

# Current Perspectives on Nonalcoholic Fatty Liver Disease in Women with Polycystic Ovary Syndrome

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**Abstract:** Polycystic ovary syndrome (PCOS) is one of the most common reproductive, endocrine, and metabolic disorders in premenopausal women. Clinically, PCOS is mainly caused by androgen excess and ovarian dysfunction, manifested by anovulatory menstrual cycles, infertility, and hirsutism. In addition, PCOS increases the risk of insulin resistance, obesity, cardiovascular disease, anxiety and depression, dyslipidemia, and endometrial cancer. Nonalcoholic fatty liver disease (NAFLD) is defined as  $\geq 5\%$  fat accumulation in the liver in the absence of remaining secondary causes and has become one of the most common chronic liver diseases worldwide. The prevalence of NAFLD is significantly higher and more severe in women with PCOS, and its pathogenesis can be associated with various risk factors such as hyperandrogenemia, insulin resistance, obesity, chronic low-grade inflammation, and genetic factors. Although there is no definitive solution for the management of NAFLD in PCOS, some progress has been made. Lifestyle modification should be the basis of management, and drugs to improve metabolism, such as insulin sensitizers and glucagon-like peptide-1 agonists, may show better efficacy. Bariatric surgery may also be a treatment of NAFLD in obese women with PCOS. This paper reviews three aspects of prevalence, risk factors, and management, in order to better understand the current state of research on NAFLD in PCOS, to explore the pathogenesis of NAFLD in PCOS, and to encourage further research on the application of drugs in this field.

**Keywords:** polycystic ovary syndrome, nonalcoholic fatty liver disease, hyperandrogenemia, insulin resistance, obesity, metformin, glucagon-like peptide-1

## Introduction

Polycystic ovary syndrome (PCOS) is one of the most common reproductive, endocrine, and metabolic disorders in premenopausal women.<sup>1</sup> PCOS is a group of syndromes caused by excessive androgens and ovarian dysfunction.<sup>2</sup> Diagnostic criteria for PCOS vary internationally and mainly follow the standards proposed by the National Institutes of Health (NIH) of the United States in 1990,<sup>3</sup> the Rotterdam standards proposed by the European Society of Reproductive Medicine and the American Society of Reproductive Medicine in 2003,<sup>4</sup> and the Androgen Excess Society (AES) standard proposed by the American Androgen Hypertrophy Society in 2006,<sup>5</sup> as shown in Table 1. The Rotterdam standard is currently the most widely used, and the worldwide prevalence of PCOS varies somewhat depending on the diagnostic criteria, ranging from 4% to 21%.<sup>6</sup> The clinical manifestations of PCOS are mainly anovulatory menstrual cycles, infertility, and hirsutism.<sup>7</sup> In addition, PCOS increases the risk of insulin resistance, obesity, cardiovascular disease, anxiety and depression, dyslipidemia, and endometrial cancer.<sup>8–12</sup>

Nonalcoholic fatty liver disease (NAFLD) is defined as  $\geq 5\%$  fat accumulation in the liver with the absence of remaining secondary causes, such as viral hepatitis, excessive alcohol consumption, drug-related liver disease, autoimmune liver disease, genetic metabolic liver disease, and other diseases.<sup>13</sup> NAFLD includes a wide range of histological changes from simple fat accumulation in the liver to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, and even hepatocellular carcinoma (HCC).<sup>14</sup> With a global prevalence of 25.24%,<sup>15</sup> NAFLD has become one of the most common chronic liver diseases worldwide and may become a major cause of end-stage liver disease in the coming decades. As a result, NAFLD has gained the attention of physicians, experts, and health policy makers worldwide.<sup>16</sup>

**Table 1** Diagnostic Criteria for PCOS

	<b>NIH</b>	<b>Rotterdam</b>	<b>AES</b>
Diagnostic criteria	1. Clinical manifestations of hyperandrogenism and/or hyperandrogenemia 2. Sporadic ovulation or anovulation	At least 2 out of 3 criteria: 1. Clinical manifestations of hyperandrogenism and/or hyperandrogenemia 2. sporadic ovulation or anovulation 3. polycystic ovarian changes	1. Clinical manifestations of hyperandrogenism and/or hyperandrogenemia 2. at least 1 out of 2 criteria (1) sporadic ovulation or anovulation (2) polycystic ovarian changes
Exclusion of disease	Hyperprolactinaemia, thyroid disorders, Cushing's syndrome, congenital adrenal hyperplasia, 21-hydroxylase deficiency, androgen-secreting tumours and other conditions causing secondary androgen elevation		

**Abbreviations:** PCOS, polycystic ovary syndrome; NIH, National Institutes of Health; AES, androgen excess society.

Recent studies have found a significant increase in the prevalence of NAFLD in PCOS. Therefore, in this review, we will discuss the research progress of NAFLD in PCOS from three aspects: prevalence, risk factors, and management.

## Prevalence of NAFLD in PCOS

In 2005, Brown et al<sup>17</sup> reported a 24-year-old patient with PCOS and chronically elevated serum transaminase levels who had a liver biopsy confirming severe NASH. Since then, there has been a gradual increase in clinical studies on NAFLD in PCOS, according to the data reported in the studies, we found that the prevalence range for NAFLD in PCOS was 14.5%–77%,<sup>18–38</sup> with relevant studies shown in Table 2. There are some differences in the prevalence of NAFLD in PCOS depending on the diagnostic criteria for PCOS. In studies with NIH as the diagnostic criteria, the prevalence ranged from 14.5%–54.5%.<sup>18,19</sup> In studies with AES as the diagnostic criteria, the prevalence range for PCOS combined with NAFLD was 23.8%–36.8%.<sup>21,22,28</sup> Lastly, in studies with Rotterdam criteria, the prevalence range for PCOS combined with NAFLD was 32.9%–77.0%.<sup>20,23–27,29–38</sup> The Rotterdam criteria have a broader definition of PCOS and incorporate more phenotypes, resulting in an increased base of PCOS diagnoses and thus more patients being screened for NAFLD. From a regional perspective, current studies of NAFLD in PCOS have focused on the Americas, Europe, and Asia, with the average prevalence in Asia being lower than that in the Americas and Europe. This regional variation may be related to dietary habits and the levels of economic development between different regions. In addition, a greater prevalence of NASH was found in PCOS compared to controls by biopsies (44.0% vs 20.8%),<sup>23</sup> and the prevalence of significant fibrosis in PCOS was 6.9%.<sup>38</sup>

## Risk Factors for NAFLD in PCOS

Results from a study of 102 women with pathologically confirmed NAFLD showed that NAFLD was more severe in PCOS, with higher rates of severe ballooning, fibrosis, and advanced fibrosis than those without PCOS; further, the median age of women with advanced liver fibrosis was 5 years earlier in those with PCOS than those without PCOS.<sup>39</sup> The main risk factors for NAFLD in PCOS include hyperandrogenemia (HA), insulin resistance (IR), obesity, chronic low grade inflammation, and genetic factors.

## Hyperandrogenemia

Pulses of sustained high-frequency gonadotropin releasing hormone (GnRH) in patients with PCOS cause an increase in the amplitude of LH pulses, resulting in excessive luteinizing hormone (LH) secretion and a relative lack of follicle stimulating hormone (FSH), which causes HA.<sup>40</sup> HA is an independent predictor of NAFLD in PCOS,<sup>34</sup> and patients with PCOS and HA have more pronounced steatosis than patients with PCOS who do not have HA.<sup>41</sup> HA is also an independent risk factor for NAFLD in non-obese patients with PCOS.<sup>30</sup> In a clinical study by Petta et al,<sup>32</sup> in which liver fibrosis was assessed with the Fibrosis 4 Score (FIB-4), higher FIB-4 was independently associated with higher FAI in nonobese PCOS patients. A low-dose dihydrotestosterone (DHT)-induced model of normal weight PCOS-like female mice with NAFLD showed that DHT enhanced the binding of an androgen receptor (AR) to an androgen response element (ARE) in sterol regulatory element-binding protein (SREBP) cleavage activating protein (SCAP) intron 8,

**Table 2** Studies on Prevalence of NAFLD in PCOS

Size		Diagnostic Criteria for PCOS	Diagnostic Basis for NAFLD	Prevalence (%)		Region	Author, Year, and Reference
PCOS	Control			PCOS	Control		
200	-	NIH	ALT	14.50	-	U.S.A	Setji, 2006 <sup>18</sup>
88	-	NIH	Ultrasonography	54.50	-	U.S.A	Gambarin-Gelwan, 2006 <sup>19</sup>
41	31	Rotterdam	Ultrasonography	41.50	19.40	Chile	Cerda, 2007 <sup>20</sup>
57	60	AES	ALT	39.00	3.20	Greece	Vassilatou, 2010 <sup>21</sup>
			Ultrasonography	36.80	20.00		
192	73	AES	LIFL	34.00	6.90	Germany	Tan, 2010 <sup>22</sup>
			CK18-M30	27.60	1.40		
34	32	Rotterdam	Liver biopsy	44.00	20.80	U.S.A	Hossain, 2011 <sup>23</sup>
45	32	Rotterdam	Ultrasonography	73.30	46.70	Brazil	Zueff, 2012 <sup>24</sup>
54	55	Rotterdam	Ultrasonography	66.70	25.40	India	Karoli, 2013 <sup>25</sup>
			ALT	31.40	7.30		
602	588	Rotterdam	Ultrasonography	32.90	18.50	China	Qu, 2013 <sup>26</sup>
184	125	Rotterdam	Ultrasonography	57.60	49.60	Poland	Bohdanowicz-Pawlak, 2014 <sup>27</sup>
			Ultrasonography	23.80	3.30		
103	34	AES	Ultrasonography	23.80	3.30	Brazil	Romanowski, 2015 <sup>28</sup>
600	125	Rotterdam	LFS	50.60	34.00	Greece	Macut, 2016 <sup>29</sup>
400	100	Rotterdam	Ultrasonography	56.25	30.80	China	Cai, 2017 <sup>30</sup>
75	75	Rotterdam	Ultrasonography	38.70	18.70	Iran	Mehrabian, 2017 <sup>31</sup>
202	101	Rotterdam	HSI	68.80	33.30	Italy	Petta, 2017 <sup>32</sup>
188	65	Rotterdam	Ultrasonography	44.68	24.62	China	Zhang, 2018 <sup>33</sup>
60	-	Rotterdam	Ultrasonography	38.30	-	India	Harsha Varma, 2019 <sup>34</sup>
98	98	Rotterdam	CAP	69.30	34.60	Mexico	Salva-Pastor, 2020 <sup>35</sup>
70	60	Rotterdam	Ultrasonography	38.57	6.67	India	Chakraborty, 2020 <sup>36</sup>
87	40	Rotterdam	Ultrasonography	77.00	52.50	Brasil	Taranto, 2020 <sup>37</sup>
101	-	Rotterdam	CAP	39.60	-	Canada	Shengir, 2020 <sup>38</sup>

**Abbreviations:** PCOS, polycystic ovary syndrome; NAFLD, nonalcoholic fatty liver disease; NIH, National Institutes of Health; AES, androgen excess society; U.S.A, United States of America; ALT, alanine aminotransferase; LIFL, liver injury implicating fatty liver; CK18-M30, cytokeratin 18-M30; LFS, liver fat score; HSI, hepatic steatosis index; CAP, controlled attenuation parameter.

elevating the SCAP-SREBP1 interaction, leading to an increase in nuclear SREBP1, and resulting in increased hepatic adipose de novo synthesis.<sup>42</sup> According to the literature, PCOS-like rats with 12 weeks of induced DHT exposure showed that chronic androgen overload leads to insulin resistance and hepatic steatosis by affecting mitochondrial function and causing apoptosis and autophagy imbalance.<sup>43</sup> In letrozole-induced PCOS-like rat models and DHT-treated HepG2 models, excess androgens cause steatosis by inhibiting the adenosine monophosphate (AMP)-activated protein kinase alpha pathway.<sup>44</sup> Androgens can also lead to impaired branched-chain amino acid metabolism and dysfunctional activity of ELOVL2, SLC22A4, and SLC16A9, contributing to the development of NAFLD.<sup>45</sup> In addition, androgens can induce mitochondrial  $\beta$ -oxidation imbalance and de novo lipogenesis through PPAR $\alpha$ / $\beta$ -Srebp1/2-Acc1 and can exacerbate liver inflammatory damage by upregulating the expressions of IL-6, TNF- $\alpha$ , MCP-1, and IL-1 $\beta$ .<sup>46</sup> Thus, HA influences the development and progression of NAFLD in PCOS by affecting hepatic lipid metabolism, apoptosis and autophagy imbalance, branched-chain amino acid metabolism, and inflammation.

## Insulin Resistance

IR occurs in 50–70% of women with PCOS who have a normal body mass index (BMI), but it is more prevalent in women with PCOS who are overweight or obese.<sup>47</sup> While there is an overlap of variants in the genetic regions of IRNS, THADA, and HMGA between PCOS and type 2 diabetes,<sup>48</sup> there are intrinsic or acquired defects in the insulin signaling pathway in PCOS.<sup>49</sup> In addition, HA and chronic low-grade inflammation in PCOS promote the progression of IR, and

therefore, there is a significant presence of IR in patients with PCOS. Among the mechanisms of NAFLD, IR has been well recognized in the pathogenesis of NAFLD, both in the traditional “second strike” theory and the more recent “multiple strike” theory. Several clinical studies have confirmed that IR is a risk factor for NAFLD in PCOS and is associated with liver fibrosis in patients with PCOS.<sup>29,31–33</sup> In IR, peripheral tissues are less sensitive and metabolically responsive to circulating insulin, and the inhibitory effect of insulin on lipolysis in peripheral adipose tissue is reduced, resulting in ectopic deposition of large amounts of free fatty acids in the liver.<sup>50</sup> Elevated glucose and insulin during IR promote de novo production of intrahepatic fat by activating ChREBP and SREBP1c, respectively.<sup>51</sup> IR causes liver damage through increased lipotoxicity, oxidative stress, and activation of the inflammatory cascade;<sup>52</sup> it also causes liver fibrosis by activating hepatic stellate cells and promoting excessive production of extracellular matrix through direct and indirect pathways.<sup>53</sup> Increased  $\alpha$ -smooth muscle actin protein expression was observed in insulin+human chorionic gonadotropin (hCG)-treated rats, both hCG-treated and insulin+hCG-treated rats had increased mRNA expression of transforming growth factor- $\beta$  and connective tissue growth factor, which were associated with liver fibrosis.<sup>46</sup> Therefore, IR is an important risk factor for NAFLD in PCOS.

## Obesity

In a clinical study by Shengir et al,<sup>38</sup> the percentage of central obesity in women with PCOS was 96% when waist circumference was used as a criterion. Using BMI as the criterion, the proportion of overweight patients was 11.9%, and the proportion of obese patients was 71.3%.<sup>38</sup> This indicates that obesity is prevalent in women with PCOS. PCOS causes weight gain and obesity, which is related to the lipolytic function of androgens on adipocytes. Testosterone contributes to the release of non-esterified fatty acids from visceral adipocytes in the body and impairs adipocyte differentiation and adipokine formation,<sup>54</sup> leading to the accumulation of local adipose tissue, especially in the abdomen. Obesity is also associated with lower postprandial thermogenesis, depressed mood and mental health, and lack of exercise in women with PCOS.<sup>55</sup> A systematic review and meta-analysis of 7148 patients included in 23 studies showed that premenopausal patients with PCOS had a 2.5-fold increased risk of nonalcoholic fatty liver disease compared to controls, with BMI being a main factor.<sup>56</sup> Obesity reduces the level of SFRP5 and its anti-inflammatory effect in the liver;<sup>57</sup> it also reduces the level of NRG4 and weakens the regulatory effect of NRG4 on hepatic lipogenesis.<sup>58</sup> Lipodystrophy occurs in obesity, and the ability of adipose tissue to store excess energy is diminished, causing hepatocytes to store excess lipids.<sup>59</sup> Furthermore, the balance of adipokines is disrupted in obesity, and the secreted adipokines are shifted towards a more adipogenic, inflammatory and fibrogenic direction.<sup>60</sup> Through these mechanisms, obesity can exacerbate NAFLD in PCOS.

## Chronic Low-Grade Inflammation

Chronic low-grade inflammation in PCOS can be mediated by obesity and HA.<sup>61</sup> The hypertrophy of adipocytes in PCOS causes interstitial vascular compression, resulting in inadequate perfusion and hypoxia in adipose tissue, which in turn stimulates the activation of NF- $\kappa$ B and regulates the expression of key genes involved in the inflammatory response.<sup>62</sup> This process induces the production and release of many mediators and triggers chronic low-level inflammation in the body, among which IL6 and IL1 $\beta$  can also stimulate the synthesis of CRP in the liver.<sup>62</sup> The compensatory process of cellular hypertrophy and proliferation of functionally impaired adipocytes produces a large number of cytokines that induce inflammatory responses, cell damage, and apoptosis.<sup>63</sup> A variety of immune cells (eg macrophages, T lymphocytes, etc) also infiltrate during adipocyte hypertrophy, producing cytokines that interact with adipokines and cause an imbalance between pro- and anti-inflammatory cytokines which leads to liver inflammation.<sup>64,65</sup> Significant increases in hepatic TNF- $\alpha$  in hepatic expression and mRNA expression of urocortin-1 were observed in the DHT-induced PCOS rat model,<sup>66</sup> confirming that PCOS can affect liver function by altering the levels of inflammatory factors and stress-related proteins.

## Genetic Factors

Genetic factors have also been associated with NAFLD in PCOS. Analysis of single nucleotide polymorphisms in cannabinoid receptor 1 (CNR1) in 173 women with PCOS and 125 age- and weight-matched healthy control patients indicated that the G allele of rs06381 was phenotypically associated with NAFLD in PCOS, suggesting a potential role

for CNR1 polymorphisms in NAFLD in PCOS.<sup>67</sup> Genetic analysis of adipose tissue from patients with NAFLD and PCOS and patients with NAFLD without PCOS showed that reduced LDLR gene expression may be associated with NAFLD in PCOS.<sup>68</sup> However, it has also been shown that the rs328 and rs268 polymorphisms of the lipoprotein lipase gene do not affect the occurrence of NAFLD in women with PCOS and in women without PCOS.<sup>69</sup> Therefore, we need further in-depth studies on the role of genetic factors in NAFLD with PCOS.

Risk factors can also interact with each other. Dehydroepiandrosterone (DHEA)-induced PCOS-like mice exhibit IR in skeletal muscle, which is associated with androgens inhibiting autophagy, damaging mitochondria, and reducing plasma membrane glucose transporter 4 (GLUT4) expression in mouse skeletal muscle through activation of mTORC1.<sup>70</sup> In cultured skeletal muscle cells and skin fibroblasts, androgens have been observed to increase serine phosphorylation of insulin receptors, affecting insulin signaling pathways and triggering IR.<sup>71,72</sup> Insulin also acts on the anterior pituitary to enhance the release of GnRH, which in turn causes increased secretion of LH and increased production of androgens.<sup>73</sup> Further, insulin can stimulate the ovaries to synthesize androgens by enhancing the activity of CYP17 $\alpha$  and other steroidogenic enzymes.<sup>74</sup> IR is negatively correlated with serum sex hormone globulin (SHBG),<sup>75</sup> which binds androgens with high affinity,<sup>76</sup> so IR can increase free androgen concentrations by reducing SHBG levels. HA and IR can exacerbate obesity,<sup>77,78</sup> and obesity can exacerbate IR by affecting the PI3K pathway.<sup>79</sup> Obesity can also exacerbate HA by affecting the abnormal function of the hypothalamic-pituitary-ovarian axis and the peripheral metabolism of sex hormones.<sup>80</sup> Visceral adipose tissue can elicit an inflammatory response and maintain an inflammatory state by increasing the production of inflammatory cytokines, the production of monocyte chemoattractant proteins, and the recruitment of immune cells.<sup>81</sup> Chronic low-grade inflammation may mediate the effects of sympathetic dysfunction on HA and IR.<sup>82</sup> The interaction between risk factors further worsens the endocrine and metabolic disorders in patients with PCOS, leading to the development and progression of NAFLD.

## Management of NAFLD in PCOS

There is no definitive approach to the management of NAFLD in PCOS. Current research on the management of NAFLD in PCOS is mainly focused on lifestyle modification, pharmacological treatments, and bariatric surgery.

### Lifestyle Modification

Lifestyle modification are the basic treatment for PCOS and NAFLD.<sup>83,84</sup> Lifestyle modification include a combination of diet control and increased exercise to achieve weight loss. Lifestyle modification can reduce weight, increase insulin sensitivity, and decrease hyperandrogenemia in women with PCOS;<sup>85–87</sup> the harmful effects of endocrine and metabolic disorders on the livers of women with PCOS are also reduced. One study confirmed that weight loss through lifestyle modification significantly reduced the characteristics of NAFLD, with reduced liver inflammation observed in subjects who lost  $\geq 5\%$  of their body weight and regression of liver fibrosis observed in subjects who lost  $\geq 10\%$  of their body weight.<sup>88</sup> Clinical studies have also shown improvements in liver function in PCOS with lifestyle modification. A 6-week, 8-hour restricted eating study in 18 women with anovulatory PCOS showed that restricted eating reduced body weight, decreased body fat, improved menstrual cycles and hyperandrogenemia, and reduced alanine aminotransferase (ALT) levels in women with PCOS.<sup>89</sup>

### Pharmacological Treatments

Although no drugs have been recommended for the treatment of NAFLD in PCOS, some drugs have been found in clinical studies to improve liver function and histology and to reduce lipid aggregation in PCOS.

### Metformin

Metformin has been used clinically for over 60 years and is also the first choice for the treatment of type 2 diabetes. Metformin acts by activating AMP-activated protein kinase (AMPK).<sup>90</sup> Activated AMPK shifts the cell from an anabolic to a catabolic state, shutting down the synthetic pathway that consumes adenosine triphosphate and restoring energy balance. As a result, glucose, lipid and protein synthesis as well as cell growth are inhibited, while fatty acid oxidation and glucose uptake are stimulated.<sup>91</sup> AMPK can mediate phosphorylation of target substrates,<sup>92</sup> attenuating NAFLD



through three pathways: inhibition of de novo lipid synthesis in the liver, increased oxidation of fatty acids in the liver, and promotion of mitochondrial function and integrity in adipose tissue.<sup>93</sup> The application of metformin in PCOS has been confirmed. Overweight women with PCOS treated with metformin showed significant improvements in endocrine and metabolic markers, including testosterone, follicle-stimulating hormone, luteinizing hormone, and low-density lipoprotein cholesterol.<sup>94</sup> Some studies also noted findings on the improvement of NAFLD in PCOS with metformin. A study that included 82 obese women with PCOS, who received metformin for 8 months, showed that metformin reduced the mean weight, serum ALT, and glutamyl transpeptidase (GGT) of these patients from 100.3 kg to 96.6 kg, 29.7 U/L to 25.8 U/L, and 21.4 U/L to 16.9 U/L, respectively.<sup>95</sup> Another study of 140 young overweight patients with hyperinsulinemia and PCOS treated with metformin for 12 months showed a reduction in the prevalence of metabolic syndrome and liver involvement in these patients.<sup>96</sup> Therefore, metformin has shown some improvement in NAFLD with PCOS, especially in overweight and obese women with PCOS and in women with hyperinsulinemia and PCOS.

## Thiazolidinediones

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptors expressed in the liver, adipose tissue, heart, skeletal muscle, and kidney that are involved in the transcriptional regulation of key metabolic pathways, such as lipid metabolism, adipogenesis, and insulin sensitivity.<sup>97</sup> Thiazolidinediones, as PPAR $\gamma$  agonists, have insulin-sensitizing effects and are widely used in the treatment of diabetes mellitus. Additionally, the role of thiazolidinedione in the treatment of NASH has been recognized. Pioglitazone alleviates NASH in diabetic and pre-diabetic patients, reduces liver fibrosis scores, lowers liver triglyceride levels from 19% to 7%, and improves hepatic insulin sensitivity.<sup>98</sup> The same effect was observed with pioglitazone in non-diabetic patients with NASH, with improvements in ALT and GGT and a decrease in histological hepatocyte damage, Mallory-Denk vesicles, and fibrosis.<sup>99</sup> Pioglitazone has also been shown to improve menstrual cycles and ovulation and to reduce glucose metabolism indicators in PCOS.<sup>74,100</sup> However, the use of thiazolidinedione in PCOS is limited by its side effects on weight gain and cardiovascular aspects.<sup>101,102</sup> Therefore, the application of thiazolidinedione to the treatment of NAFLD in non-obese patients with PCOS will probably have more positive results.

## GLP1 Receptor Agonists

Incretin peptides are intestinal hormones that promote postprandial insulin secretion in a glucose-dependent manner, including glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), and have effects on the regulation of islet hormone secretion, glucose concentration, lipid metabolism, intestinal motility, appetite, and body weight.<sup>103</sup> By performing an oral glucose tolerance test on women with PCOS and healthy controls, it was detected that blood GLP1 concentrations at 180 minutes were significantly lower in women with PCOS than in healthy controls.<sup>104</sup> Therefore, the use of GLP1 receptor agonists in PCOS is feasible. Liraglutide reduces body weight in overweight or obese women with PCOS,<sup>105</sup> improves IR in women with PCOS,<sup>106</sup> reduces free testosterone levels, elevates SHBG levels, and improves menstrual cycle and ovarian function in women with PCOS.<sup>107</sup> The improvement of NAFLD in PCOS by liraglutide has also been clinically demonstrated. A double-blind, placebo-controlled, randomized clinical trial of women with PCOS treated with liraglutide for 26 weeks showed that liraglutide reduced liver fat content by 44%, visceral adipose tissue by 18%, and the prevalence of NAFLD by two-thirds in these patients.<sup>108</sup> For NAFLD in obese patients with PCOS, liraglutide may provide additional beneficial effects.<sup>109</sup>

## Spirolactone

Spirolactone mainly acts as an antagonist binding to androgen receptors and can inhibit ovarian and adrenal steroid production as well as 5-alpha-reductase activity, thus exerting an anti-androgenic effect to achieve a therapeutic effect on PCOS.<sup>110,111</sup> Clinical studies show that spiroolactone can improve HA and hirsutism and restore menstrual cycles in PCOS.<sup>112,113</sup> Spirolactone also reduces serum free fatty acid levels in PCOS.<sup>114</sup> In a letrozole-induced rat model, spiroolactone was observed to reduce uric acid and malondialdehyde in the liver, elevate glutathione reductase in the liver, reduce hepatic triglyceride accumulation, and alleviate NAFLD.<sup>115</sup> However, spiroolactone is often used in

combination with oral contraceptives for the treatment of PCOS because it can cause irregular menstruation when used in high doses alone and has the risk of feminizing the male fetus in pregnant patients.<sup>110,111</sup>

## Nutritional Supplements

Recent studies have shown that some nutritional supplements can be helpful in the treatment of NAFLD in PCOS. A 12-week combination of 1000 mg omega-3 fatty acids (containing 400 mg of  $\alpha$ -linolenic acid) and 400 IU vitamin E supplementation in women with PCOS significantly improved IR index and reduced total and free testosterone.<sup>116</sup> The combination also downregulated lipoprotein(a) and oxidized low-density lipoprotein (Ox-LDL) expression, reduced triglycerides and very low-density lipoproteins, and improved overall plasma antioxidant capacity.<sup>117</sup> An 8-week supplementation of 4 g/d of omega-3 fatty acids and measurement of hepatic fat content by proton magnetic resonance spectroscopy in 25 women with PCOS showed that omega-3 fatty acids reduced liver fat by  $\geq 5\%$  in women with PCOS.<sup>118</sup> In addition, vitamin E can also reduce hepatic steatosis, inhibit liver inflammation, and improve NAFLD by inhibiting lipid accumulation and peroxidation in the liver.<sup>119</sup> Vitamin D supplementation of 3200 IU/d for 3 months in 40 patients with PCOS showed that vitamin D reduced ALT levels in PCOS patients, and a downward trend was observed for hyaluronic acid, type III procollagen N-terminal pro-peptide, and enhanced liver fibrosis (ELF) scores.<sup>120</sup> Although some clinical studies have observed the therapeutic effect of nutritional supplements on NAFLD in PCOS, there is still no evidence that they can be used alone in the treatment of PCOS, and additional clinical studies are needed to confirm their therapeutic value in PCOS.

## Bariatric Surgery

Bariatric surgery has proven valuable in the treatment of obese women with PCOS. Bariatric surgery can improve menstrual abnormalities, restore ovarian morphology, improve HA and hirsutism, reduce body weight, and improve glucose metabolism and dyslipidemia in obese patients with PCOS.<sup>121–123</sup> In addition, clinical studies have confirmed that bariatric surgery can significantly reduce ALT and aspartate aminotransferase (AST) levels in women with PCOS.<sup>124</sup> However, more studies are needed to further confirm the effects of bariatric surgery on hepatic lipid metabolism and hepatic histological improvement in women with PCOS.

## Conclusion

There is growing evidence that PCOS can increase the prevalence of NAFLD, mainly associated with HA and IR. Therefore, screening for NAFLD should be enhanced in patients with PCOS, especially those with HA and IR features. Although there is no clear protocol for the treatment of NAFLD in PCOS, it appears that lifestyle modification should be the basis, and drugs to improve metabolism represented by insulin sensitizers and GLP1 receptor agonists may have positive application prospects.

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## Disclosure

The authors declare no conflicts of interest in this work.

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