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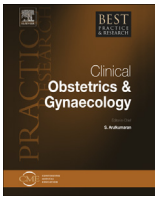

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Hepatic manifestations of women with polycystic ovary syndrome

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Women with polycystic ovary syndrome (PCOS) have a higher prevalence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) than the general population. The link between NAFLD/NASH and PCOS is not just a coincidence. Indeed, both of these disorders comprise common risk factors, including central obesity, insulin resistance, chronic low-grade inflammation, and hyperandrogenemia. The characteristics of hyperandrogenemia in women with PCOS include elevated total and free testosterone levels and low sex hormone-binding globulin levels and are reported to be associated with NAFLD and elevated liver enzymes; however, not all elevated androgen levels in women with PCOS have the same adverse effects on the liver. With the exception of weight loss and encouraging exercise in obese women, few evidence-based effective treatments target NAFLD/NASH in women with PCOS. Selective antiandrogens and insulin sensitizers might be beneficial in treating NAFLD/NASH in women with PCOS, but further elucidation is needed.

Introduction

The liver is a unique organ that has regulatory function for detoxification and metabolism. Consequently, it is a target for multiple metabolic and endocrine disorders, including hypertension, type 2 diabetes, obesity, hyperlipidemia, hypothyroidism, hyperthyroidism, adrenal dysfunction,

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autoimmune disease, excess alcohol or heavy metal consumption, substance and/or drug abuse, and polycystic ovary syndrome (PCOS) [1,2].

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disorder in Western industrialized countries (affecting 20–40% of the general population) and with a growing prevalence in Asian countries (12–29% in the population subgroups according to different age, ethnicity, gender, and location) [2,3]. According to the longitudinal studies conducted in east Asia, the prevalence of NAFLD has almost doubled in the most recent 12-year period [4]. There is strong evidence that the presence of NAFLD increases in parallel with the prevalence of obesity, type 2 diabetes, and metabolic syndrome [5–8]. NAFLD has become an emerging problem in the Asia-Pacific region and also an endemic disorder worldwide [3,5]. NAFLD includes a spectrum of hepatic manifestations, ranging from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), according to the severity. The characteristic features of NASH include hepatocellular ballooning, mixed acute and chronic lobular inflammation, and perisinusoidal fibrosis, which is indistinguishable from alcoholic steatohepatitis, excluding a history of alcohol consumption [9]. The general impression is that most individuals with NAFLD are unlikely to develop significant hepatic decompression. Although rare, the natural history of NASH can progress to more progressive complications (cirrhosis and hepatocellular carcinoma) [2,9,10]. NAFLD can also progress to severe complications in not only Western countries [2,10,11] but also a region in Japan with a low prevalence of obesity [12]. A cohort study conducted in a Japanese population reported 36% with advanced hepatic fibrosis, 20% with a 5-year cumulative incidence of hepatocellular carcinoma, and a 2.4% mortality rate due to liver-related complications, such as variceal bleeding, ascites and hepatic encephalopathy among patients diagnosed with NAFLD [12]. The elevated liver enzymes have been proposed as a biomarker that correlates with the occurrence of diabetes and cardiovascular disease and an increased risk of mortality from liver disease after a long-term follow-up [13,14]. Because NAFLD is also common in children and adolescents, clarifying the potential risk factors in a young population might be helpful in an effort to prevent liver damage progression at an early age [15,16].

PCOS is one of the most common endocrinopathies among women of early reproductive age, and it is characterized by chronic anovulation (oligomenorrhea or amenorrhea), clinical and/or biochemical hyperandrogenism, and the presence of polycystic ovaries [17]. The phenotypic characteristics of women with PCOS, including hyperandrogenism, polycystic ovaries, and anovulation, are apparent at a young age and may disappear with aging [18–20]; however, the metabolic disturbances persist and deteriorate with aging [21–23]. Therefore, further investigation of the potential metabolic dysfunction with early intervention in young women might help prevent disease. Women with PCOS are well known to have a higher prevalence of infertility, insulin resistance, obesity, dyslipidemia [24,25], hypertension [26], and disturbed metabolic profile that may lead to subsequent cardiometabolic diseases [27] than women without PCOS. Recently, there has been growing evidence demonstrating a strong association among PCOS, NAFLD, and NASH [28–30]. Most of the endocrine and metabolic characteristics of women with PCOS, including elevated androgen levels, insulin resistance, dyslipidemia, and elevated low-grade inflammation levels, are thought to contribute to the presence and progression of NAFLD [1,2,31–33]. Women with PCOS have been reported to have a higher prevalence of NAFLD and NASH diagnosed by liver biopsy [31], magnetic resonance spectroscopy [34], computed tomography [16], and abdominal ultrasonography [28]. In addition, common treatments of women with PCOS include oral contraceptives, antiandrogens, and insulin sensitizers, which may have diverse effects on liver function [1,35]. In this review, we discuss all the hepatic manifestations that might be related to the phenotypic characteristics and treatments of women with PCOS (Table 1 and Fig. 1).

Obesity and metabolic syndrome in relation to NAFLD and PCOS

The link between metabolic syndrome and PCOS has been greatly emphasized because insulin resistance and visceral obesity are characteristic features of women with PCOS [36,37]. The prevalence of metabolic syndrome in women with PCOS is 40–50%, which is approximately seven times the female population of similar age in the US [38]; however, even in regions in which metabolic syndrome is less common than the USA, such as Italy [37] and Taiwan [25], metabolic syndrome is still four and two times more common than similar-aged young women, respectively. In the Multi-ethnic Study of Atherosclerosis (MESA), more patients with NAFLD have metabolic syndrome than the NAFLD-free

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