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Review article

Association Between Polycystic Ovary Syndrome and Fatty Liver Disease in Women: A Literature Review

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Abstract

Introduction: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a multisystem condition with a spectrum that begins with simple steatosis, followed by nonalcoholic steatohepatitis, and may progress to fibrosis. Its prevalence among women with polycystic ovary syndrome (PCOS) ranges from 34% to 70%, a relationship explained pathophysiologically by insulin resistance, obesity, hyperandrogenism, and other contributing factors. Currently, there is no approved treatment for either condition; therefore, management should focus on lifestyle modifications, including proper nutrition, weight loss, and physical activity—either as stand-alone strategies or in combination with pharmacological therapy. **Materials and methods:** This article reviews current evidence on the association between fatty liver disease and PCOS. A literature search was conducted using DeCS and MeSH terms in both Spanish and English, including studies published from 2014 to date. **Conclusion:** It is recommended that all women with PCOS undergo liver function testing and imaging studies (such as ultrasound and elastography) for the diagnosis of MAFLD.

Keywords

Nonalcoholic fatty liver disease, polycystic ovary syndrome, insulin resistance, obesity, hyperandrogenism.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a multisystem disorder encompassing various hepatic manifestations, including simple steatosis, nonalcoholic steatohepatitis (NASH), and progressive fibrosis. Its prevalence is rising and is characterized by hepatic steatosis affecting more than 5% of hepatocytes in the absence of other causes, such as excessive alcohol consumption, and may progress to cirrhosis[(1)]. Diagnosis is confirmed through histology or imaging studies[(1)]. NAFLD has been associated with obesity, insulin resistance, type 2 diabetes *mellitus* (T2DM), hypertension, and dyslipidemia[(2)].

A new terminology has been proposed for these conditions: metabolic dysfunction-associated steatotic liver disease (MASLD) instead of NAFLD, and metabolic dysfunction-associated steatohepatitis (MASH) instead of NASH. This updated nomenclature includes hepatic steatosis in the presence of at least one of five cardiometabolic criteria, such as overweight, hyperglycemia, hypertension, and dyslipidemia[(3)]. The diagnostic criteria for NAFLD/NASH remain valid for MASLD/MASH, particularly since studies show that up to 98% of NAFLD patients meet MASLD criteria[(4)]. This review uses the term MASLD instead of NAFLD and MASH for conditions related to NASH.

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in reproductive-age women and the leading cause of oligoovulatory infertility. It is characterized by hyperandrogenemia, anovulation, elevated luteinizing hormone (LH) levels, and polycystic ovarian morphology on imaging[5]. Its prevalence varies depending on diagnostic criteria: 6%–10% using classic definitions[6], while the Rotterdam criteria identify 18%–20% of cases. The latter offers greater sensitivity and clinical utility by capturing a broader range of phenotypes beyond hyperandrogenism alone[7].

Multiple studies report a higher prevalence of NAFLD in women with PCOS (34%–70%) compared to the general population (14%–34%)[8]. Both conditions share common risk factors, including elevated serum androgens, obesity, and insulin resistance[9]. The liver-ovary axis theory suggests PCOS is an independent risk factor for NAFLD development and vice versa[10] (**Figure 1**).

METHODOLOGY

A narrative review was conducted, beginning with a literature search using the following DeCS (Health Sciences Descriptors) and MeSH (Medical Subject Headings) terms, as well as keywords in the search strategy: nonalcoholic fatty liver disease (NAFLD), polycystic ovary syndrome, insulin resistance, obesity, hyperandrogenism.

The search was limited to human studies published in Spanish and English from 2014 to the present. Animal studies and pediatric populations were excluded. Electronic databases including PubMed/Medline, Scopus, Embase, SciELO, and Science Direct were consulted. Additionally, manual searches were performed in gray literature databases and Google Scholar. All studies included in the review were thoroughly analyzed for scientific quality, considering their design and methodology. Ultimately, 21 articles were selected to complete the information presented in this text.

INSULIN RESISTANCE

Multiple studies have demonstrated an association between insulin resistance and fatty liver in women with PCOS[11]. Excess lipids lead to insulin resistance, which can result in cardiometabolic complications such as diabetes *mellitus*, cardiovascular disease, and fatty liver[9]. Similarly, increased insulin resistance has been observed in women with PCOS and hepatic steatosis[12].

Several associated mechanisms have been proposed. First, insulin resistance causes adipocyte dysfunction, disrupting lipolysis, increasing free fatty acids, reducing adiponectin secretion, and promoting the release of proinflammatory cytokines. These effects lead to lipid overload and accumulation in the liver, exacerbating hepatic steatosis and insulin resistance[13]. Decreased leptin and adiponec-

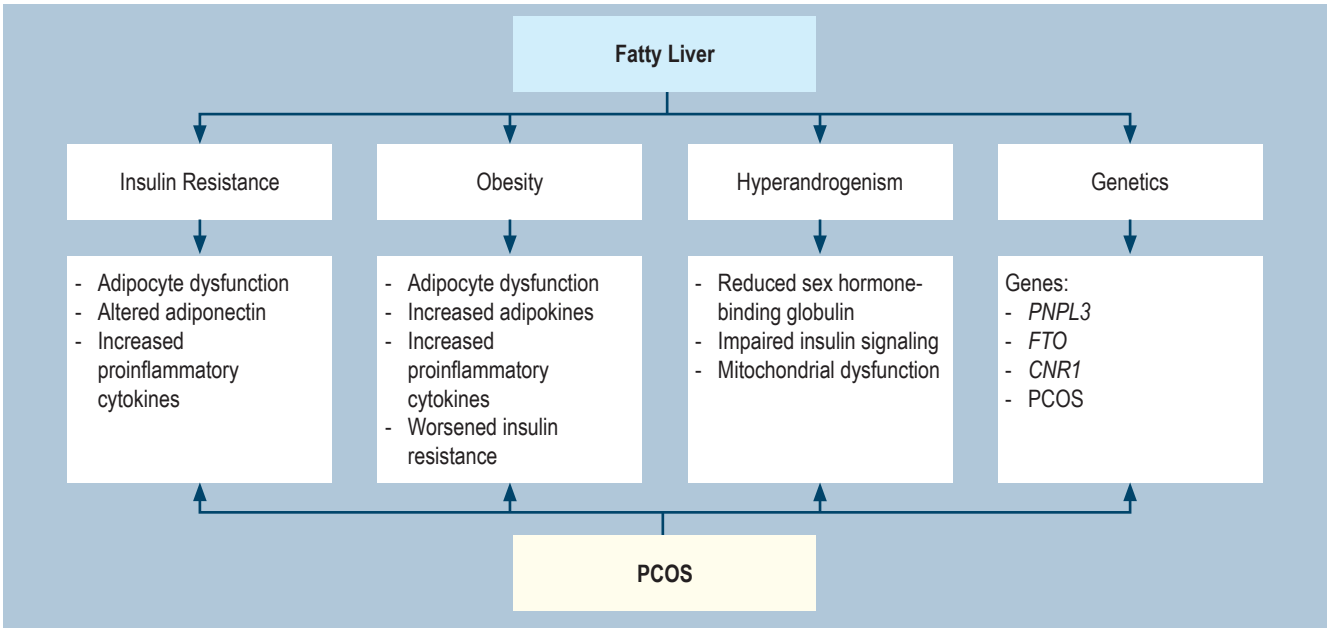

Figure 1. Pathophysiology of Fatty Liver and Polycystic Ovary Syndrome (PCOS). Image property of the authors.

tin levels are also associated with impaired insulin sensitivity[14]. Second, insulin resistance exerts both direct and indirect effects on the pituitary gland[15], stimulating androgen production, which reduces insulin clearance and leads to hyperinsulinemia[16]. Finally, MASLD and PCOS trigger a systemic inflammatory response involving nuclear factor kappa beta (NF-κB) activation and elevated proinflammatory cytokines. This activates stress-related protein kinases and induces phosphorylation of insulin receptor substrate 1 (IRS-1), impairing insulin signaling[17]. Proinflammatory cytokines and oxidative stress further inhibit signaling through IRS-1 and IRS-2[14].

When measuring insulin resistance, significantly higher values have been found in women with PCOS and hepatic steatosis compared to those with PCOS alone (HOMA-IR = 4.66 ± 2.78 vs. 2.26 ± 1.45; $p < 0.001$)[12]. A Chinese study found that NAFLD was significantly more prevalent in women with PCOS, and insulin resistance was also markedly more frequent[18]. Karoli et al. identified that women with PCOS had a higher prevalence of hepatic steatosis (67% vs. 25%; $p = 0.001$) and elevated transaminases (31% vs. 7%; $p = 0.03$), along with increased insulin resistance indices[19].

OBESITY

Obesity is a well-established risk factor for both hepatic steatosis and PCOS. Studies report that 50% of NAFLD patients and 80% of MASH patients are overweight or obese[20]. Among PCOS patients specifically, approximately 50% present with overweight or obesity[21]. Furthermore, excess weight has been linked to various cardiovascular risk factors shared by MASLD and PCOS patients[22].

Increased adipose tissue leads to elevated secretion of adipokines and cytokines—including leptin, adiponectin, tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6)—resulting in higher circulating free fatty acids and leptin levels alongside reduced adiponectin. These changes promote insulin resistance and androgen production. Additionally, elevated follicular fluid insulin levels are observed, along with decreased sex hormone-binding globulin (SHBG), glucose transporter 4 (GLUT-4), and IRS-2 in granulosa and cumulus cells, exacerbating insulin resistance and fat accumulation. Ultimately, increased androgens and insulin resistance drive abdominal fat deposition, creating a self-perpetuating cycle[23].

A 2019 study found that abdominal obesity—defined as waist circumference >80 cm and BMI ≥25.0 kg/m^2—predicted fatty liver in PCOS patients versus healthy controls (p <0.001 for both parameters)[24]. Similar findings emerged in Petta et al.'s study, where PCOS patients had higher BMI (25.7 ± 2.9 vs. 23.9 ± 3.0 kg/m^2, p <0.001) and greater abdominal obesity prevalence (48.2% vs. 34.6%, p = 0.01) than controls. Steatosis independently correlated with waist circumference (OR: 1.04; 95% CI: 1.01–1.08; $p = 0.006$)[25].

HYPERANDROGENISM

SHBG is a sex steroid transporter with high affinity for testosterone in circulating plasma, regulating its bioavailability in target tissues[26]. PCOS patients characteristically demonstrate low SHBG levels–a hallmark feature associated with clinical manifestations of hyperandrogenism including hirsutism, alopecia, and acne[27]. Moreover, PCOS patients with reduced SHBG levels show increased risk of developing NAFLD[28].

Cellular studies demonstrate that decreased SHBG is associated with lower messenger RNA (mRNA) and protein levels of IRS-1, IRS-2, and PI3K, suggesting SHBG may be involved in insulin signaling pathways and insulin resistance[29]. Insulin resistance affects ovarian theca cells by increasing androgen production while decreasing hepatic SHBG synthesis, thereby elevating levels of free or biologically active testosterone[30]. Thus, reduced SHBG, hyperandrogenism, and insulin resistance form a vicious cycle that contributes to the increased prevalence and severity of both fatty liver disease and PCOS[10].

In Hong et al.'s study of 667 women diagnosed with PCOS and 289 controls with regular menstrual cycles, women with PCOS were 2.46 times more likely to have NAFLD (95% CI: 5.12-26.96). Total testosterone, free testosterone, and free androgen index showed the strongest correlation with this increased likelihood[31]. Another study in women with PCOS found that androgenicity, represented by free testosterone or free androgen index, was associated with nonalcoholic fatty liver disease (p <0.001) after adjusting for age, BMI, lipid profile, insulin resistance, and glycemic status[32].

OTHER FACTORS

Environmental factors have been linked to metabolic dysfunction, PCOS, and MASLD. A sedentary lifestyle and poor dietary habits can lead to overweight, obesity, and insulin resistance, resulting in cardiometabolic and reproductive disturbances[10]. Evidence suggests that diets high in sugar, particularly those rich in sucrose or high-fructose corn syrup, increase the risk of developing NAFLD and MASH[33].

Elevated thyroid-stimulating hormone (TSH) levels correlate with obesity, dyslipidemia, insulin resistance, fatty liver disease, and higher plasma total cholesterol concentrations[34]. Hypothyroidism frequently occurs in both MASLD patients and women with PCOS. Furthermore, elevated TSH levels may impair oocyte maturation and fer-

tilization in women with PCOS undergoing in vitro fertilization[35], and have been associated with increased all-cause and cardiovascular mortality in MASLD patients[36].

At the genetic level, mutations have been identified in the endocannabinoid receptor 1 gene (CNR1), patatin-like phospholipase domain-containing protein 3 (PNPLA3), and the fat mass and obesity-associated gene (FTO). Endocannabinoid system activity, influenced by the CNR1 gene, is significantly higher in overweight and obese patients with PCOS and metabolic dysfunction[37]. The *CNR1 rs12720071* variant has been associated with a threefold increased risk of PCOS (OR: 3.01), while the *CNR1 rs806368* variant correlates with an eightfold higher PCOS risk (OR: 8.81). Additionally, the *CNR1 rs12720071* variant has also been linked to a 3.6-fold increased risk of hyperandrogenism[38]. *CNR1* activation induces abdominal obesity, dyslipidemia, and insulin resistance in MASLD patients, whereas its blockade reduces transaminase levels and hepatic inflammation markers in women with PCOS[39].

DIAGNOSIS

PCOS should be suspected in women with irregular menstruation, acne, alopecia, and hirsutism[40]. Diagnosis is confirmed using Rotterdam criteria, requiring at least two of the following three criteria: oligo-anovulation, hyperandrogenism (clinical or biochemical), and polycystic ovarian morphology on ultrasound[41].

Hyperandrogenism is confirmed through the presence of hirsutism and biochemical assessment of circulating androgen levels, including free and total testosterone, as well as dehydroepiandrosterone sulfate. Ovulatory dysfunction is suspected in cases of polymenorrhea or oligomenorrhea and confirmed by measuring progesterone levels on days 22-24 of the menstrual cycle. Additionally, anti-Müllerian hormone (AMH) may be measured to assess increased antral follicle count. Transvaginal ultrasound helps identify polycystic ovarian morphology[42]. Following diagnosis confirmation, an oral glucose tolerance test and serum glucose measurements are recommended to evaluate insulin resistance[43]. Liver enzyme tests should also be performed to detect NAFLD-related abnormalities[6].

NAFLD diagnosis is based on histological, imaging, or serological evidence of hepatic steatosis, along with at least one of the following criteria: overweight/obesity, presence of type 2 diabetes, or at least two metabolic risk abnormalities[44]. Diagnostic evaluation includes liver function tests and hepatic imaging studies[45].

Liver biopsy remains the gold standard for NAFLD diagnosis and staging. However, due to its invasive nature, associated morbidity, and sampling error risk, noninvasive methods are preferred[46]. Ultrasound is the first-line imaging modality, though its sensitivity is limited (approximately 80% in cases with >30% fat infiltration) and performance decreases in subjects with BMI >40 or patients with mild steatosis (65% sensitivity)[47]. Transient elastography provides noninvasive measurement of liver stiffness and has been used to identify fibrosis. Similarly, magnetic resonance elastography is useful for assessing both hepatic steatosis and fibrosis[48].

We recommend the following algorithm for evaluating PCOS patients with suspected fatty liver disease (**Figure 2**).

MANAGEMENT STRATEGIES

The primary recommendations for managing PCOS and metabolic dysfunction-associated steatotic liver disease (MASLD) include lifestyle modifications, dietary adjustments, weight loss, and exercise—either alone or in combination with pharmacotherapy[49].

For women with PCOS, a 5%–10% weight loss over six months—particularly targeting abdominal fat—has been shown to: improve insulin sensitivity, restore ovulation, reduce testosterone levels, enhance conception rates, and lower miscarriage risk[50].

In NAFLD patients, a 3%–5% body weight loss correlates with improved hepatic steatosis, though a 10% reduction may be needed to ameliorate necroinflammation and fibrosis in some cases[51]. Notably, 90% of patients losing >10% of their weight achieved resolution of steatohepatitis, while 45% showed fibrosis regression[52].

The Mediterranean diet—characterized by reduced carbohydrate intake (especially sugars and refined carbs) and high monounsaturated fatty acid consumption—has demonstrated efficacy in reducing steatosis in fatty liver patients, even without significant weight loss[53]. However, evidence for dietary superiority in PCOS remains limited, with caloric restriction being the only universal recommendation[50].

Currently, no drugs are specifically approved for MASLD. Available pharmacologic options for PCOS aim to: reduce hepatic fat accumulation, improve insulin resistance, mitigate liver injury, and regulate ovulation and menstruation[49].

Pharmacological Therapy

- *Metformin*: This biguanide improves insulin sensitivity and helps control blood glucose by inhibiting gluconeogenesis. It activates AMP-activated protein kinase (AMPK) through a lysosomal pathway, suppresses gluconeogenic gene expression, and stimulates glucagon-like peptide-1 (GLP-1) release, thereby enhancing insulin secretion and GLUT-4 translocation in skeletal muscle[54,55]. While it has not proven effective for hepa-

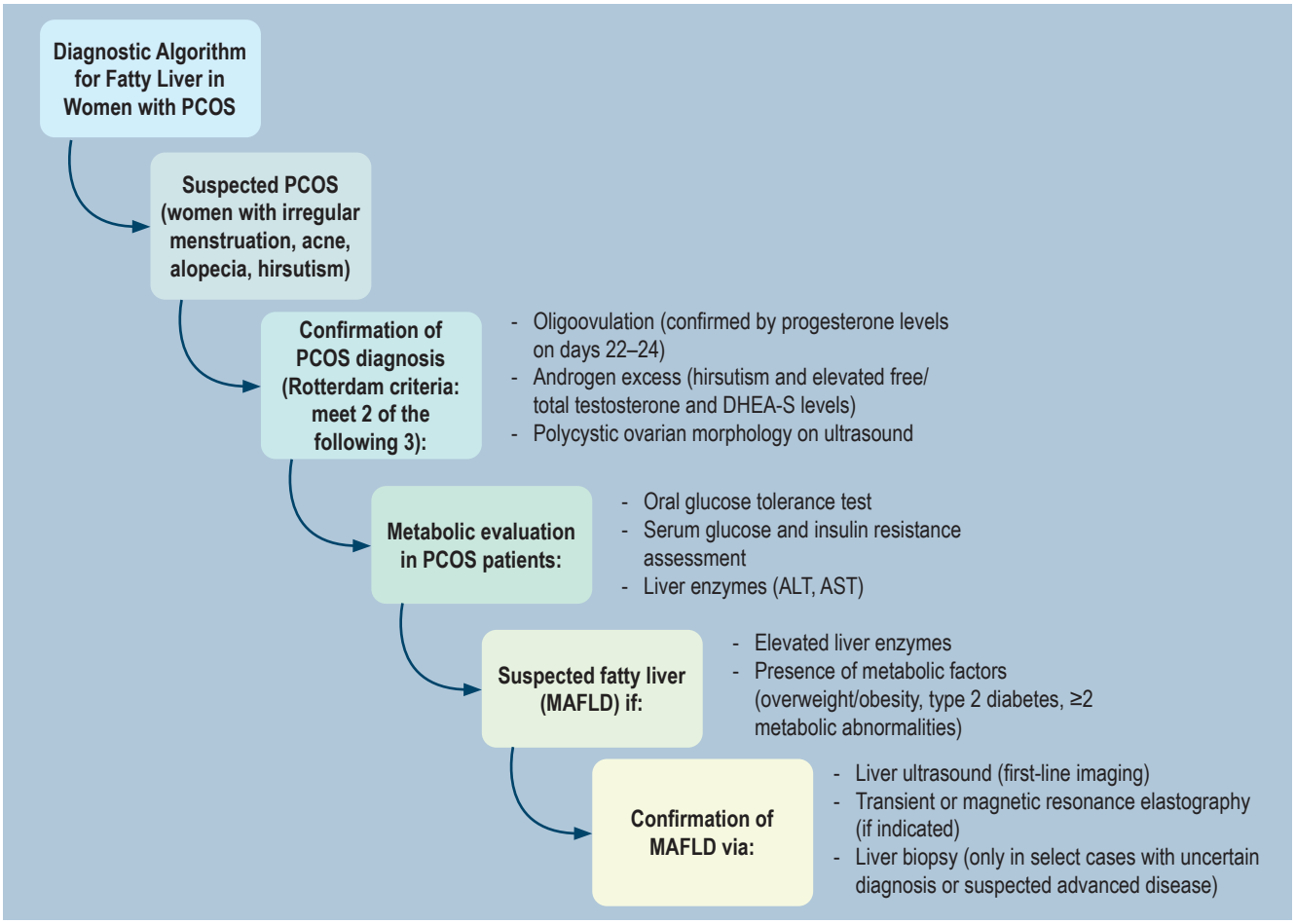

Figure 2. Diagnostic algorithm for nonalcoholic fatty liver disease in women with polycystic ovary syndrome. ALT: alanine aminotransferase; AST: aspartate aminotransferase; DHEA-S: dehydroepiandrosterone sulfate; MAFLD: metabolic dysfunction-associated fatty liver disease; PCOS: polycystic ovary syndrome. Image property of the authors.

tic steatosis—showing no superiority in histological or biochemical parameters for NAFLD patients[56]—it has demonstrated benefits in women with PCOS, including improved menstrual and ovulatory function, as well as potential advantages for insulin resistance and glucose control. Its use may be considered for women with metabolic abnormalities or those who fail to achieve therapeutic goals through lifestyle changes alone[50].

- *GLP-1 Receptor Agonists*: These agents may benefit both MASLD and PCOS, particularly in patients with insulin resistance, type 2 diabetes (T2DM), and dyslipidemia. They improve glycemic control, stimulate insulin secretion, protect pancreatic β-cells, and promote weight loss[57]. In MASH, they reduce steatosis, alleviate inflammation, and slow fibrosis progression[58]. Liraglutida has been associated with reduced liver enzyme levels[59], while semaglutida has shown decreases in alanine aminotransferase (ALT) and inflammatory markers[60]. For PCOS, these drugs may aid in weight and testosterone reduction[61]. One liraglutide study reported a 39% decrease in hepatic fat content and 5.6% body weight loss in PCOS patients after 26 weeks of treatment[62].
- *SGLT2 Inhibitors*: By inhibiting renal glucose reabsorption in the proximal tubule, these drugs lower serum glucose and promote urinary excretion of glucose and sodium. They also contribute to weight loss, improve diet-induced hepatic steatosis, and prevent MASH progression while reducing cardiovascular risk and improving blood pressure[63]. Though not specifically indicated for PCOS or MASLD, they show promise for these conditions. In a clinical trial with empagliflozin, significant reductions in anthropometric parameters (waist/hip circumference, BMI, lean mass) were observed in

women with PCOS, though hormonal and metabolic variables remained unchanged[64]. Caution is warranted for adverse effects, including urinary tract infection risk and euglycemic ketoacidosis in diabetic patients[65].

- *Vitamin E*: As an antioxidant, it may reduce inflammation and oxidative stress. While it has been shown to decrease steatosis, it lacks significant effects on liver fibrosis[48]. Its use may be considered for MASH in non-diabetic patients, but evidence is insufficient for T2DM or advanced fibrosis cases. The stroke risk associated with long-term use should be evaluated[66].
- *Hormonal Therapy for PCOS*: Combined oral contraceptives are recommended to regulate menstrual cycles, reduce hirsutism, and improve acne[67]. For contraindicated or intolerant patients, antiandrogens may be used[40]. Aromatase inhibitors (e.g., letrozole, clomiphene) are first-line for ovulation induction[68]. Infertility treatment-resistant cases may warrant laparoscopic ovarian surgery as second-line therapy, with *in vitro* fertilization as a last option[69,70].

CONCLUSIONS

A clear association exists between metabolic dysfunction-associated steatotic liver disease (MASLD) and PCOS. We therefore recommend that all women with PCOS undergo liver dysfunction screening via transaminase measurement and imaging—ultrasound as first-line, with elastography if fibrosis is suspected—for MASLD diagnosis.

Timely identification and treatment of this association enable a comprehensive approach centered on weight reduction, dietary modification, and regular exercise. Currently, no approved therapy specifically targets both conditions, underscoring the need for further research to develop future therapeutic strategies.

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