NAFLD, Diabetes, and Other Endocrine Diseases: Clinical Implications

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8.1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is a metabolic liver disease that encompasses a spectrum of progressive pathologic conditions, ranging from simple steatosis to steatohepatitis (NASH), fibrosis, and cirrhosis. NAFLD is the most common liver disease in high-income countries affecting at least 25% of the general adult population. This liver disease affects up to 70–80% of patients with type 2 diabetes mellitus (T2DM) and up to 30–40% of adults with type 1 diabetes mellitus (T1DM) [1–3].

It is well known that NAFLD and T2DM often coexist and may act synergistically to drive adverse hepatic and extrahepatic clinical outcomes [1–3]. However, the link between NAFLD and T2DM is more complex than previously thought. It is now becoming clear that there is a close, bi-directional relationship between NAFLD and T2DM, and that NAFLD may also precede and/or promote the development of incident T2DM [4].

Abnormalities in various endocrine axes have been also associated with NAFLD [5]. In addition to diabetes, NAFLD is often present in patients with other common endocrine diseases, such as polycystic ovary syndrome (PCOS) and primary hypothyroidism [6–8]. NAFLD may be also present in patients with hypogonadism, growth hormone deficiency, acromegaly, or Cushing's syndrome, but the associations between NAFLD and these less frequent endocrine diseases have not been extensively explored in large series of patients [6].

It is possible to assume that the significant associations between NAFLD and common metabolic and endocrine diseases might also shed light in the aetiological

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mechanisms underpinning the pathogenesis of NAFLD. Moreover, understanding the hormonal regulation of NAFLD might lead to advances in the pharmacological treatment of this liver disease in the near future.

This chapter focuses on the significant relationships of NAFLD with type 1 and type 2 diabetes and other two common endocrine diseases (i.e., PCOS and primary hypothyroidism), and the adverse effects of NAFLD on the risk of developing chronic vascular complications of diabetes (mainly cardiovascular disease and chronic kidney disease).

NAFLD is an increasingly prevalent and burdensome liver disease that has been often overlooked by diabetologists and endocrinologists. Therefore, the major aim of this chapter is to not only to examine the rapidly expanding body of clinical evidence that supports a strong association of NAFLD with diabetes and other common endocrine diseases but also to raise awareness within the endocrine/gastroenterology community.

8.2 Epidemiological Evidence Linking NAFLD to Polycystic Ovary Syndrome

PCOS is a complex endocrine disorder that affects a significant proportion of women of reproductive age (affecting up to nearly 10% of these women) in the Europe and worldwide [9]. PCOS is one of the leading causes of fertility problems in women, and can lead to additional health problems in later life (i.e., with increased rates of T2DM, hypertension, and cardiovascular events). Women with PCOS have hyperandrogenism (clinical, biochemical, or both), ovulatory dysfunction, and polycystic ovarian morphologic features; additionally, these women are often overweight or obese and have greater insulin resistance [9].

To date, several cross-sectional and case–control studies have assessed the relationship between PCOS and NAFLD (for review see [7]). In most of these published studies, PCOS was diagnosed using the Rotterdam criteria (i.e., the most widely used criteria for diagnosing the disease) [9], except for few studies, which used other diagnostic criteria. Over a dozen cross-sectional studies showed that the prevalence of NAFLD (mostly detected by ultrasonography) is markedly increased in young women with PCOS, independent of overweight/obesity and other metabolic syndrome features. In these studies, the prevalence of NAFLD in women with PCOS ranges from approximately 35 to 70% compared with approximately 20 to 30% in age- and body mass index (BMI)-matched control women [7].

A comprehensive meta-analysis of 17 case–control studies published through 2017 (involving a total of approximately 2700 women with PCOS and 2600 matched control women) confirmed that PCOS women had a ~2.5-fold increased rate of NAFLD (fixed-effects odds ratio 2.25, 95% CI 1.95–2.60; I^2 = 5%) compared to control women, irrespective of age and BMI [10]. In addition, PCOS women with hyperandrogenism had a significantly higher risk of having NAFLD than controls. Conversely, normo-androgenic PCOS women did not seem to have

a higher prevalence of NAFLD when compared to controls [10]. Similar results were observed in another recent meta-analysis [11]. Accordingly, in a small case–control study involving 29 obese women with PCOS and 22 healthy controls who were matched for age, BMI, and waist circumference, Jones et al. found that hyper-androgenic PCOS women had a significantly higher intrahepatic fat content on magnetic resonance spectroscopy compared to both normo-androgenic PCOS women and matched controls (mean intrahepatic fat content: 12.9% vs. 0.6% vs. 1.9%, respectively) [12]. In a case–control study of 275 young nonobese women with PCOS and 892 nonobese control women, Kim et al. found that the prevalence of ultrasound-diagnosed NAFLD was significantly greater in women with PCOS than in controls (5.5% vs. 2.8%), and that the presence of hyperandrogenemia (i.e., higher levels of free testosterone or free androgen index) was significantly associated with NAFLD even after adjustment for age, BMI, plasma lipid profile, insulin resistance, or glycemic status [13]. More recently, Kumarendran et al. performed a population-based retrospective cohort study utilizing a large UK primary care database and included more than 63,000 women with PCOS and 121,000 matched controls registered between 2000 and 2016. Notably, these authors found that rates of NAFLD were significantly increased in women with PCOS (even after adjusting for BMI and dysglycemia), and identified androgen excess as a potential additional contributing risk factor for NAFLD development in PCOS [14].

All these findings suggest that androgen excess might represent a possible causative mechanism linking PCOS to the development and progression of NAFLD (in addition to coexisting abdominal obesity and insulin resistance). However, future larger studies are needed to determine if androgen excess also drives the progression of NAFLD to liver inflammation and fibrosis, and to establish whether anti-androgen treatment may reduce the risk of NAFLD.

Notably, some small case–control studies performed at tertiary gastroenterology centers showed that PCOS is also a common pathologic condition in patients with biopsy-proven NAFLD [15–17]. Among these patients the prevalence of PCOS ranged from approximately 50% to 70%, and these women were also more likely to develop the more severe histologic forms of NAFLD (i.e., NASH with varying degrees of fibrosis on liver histology) [15–17].

Collectively, although further well-conducted studies on larger series of carefully characterized women with PCOS are needed to corroborate these findings and to better elucidate the biological mechanisms underlying the association between PCOS and NAFLD, the aforementioned studies clearly indicate that the prevalence of NAFLD is significantly higher in women with PCOS than in control women, independent of age, overweight/obesity, and other coexisting metabolic syndrome features. Furthermore, the young age of many women with PCOS and the relatively advanced stage of NASH (as revealed by liver biopsies from these patients) clearly suggest the possibility of an increased risk for long-term liver-related complications in this group of patients over the course of their lives. Therefore, we believe that the currently available literature argues for a systematic screening for NAFLD in young women with PCOS (especially in those with PCOS-related androgen excess).

8.3 Epidemiological Evidence Linking NAFLD to Primary Hypothyroidism

Overt primary hypothyroidism is an endocrine disorder affecting up to nearly 3–4% of individuals living in iodine-replete communities that is defined by insufficient levels of serum thyroid hormones. Primary hypothyroidism has multiple aetiologies and manifestations [18].

It is known that the development and progression of NAFLD usually occur in the presence of profound derangements of lipid and glucose metabolism, and dysregulation of energy homeostasis [1, 2, 5]. Thyroid hormones are critical regulators of energy homeostasis and have prominent direct effects on lipid and glucose metabolism [19].

To date, several observational studies have explored the association between primary subclinical/overt hypothyroidism and imaging-defined or biopsy-proven NAFLD [20]. However, the findings from these studies have been conflicting so far, with some studies reporting that the prevalence of primary hypothyroidism, especially subclinical hypothyroidism, was extremely common among patients with NAFLD (occurring in up to 20–25% of these patients) [21, 22], while other studies failing to find any significant association between primary hypothyroidism and risk of NAFLD [23–25]. On this background of evidence, it remains uncertain whether subclinical hypothyroidism is a risk factor for NAFLD.

Recently, we carried out a systematic review and meta-analysis of observational, cross-sectional and longitudinal studies examining the association between primary hypothyroidism and risk of NAFLD [26]. This meta-analysis involved a total of 15 observational studies using either liver biopsy or imaging techniques (mostly ultrasonography) to diagnose NAFLD with aggregate data on 44,140 individuals with nearly 15% of them who were either taking levothyroxine replacement therapy or had either subclinical or overt hypothyroidism based on thyroid function tests [26]. As shown in Fig. 8.1, meta-analysis of data from the 12 cross-sectional studies has shown that the presence of variably defined hypothyroidism was significantly associated with a 42% increased risk of imaging-defined or biopsy-proven NAFLD (n = 12 studies; random-effects odds ratio 1.42, 95% CI 1.15–1.77; I^2 = 51.2%), independently of age, sex, BMI, diabetes, or metabolic syndrome. This risk tended to increase across the different definitions used for diagnosing hypothyroidism (i.e., a self-reported history of hypothyroidism with use of levothyroxine replacement therapy > newly diagnosed overt biochemical hypothyroidism > newly diagnosed subclinical hypothyroidism), and appeared to further increase with greater histologic severity of NAFLD (Fig. 8.2). Conversely, meta-analysis of data from the three longitudinal studies has shown that subclinical hypothyroidism was not significantly associated with the risk of incident NAFLD (assessed by ultrasonography) over a median follow-up of 5 years (n = 3 studies; random-effects hazard ratio 1.29, 95% CI 0.89–1.86; I^2 = 83.9%), after adjusting for age, sex, BMI, diabetes, or other known metabolic risk factors [26]. However, on the basis of these three longitudinal studies included in the meta-analysis [23, 27, 28], it is likely that this finding could be due to the lack of adequate statistical power, and that larger

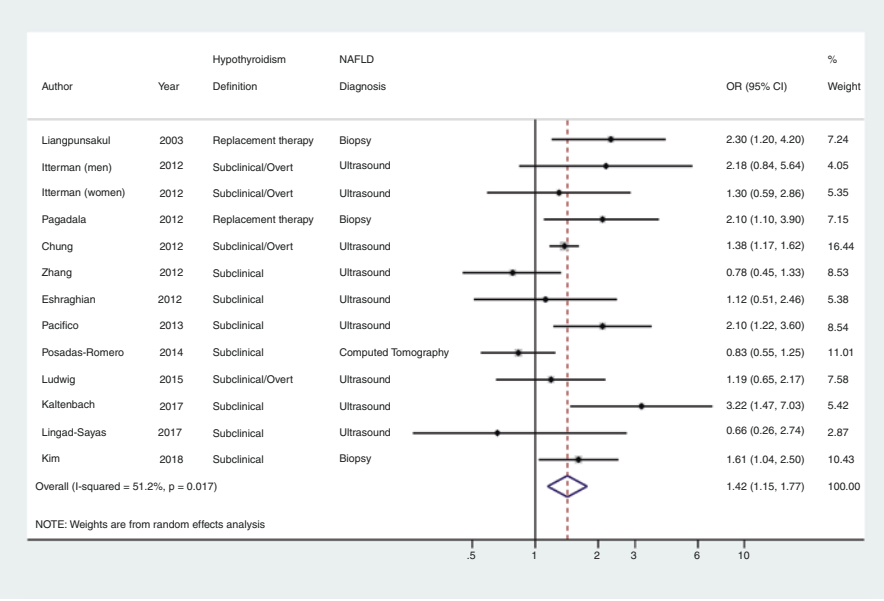

Fig. 8.1 Forest plot and pooled estimates of the effect of variably defined primary hypothyroidism (defined as either self-reported use of levothyroxine replacement therapy or abnormal concentrations of serum thyroid stimulating hormone and/or free thyroxine) on the risk of prevalent NAFLD in 12 eligible cross-sectional studies. (Reproduced with permission [26])

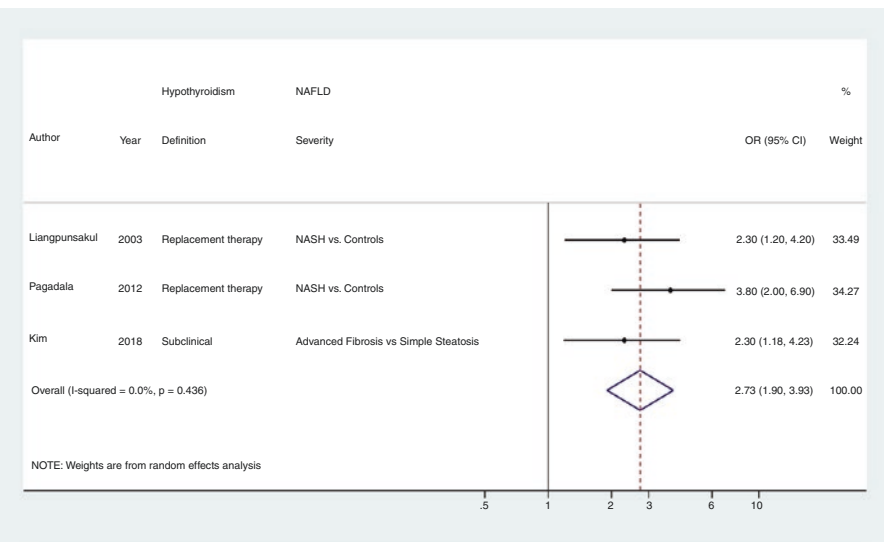

Fig. 8.2 Forest plot and pooled estimates of the effect of variably defined primary hypothyroidism on the severity of NAFLD on liver histology in three eligible cross-sectional studies. (Reproduced with permission [26])

(n > 10,000 individuals) prospective cohort studies with longer follow-up periods (≥10 years) will be needed to better elucidate this important topic. As expected, no sufficient data were available in most of the studies included in the meta-analysis to examine the effect of newly diagnosed overt hypothyroidism on the risk of developing incident NAFLD. Nevertheless, it should also be noted that Bano et al. found that both subclinical and overt hypothyroidism were independently associated with an increased 10-year risk of developing incident NAFLD with clinically significant hepatic fibrosis (assessed by Fibroscan®) in a large population-based cohort of elderly Dutch individuals [28].

Collectively, we believe that the findings of this updated meta-analysis support the view that the presence of variably defined primary hypothyroidism is significantly associated with NAFLD, and may also have clinical practice implications for the potential screening of hypothyroidism and NAFLD. Indeed, these findings suggest that patients with NAFLD should probably be screened for primary hypothyroidism (a disease necessitating hormone replacement therapy); and that NAFLD should be looked for in patients with hypothyroidism, given that these patients are at higher risk of having NASH and advanced fibrosis.

However, on the basis of the currently available literature, it should also be noted that the temporal relationship between liver and thyroid diseases is not clear, and that a causal relationship between NAFLD and primary hypothyroidism cannot be definitely established [26]. Again, it should be noted that the levels of thyroid antibodies were not consistently measured in any of the aforementioned studies (except for the study by Bano et al. [28], who measured serum thyroid peroxidase antibodies, but did not find any significant association between levels of thyroid peroxidase antibodies and risk of incident NAFLD); hence, the cause of hypothyroidism is not clear. In addition, none of the included studies examined the effects of levothyroxine replacement therapy when exploring the risk of NAFLD in patients with subclinical or overt hypothyroidism. Further large prospective studies to confirm these findings should be undertaken, and mechanistic studies to better elucidate the mechanisms underlying the association between hypothyroidism and NAFLD are also warranted.

A detailed description of the multifactorial pathogenesis involved in the hypothyroidism-induced NAFLD is beyond the scope of this chapter. To date, however, there is convincing evidence of biological plausibility that overt hypothyroidism can promote the development of NAFLD through multiple extrahepatic and intrahepatic mechanisms [19, 20]. Indeed, hypothyroidism can induce NAFLD through the systemic development of metabolic disorders, low-grade inflammation, and increased oxidative stress [19, 20]. Moreover, thyroid hormones also have direct effects on hepatic lipid and glucose metabolism [19]. In addition to the adverse effects of decreased serum thyroid hormones on hepatic glucose and lipid metabolism, it is also possible that increased serum TSH levels *per se* could promote the development of NAFLD by stimulating hepatic *de novo* lipogenesis [29]. Additionally, the intrahepatic thyroid hormone concentration and/or thyroid hormone signaling could be decreased in the livers of patients with NAFLD [20, 30]. On this background of evidence, it is possible to assume that thyroid hormone analogs or mimetics could be useful for the treatment of NAFLD [19, 20]. In a

recent phase 2b single-arm trial performed in six hospitals in Singapore, it has been reported that low-dose levothyroxine significantly decreased intrahepatic lipid content (with a relative reduction of 12% of IHLC as measured by magnetic resonance spectroscopy) in 20 euthyroid patients with type 2 diabetes and NAFLD [31]. A double-blinded, randomized, placebo-controlled phase 2 trial is also ongoing to evaluate the efficacy and safety of MGL-3196, i.e., a selective liver-directed, thyroid hormone receptor-β agonist, in patients with biopsy-proven NASH.

8.4 Epidemiological Evidence Linking NAFLD to Diabetes Mellitus

NAFLD and diabetes mellitus are common diseases that often coexist and act synergistically to drive adverse hepatic and extrahepatic clinical outcomes [1–3, 32]. The coexistence of NAFLD and diabetes increases the risk of developing both microvascular and macrovascular complications of diabetes as well as increasing the risk of developing more severe forms of NAFLD (as extensively reviewed in [32]). In addition, patients with NAFLD and diabetes have an increased risk of all-cause and cause-specific (cardiovascular, cancer, and liver) mortality compared to those without NAFLD [1, 2, 32].

8.4.1 Prevalence of NAFLD in Diabetes and Risk of Liver-Related Complications

Patients with established T2DM have a high prevalence of NAFLD. Indeed, in these patients imaging-diagnosed NAFLD ranges from approximately 45 to 75% in large hospital-based studies and from 30 to 70% in population-based studies [32]. For example, in the Valpolicella Heart Diabetes Study, involving nearly 2800 Italian outpatients with T2DM (mean age: 63 years, mean BMI: 27 kg/m^2), the prevalence of NAFLD on ultrasonography was nearly 70% [33].

In patients with T2DM, the coexistence of NAFLD is associated with poorer glycemic control, more severe hyperinsulinemia, and greater insulin resistance in the skeletal muscle, adipose tissue, and liver compared with their counterparts without NAFLD [34]. In clinical practice, it is well established that T2DM patients with NAFLD have a poorer quality of glycemic control and require a higher daily amount of insulin to get a good glycemic control than their counterparts without NAFLD [34]. It is believed that increased intrahepatic fat accumulation is an important determinant of insulin resistance in the liver and affects both the daily dosage of glucose-lowering therapy and the achieving good glycemic control in patients with T2DM [32, 34]. These considerations suggest that treatment strategies that decrease intrahepatic fat accumulation and improve insulin sensitivity might partly contribute to improved glycemic control in patients with T2DM and NAFLD.

Substantial evidence indicates that people with T2DM are also at higher risk of developing NASH, and a twofold to fourfold higher risk of developing serious

liver-related complications, such as cirrhosis, liver failure, and hepatocellular carcinoma [1, 2, 32, 35, 36]. It is also notable that, in dual biopsy studies, the development of incident T2DM was the strongest clinical predictor of faster progression to NASH, advanced fibrosis and cirrhosis [37].

A recent study that used magnetic resonance imaging to assess hepatic fat content and magnetic resonance elastography (MRE) to estimate liver stiffness has reported high rates of both hepatic steatosis (defined as MRI-PDFF ≥5%) and advanced fibrosis (defined as MRE ≥3.6 kPa) in a cohort of 100 consecutive patients with T2DM in primary care, who did not have any other aetiology of liver disease (i.e., 65% of these patients had hepatic steatosis and 7.1% had advanced fibrosis, respectively) [38]. A high prevalence of NAFLD and advanced fibrosis was also reported in a hospital cohort of 1918 Chinese adult patients with T2DM (mean age: 60.6 years, mean BMI: 26.6 kg/m^2) where hepatic fat and fibrosis were simultaneously assessed with FibroScan® (i.e., ~73% of them had CAP ≥222 dB/m and 17.7% had LSM ≥9.6 kPa, respectively) [39]; notably, as shown in Fig. 8.3, in a subset of these patients with T2DM submitted to liver biopsy (n = 94), 56% had NASH and 50% had advanced fibrosis [39]. In the NASH-Clinical Research Network cohort study enrolling nearly 1300 US adult patients with biopsy-proven NAFLD, the authors found that the prevalence of NASH and advanced fibrosis in the subgroup of those with T2DM and NAFLD (n = 346; mean age: 53 years, mean

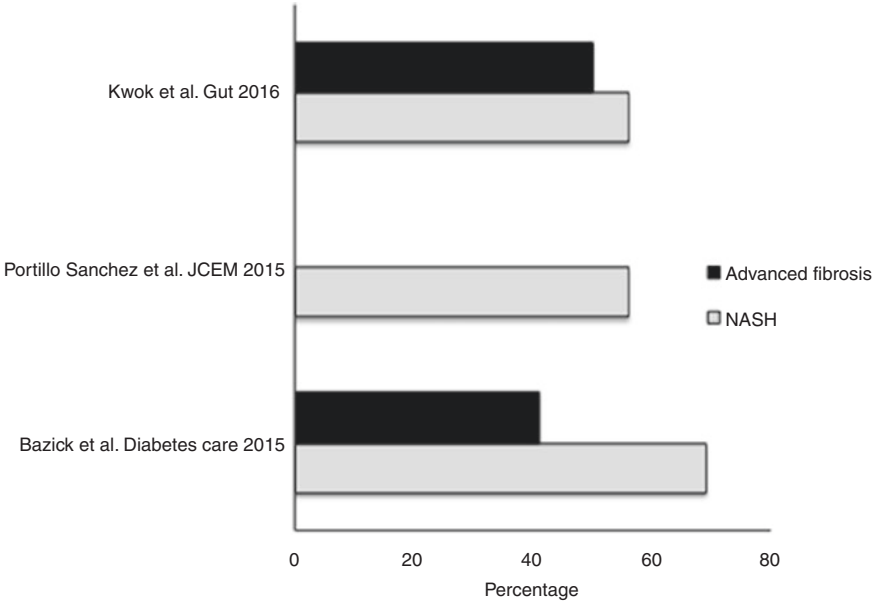

Fig. 8.3 Prevalence of NASH and advanced fibrosis on liver histology in patients with type 2 diabetes (irrespective of serum aminotransferase concentrations). (Data are derived from studies published by Kwok et al. [39], Bazick et al. [40], and Portillo-Sanchez et al. [41], respectively. Reproduced with permission [4])

BMI: 35.8 kg/m^2) was 69.2% and 41%, respectively [40]. Similarly, the prevalence of NASH was found to be as high as 56% in a small study of obese patients with T2DM and normal serum aminotransferase concentrations (n = 103; mean age: 60 years, mean BMI: 33 kg/m^2) [41]. Notably, a large administrative health database (involving almost 2.5 million people) documented that Canadian adults with newly diagnosed T2DM had an approximately twofold higher risk of developing cirrhosis, liver failure, or liver transplantation than matched individuals without diabetes over a follow-up period of 12 years [42]. Finally, prospective studies have shown that there is also a strong link among T2DM, NAFLD/NASH, and risk of hepatocellular carcinoma (HCC) [43, 44]. In fact, the coexistence of T2DM increases the risk of developing HCC (approximately from 1.5 to 4-fold) [35, 36, 43, 44]. Preclinical and observational studies also suggested that hypoglycemic agents can modulate the risk of incident HCC in patients with T2DM [45, 46]. However, the effect of each individual hypoglycemic agent should be interpreted cautiously owing to inherent cancer-modifying effect of the comparator group. Further large randomized clinical trials are needed to confirm these findings.

Worryingly, it is also well known that the coexistence of NAFLD may also adversely influence the prognosis of diabetes [32, 35]. Using the electronic administrative database of death certificates of the Veneto Region (Northern Italy), Zoppini et al. found that people with diabetes (n = 167,621 diabetic individuals aged 30–89 years) had a nearly threefold higher risk of dying of chronic liver diseases, mainly due to NAFLD [47]. In line with these findings, Adams et al. found that the coexistence of NAFLD (diagnosed by imaging or biopsy) carried an approximately twofold increased risk of all-cause mortality (mainly due to cardiovascular disease, malignancy, and liver-related complications) over a mean follow-up of 11 years in a community-based cohort of 337 residents of Olmsted County, Minnesota, with diabetes mellitus [48]. Again, a national cohort study of Scottish people aged 40–89 years documented that NAFLD was the most common liver disease in people with T2DM, and that T2DM was closely associated with an increased risk of hospital admissions or death for NAFLD [49].

All the aforementioned considerations fully support a screening for NAFLD in patients with established T2DM, and the need for close and intensive surveillance for advanced liver disease in those with NAFLD [1, 3, 32]. It is also reasonable to assume that an early diagnosis and treatment of NAFLD, if any, may have a beneficial clinical impact on survival rates of patients with T2DM.

At present, few data are available regarding the prevalence and natural history of NAFLD in patients with T1DM. However, the epidemiological impact of both NAFLD and the metabolic syndrome seems to be relevant also in adult patients with T1DM since the prevalence of the metabolic syndrome is steadily growing in these patients, being nowadays approximately of 40% [32]. Although there are conflicting results, some studies reported that NAFLD on ultrasonography is present in approximately 30–40% of adult patients with T1DM [32, 50]. In a longitudinal cohort of T1DM and T2DM patients who undergone a liver biopsy, it was demonstrated that adult patients with T1DM had a high risk of developing cirrhosis and portal hypertension, and that this risk was even comparable with that observed in

patients with T2DM, who were matched for duration of diabetes, obesity, and other comorbidities [51]. However, further studies are required to better characterize the relationship between NAFLD and T1DM.

8.4.2 NAFLD and Risk of Chronic Kidney Disease and Other Microvascular Complications

Accumulating epidemiological evidence indicates that the presence of imaging-diagnosed NAFLD is associated with an increased risk of microvascular complications of diabetes, such as chronic kidney disease (CKD), retinopathy, and distal symmetric polyneuropathy [32].

For instance, in a large cohort study involving 2103 ambulatory patients with T2DM, it has been reported that those with ultrasound-diagnosed NAFLD had remarkably higher age- and sex-adjusted prevalence rates of both non-proliferative and proliferative/laser-treated retinopathy and CKD than patients without NAFLD. Logistic regression analysis showed that NAFLD was associated with increased rates of CKD (adjusted-odds ratio 1.87; 95% CI 1.3–4.1) and proliferative/laser-treated retinopathy (adjusted-odds ratio 1.75; 95% CI 1.1–3.7), even after adjustment for multiple cardiometabolic risk factors, diabetes-related variables, and other potential confounders [52]. Other studies have clearly shown that the presence and severity of NAFLD was associated with an increased prevalence of abnormal albuminuria or decreased kidney function in patients with T2DM or pre-diabetes [32, 53]. Similarly to what reported in T2DM patients, some studies also showed that NAFLD was independently associated with a higher prevalence of both CKD and diabetic retinopathy in adult patients with T1DM [54].

To date, there is a paucity of published data regarding the risk of developing CKD in diabetic patients with NAFLD. The Valpolicella Heart Diabetes Study showed that patients with T2DM and NAFLD had a higher risk of developing incident CKD (i.e., CKD stage ≥3 with/without accompanying overt proteinuria) compared with their counterparts without NAFLD over a mean follow-up period of 6.5 years. Notably, this risk remained significant even after adjusting for a broad range of coexisting cardio-renal risk factors (including also diabetes duration, hemoglobin A1c, hypertension, baseline e-GFR, albuminuria, and current use of medications) [55].

In line with this finding, in a small follow-up cohort study involving 261 T1DM adult patients with preserved kidney function and without overt proteinuria at baseline, who were followed for a mean period of 5.2 years, the presence of ultrasound-diagnosed NAFLD was independently associated with an increased incidence of CKD (hazard ratio 2.85, 95% CI 1.6–5.1). Notably, addition of NAFLD to traditional cardio-renal risk factors significantly improved the discriminatory capability of the regression models for predicting CKD [56].

We recently performed a systematic review and meta-analysis of nine observational studies, involving 96,595 adult individuals (~34% with either imaging-diagnosed or biochemistry-based NAFLD) of predominantly Asian descent and nearly 5000 cases of incident CKD (i.e., CKD stage ≥3) over a median follow-up

of 5.2 years [57]. No studies with biopsy-proven NAFLD were available in the literature for the analysis. As shown in Fig. 8.4, patients with imaging-diagnosed NAFLD had a significantly higher long-term risk of incident CKD compared with those without NAFLD (pooled random-effects hazard ratio 1.37, 95% CI 1.20–1.53; $I^2 = 33.5\%$), even after adjustment for common cardio-renal risk factors [55]. Patients with more "severe" NAFLD (according to ultrasonographic steatosis scores or non-invasive biomarkers of liver fibrosis) were also more likely to develop incident CKD (random-effects hazard ratio 1.50, 95% CI 1.25–1.74; $I^2 = 0\%$). Interestingly, as also shown in Fig. 8.4, when the analysis was stratified by the study population, the association between NAFLD and the risk of incident CKD appeared to be stronger in studies that enrolled patients with established diabetes (random-effects hazard ratio 1.56, 95% CI 1.07–2.05; $I^2 = 0\%$) [57].

Finally, preliminary evidence also suggests that NAFLD is associated with an increased prevalence of distal symmetric polyneuropathy and cardiovascular autonomic neuropathy in patients with T1DM or T2DM [58, 59]. However, further research is needed to confirm these data.

Despite the growing evidence of biological plausibility linking NAFLD with CKD and other microvascular complications in adult patients with T1DM or T2DM,

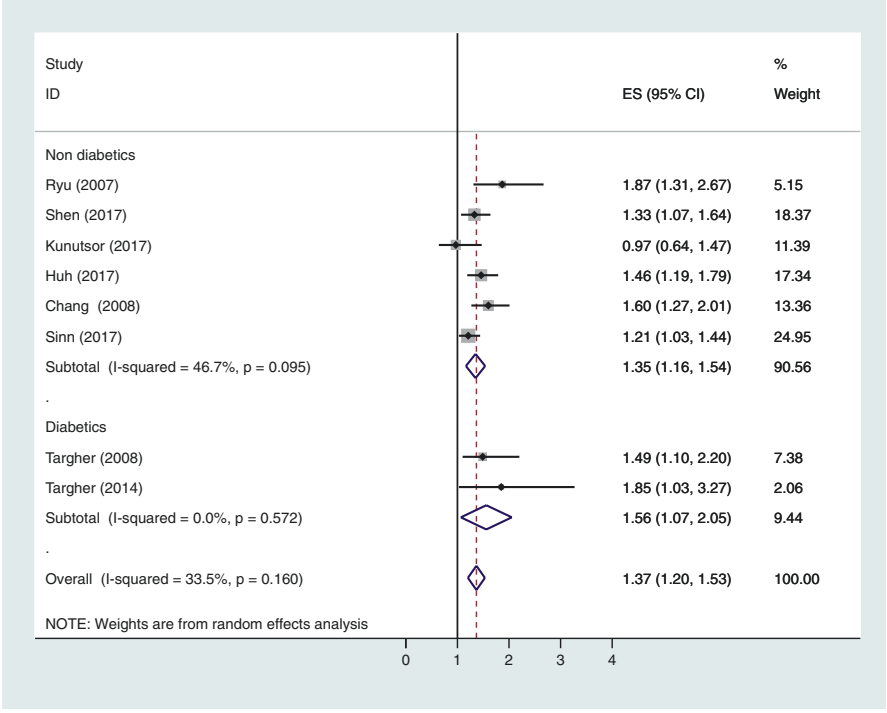

Fig. 8.4 Forest plot and pooled estimates of the effect of NAFLD on the risk of incident chronic kidney disease (CKD stage ≥3) in eight eligible prospective studies, stratified by study population (diabetes vs. no-diabetes). (Reproduced with permission [57])

it still remains to be definitively established whether a causal association also exists [60]. Additional prospective and mechanistic studies are needed to better elucidate the independent contribution of NAFLD to the increased risk of developing microvascular diabetic complications in patients with NAFLD. In the meantime, however, all the aforementioned studies provide further support for the view that a diagnosis of NAFLD identifies a subset of individuals, who are at higher risk of incident CKD (stage ≥3), and who need more intensive surveillance and early treatment to decrease the risk of developing CKD [32, 60].

8.4.3 NAFLD and Risk of Macrovascular Complications

Strong evidence indicates that cardiovascular disease dictates the outcome(s) in patients with NAFLD more frequently and to a greater extent than does the progression of liver disease in both patients with and without diabetes [2–4, 61, 62]. Recent cohort studies of patients with histologically confirmed NAFLD have clearly demonstrated that cardiovascular disease is the leading cause of mortality in these patients (~40–45% of the total deaths), and that fibrosis stage is the strongest histologic predictor for overall and disease-specific mortality in NAFLD [63].

Several cross-sectional studies have consistently shown that NAFLD was closely associated with both various markers of subclinical atherosclerosis and clinically manifest CVD across a wide range of patient populations, including also patients with diabetes [4, 61, 62]. For example, in the Valpolicella Diabetes Heart Study, it has been reported that type 2 diabetic patients with NAFLD (detected by ultrasonography) had a remarkably higher prevalence of clinically manifest coronary, cerebrovascular, and peripheral vascular disease compared to their counterparts without NAFLD, even after adjustment for traditional cardiovascular risk factors, hemoglobin A1c, use of medications, and other important diabetes-related confounders [33]. Almost identical findings were also reported in adult patients with T1DM [50].

Notably and most importantly, a number of hospital-based and population-based studies also reported that NAFLD (diagnosed by imaging techniques) was significantly associated with an increased incidence of fatal and nonfatal cardiovascular events, independent of established cardiovascular risk factors, both in patients with T2DM and in those without T2DM (as extensively reviewed in [4, 62]).

For instance, the Valpolicella Diabetes Heart Study documented that patients with T2DM and NAFLD (who were free from prior cardiovascular disease at baseline) had a nearly twofold increased risk of developing nonfatal ischemic heart disease, ischemic stroke, or cardiovascular death compared with patients without NAFLD over a 6.5-year follow-up period [64]. Notably, this relationship was independent of traditional cardiovascular risk factors, diabetes duration, hemoglobin A1c, and use of hypoglycemic, anti-hypertensive, lipid-lowering, and antiplatelet drugs [64]. Similarly, in a retrospective cohort of 286 adult patients with T1DM, who were followed for a mean period of 5.3 years for the occurrence of incident CVD events (i.e., a combined endpoint inclusive of nonfatal ischemic heart disease, ischemic stroke, or coronary/peripheral artery revascularizations), the presence of

NAFLD on ultrasonography was associated with an increased risk of incident CVD events, independent of established cardiovascular risk factors and diabetes-related variables [65].

A comprehensive meta-analysis that incorporated almost 34,000 individuals in 16 observational cohort studies concluded that the presence of NAFLD (diagnosed either by imaging methods or by histology) was significantly associated with a nearly 65% increased risk of developing fatal and nonfatal cardiovascular events over a median follow-up of 6.9 years (Fig. 8.5), and that this risk increased further with greater severity of NAFLD (defined either by presence of hepatic steatosis on imaging *plus* either increased serum gamma-glutamyltransferase concentrations or high NAFLD fibrosis score or high ^{18}F-fluoro-2-deoxyglucose uptake on positron emission tomography, or by increasing fibrosis stage on liver histology) [66].

Although the results of this updated meta-analysis strongly support the existence of a significant association between NAFLD and the risk of developing fatal and

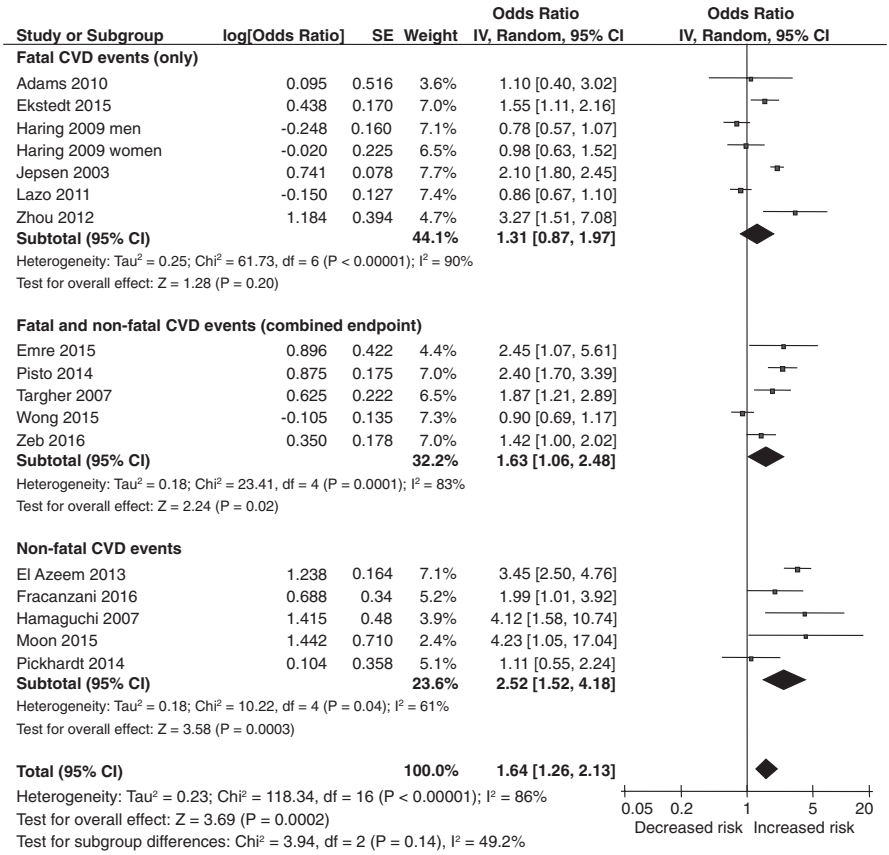

Fig. 8.5 Forest plot and pooled estimates of the effect of NAFLD on the risk of incident cardiovascular events (fatal, nonfatal, or both) in 16 eligible prospective studies. (Reproduced with permission [66])

nonfatal CVD events both in patients with and without diabetes, it is important to underline that the observational design of the eligible studies does not allow for proving causality [66]. Moreover, the key question of whether the prognostic role of NAFLD in the development of cardiovascular disease is restricted to NASH/advanced fibrosis or is also associated with simple steatosis remains partly unresolved. More research is needed to address this issue.

In the past few years, compelling evidence has also emerged for a strong association between NAFLD and risk of cardiomyopathy (mainly left ventricular diastolic dysfunction and hypertrophy, possibly leading to the development of congestive heart failure over time), cardiac valvular calcification (mainly aortic-valve sclerosis and mitral annulus calcification), cardiac arrhythmias (mainly permanent atrial fibrillation), and some cardiac conduction defects (mainly persistent first-degree atrio-ventricular block, right bundle branch block, and left anterior hemi-block) both in patients without diabetes and in those with T2DM [67]. All of these additional NAFLD-related heart diseases could further contribute to the increased risk of cardiovascular morbidity and mortality observed among patients with NAFLD.

A detailed description of the complex and multifactorial pathogenesis linking NAFLD to cardiovascular disease is beyond the scope of this chapter. However, there are a myriad of possible underlying mechanisms that plausibly link NAFLD to the development and persistence of coronary atherosclerosis, cardiomyopathy, cardiac arrhythmias, and certain cardiac conduction defects. Indeed, NAFLD, especially in its more advanced forms (NASH with varying amounts of liver fibrosis), exacerbates systemic and hepatic insulin resistance, predisposes to atherogenic dyslipidemia, and causes the release of multiple pro-inflammatory, pro-fibrogenic, and vasoactive mediators that can promote the development and progression of cardiovascular, cardiac, and arrhythmic complications [4, 61, 62, 67]. To date, however, it should be noted that no studies have definitely established a cause–effect relationship, and further research is required to gain mechanistic insights into the pathophysiology linking NAFLD to these cardiovascular, cardiac, and arrhythmic complications. Moreover, it is not yet established whether addition of NAFLD to the currently available risk assessment equations improves CVD risk prediction. Finally, since NAFLD is heterogeneous and may be also caused by common genetic variants (e.g., patatin-like phospholipase domain-containing 3 [PNPLA3] variants or trans-membrane 6 superfamily member 2 [TM6SF2] variants), it will be also interesting to ascertain whether obese/metabolic NAFLD and genetic-related NAFLD produce the same risk of developing cardiovascular events [4, 62, 67].

Collectively, we believe that the current evidence from the published studies clearly indicates that a diagnosis of NAFLD identifies a subset of individuals, which are exposed to at higher risk of fatal and nonfatal cardiovascular events. These findings further reinforce the notion that NAFLD is a *multisystem* disease that affects many extrahepatic organ systems, including the heart and vasculature, by disrupting the regulation of several metabolic and inflammatory pathways [4, 61, 62, 67]. This concept also implies that all individuals with NAFLD should undergo careful cardiovascular surveillance as recommended by the most recent European, American, and Italian clinical practice guidelines for the management of NAFLD [68–70]. A more accurate, patient-centered, team-based approach to the management and treatment

of individuals with NAFLD, based on a careful evaluation of related cardiometabolic risk factors and monitoring for cardiovascular and liver complications, will be needed.

8.4.4 NAFLD and Risk of Developing Type 2 Diabetes

The link between NAFLD and T2DM is more complex than previously thought. Accumulating evidence now suggests that there is a mutual and bi-directional relationship between NAFLD and T2DM, and that NAFLD may also precede and/or promote the development of T2DM [4, 35, 71].

A large and updated meta-analysis of 19 longitudinal studies (including nearly 300,000 individuals and approximately 16,000 new cases of incident diabetes) confirmed that patients with imaging-defined NAFLD had a 2.2-fold increased risk of developing incident diabetes than those without NAFLD over a median follow-up of 5 years (Fig. 8.6), even after adjustment for age, sex, adiposity measures, and

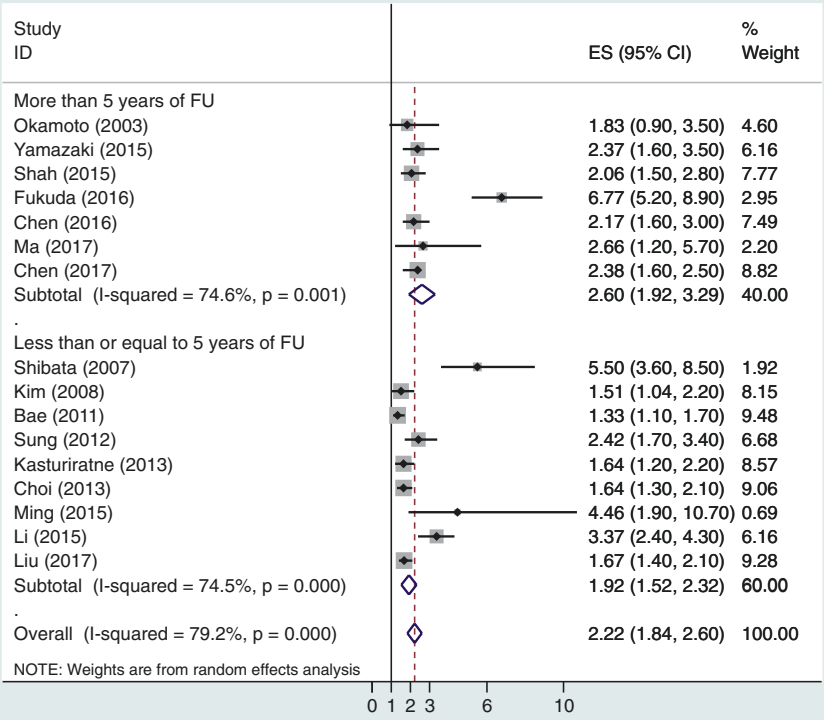

Fig. 8.6 Forest plot and pooled estimates of the effect of NAFLD on the risk of incident diabetes in 16 eligible studies, stratified by duration of follow-up (based on the median follow-up of the eligible studies). (Reproduced with permission [72])

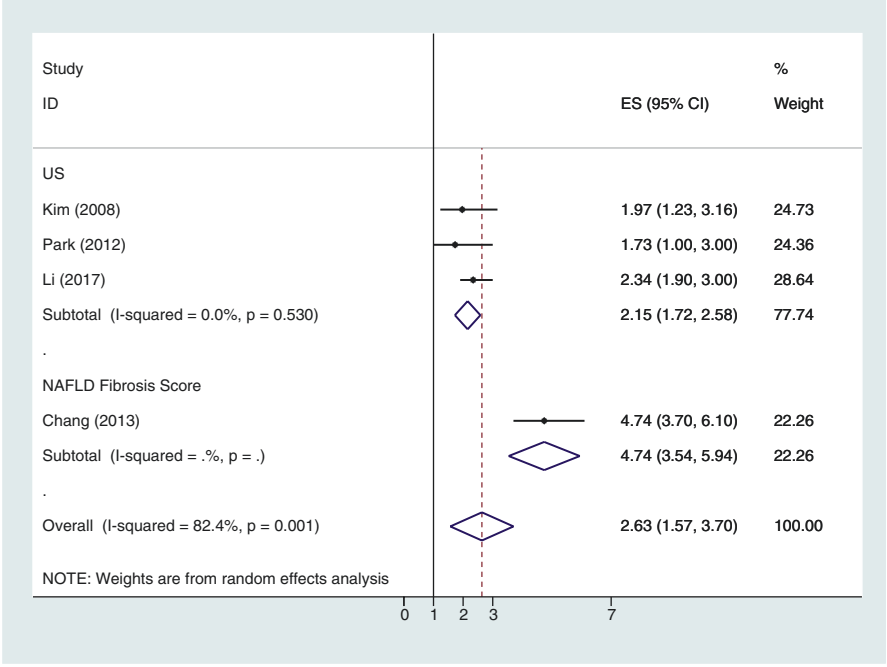

Fig. 8.7 Forest plot and pooled estimates of the effect of the severity of NAFLD (defined by ultrasonography [US] or high NAFLD fibrosis score [NFS]) on the risk of incident diabetes in four eligible studies. (Reproduced with permission [72])

other common metabolic risk factors [72]; the magnitude of this risk paralleled the underlying severity of NAFLD based on ultrasonographic steatosis scores and non-invasive biomarkers of fibrosis (Fig. 8.7) [72].

Notably, some large Asian cohort studies also showed that the risk of incident T2DM appears to diminish over time following the improvement or resolution of NAFLD on ultrasonography, adding weight to causality and suggesting that liver-focused treatments might reduce risk of developing some important extrahepatic complications of NAFLD [73, 74].

To date, there is convincing evidence regarding the biological plausibility of the role of NAFLD in the development of incident T2DM. Indeed, NAFLD, especially in its more severe histologic forms, may interact with the regulation of multiple metabolic pathways, and may be involved in the development of incident T2DM possibly via its direct contribution to hepatic insulin resistance and the systemic release of multiple hepatokines (e.g., fetuin-A, fetuin-B, retinol binding protein-4, selenoprotein P) that may adversely affect glucose metabolism and insulin action [4, 35, 72, 75].

However, it remains currently uncertain whether NAFLD is causally related to the development of incident T2DM or is simply a marker of other shared metabolic risk factors, such as expended visceral adipose tissue. Further large prospective studies are also needed in non-Asian populations, as most of the published studies have been conducted in Asian populations (especially in South Korean

people), where large populations undergo regular health check-ups, including liver ultrasonography. Finally, additional prospective studies are also required to establish whether adding NAFLD to the currently available algorithms will improve risk prediction for diabetes.

Despite the abovementioned caveats, there is now increasing evidence suggesting that NAFLD is associated with an approximate doubling of risk of incident T2DM. This association appears to be dose-dependent and is ameliorated with improvement or resolution of NAFLD over time. Consequently, current clinical guidelines do recommend routine screening of NAFLD patients for T2DM with fasting plasma glucose and hemoglobin A1c levels, or with a 75-g oral glucose tolerance test in high-risk patient groups [68–70].

8.5 Conclusions

NAFLD is a multisystem disease that affects many extrahepatic organ systems by disrupting the regulation of multiple metabolic and inflammatory pathways [62, 76]. It is important that clinical endocrinologists/diabetologists recognize the presence of NAFLD and its potentially devastating hepatic and extrahepatic consequences.

These clinicians have to keep in mind that NAFLD is very common in patients with T2DM and T1DM (affecting about 70–80% of those with T2DM and up to 30–40% of adult patients with T1DM), and that these patients are also more likely to develop the more severe histological forms of NAFLD (i.e., NASH, cirrhosis, and HCC). In addition, because of the close link between diabetes, NAFLD, and adverse vascular complications, more careful surveillance of these at-risk patients will be needed. Therefore, a more accurate, patient-centered, multidisciplinary-team-based approach to the management and treatment of diabetic patients with NAFLD, based on a careful evaluation of related cardiometabolic risk factors and monitoring for cardiovascular, kidney, and liver complications, is warranted.

Accumulating evidence suggests that NAFLD is a frequent condition also in patients with other common endocrine diseases, such as PCOS and primary hypothyroidism. Worryingly, these patients seem to be also more likely to develop NASH and advanced fibrosis. Although the observational design of the available studies does not allow for proving causality, and more mechanistic studies are required to better clarify the underlying mechanisms linking NAFLD to PCOS and primary hypothyroidism, we believe that the currently available literature argues for a systematic screening for NAFLD both in young women with PCOS (especially in those with PCOS-related androgen excess) and in patients with primary hypothyroidism. It is plausible to hypothesize that a better understanding of both the hormonal regulation(s) of NAFLD and the links of NAFLD with these common endocrine diseases will also result in future advances in the pharmacological treatment of this increasingly prevalent and burdensome liver disease.

Conflict of Interest All authors have no conflicts of interest to disclose.

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