Obesity-Associated Liver Disease

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Context: In the last few years, several data have accumulated suggesting that obesity may be associated with liver disease and disease progression. Accordingly, the worldwide epidemic of obesity is likely to become a relevant source of morbidity and mortality in the general population.

Evidence Acquisition: We reviewed the literature on two main issues: 1) the evidence that obesity carries out an increased risk of liver disease, both in the general population and in selected cohorts; and 2) the evidence that obesity is a risk factor for nonalcoholic fatty liver disease and its progression in a series observed in liver units.

Evidence Synthesis: The presence of obesity increases the risk of elevated liver enzymes by a factor of two to three, whereas the risk of steatosis at ultrasonography is increased by a factor of 3 in the presence of overweight and peaks at a factor of approximately 15 in the presence of obesity. Both cirrhosis (cryptogenic cirrhosis) and hepatocellular carcinoma are also associated with obesity in the general population. In patients with nonalcoholic fatty liver disease observed in liver units, obesity and weight gain are systematically associated with advanced fibrosis and fibrosis progression.

Conclusion: Liver disease of metabolic origin, associated with obesity, is now recognized as the most prevalent liver disease in Western countries. Strategies are needed to approach obesity-associated liver disease by behavior programs, motivating people to adopt a healthier lifestyle. Such programs should be coupled with public policies at a societal level to obtain the maximum effects in lifestyle changes. **(*J Clin Endocrinol Metab* 93: S74–S80, 2008)**

In 1980 Ludwig *et al.* (1) originally described a sequence of clinical and histological events characterized by liver fat accumulation [nonalcoholic fatty liver disease (NAFLD)] and culminating in advanced liver disease. The disease is the product of an altered substrate metabolism and has obesity as a pivotal pathogenic component. Excluding cases due to excessive alcohol intake, liver fat deposition may either be isolated (pure fatty liver or steatosis) or associated with a variable degree of necroinflammation and fibrosis [nonalcoholic steatohepatitis (NASH)], progressing to advanced fibrosis and cirrhosis (cryptogenic cirrhosis) and finally to hepatocellular carcinoma (HCC) (2).

In the last 20 yr, many more data have accumulated indicating that obesity may definitely be a risk factor for liver disease, requiring careful consideration. We shall briefly outline the pathogenic mechanism(s) involved in metabolic liver disease and in disease progression and will review the existing evidence.

The literature indicates that the burden of obesity-associated liver disease is significant; it constitutes a rather novel condition that must be carefully considered by physicians caring for obese subjects.

Evidence Acquisition

We did an extensive search on MEDLINE, using a variable combination of the following search terms (in the titles and the abstracts): (liver disease, steatosis, fatty liver, steatohepatitis, NAFLD, NASH) AND (body mass index, overweight, obesity). In addition, we checked the bibliographies of relevant published articles and the abstracts of the annual meetings of the European Association for the Study of the Liver and the American Association for the Study of Liver Disease (from January 2002 to April 2008), but we excluded the abstracts not followed by a publication *in extenso*.

The search was restricted to humans. Two sources of evidence were retrieved: 1) the evidence that obesity carries out an in-

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Abbreviations: ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; FFA, free fatty acid(s); GGT, γ-glutamyltransferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio.

creased risk of liver disease, both in the general population and in selected cohorts; and 2) the evidence that in subjects referred to liver units, obesity is a risk factor for NAFLD and NAFLD progression. The two groups of studies will be analyzed separately. A brief section was also dedicated to the role of obesity as a risk factor for liver diseases of other well-defined etiology [namely, hepatitis C virus (HCV) infection], which constitutes an important source of obesity-related morbidity.

Pathogenesis of Metabolic Liver Disease

The role of adipose tissue, namely the central (or upper body) obesity phenotype associated with increased visceral fat, in the pathogenesis of NAFLD is primary. Liver fat accumulation is largely dependent on recirculating free fatty acids (FFAs) from the adipose tissue pool. The visceral adipose tissue has greater lipolytic potential than the more abundant sc adipose tissue, and the release of FFA from visceral fat depots directly into the portal circulation is one of the mechanisms of hepatic injury (Fig. 1). Studies based on proton magnetic resonance spectroscopy have shown that the amount of intrahepatocellular lipids increases by approximately 20% for any 1% increase in total or sc adipose tissue, but doubles for any 1% increase in intraabdominal adipose tissue (3), thus explaining why even modest changes in visceral fat [in the absence of increased body mass index (BMI)] may cause steatosis (4). Accumulation of triglycerides in the hepatocytes is the result of both increased inflow of FFA and *de novo* lipogenesis. By stable isotope techniques, it has been estimated that in the presence of steatosis 59% of the triglycerides present in the liver arise from recirculation from adipose tissue, 26% from *de novo* lipogenesis from dietary carbohydrates—a value much higher than reported in normal subjects—and 15% from dietary lipids (5). In a few cases, steatosis leads to lipotoxicity, which causes apoptosis, necrosis, generation of oxidative stress, and inflammation. The resulting chronic injury activates a fibrogenic response that eventually leads to end-stage liver disease (6). Increased FFA concentrations, in turn, may be responsible for insulin resistance in muscle tissue, whereas in adipose tissue insulin resistance further prevents the insulin-mediated suppression of lipolysis. The sequence of events and the mediators linking visceral fat to insulin resistance and liver disease progression are not well defined. Adipose tissue is an endocrine organ, and over 100 factors secreted by adipose tissue have been identified as potentially responsible for liver lipotoxicity (7). Their secretion is increased with increased visceral fat mass, with the notable exception of adiponectin (8); and chronic inflammation, characterized by the infiltration of adipose tissue by macrophages, endoplasmic reticulum stress, and oxidative stress, plays a relevant part (9). Animal models of NAFLD have also suggested a possible role of FFA, not triglycerides, in the hepatocytes as factors promoting hepatocellular injury (10). However, the key issue of factors triggering the progression from pure steatosis to NASH and fibrosis is not solved yet. It is also possible that different factors may be operative in individual subjects, but excess visceral body fat remains a nearly necessary condition.

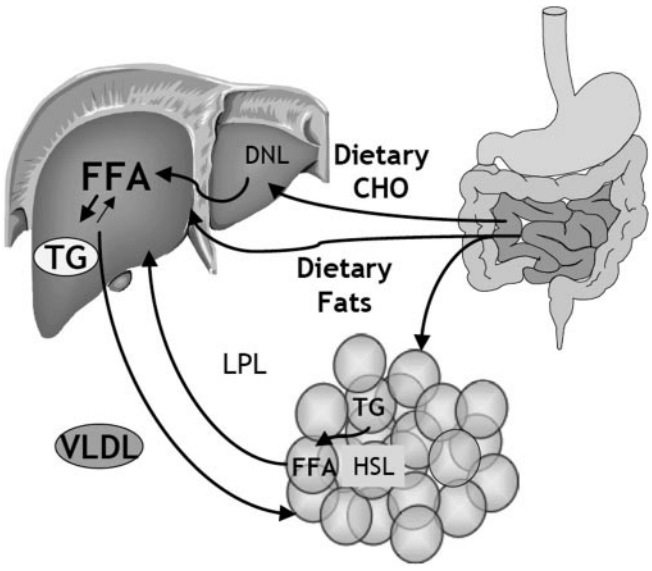

FIG. 1. Hepatic triglycerides originate either from FFA—accumulating in the liver either from recirculation from adipose tissue (namely visceral adipose tissue) or from chylomicron remnants from dietary lipids—or from *de novo* lipogenesis from absorbed carbohydrates. CHO, Carbohydrates; DNL, *de novo* lipogenesis; HSL, hepatic sensitive lipase; LPL, lipoprotein lipase; TG, triglycerides; VLDL, very low density lipoproteins.

Liver Disease in Obese Subjects

A bright liver at ultrasound and increased levels of hepatic enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), or γ-glutamyltransferase (GGT)] are the hallmarks of the whole spectrum of NAFLD. They are common in obesity, and their prevalence increases progressively with increasing BMI. At liver biopsy, subjects with moderate or severe fatty change, lipogranulomas, focal necroses, or parenchymal inflammation are significantly more obese than patients without these changes (11). In the general population of the Dionysos study, fatty liver at ultrasonography was documented in 10–15% of normal individuals and in up to 76% of obese subjects not drinking alcohol in toxic amounts (12). Compared with controls, the risk for steatosis was 4.6-fold increased in obese persons and only 5.8-fold higher in persons who were obese and drank heavily (12). However, in a subsequent analysis, the prevalence of steatosis was not different in subjects with and without elevated liver enzymes (25 *vs.* 20%) (13).

Large differences in the prevalence of steatosis exist in the general population. In a large, multiethnic, population-based sample where the distribution of hepatic triglyceride content was analyzed by the sensitive proton magnetic resonance spectroscopy, almost one third of the population had hepatic steatosis, and most subjects with hepatic steatosis had normal levels of ALT (79%). The frequency of hepatic steatosis varied significantly with ethnicity (45% in Hispanics, 33% in whites, 24% in blacks) and sex (42% in white men, 24% in white women), and the higher prevalence of steatosis in Hispanics was due to the higher prevalence of obesity and insulin resistance (14). In populations of Eastern ethnic origin (Korean population), the age-

adjusted ultrasonographic prevalence of fatty liver (21.6% in men, 11.2% in women) was reported to be similar to that seen in more developed countries (15), and a scoring system with abdominal ultrasonography was developed to provide accurate information on hepatic steatosis and visceral obesity in apparently healthy people who do not consume alcohol (16). Finally, liver fat varies with the degree of obesity, and in longitudinal studies even small changes in body weight (on average 1.3–2.5 kg) are associated with the ultrasonographic appearance/disappearance of steatosis (17).

Compared with ultrasonography, the sensitivity of ALT for the diagnosis of primary NAFLD is much lower. In a cross-sectional study of a subsample of the Israeli national health survey, the prevalence of steatosis was 30%, but the sensitivity of ALT was only 8.2%; again however, abdominal obesity was one of the most predictive factors of NAFLD (18).

Nonetheless, elevated liver enzymes of unexplained origin remain the most common cause for specialist referral. Although an association between the severity of liver disease and high levels of enzymes is not unequivocally demonstrated (19), their increase is the most sensitive biochemical indicator of the presence of hepatic steatosis in populations of different ethnic origin (12, 20) and is currently used as a surrogate marker of liver injury. In adults aged 17 yr and older from the Third National Health and Nutrition Examination Survey (NHANES III) (1988–1994), elevated ALT or AST of unexplained origin (nearly 8% of over 15,000 samples) was significantly associated with high BMI and large waist circumference, as well as with other features of the metabolic syndrome, in keeping with the primary role of adiposity in the pathogenesis of liver disease (21). In the same population, the proportion of elevated ALT activity due to overweight and obesity was estimated to be 65%, and central adiposity, measured by the waist to hip ratio, was a major determinant of the association of overweight with elevated serum ALT activity (22). Also, Stranges *et al.* (23) confirmed an independent role of abdominal height, a measure of central adiposity, as a predictor of elevated ALT and GGT levels, a possible expression of unrecognized fatty liver.

In the large QUOVADIS cohort including nearly 800 obese subjects attending medical obesity clinics in Italy, elevated liver enzymes were a common finding in the absence of any symptom, sign, and previous history of liver disease. Median AST and ALT increased with increasing obesity class and on average exceeded normal limits in 21% and 10% of cases, but the higher the BMI, the higher the prevalence of elevated liver enzymes (Fig. 2) (24). In the same setting also, the presence of insulin resistance was highly predictive of elevated enzymes, confirming the role of insulin resistance in NAFLD and the concept that NAFLD is the hepatic expression of the insulin resistance (metabolic) syndrome (25). In a Japanese cohort free of previous liver injury and with no other causes of incidental liver disease, weight gain preceded the rise of aminotransferase levels and the appearance of other insulin resistance-related features, confirming the pivotal role of fat mass in liver disease of metabolic origin (26).

A comprehensive review of the literature indicates that the presence of obesity increases the risk of elevated liver enzymes by a factor of two or three, whereas the risk of steatosis at ultrasonography is increased by a factor of 3 in the presence of overweight and peaked at a factor of approximately 15 in the presence of obesity. This indicates that a large number of cases with ultrasonographically detectable liver disease will have normal liver enzymes and that liver enzymes are a poor predictor of the severity of liver disease.

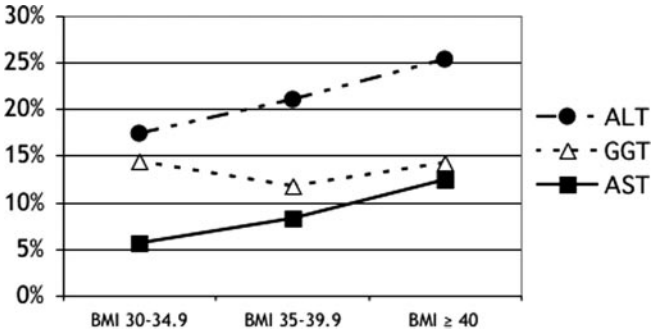

FIG. 2. Prevalance of AST, ALT, and GGT at various BMI levels. Median AST and ALT increased with increasing obesity class and on average exceeded normal limits in 21% and 10% cases respectively, but the higher the BMI, the higher the prevalence of elevated liver enzymes.

The importance of liver disease in obesity is not limited to initial NAFLD stages. Both cirrhosis and HCC are associated with obesity. In an specific analysis of the First National Health and Nutrition Examination Survey (NHANES I), cirrhosis-related deaths or hospitalizations were more common in obese [0.81/1000 person-years; adjusted hazard ratio (HR), 1.69] and in overweight persons [0.71/1000 person-years; adjusted HR, 1.16; 95% confidence interval (CI), 0.7–1.9] compared with normal-weight persons (0.45/1000 person-years). Among persons who did not consume alcohol, there was a strong association between obesity (adjusted HR, 4.1; 95% CI, 1.4–11.4) or being overweight (adjusted HR, 1.93; 95% CI, 0.7–5.3) and cirrhosis-related death or hospitalization (27).

In both men and women belonging to a prospectively studied population of more than 900,000 U.S. adults who were free of cancer at enrollment in 1982, high BMI was also significantly associated with higher rates of liver cancer-related death. A BMI greater than 35 kg/m^2 carried a relative risk of HCC death of 4.52 in comparison to normal weight (28). Similarly, in patients undergoing liver transplantation for HCC, obesity was an independent predictor for HCC in patients with alcoholic cirrhosis [odds ratio (OR), 3.2; 95% CI, 1.5–6.6] and cryptogenic cirrhosis (OR, 11.1; 95% CI, 1.5–87.4) (29). It is likely that the association of HCC with obesity represents the progression of underlying NAFLD to cirrhosis, but it remains unclear whether cirrhosis is a necessary prerequisite for the development of HCC (30). Animal models of NAFLD support the hypothesis that obesity-related metabolic abnormalities, rather than cirrhosis, initiate the hepatic neoplastic process during obesity (31).

Finally, elevated liver enzymes and steatosis are also common in morbidly obese subjects undergoing bariatric surgery. This population constitutes an important cohort because liver biopsy can be easily obtained at surgery. Marceau *et al.* (32) first reported a systematic assessment of liver histology in over 500 subjects undergoing bariatric surgery. Steatosis was present in 86% of cases, fibrosis in 74%, mild inflammation or NASH in

24%, and unexpected cirrhosis in 2%. The risk of steatosis increased systematically with each addition of the four components of the metabolic syndrome, and patients with diabetes or impaired glucose tolerance had a 7-fold increased risk of fibrosis. Dixon *et al.* (33) confirmed that 25% of cases submitted to laparoscopic antiobesity surgery have NASH, and 42% of these have advanced fibrosis. Raised presurgery ALT levels (OR, 8.6; 95% CI, 3.1–23.5) predict NASH independently of insulin resistance, whereas the improvement of insulin resistance after surgery is associated with a reduced amount of liver fat (34). A review of 12 observational and cross-sectional studies, summing up 1620 patients with severe obesity, has shown that steatosis is nearly universally present in morbid obesity (91%; range, 85–98%), NASH is present in over one third of cases (37%; range, 24–98%), with unexpected cirrhosis in 1.7% (range, 1–7%) (35). Interestingly, whereas AST levels were associated with NASH and advanced fibrosis, the majority of patients with either NASH or advanced fibrosis had normal AST (36). Of note, weight loss induced by gastric bypass surgery normalizes the metabolic abnormalities involved in the pathogenesis and pathophysiology of NAFLD and decreases the hepatic expression of factors involved in the progression of liver inflammation and fibrosis (37).

More data on follow-up liver biopsies have been recently reported in subjects after bariatric surgery, and a clinical scoring system for morbid obesity was derived to score the probability of NASH into four categories (low, intermediate, high, and very high), thus allowing a better definition of liver disease risk (38).

Obesity in Subjects with Nonalcoholic Fatty Liver Disease

The above data on the potential impact of obesity on liver disease, derived from population and cohort studies, are remarkably confirmed by reports from liver units where obesity or weight gain is identified as a primary factor associated with liver disease, namely with progressive liver disease and advanced fibrosis (Table 1) (39). Several cross-sectional studies of NAFLD cohorts suggest that the degree of obesity, together with insulin resistance, older age (>40–50 yr), diabetes, and high triglycerides are strong indicators of advanced stages of liver fibrosis. In 93 consecutive patients with abnormal liver function tests and no alcoholic, viral, autoimmune, drug-induced, or genetic liver disease, a BMI of at least 28 kg/m^2 was highly predictive of advanced fibrosis (OR, 5.7) (40). In NASH, obesity was selected by multivariate analysis as a variable independently associated with both severe liver fibrosis (bridging/cirrhosis) and the degree of fat infiltration (41). In most NAFLD patients, obesity is associated with other metabolic abnormalities, and the risk of NASH increases linearly with the number of additional features of the metabolic syndrome (25). However, the presence of NAFLD might also predict the development of metabolic disorders due to insulin resistance, heralding the development of obesity, hypertension, high triglycerides, and glucose abnormalities (42). This opens the question as to whether insulin resistance or obesity *per se* is the cause of liver disease (43), a question which is so far unanswered.

TABLE 1. Number of retrospective and follow-up studies that identified independent predictors of advanced fibrosis in NAFLD/NASH

Predictors of advanced fibrosis	Retrospective studies (n = 17)	Follow-up studies (n = 5)
Obesity/BMI/weight gain	7	3
Diabetes/high glucose	5	2
High insulin, insulin resistance	7	2
Insulin resistance/metabolic syndrome	3	
Age	3	1
High triglycerides	2	
Male gender	1	
Female gender	1	
AST, ALT, or AST/ALT	7	1

The analysis is derived from Ref. 39.

Although NAFLD is likely to be a slowly progressive disease (44), cryptogenic cirrhosis is expected to develop from advanced forms of NASH. Three studies examined the presence of metabolic risk factors among patients with cryptogenic cirrhosis; the prevalence of obesity, diabetes, or both was similar compared with patients with NASH, but higher compared with patients with cirrhosis from other causes, thereby suggesting that cryptogenic cirrhosis may represent burned-out NASH (45–47). Furthermore, NAFLD tends to recur after liver transplantation, and obesity is common in patients with post-orthotopic liver transplantation NAFLD (48).

Finally, patients with superimposed on developing cryptogenic cirrhosis have a higher prevalence of obesity and diabetes, compared with patients with carcinoma superimposed on cirrhosis that is alcohol- or virus-related (49), suggesting that NAFLD is the underlying disease in many patients with cryptogenic cirrhosis complicated by HCC. One small retrospective analysis in patients with obesity-related cryptogenic cirrhosis revealed that severe liver disease was as frequent in these cases as in patients with HCV-related cirrhosis (50). Also HCC was detected in 27% of obese patients *vs.* 21% of matched HCV cases, suggesting a carcinogenic potential of obesity comparable to that of HCV in the presence of cirrhosis (50).

A number of longitudinal studies based on retrospective and prospective serial liver biopsies are now available to depict the progression of fibrosis in patients with NAFLD and the factors associated with it, since the first analysis of Powell *et al.* (2). Progressive fibrosis was much more common in patients with NASH (8%), compared with those with simple steatosis (0%), in a follow-up of 7–16 yr (median, 11) in a cohort of NAFLD cases (30% with obesity) (51). In 22 NAFLD cases where a second biopsy was available at least 3 yr after initial assessment, obesity was significantly more prevalent in subjects with fibrosis progression (86%) than in nonprogressors (27%), and high BMI was the only factor associated with progression (52). In 103 patients who underwent serial liver biopsies after a mean interval of 3.2 yr (range, 0.7–21.3), fibrosis progressed in 37%, remained stable in 34%, and regressed in 29%. Diabetes and low initial fibrosis stage were associated with higher rates of fibrosis progression, as was obesity when cases with cirrhosis were excluded (53).

Diabetes and obesity are also associated with poor survival in NAFLD. In the 420 NAFLD cases of the Olmsted county cohort, liver disease was the third leading cause of death (as compared with the 13th leading cause of death in the general Minnesota population), and the presence of glucose abnormalities was significantly associated with liver-related death (54). However, the risk of death might be overestimated due to the presence of cirrhosis in a few cases at initial diagnosis. In a cohort study of 129 consecutive patients with biopsy-proven NAFLD and followed up for a mean period of 13.7 yr, mortality was not different from that observed in the general population in subjects with pure fatty liver, but it was significantly increased in subjects with NASH. Progression of fibrosis occurred in 41% of cases; these subjects more often had a weight gain exceeding 5 kg, were more insulin resistant, and had more pronounced hepatic fatty infiltration at follow-up (55).

Obesity as Risk Factor in Liver Diseases of Different Etiology

Several studies in selected cohorts have extensively demonstrated that obesity may also play a role in the development and progression of liver disease of well-defined etiology (56).

The setting of HCV infection is paradigmatic (57). Whereas HCV genotype 3 infection is likely to produce steatosis through a virus-mediated mechanism (58), in subjects with genotype non-3 HCV infection steatosis is generally considered the effect of coexisting metabolic conditions (59), possibly exacerbated by viral infection (60). The presence of obesity and obesity-associated insulin resistance and steatosis facilitates the development of diabetes in the precirrhotic stage, carries a higher risk of failure during interferon treatment (61) or recurrence after initial response (62), and increased fibrosis (63–65). Treatment failure in obesity might result from lower interferon concentrations and a milder biological response upon exposure to exogenous interferon-α in obese patients (66). In a meta-analysis on individual data from 3068 patients with histologically confirmed chronic hepatitis C recruited by 10 clinical centers in different ethnic settings, steatosis was independently associated with several variables, including higher BMI, and predicted fibrosis (67). On this basis, a pretreatment of insulin resistance with insulin-sensitizing agents and/or weight loss by dietary intervention have been proposed as preinterferon strategies to increase sustained virological response (62).

Very recently, the contribution of obesity and steatosis to the expression of inflammatory markers in chronic HCV has been reassessed. In comparison with lean patients, overweight and obese subjects had increased circulating and hepatic C-reactive protein levels. Obesity and steatosis were also associated with increased circulating, but not hepatic, IL-6, and an independent relationship was seen between hepatic TNF-α mRNA levels and higher total inflammatory score and stage of fibrosis (68). These data support the key role of obesity and obesity-derived proinflammatory cytokine in liver injury in chronic HCV.

A similar detrimental effect of obesity probably occurs in subjects with familial hemochromatosis or in subjects with alcohol-induced liver disease, where the presence of obesity further increases the risk of steatosis (12).

Conclusions

The whole spectrum of NAFLD, from steatosis to cryptogenic cirrhosis, was barely known in 1981 and is now recognized as the most prevalent liver disease in Western countries, particularly where the prevalence of hepatitis viruses is low (69). These NAFLD individuals have an increased calculated risk of coronary artery disease (70), as well as an increased risk of type 2 diabetes (71). Population studies have confirmed a higher cardiovascular risk (72, 73), both in the presence and the absence of diabetes.

Although specific genotypes may facilitate the phenotypic expression of liver disease, an excess fat mass remains the most common background condition, favoring the development of steatosis and its progression to advanced liver disease, as well as promoting the development of the metabolic syndrome. The obesity epidemic is likely to put a very high number of patients at risk of liver disease in the future, and strategies are needed to approach NAFLD by behavior programs, to reduce excess nutrition, and increase exercise. There is a need for multidisciplinary teams including dietitians, psychologists, and physical activity supervisors caring for patients with NAFLD, motivating persons to adopt a healthier lifestyle. These programs should be coupled with public policies at a societal level to obtain the maximum effects in lifestyle changes (74).

Acknowledgements

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