

Association between Non Alcoholic Fatty Liver Disease and Polycystic Ovarian Syndrome: A Systematic Review

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Abstract

Nonalcoholic fatty liver disease (NAFLD), has emerged as one of the most common causes of chronic liver disease and is increasingly being attributed to cirrhosis in a large number of patients. NAFLD is characterized by accumulation of fat in hepatocytes without a significant history of alcohol consumption. Since the prevalence of NAFLD is markedly increased in obesity, type 2 diabetes mellitus and dyslipidemia, the role of insulin resistance in the pathogenesis of this disease has been studied and a strong association has been found between insulin resistance and NAFLD. It is now established that NAFLD is the hepatic component of the metabolic syndrome. On the other hand, polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in premenopausal women. Insulin resistance which is the hallmark of metabolic syndrome, has also been documented in about 50% to 80% of women with PCOS. Over the past few years evidence has accumulated showing an association between nonalcoholic fatty liver disease and polycystic ovary syndrome. The pathophysiologic link and the clinical significance of this relationship are still not very well understood, however, there is sufficient data to support the same. We present here a systematic review of studies which have evaluated this association and have underlined the clinical implications of this co-existence.

Keywords: Nonalcoholic fatty liver disease NAFLD; Polycystic ovary syndrome (PCOS); Hepatocytes; Dyslipidemia; Non-alcoholic steatohepatitis (NASH)

Introduction

Nonalcoholic fatty liver disease (NAFLD), has emerged as one of the most common causes of chronic liver disease in western countries, and is increasingly being attributed to Cirrhosis in a large number of patients in the

developing countries like India. A large subset of patients previously assigned to have cryptogenic cirrhosis is now assumed to be due to NAFLD. NAFLD is characterized by accumulation of fat in hepatocytes without a significant history of alcohol consumption [1]. The spectrum of this disease varies from simple steatosis, which can progress

to non-alcoholic steatohepatitis (NASH) and ultimately can culminate into liver cirrhosis, and even hepatocellular carcinoma [2]. Since the prevalence of NAFLD is markedly increased in obesity, type 2 diabetes mellitus and dyslipidemia, the role of insulin resistance in the pathogenesis of this disease has been studied and a strong association has been found between insulin resistance and NAFLD [3]. It is now established that NAFLD is the hepatic component of metabolic syndrome [4].

On the other hand, Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in premenopausal women, which affects nearly 5%-18% of this population [5]. Insulin resistance which is the hallmark of metabolic syndrome has been documented in about 50% to 80% of women with PCOS [6]. In PCOS, Insulin resistance is an active contributor to its pathogenesis rather than being a simple biomarker thereof. It is a known fact that Insulin receptors are abundant in ovaries and dysregulation of insulin signalling in theca cells increases the production of androgens and contributes in the pathogenesis of PCOS.

Over the past few years evidence has accumulated showing an association between nonalcoholic fatty liver disease and polycystic ovary syndrome. The pathophysiologic link and the clinical significance of this relationship are still not very well understood, however, there is sufficient data to support the same and the management principles may be common when it comes to a concerted treatment of both the diseases if they co-exist. In the current review, we have tried to discuss the studies which have shown this relationship and the potential treatment options which can be made available to the patient in concert with each other, keeping the common pathophysiologic mechanisms of Insulin Resistance in mind.

Insulin Resistance: The Common Linage

By using proton magnetic resonance spectroscopy (1H-MRS), which is a method to accurately measure hepatic triglyceride content, it was shown that the prevalence of NAFLD is higher in Obesity [7] and in diabetic patients [8]. This observation led to the opinion that insulin resistance and hyperinsulinemia may have a role in the pathophysiology of NAFLD. Insulin resistance was later evaluated in these patients using the homeostasis model popularly known as HOMA-IR [9]. These findings were further confirmed by studies involving non-obese, non-diabetic patients who had NAFLD. In this evaluation,

euglycemic insulin clamp technique was used, which is the gold standard method for the assessment of insulin sensitivity [10]. These studies have shown that insulin resistance is the primary mechanism behind the pathogenesis of NAFLD. Proinflammatory cytokines like interleukin-6 and tumor necrosis factor- α are also elevated in these patients, whereas leptin resistance and decreased levels of adiponectin are also documented in these patients underlining their role as mediators of insulin resistance [11].

On the other hand, Burghen *et al.* were the first to report the presence of hyperinsulinemia in obese PCOS patients [12]. Further analyses using the euglycemic insulin clamp technique, as discussed with NAFLD, demonstrated peripheral insulin resistance as an accompaniment of PCOS [13]. It was further shown that patients with PCOS have an increased prevalence of impaired glucose tolerance as well as diabetes mellitus, abdominal adiposity and dyslipidemia [14,15]. Insulin resistance in PCOS has been postulated to be due to a post-receptor defect in insulin signal transduction pathway which otherwise is important for glucose and lipid metabolism [15]. As a result of selective insulin resistance, tissues other than skeletal muscles which express insulin receptors like the ovaries are also sensitive to insulin and are exposed to increased levels of circulating insulin. This hyperinsulinemia decreases the production of sex-hormone binding globulin (SHBG) from the liver. SHBG is the main protein which binds testosterone and prolongs its metabolic clearance. Thus there is increased testosterone bioavailability in these patients. Therefore, insulin resistance, which is a prominent finding in PCOS patients, is an important factor that contributes to ovarian androgen excess which is the hallmark of PCOS. Thus we see that insulin resistance is a common link between NAFLD and PCOS. It accounts for most of the concerns with respect to both these conditions and is a common pathophysiologic mechanism behind both these disorders.

Clinical Data and Prevalence of NAFLD in Patients of PCOS

The co-existence of NAFLD with PCOS was first noted in a patient in 2005 by Brown *et al* [16]. At that time, it was opined that NAFLD might be a common accompaniment in certain patients of PCOS considering the fact that insulin resistance was a known feature in both NAFLD and PCOS and both these disorders had already been linked with metabolic syndrome. Therefore

a search was later started to look for the frequency of NAFLD in PCOS patients and the importance of screening PCOS patients with liver function tests was underlined. Various clinical studies have demonstrated an association of elevated ALT levels in patients of PCOS, and the degree of insulin resistance has been assessed in many studies using indices like quantitative insulin sensitivity index (QUICKI) and HOMA-IR and by the euglycemic insulin clamp technique, as discussed earlier [17]. There is sufficient data to support that obesity and insulin resistance are central in the etio-pathogenesis of both NAFLD and PCOS. In addition to that, there is sufficient data to support the fact that lifestyle modifications such as diet, weight loss, exercise and metformin have benefits in both PCOS as well as NAFLD [16].

It is a known fact that PCOS is a hyperandrogenic syndrome, and therefore if it can be demonstrated that androgens play any role in the development of NAFLD it may also add to the common linkage as discussed. Hence, studies were carried out that demonstrated an association of NAFLD with androgens. In one study, it was shown that ALT levels were elevated in patients having of hirsutism which is one of the main clinical manifestations of hyperandrogenism [18]. In another study, it was seen that a positive correlation existed between ALT levels and total testosterone levels and free-androgen index (FAI) values in overweight/obese PCOS patients [19].

Some other studies which used imaging for the diagnosis of NAFLD in PCOS patients showed a significant association of NAFLD with hyperandrogenism. A recent study to evaluate the effects of metformin on NAFLD in PCOS patients showed that PCOS patients with NAFLD (which was detected by abdominal ultrasonography) had significantly higher FAI values compared to PCOS patients without NAFLD [20]. Another longitudinal study on obese PCOS patients and age-matched controls showed that presence of NAFLD in these patients, detected by ultrasonography was positively correlated with FAI values and negatively correlated with SHBG levels [21]. Another study has recently shown that levels of the serum apoptotic markers like M30 [caspase 3-cleaved fragment of cytokeratin 18 (CK18)] are markedly increased in PCOS patients who also have NAFLD [22]. This finding shows that there is a strong pro-apoptotic environment in PCOS patients who have concomitant NAFLD. This study also demonstrated an altered expression of two important genes in the adipose tissue of NAFLD patients with PCOS compared to NAFLD patients without PCOS: a decrease in

LDL receptor mRNA expression, and an increase in protein ninein (NIN) mRNA expression [22].

The Genetic Link between NAFLD and PCOS

Genetic susceptibility to PCOS has previously been shown with twin records and family studies and it has been shown that there is a heritability of approximately 70%. Genome-wide association studies (GWAS) have localized susceptibility genes for PCOS. The first GWAS in PCOS was conducted in Chinese PCOS patients and susceptibility loci were identified on chromosome 2p16.3, 2p21 and 9q33.3 [23]. GWAS in NAFLD identified a missense mutation (I148M) in patatin-like phospholipase domain-containing (*PNPLA*) 3 gene (adiponutrin gene). This gene mutation was strongly associated with increased hepatic steatosis [24]. Further studies confirmed that the I148M variant of *PNPLA3* gene is a major determinant of liver fat content as well as a predisposing factor for steatohepatitis and progressive fibrosis [25].

Evaluation of Patients with NAFLD and Concomitant PCOS

Aminotransferase level stands out as the most important screening tool to evaluate the presence of NAFLD in patients presenting with PCOS. However, aminotransferase levels may be normal in a large subset of patients who have NAFLD and do not have steatohepatitis. A prospective study from Chile has shown that there is a significant difference in elevated ALT levels between PCOS patients compared to age matched healthy women [26]. In concert with this study, a Greek study has also shown a significant difference of ALT and/or AST levels between PCOS patients compared to age matched healthy women [27]. Thus existing evidence explicitly suggests a significantly higher prevalence of elevated aminotransferase levels in PCOS patients.

Other laboratory markers may also be utilized for identifying the risk for NAFLD in patients of PCOS. A recent study has demonstrated that the caspase 3-cleaved fragment of cytokeratin 18 (CK18), which is a marker for NASH was significantly elevated in PCOS patients compared to age-matched controls [28]. In yet another study the presence of hepatic steatosis was calculated by the fatty liver index (FLI), which is an algorithm based on

BMI, waist circumference, triglycerides and gamma-glutamyl transferase. Significantly higher FLI levels were detected in PCOS patients than in BMI-matched controls [29].

Imaging modalities are the mainstay for the detection of NAFLD and these include ultrasonography, computerised tomography (CT), magnetic resonance imaging (MRI) and Magnetic Resonance Spectroscopy (MRS). However most of these imaging modalities cannot assess hepatic fibrosis. Few studies have evaluated the presence of hepatic steatosis in PCOS patients using abdominal ultrasonography. In one study, hepatic steatosis was seen in 55% of PCOS patients [30]. In a recent study CT evaluation of fatty liver was carried with obese adolescent patients having PCOS. Fatty liver was determined by a ratio of liver to spleen Hounsfield attenuation units [31]. Another recent study demonstrated statistically significant hepatic steatosis in PCOS patients compared to age and BMI-matched healthy women [32].

Management of Patients Having Co-existent NAFLD and PCOS

Early detection of NAFLD in patients presenting with PCOS is important. Early intervention at the stage of simple steatosis or steatohepatitis may decrease the risk of progression to cirrhosis. Therefore all PCOS patients should get evaluation of liver functions by assessment of aminotransferase levels and ultrasonography. Lifestyle modifications have been shown to exert beneficial effects in patients with simple steatosis or NASH. So dietary modifications, weight loss and exercise should be explained to patients of PCOS having NAFLD/ NASH. Diet, weight loss and exercise are central in the treatment of such patients and may be combined with insulin-sensitizers like metformin or pioglitazone, hepatoprotective agents like antioxidants and anti-inflammatory agents. Few recent studies have evaluated the effects of omega-3 fatty acid supplementation on liver fat content in obese PCOS patients. A beneficial effect was found with omega-3 fatty acids supplementation and this was attributed to modification of intrahepatic lipid metabolism by activation of peroxisome proliferator-activated receptor- α (PPAR- α) [33].

The effect of metformin on NAFLD in obese PCOS patients has also been assessed in prospective studies [34]. In most of these studies a significant reduction of

liver enzyme levels was shown in such patients [34]. In addition to this there was a reduction of insulin resistance in these patients also, which was assessed by HOMA-IR and FAI values. Also, there was an increase in SHBG and HDL levels [20]. Several studies have also propounded that in addition to beneficial effects on glucose metabolism metformin also has beneficial effects on lipid metabolism and androgen excess by increasing SHBG levels and decreasing androgen levels [35]. Thus it is being inferred that metformin might be the drug of choice for treating patients of NAFLD who also have PCOS.

Conclusion

Polycystic ovary syndrome is a disorder, involving multiple genetic, metabolic and hormonal controls that fail to interact properly and manifest as PCOS. As per the data available, the prevalence of both PCOS and NAFLD rises proportionally to the degree of insulin resistance. It has been proven now, that both NAFLD and PCOS are accompanied by metabolic syndrome and obesity. NAFLD has already been proposed to be the hepatic manifestation of metabolic syndrome, it however, seems prudent to label PCOS as the ovarian manifestation of metabolic syndrome. PCOS patients, especially if they are obese or have features of metabolic syndrome, should undergo liver evaluation by assessment of aminotransferase levels and abdominal ultrasound. Lifestyle modifications such as diet, weight loss and exercise are important initial therapeutic interventions for PCOS patients with NAFLD. Metformin may be used in a subset of these patients, although there is still no proven effective medication for NAFLD. Long-term follow up studies are needed to evaluate the implications of these two conditions concomitantly and may guide about appropriate evaluation and standard treatment for PCOS patients with NAFLD.

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