feasible to perform a liver biopsy in all patients with NAFLD, several noninvasive markers and algorithms have been introduced for the prediction of NASH and fibrosis [9]. IR is a critical component in the development of NAFLD; its prevalence parallels the increasing prevalence of obesity, diabetes and MetS [9–11]. The progression from SS to NASH is also affected by IR and hyperinsulinemia [12, 13]. It seems that a bidirectional association exists between NAFLD and IR; NAFLD is affected by IR and, subsequently, affects IR [14].

The aim of this review is to summarize and critically appraise the literature regarding the associations between NAFLD and PCOS; more specifically to discuss: (1) the prevalence of co-existence of the two entities, (2) the possible pathophysiological links, (3) the proper diagnostic assessment, and (4) the appropriate management of women with NAFLD and PCOS.

Co-existence of NAFLD and PCOS

The first case of NAFLD in a woman with PCOS was reported in 2005. It was a young, 24 year old obese woman who underwent a liver biopsy due to elevated liver function tests (LFTs). As severe NASH was revealed, concern was raised for the prevalence of NAFLD in patients with PCOS [15, 16]. Since 2005, many studies used laboratory [alanine aminotransferase (ALT), aspartate aminotransferase (AST)] and imaging modalities [ultrasonography (US)] for the diagnosis of NAFLD [17–30]. Indices combining different parameters have also been applied, for the noninvasive diagnosis of steatosis, such as the NAFLD liver fat score (NAFLD-LFS) [31], the fatty liver index [27], or fibrosis, such as the fibrosis index based on four factors (FIB-4) [32], the NAFLD fibrosis score [33], the BMI, AST/ALT ratio, diabetes score [34], and the visceral adiposity index [35, 36]. Only a few studies performed a biopsy for the confirmation of NAFLD in women with PCOS.

Growing evidence from primary studies and meta-analyses indicates a high prevalence of NAFLD in women with PCOS ranging from 34% to 70% compared with 14–34% in women of the general population [17, 37–44]. A cross-sectional study of 600 Caucasian women with PCOS and 125 controls matched for body mass index (BMI) identified NAFLD in 51% of women with PCOS, compared with 34% of controls. Women with PCOS had larger waist circumference, lipid accumulation product (LAP; a non-invasive index of steatosis, consisting of waist circumference and fasting triglyceride concentrations), IR, total cholesterol, and triglycerides compared with controls. Upon further analysis, IR and LAP were independently associated with NAFLD [37]. A retrospective cohort study in women with PCOS ($n = 63{,}000$) reported that serum testosterone >3.0 nmol/L was associated with an increase in NAFLD rates (hazard ratio [HR] 2.30, 95% CI 1.16–4.53, for testosterone 3.0–3.5 nmol/L and HR 2.40, 95% CI 1.24–4.66, $p = 0.009$ for testosterone >3.5 nmol/L) [45]. The prevalence of NAFLD may be even higher in adolescent girls with PCOS compared with those without the syndrome [46, 47]; the investigators try to develop new indexes for identification of NAFLD in such populations [47]. Postmenopausal women without a history of PCOS have a similar prevalence of NAFLD compared with premenopausal women with PCOS [48]. In premenopausal women, those with NAFLD are more often diagnosed with PCOS (43.7%) compared with women without NAFLD (23.1%) [42].

Pathophysiological associations between NAFLD and PCOS

It is still unclear how PCOS and NAFLD may influence each other [14, 15]. Although genetic associations are not apparent, common genes are implicated in both NAFLD and PCOS. The fact that NAFLD presents racial and ethnic differences, being more prevalent in Hispanic women for example, highlights the importance of the genetic component. In this regard, the patatin-like phospholipase domain containing 3 (*PNPLA3*) polymorphisms, which are more common in Hispanics, are strongly associated with NAFLD and its severity [7, 49–51]. Apart from genes adding a racial predisposition, genes that may possibly affect both NAFLD and PCOS could be grossly classified into three categories: (1) genes involved in androgen synthesis and availability (*CYP17, CYP11A*, *SHBG)*, (2) genes involved in the secretion and action of cytokines (IL-6, TNF-α, TNF-R), and (3) genes involved in the secretion and action of insulin (insulin, insulin-receptor) [15, 43].

Obesity and IR seem to represent common pathogenetic factors of PCOS and NAFLD [15, 43]. In patients with PCOS, elevated ALT concentrations have been associated with age [26], obesity [19, 24, 26, 27] and waist circumference [19, 27]. Similarly, IR assessed by quantitative insulin sensitivity index (QUICKI), HOMA-IR or the euglycemic insulin clamp technique, has been independently associated with NAFLD [19, 23, 26, 27, 37, 52]. NAFLD can further deteriorate hepatic and general IR [53],

thus aggravating IR in women with PCOS. On the other hand, IR induces lipolysis mainly in visceral adipose tissue and increases the hepatic flow of free fatty acids, thus augmenting hepatic fat accumulation [14, 54]. Finally, insulin stimulates the production of collagen and fibrinogen from hepatic stellate cells, which may contribute to fibrosis [13, 14, 54].

The link between hyperandrogenism and IR is of interest too. Insulin can act as a co-gonadotropin on the ovary, stimulating the CYP17α activity and leading to androgen overproduction [5]. Insulin can also act as a modulator of adrenal secretory activity, increasing the secretion of 17-hydroxy-progesterone and dehydroepiandrosterone sulfate [55]. In addition, hyperinsulinemia directly inhibits sex hormone-binding (SHBG) production, thus increasing the concentrations of circulating free androgens [5]. Although there are no apparent differences in circulating androgens, SHBG concentrations are usually lower and free androgen index (FAI) higher in PCOS women with NAFLD compared with those without NAFLD [22, 38, 56–58]. FAI, high sensitivity C-reactive protein and osteopontin were shown to predict NAFLD better than the waist-to-hip ratio in both normal-weight PCOS women and controls [59]. Although IR and high androgen levels are associated, hyperandrogenism has been shown to affect NAFLD independently of IR; more specifically, hyperandrogenic women with PCOS were shown to have higher fat in the liver compared with women with normo-androgenic PCOS after adjustment for BMI and HOMA-IR [38].

It has been hypothesized that hyperandrogenism has a direct effect on low-density lipoprotein receptor in the liver, thus making PCOS women more prone to develop dyslipidemia and NAFLD [60]. Moreover, androgens may exert a direct effect on adipokine production [61]. Hyperandrogenism in women with PCOS has been associated with lower concentrations of serum adiponectin, while the latter has also been shown in patients with NAFLD [62]. Other adipokines, including leptin and resistin, could be involved in the metabolic alterations of PCOS and the pathogenesis of NAFLD [63]. There are also in utero animal studies favoring an association between hyperandrogenism and liver damage. Prenatal androgenization of female rat fetuses with consequent development of a PCOS-like phenotype resulted in tissue-specific molecular changes, including the liver [64, 65], while maternal exposure to testosterone caused histologically confirmed fat deposition into the liver in sheep, independently of central obesity [66].

Data on the hepatic effect of oral contraceptives, which is a common treatment for PCOS women, in PCOS women with NAFLD are limited and conflicting. In a population-based cross-sectional study form the Third National Health and Nutrition Examination Survey, lower rates of NAFLD were shown in current (6.7%) than in former (12.0%) or never users (15.6%) of oral contraceptives [67]. On the contrary, in a more recent study, premenopausal women on oral contraceptives were reported to have higher rates of lobular inflammation [68], which characterizes NASH. Prospective cohort studies of adequate power are required to clarify whether oral contraceptives have an effect on NAFLD, specifically in PCOS women. This effect may differ depending mainly on the different progestins the oral contraceptives contain, being more adverse in oral contraceptives containing progestins with higher androgen activity. However, this also remains to be shown.

Diagnostic assessment

Recommendations regarding screening for NAFLD in women with PCOS specifically are lacking, and there are not recommended modalities or algorithms specifically for this population. NAFLD is mostly an asymptomatic disease. Elevation of LFTs, especially ALT, is a common finding, but still unspecific for the disease severity. Liver biopsy remains the gold standard, as the staging and grading of NAFLD are histological [8, 9]. Nonetheless, it is not feasible to perform a biopsy in all patients with a suspicion of NAFLD, mainly due to the high disease prevalence [69]. Furthermore, the performance of serial liver biopsies in the setting of follow-up for a disease without any approved medication meets ethical considerations. Sampling error and inter-assessment variability have also been reported in up to 30% of biopsies [70]. Moreover, liver biopsy is interventional, albeit serious complications have been rarely reported. Because of the above, several noninvasive indices have been proposed [31–35, 71]. Less used biomarkers such as hyaluronic acid, osteopontin, type IV collagen and matrix metalloproteinase, have been proposed for the estimation of NAFLD severity. Furthermore, cytokeratin-18 (CK-18) has been gaining increasing interest in the noninvasive diagnosis of NASH. Concentrations of caspase-generated CK-18 fragments reflect hepatocellular apoptosis, thus CK-18 has been proposed as a biomarker for NASH, since increased apoptosis is a hallmark of NASH [55, 72]. However, to-date no single parameter can provide acceptable accuracy in the noninvasive diagnosis of NASH and importantly, liver fibrosis, regarded as the main prognostic histological endpoint. For this reason, algorithms combining more than one parameters have been proposed for the noninvasive diagnosis of NASH and fibrosis (e.g., NAFLD fibrosis score, fibrosis 4 index [FIB-4], enhanced liver fibrosis (ELF) etc.) [7].

Although imaging modalities have been tested for NAFLD diagnosis, these techniques can provide information for the presence of steatosis, but not for the fibrosis, the main histological predictor of advanced disease. US has

lower diagnostic accuracy than computed tomography (CT) and MRI, which is further limited in obese individuals, who are the majority of NAFLD patients [73, 74]. The advantages of simplicity, safety and low cost have indicated US as the most widely initially imaging modality, still with low sensitivity. Transient elastography (FibroScan®) with controlled attenuation parameter is an FDA-approved modality for the diagnosis and assessment of the severity of hepatic steatosis and fibrosis. Briefly, a vibration device induces a shear wave in the liver, thereby measuring the hepatic elasticity or stiffness, which is correlated with the severity of fibrosis. Nonetheless, a limitation of transient elastography is that it has lower diagnostic accuracy in obese individuals, because the adipose tissue interferes with the elastic wave properties. It is regarded as important, since most of NAFLD and PCOS women are obese [7–9, 75].

To summarize, women with PCOS are suggested to be screened for NAFLD, particularly if they are obese with features of MetS. Liver US in combination with noninvasive indices, mainly of fibrosis, can be also applied. Liver biopsy should be used in women with suspected fibrosis, e.g., in those indicated by transient elastography and/or noninvasive indices of fibrosis. Conversely, premenopausal women with NAFLD may need screening for PCOS [1, 8, 9].

Management of NAFLD in PCOS women

Lifestyle interventions, with dietary modifications and daily exercise, constitute the cornerstone of management in patients with NAFLD [8, 9]. A sustained reduction of 5–7% of body weight has resulted in improvement in steatosis and inflammation, but a sustained reduction of more than 10% is required to improve fibrosis [76]. This can be achieved by an energy deficit of 500–750 kcal per day, along with aerobic exercise [77]. Although the energy deficit seems to be the primary drive toward NAFLD improvement, the dietary macro- and micro-nutrients may also play a role, at least in reducing other cardio-metabolic risk factors, closely associated with NAFLD. In this regard, the Mediterranean diet was shown to reduce steatosis at a greater extent compared with the low-fat diet in a NAFLD population, but not specifically PCOS [78]. Furthermore, data assessing fibrosis with paired liver biopsies are lacking. Data from PCOS-specific studies regarding the effects of dietary regiments on liver steatosis and NAFLD or NASH are scarce. Women with biopsy-confirmed NASH showed histological improvement in response to diet [79] as well as normalization of LFTs in response to diet and exercise with or without combination with metformin [80].

Regarding pharmacotherapy, pioglitazone and vitamin E have shown promising results in patients with NAFLD [8, 9]. The PIVENS trial, comparing low-dose pioglitazone or vitamin E vs placebo for 2 years in patients without overt T2DM, showed that pioglitazone improved histological features, albeit not fibrosis, and achieved resolution of NASH more often than placebo [81]. The histological benefits occurred together with ALT and IR improvement. Similar results were reported in other, mostly smaller and shorter, randomized-controlled trials (RCTs) [82, 83]. In the PIVENS trial, vitamin E (800 IU/day) improved steatosis, inflammation and ballooning and induced resolution of NASH in 36% of patients compared with 21% in the placebo arm [81]. Thiazolidinediones (TZDs) present a favorable effect on insulin sensitivity and result in improved glucose tolerance and in reduction of circulating androgens. However, there are considerations on pioglitazone, including weight gain and an adverse effect on bone metabolism, which may limit their use generally and specifically in obese women with PCOS [84, 85].

Metformin is widely used in women with PCOS. Primarily, it decreases hepatic glucose production by inhibiting key enzymes for gluconeogenesis; secondarily, it enhances peripheral insulin sensitivity. These two actions result in the reduction of insulin concentrations, therefore in improvement of metabolic parameters. The reduction in insulin concentrations can result in a decrease in endogenous androgen production and an increase in SHBG concentrations [86]. Metformin has a favorable safety profile, and most caregivers are very familiar with its use. Nonetheless, metformin did not meet the pathophysiologically awaited expectations to improve liver histology in patients with NAFLD [87]. Regarding glucagon-like peptide-1 receptor agonists (GLP-1RA), a recent RCT showed that the daily use of liraglutide 1.8 mg in overweight women with PCOS leads to 5.6% weight loss, reduction in NAFLD rates by 66%, and reduction in liver fat content and visceral adipose tissue by 44% and 18%, respectively [88]. However, more studies are required to evaluate the efficacy and safety of liraglutide, especially in the long-term in PCOS women without diabetes, as well as those of other GLP-1RA, in liver histology of PCOS women with NAFLD. A recent RCT of vitamin D supplementation (3200 IU or placebo daily for 3 months) in 40 women with PCOS demonstrated decreases in ALT ($p = 0.042$) in the vitamin D arm, with no differences in other liver markers [89]. However, current data do not support vitamin D monotherapy in PCOS women specifically for NAFLD treatment. However, vitamin D may be supplemented in PCOS women, following the guidelines for the general population.

To summarize, lifestyle recommendations targeting essential and sustained weight loss are recommended for women with PCOS and NAFLD. Vitamin E and pioglitazone have provided promising results, as well as one study with liraglutide. However, more RCTs are explicitly required for non-diabetic women with PCOS and NAFLD.

Conclusions

A growing body of evidence suggests that NAFLD and PCOS often co-exist. A bidirectional association seems to exist between IR and NAFLD, which may contribute to the pathophysiology of PCOS. Inversely, PCOS characterized by IR and hyperandrogenism may affect NAFLD. Women with PCOS, particularly obese with features of MetS, should be screened for NAFLD, while premenopausal women with NAFLD should be screened for PCOS. Lifestyle recommendations targeting weight loss constitute the cornerstone of the management of both PCOS and NAFLD. Vitamin E, pioglitazone and liraglutide have produced promising results, but more data specifically in women with PCOS and NAFLD are required.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human or participants or animals performed by any of the authors.

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