

## Nonalcoholic fatty liver disease and polycystic ovary syndrome

Stergios A. Polyzos,\* Dimitrios G. Goulis,\*\* Jannis Kountouras\*

\* Second Medical Clinic, Aristotle University of Thessaloniki, Ippokration Hospital, Thessaloniki, Greece.

\*\* Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Papageorgiou Hospital, Thessaloniki, Greece.

### Article commented:

Targher G, Rossini M, Lonardo A. Evidence that non-alcoholic fatty liver disease and polycystic ovary syndrome are associated by necessity rather than chance: a novel hepatoovarian axis? *Endocrine* 2015. Doi:10.1007/s12020-015-0640-8.

### Comment

Targher, *et al.* reviewed the clinical and biological evidence supporting an association between nonalcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS).<sup>1</sup> The topic is of great interest, first, because of the high prevalence of both diseases. NAFLD has a prevalence of 6-45% depending on the population and the method of diagnosis.<sup>2</sup> PCOS is the most common endocrine disorder in the women of reproductive age, with a prevalence up to 18% by using the ESHRE/ASRM criteria.<sup>3</sup> Second, NAFLD and PCOS share common pathogenetic mechanisms, such as insulin resistance (IR) that seems to play a central role in both conditions.<sup>4,5</sup> Last but not least, both PCOS and NAFLD seem to have profound medical implications, including cardiovascular morbidity and mortality.<sup>6,7</sup>

Targher, *et al.* first summarized epidemiologic evidence linking NAFLD to PCOS. They included 17 cross-sectional and case-control studies, in which NAFLD was evaluated in PCOS women (15 studies; one of the earliest published in *Annals of Hepatology*<sup>8</sup>), or, vice versa, PCOS was evaluated in women with NAFLD (two studies). All but two studies reported a higher prevalence of NAFLD in PCOS

women (35-70%) compared with the control groups (20-30%).<sup>1</sup> Conversely, both studies evaluating PCOS in NAFLD women showed a high prevalence of PCOS (50-70%).<sup>9,10</sup>

Subsequently, Targher, *et al.* proposed some plausible pathogenetic mechanisms linking NAFLD to PCOS, though not fully elucidated yet.<sup>1</sup> Although this part becomes to an extent speculative due to the limited existing evidence, at the same time it provides strong stimuli for further research. Obesity, IR (both hepatic and systemic) and subsequent hyperinsulinemia are proposed to be centrally involved, affecting both lipid and glucose metabolism, and leading to:

- Hepatic steatosis and later progression to nonalcoholic steatohepatitis (NASH).
- Chronic anovulation and hyperandrogenemia, typical manifestations of PCOS.
- A mild but chronic inflammation of adipose tissue, which alters the profile of secreted adipokines and cytokines.

As a consequence, lipid profile becomes atherogenic, coagulant factors and oxidative stress are increased, which all might contribute to increased cardiovascular morbidity later in life; evidence-based interventions and recommendations for screening tests are also needed to address cardiovascular disease risk in adolescents and young women with PCOS.

A limitation of the current relative literature is the scarce data on liver histology; although the diagnosis of PCOS is based on relatively simple criteria,<sup>3</sup> the severity of NAFLD needs histological confirmation, which remains the diagnostic gold standard. Among all the studies evaluating NAFLD in PCOS populations, only six PCOS women had been subjected to liver biopsy in a single, retrospective study.<sup>11</sup> Liver biopsy was also performed in subgroups of both studies evaluating PCOS in NAFLD populations,<sup>9,10</sup> but the absolute numbers of patients

Correspondence and reprint request: Stergios A. Polyzos, MD, MSc, PhD. 13 Simou Lianidi, 551 34 Thessaloniki, Greece. Tel./Fax: +302310424710. E-mail: stergios@endo.gr

Manuscript received: September 03, 2015.  
Manuscript accepted: September 03, 2015.

were low ( $n = 7^9$  and  $n = 50^{10}$ ). Since the liver biopsy in young women with PCOS meets obvious ethical consideration, studies with alternative methods of NAFLD diagnosis are of importance. Ultrasonography, used in the majority of studies, has limited sensitivity, especially in low steatosis grade and more obese individuals, who are most of NAFLD and PCOS patients.<sup>12</sup> Magnetic resonance techniques are more sensitive to detect steatosis, but cannot differentiate simple steatosis from NASH.<sup>12</sup> An appealing alternative could be the use of noninvasive indices for steatosis, NASH and fibrosis, as reviewed elsewhere.<sup>13</sup>

In this regard, we previously published a case-control study with 314 PCOS women and 78 controls,<sup>14</sup> aiming to evaluate noninvasive indices of hepatic steatosis and fibrosis between groups. Our series was the first to report noninvasive indices of NAFLD in PCOS women and included the second larger population of PCOS women evaluating for NAFLD, after Qu, *et al.* study, in which the diagnosis of NAFLD was based on ultrasonography.<sup>15</sup> Specifically, we compared three noninvasive indices for hepatic steatosis [NAFLD liver fat score, lipid accumulation product (LAP), hepatic steatosis index (HIS)] and four for fibrosis [FIB-4, aspartate aminotransferase (AST)-to-Platelet Ratio Index (APRI), body mass index (BMI)-Age-Alanine aminotransferase (ALT)-Triglycerides (BAAT), BMI AST/ALT Ratio Diabetes (BARD)] between PCOS and control groups. All steatosis indices were higher in PCOS compared with the control group. FIB-4 and BAAT were higher in PCOS group, whereas APRI and BARD were not. Within PCOS group, all steatosis indices were higher in women with than without metabolic syndrome (MetS). However, among fibrosis indices, only BAAT was higher in PCOS women with MetS.<sup>14</sup> The results remained essentially unchanged when adjusted for age. Moreover, all indices of hepatic steatosis were positively correlated with testosterone and free androgen index, whereas inversely with sex hormone-binding globulin (SHBG). Although correlations cannot prove a causative association, we could hypothesize that hyperandrogenemia and low SHBG, usually observed in PCOS women, but also in NAFLD,<sup>16</sup> might play a role in the pathogenesis of hepatic steatosis. The observed discordance in fibrosis indices might be partly attributed to the low rates of hepatic fibrosis expected in this cohort of young premenopausal women (mean age 26.1 years) with low rate of type 2 diabetes (1.9%) and low triglycerides levels (mean 98 mg/dL). Based on fibrosis indices, only a minori-

ty of PCOS women is expected to have advanced fibrosis in the third decade of life; however, the higher rates of hepatic steatosis, together with higher IR and obesity indices in women with PCOS than controls, which were also observed in our study, might render women with PCOS at higher risk for NASH, or even NASH-related cirrhosis and hepatocellular carcinoma, later in their life. However, prospective cohort studies are required to elucidate this aspect (PCOS *vs.* controls on a longitudinal basis). Prospective cohort studies are also needed (PCOS women with *vs.* without NAFLD) to investigate whether PCOS women with NAFLD are at a greater risk of cardiovascular morbidity and mortality, especially after menopausal transition, which is of high clinical implication.

Furthermore, an important question is whether the I148M polymorphism of the patatin-like phospholipase domain-containing protein (*PNPLA*) gene, the strongest to-date genetic factor in the pathogenesis of NAFLD,<sup>17</sup> is also associated with PCOS; this needs studies of simpler design (case-control or cross-sectional), albeit of large samples. A positive association between I148M polymorphism and PCOS will definitely provide strong genetic evidence for the interplay between NAFLD and PCOS.

Until the consequences of their long-term co-existence, if any, are established, the physicians should be aware that PCOS women are at higher risk of NAFLD, as the review of Targher, *et al.* summarized,<sup>1</sup> and they need to be screened appropriately, especially if other predisposing factors for NAFLD, such as obesity, IR, dyslipidemia and diabetes, co-exist in PCOS women.

## ABBREVIATIONS

- **ALT:** alanine aminotransferase.
- **APRI:** AST-to-Platelet Ratio Index.
- **AST:** aspartate aminotransferase.
- **BAAT:** BMI-Age-ALT-Triglycerides.
- **BARD:** BMI AST/ALT Ratio Diabetes.
- **BMI:** body mass index.
- **HIS:** hepatic steatosis index.
- **IR:** insulin resistance.
- **LAP:** lipid accumulation product.
- **MetS:** metabolic syndrome.
- **NAFLD:** nonalcoholic fatty liver disease.
- **NASH:** nonalcoholic steatohepatitis.
- **PCOS:** polycystic ovary syndrome.
- **PNPLA:** patatin-like phospholipase domain-containing protein.
- **SHBG:** sex hormone-binding globulin.

## GRANTS OF FINANCIAL SUPPORT

No source of support or funding for this study.

## DISCLOSURE STATEMENT

The authors declare that they have no conflict of interest.

## REFERENCES

1. Targher G, Rossini M, Lonardo A. Evidence that non-alcoholic fatty liver disease and polycystic ovary syndrome are associated by necessity rather than chance: a novel hepato-ovarian axis? *Endocrine* 2015; 10:1007/s12020-015-0640-8.
2. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; 34: 274-85.
3. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004; 19: 41-7.
4. Polyzos SA, Kountouras J, Zavos C. Nonalcoholic fatty liver disease: the pathogenetic roles of insulin resistance and adipocytokines. *Curr Mol Med* 2009; 9: 299-314.
5. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr Rev* 2012; 33: 981-1030.
6. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA* 2015; 313: 2263-73.
7. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. *J Clin Endocrinol Metab* 2015; 100: 911-9.
8. Gutierrez-Groble Y, Ponciano-Rodriguez G, Ramos MH, Uribe M, Mendez-Sanchez N. Prevalence of non alcoholic fatty liver disease in premenopausal, posmenopausal and polycystic ovary syndrome women. The role of estrogens. *Ann Hepatol* 2010; 9: 402-9.
9. Brzozowska MM, Ostapowicz G, Weltman MD. An association between non-alcoholic fatty liver disease and polycystic ovarian syndrome. *J Gastroenterol Hepatol* 2009; 24: 243-7.
10. Hossain N, Stepanova M, Afendy A, Nader F, Younossi Y, Rafiq N, Goodman Z, et al. Non-alcoholic steatohepatitis (NASH) in patients with polycystic ovarian syndrome (PCOS). *Scand J Gastroenterol* 2011; 46: 479-84.
11. Setji TL, Holland ND, Sanders LL, Pereira KC, Diehl AM, Brown AJ. Nonalcoholic steatohepatitis and nonalcoholic Fatty liver disease in young women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2006; 91: 1741-7.
12. Polyzos SA, Mantzoros CS. Necessity for timely noninvasive diagnosis of nonalcoholic fatty liver disease. *Metabolism* 2014; 63: 161-7.
13. Machado MV, Cortez-Pinto H. Non-invasive diagnosis of non-alcoholic fatty liver disease. A critical appraisal. *J Hepatol* 2013; 58: 1007-19.
14. Polyzos SA, Goulis DG, Kountouras J, Mintziori G, Chatzis P, Papadakis E, Katsikis I, et al. Non-alcoholic fatty liver disease in women with polycystic ovary syndrome: assessment of non-invasive indices predicting hepatic steatosis and fibrosis. *Hormones (Athens)* 2014; 13: 519-31.
15. Qu Z, Zhu Y, Jiang J, Shi Y, Chen Z. The clinical characteristics and etiological study of nonalcoholic fatty liver disease in Chinese women with PCOS. *Iran J Reprod Med* 2013; 11: 725-32.
16. Polyzos SA, Kountouras J, Tsatsoulis A, Zafeiriadou E, Katsiki E, Patsiaoura K, Zavos C, et al. Sex steroids and sex hormone-binding globulin in postmenopausal women with nonalcoholic fatty liver disease. *Hormones (Athens)* 2013; 12: 405-16.
17. Polyzos SA, Mantzoros CS. An update on the validity of irisin assays and the link between irisin and hepatic metabolism. *Metabolism* 2015; 64: 937-42.