Non-alcoholic fatty liver disease–From the cardiologist perspective

Oana Sîrbu[1], Mariana Floria[1,2], Petru Dăscălița[1], Victorița Şorodoc[1,2], Laurențiu Şorodoc[1,2]

[1]Gr. T. Popa University of Medicine and Pharmacy and [2]Sf. Spiridon Emergency Hospital; Iaşi-*România*

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) includes a range of disorders characterized by excess accumulation of triglycerides within the liver. While simple steatosis may be clinically stable, non-alcoholic steatohepatitis (NASH) can be progressive. Inflammation is believed to be the driving force behind NASH and the progression to fibrosis and subsequent cirrhosis. NAFLD is globally considered a significant health concern not only because of its incidence but also because of its economic impact. The fact that NAFLD is associated with cardiovascular disease is widely recognized, as well as the fact that NAFLD patient mortality rises when such an association is present. In particular, NAFLD is associated with coronary and carotid atherosclerosis, endothelial dysfunction and arterial rigidity, ventricles function, valves morphology, congestive heart failure, and arrhythmias (especially atrial fibrillation). Additionally, the hypercoagulability status in NAFLD patient may be suggested by the presence of inflammatory and coagulation markers. In order to differentiate between milder forms and the more severe ones that necessitate aggressive therapy, individualized risk scores may be used. This narrative review will analyze and interpret the papers published in PubMed in the last 16 years, in an attempt to expand our understanding of the NASH as a possible cardiovascular risk factor. *(Anatol J Cardiol 2016; 16: 534-41)*

Keywords: non-alcoholic fatty liver disease, cardiovascular disease, cardiovascular risk, risk score

Introduction

Non-alcoholic fatty liver disease (NAFLD) is globally the most prevalent chronic liver disease, and it encompasses a wide array of diseases, including simple steatosis. The spectrums of disorders included in NAFLD are benign macrovesicular hepatic steatosis, non-alcoholic steatohepatitis (NASH), hepatic fibrosis, cirrhosis of liver, and hepatocellular carcinoma. While simple steatosis may be clinically stable, NASH can be progressive (1). At present, there is no specific test that can predict progression of simple steatosis to NASH. Inflammation is believed to be the driving force behind NASH and the progression to fibrosis and subsequent cirrhosis. NAFLD is strongly associated with obesity, insulin resistance, hypertension, and dyslipidemias. It is currently considered the liver component of the metabolic syndrome, an acutely atherogenic component (2). This paper is a narrative review about cardiovascular disease associated with NAFLD and subsequent cardiovascular risk. We selected the papers published in PubMed since 2000 using the following key words: non-alcoholic fatty liver disease and cardiovascular disease. We found 1231 papers; 435 and 39, respectively, out of these were reviews and clinical trials. Due to a large variety of cardiology fields and inhomogeneous outcomes, it was impossible to perform a systematic review.

Prevalence, pathogenesis, and diagnosis of non-alcoholic fatty liver disease

In eastern countries, NAFLD is present in approximately 12–24% of the general population, in 25–90% of obese patients and, in 70% of patients with type 2 diabetes mellitus (3). However, the real prevalence of this disease may only be estimated as precise non-invasive diagnostic methods are not yet available (2).

Recently were identified the major inherited factors of hepatic fat accumulation and susceptibility to progressive NASH; these abnormal gene variants are also the major factors of inter-individual differences in liver steatosis (4). The theory of systemic lipotoxicity has been applied to NASH, where excessive or dysfunctional regulation of free fatty acids and/or their metabolites induces cellular injury and death. The presence of inflammation on liver biopsy is associated with the development

Anatol J Cardiol 2016; 16: 534-41

Sirbu et al.
Non-alcoholic fatty liver disease   535

of advanced fibrosis in NASH. The presence of acinar inflammation is essential for histological diagnosis of adult NASH. Portal inflammation is increasingly recognized as an important feature of NASH, probably mediated by hepatic macrophages.

NAFLD diagnosis requires no significant alcohol drinking history and fatty liver presence on imaging (5). After this first step, it is mandatory to establish how severe the fatty liver disease is—simple steatosis, steatohepatitis, hepatic fibrosis, or cirrhosis of liver. Even though liver biopsy is the gold standard method for NAFLD diagnosis, which is often refused by the patients, abnormal liver chemistry and imaging studies are very important (6).

However, abnormal values of liver function parameters such as aspartate aminotransferase (AST) and alanine transaminase (ALT) do not have significance for NASH diagnosis. Even though the AST:ALT ratio increases with NAFLD stages, these biological markers can be normal even in advanced NAFLD.

Abdominal ultrasound is the first step in NAFLD diagnosis in daily practice because it is easily available, without radiation exposure, and inexpensive (5). The criteria suggesting NAFLD, observed on abdominal ultrasound, were hepatomegaly, hyperechogenity of the liver parenchyma, and blurred vascular margins. However, this imaging modality cannot detect and differentiate NASH stages; in addition, it has other limitations like operator experience and technical difficulties in obese patients. It seems that computed tomography is not more sensitive than abdominal ultrasound in detecting hepatic steatosis (6).

Imaging techniques like conventional magnetic resonance is not recommended because it assesses the liver fat signal, which is not a reliable method (6). The proton density fat-fraction assessed directly by new magnetic resonance imaging techniques seems to be correlated with histologic grades of NAFLD. Therefore, magnetic resonance imaging is superior in differentiating different stages of fibrosis (7). Similarly, Fibroscan can detect the stages of hepatic fibrosis (5). The main challenge faced by physicians is to differentiate between mild, benign forms of fatty liver disease and the more progressive, severe forms that necessitate aggressive therapy. In this context, risk scores are an efficient tool for the physician, as a relatively simple method that relies on identifying and measuring objective factors.

There are some non-invasive scoring systems to predict NASH/NAFLD in patients with severe or morbid obesity or in general population, to select patients for liver biopsy or to find out whether patients have advanced hepatic fibrosis (7-11).

The HAIR score (8) (the acronym for: **H**ypertension, **A**LT and **I**nsulin **R**esistance) is useful in predicting NASH in patients with severe obesity (body mass index or BMI ≥35 kg/m^2). It facilitates the selection of individuals who may benefit from liver biopsy and auxiliary therapies. The HAIR score (8) is based on three parameters, whose presence is scored as follows:

   1. Hypertension: 1 point
   2. ALT >40 µl/L: 1 point
   3. Insulin Resistance Index >5.0: 1 point

The presence of a minimum of two parameters has high diagnostic sensitivity (80%) and specificity (89%) for NASH. The presence of all three factors establishes the NASH diagnosis (8).

The BAAT score (9) may be used to select patients presenting with abnormal liver function tests for liver biopsy. Detection of only one of the following parameters excludes septal fibrosis or hepatic cirrhosis.

   1. BMI ≥28 kg/m^2: 1 point
   2. Age ≥50 years: 1 point
   3. ALT ≥2 x normal value: 1 point
   4. Triglycerides ≥1.7 mmol/L (150 mg/dL): 1 point

A final score of either 0 or 1 has 100% negative predictive value for septal fibrosis (100% sensitivity and 46% specificity) (9).

The NICE model (10) is based on the presence of the metabolic syndrome (as defined by International Diabetes Federation—IDF criteria), AST and cytokeratin-18 fragment serum levels. The IDF criteria that define the metabolic syndrome are central obesity (waist circumference of over 80 cm in women and 94 cm in men) and any two of the following:

   1. Triglycerides ≥1.7 mmol/L or under treatment for hypertriglyceridemia;
   2. HDL-cholesterol <1.29 mmol/L in women or <1.03 mmol/L in men;
   3. Systolic arterial tension ≥130 mm Hg or diastolic ≥85 mm Hg or under treatment for hypertension;
   4. Fasting glycemia ≥5.6 mmol/L or previous diagnosis of Type II Diabetes.

The formula (10) to determine this score is 5.654+3.78E^{-02}xAST (UI/L)+2.215E^{-03}xCK18 fragment level (UI/L)+1.825x(metabolic syndrome present=1)

A score value of ≥5 allows for an accurate diagnosis of NAFLD in patients with morbid obesity (8).

Another model that incorporates the presence of diabetes, ALT levels, hypertriglyceridemia, and sleep apnea may be useful in selecting patients with morbid obesity for liver biopsy and establishing the NASH diagnosis. This particular model has a negative predictive value of 89.7% in low-risk patients and a positive predictive value of 75% in patients with extremely high risk (10).

Another risk score used is the fatty liver index (FLI) score (11), which is designed to aid the diagnosis of NASH in the general population. It uses the serum levels of the triglycerides and gamma-glutamyl transpeptidase, BMI, and waist circumference. The score is determined based on the following formula:
FLI=(e 0.953 x loge$^{(triglycerides)}$+0.139xBMI+0.718xloge$^{(GGT)}$+ 0.053 x waist circumference-15.745)/(1+e 0.953xloge$^{(triglycerides)}$+0.139xBMI+0.718xloge$^{(GGT)}$+0.053xwaist circumference-15.745)x100

An FLI under 30 may be used to exclude hepatic steatosis (87% sensitivity). A value ≥60 has 86% specificity for the diagnosis of hepatic steatosis (11).

BARD score uses the following parameters: BMI >28 (yes=1, no=0), AST/ALT ≥0.8 (>0.8=2, ≤0.8=0) and diabetes mellitus (yes=1, no=0) (7). It ranges from 0 to 4. A BARD score of 0 to 1 means low probability of advanced hepatic fibrosis (negative

predictive value 96%) and score 2 to 4 means high probability of hepatic fibrosis (positive predictive value 43%) (7).

NAFLD fibrosis score depends on age year, BMI (kg/m^2), diabetic status (yes=1, no=0), AST, ALT, platelet count and albumin (7). The following formula is used to calculate it: −1.675+0.037x age+0.094xBMI+1.13ximpaired fasting blood glucose/diabetes +0.99xAST/ALT ratio-0.013xplatelet (10^9/L)-0.66xalbumin (g/dL). If the score is less than −1.455, there is low probability of advanced hepatic fibrosis (negative predictive value ≥87%); and if the score is >0.676, there is high probability of advanced hepatic fibrosis (positive predictive value ≥78%). If the score is intermediate (between −1.455 and 0.676), there is indeterminate probability and these patients need to have liver biopsy for further assessment.

Fibrosis 4 index uses age, AST, ALT, and platelet count for assessing the necessity of liver biopsy (7). The formula this score is age (years)xAST (U/L)/platelet (10^9/L)x[ALT (U/L)]$^{1/2}$. If the score is <1.30, there is low probability of advanced hepatic fibrosis (negative predictive value 90%); and if the score is >2.67, there is high probability of advanced hepatic fibrosis (positive predictive value 80%) (7). If the score is intermediate (1.30 to 2.67), the possibility of having advanced hepatic fibrosis is indeterminate and liver biopsy is warranted.

APRI score uses the following formula: AST level (IU/L)/AST upper limit of normal (IU/L)/[platelet count (10^9/L)]x100 (7). If the score is ≤0.5, there is low probability of hepatic fibrosis (negative predictive value 83%) and if the score is >1.5, there is high probability (positive predictive value 68.4%) of hepatic fibrosis (7). The intermediate score (0.5 to 1.5) do not indicates a clear probability for liver fibrosis, therefore liver biopsy should be done in those patients.

Non-alcoholic fatty liver disease and cardiovascular disease

Many studies have underlined the association between NAFLD and cardiovascular disease (1–3). The most important characteristic of this association is the rise in mortality and morbidity. Studies have shown that mortality in NAFLD patients is higher than that in the general population and is mainly determined by the concomitant cardiovascular disease and by the hepatic dysfunction. The two main causes of mortality have been identified as neoplasia and ischemic heart disease. The third-ranked cause of mortality identified was non-liver neoplasia. On the contrary, data from a National Health and Nutrition Examination Survey study, which included 11,000 adults screened for an average period of 14 years, suggested no independent associations between NAFLD and number of deaths caused by cardiovascular disease (2).

Non-alcoholic fatty liver disease and coronary atherosclerosis

A strong association between NAFLD and CAD has been suggested. In patients diagnosed with both pathologies, who have underwent a coronary angiography investigation, a strong connection between NAFLD and CAD has been shown, an as-

sociation that is independent of risk factors common to both diseases (age, male sex, hyperglycemia, diabetes mellitus, and abnormal lipid profile) (12). The association between NAFLD and CAD involves the severity of the stenosis; there is a 51% increase in NAFLD patients in those with mild and insignificant coronary stenosis to 100% in patients with three affected coronary arteries (13). Even if these studies have identified an association between NAFLD and angiography detected CAD, after adjusting for traditional cardiovascular risk factors and metabolic syndrome components, none of the above has evaluated the functional significance of the coronary lesions. In any case, this association should not be overestimated, given the fact that the clinical effect is determined by ischemia rather than by coronary anatomy (12).

Coronary arterial calcification assessed by computed tomography represents a marker for sub-clinical atherosclerosis (1). It seems that there is an association between NAFLD and a high score for coronary artery calcifications, irrespective of traditional cardiovascular risk factors or metabolic syndrome components (14). However, one of these studies has pointed towards much stronger association between NAFLD and vulnerable plaques than coronary stenosis (1). Nevertheless, a recent study conducted on a sample of 2424 patients has not detected any significant correlations between NAFLD and sub-clinical cardiovascular disease, the discrepancies having been interpreted by the authors as racial differences amongst study participants (15).

Even more, patients with NAFLD have microcirculatory dysfunction reflected by a reduction in coronary flow reserve, independent of metabolic risk factors. NAFLD fibrosis score correlates with the severity of microcirculatory dysfunction and is predictive of impaired coronary flow reserve (2).

Non-alcoholic fatty liver disease and carotid artery atherosclerosis

Intima-media thickness (IMT) of carotid arteries represents a marker for subclinical atherosclerosis, regardless of insulin resistance, metabolic syndrome components, and traditional cardiovascular risk factors (16). An ultrasonographic, non-invasively measured carotid artery IMT has been associated with an increasing in cardiovascular risk. A recent meta-analysis of 4 studies including 1947 cases has revealed a strong association with both: a pathologic carotid artery IMT and the presence of carotid plaque (17). The main characteristics of the studies that analyzed the link between NAFLD and IMT are shown in Table 1 (16–27). Because atherosclerosis is accelerated in diabetic patients, we have excluded studies on patients with this pathology. Even if NAFLD is ultrasonographically diagnosed (a subjective method that may only detect steatosis once the presence of fat is over 33% in the liver biopsy), the two studies (18,19) that used biopsy for the diagnosis of NAFLD confirm the data from the other studies, specifically the association between NAFLD and carotid artery IMT, whose value increases together with

Anatol J Cardiol 2016; 16: 534-41

Sirbu et al.
Non-alcoholic fatty liver disease   *537*

Table 1. Association between carotid intima-media thickness (IMT) and non-alcoholic fatty liver disease (NAFLD) on studies with at least 100 non-diabetic subjects

Reference	Study design	No. of pts	NAFLD diagnosis	Carotid phenotype	Adjusted for	Conclusion
Volzke et al. 2005 (18)	Population based cross-sectional	4222	US	IMT, CP	Age, gender, alcohol consumption, smoking, diabetes, Hypertension, BMI, total cholesterol/HDL ratio, plasma fibrinogen levels	NAFLD was independently associated with carotid plaques, but not with IMT
Targher et al. 2006 (20)	Prospective matched cohort	245	Biopsy	IMT, CP	Age, gender, smoking, diabetes, BMI, LDL cholesterol ratio metabolic syndrome, HOMA-IR score	The histological severity of NAFLD independently predicts carotid IMT
Fracazany et al. 2008 (16)	Prospective case-control	375	US	IMT, CP		Mean IMT was significantly higher among NAFLD patients
Gastaldelli et al. 2009 (19)	Population based study	1307	FLI	IMT	Insulin sensitivity index, Framingham risk score	Independent association between FLI and IMT on subjects without diabetes or hypertension
Mohammandi et al. 2011 (22)	Prospective case-control	149	US	IMT	Metabolic syndrome	NAFLD strongly associated with IMT
Neri et al. 2011(23)	Prospective cross-sectional	150	Biopsy	IMT		An increased IMT was significantly associated with the degree of liver steatosis and fibrosis in HD patients
Huang et al. 2011 (27)	Population-based cross-sectional	8632	US	IMT	Age, sex, metabolic syndrome, conventional cardiovascular risk factors	NAFLD was independently associated with elevated IMT
Kang et al. 2012 (24)	Prospective cross-sectional	633	US	IMT	Age, BMI, blood pressure, waist circumference, lipid profile, liver enzyme, hs-CRP	NAFLD is significantly associated with carotid atherosclerosis in non-diabetic outpatient even without metabolic syndrome
Kim et al. 2013 (25)	Cross-sectional	769	US	IMT	Age, systolic blood pressure, triglycerides, HDL-cholesterol, BMI	Women with an ALT level above the middle of the reference range had a higher IMT only when they also had NAFLD
Lankarani et al. 2013 (26)	Population-based case-control	580	US	IMT		Patients with NAFLD had a significantly higher prevalence of increased IMT
Sesti et al. 2014 (21)	Cross-sectional	400	US	IMT	Age, gender, smoking, metabolic syndrome, statin and antihypertensive therapy	Individuals with high and intermediate probability of liver fibrosis had higher value of IMT

ALT - alanine transaminase; BMI - body mass index; CP - carotid plaques; hs-CRP - high sensitivity-C Reactive Protein; FLI - fatty liver index; HD - hemodialysis; HDL - high density lipoprotein; HOMA-IR - homeostasis model assessment-estimated insulin resistance; IMT - intima media-thickness; LDL - low density lipoprotein; NAFLD - non-alcoholic fatty liver disease; pts - patients; US - ultrasound

the severity of hepatic lesions. Moreover, Gastaldelli et al. (19) has used FLI score for the NAFLD diagnosis, and has concluded that patients with an FLI over 60 have an increased probability of suffering from both hepatic steatosis and early carotid artery atherosclerosis. In this study, subjects did not present with manifest cardiovascular disease, type II diabetes mellitus, or hypertension.

Non-alcoholic fatty liver disease and endothelial dysfunction

The earliest detectable component in the development of atherosclerosis is endothelial dysfunction (20). The most common way to detect it is by using flow-mediated dilatation (FMD) of the brachial artery. There was evidence that FMD was significantly reduced in patients with NAFLD after adjustment for age,

sex, BMI, and insulin resistance, and this reduction was parallel with histological progression (21). In 84 patients with NAFLD, Mohammadi et al. (22) showed that even in the absence of the metabolic syndrome, NAFLD is associated with endothelial dysfunction quantified by FMD. Another study conducted on Indians has shown an association between endothelial dysfunction and NAFLD. The presence of NAFLD has been independently associated with impaired FMD even after factoring in adiposity, blood pressure, lipid levels, and the presence of the metabolic syndrome (28). Furthermore, it has been proved that histological severity of NAFLD is independently associated with FMD (29). In addition, endothelial function, evaluated by strain-gauge plethysmography, is significantly reduced in hypertensive patients with associated liver steatosis comparing with those without (30).

An elevated level of asymmetric dimethyl arginine (ADMA), an endogenous competitive inhibitor of nitric oxide synthase, is a risk factor for endothelial dysfunction. A study, which evaluated endothelial dysfunction by IMT, FMD, and plasma ADMA levels in 51 biopsy proven NAFLD subjects and 21 age- and sex-equivalent subjects in the control group, found significantly impaired endothelial dysfunction in patients with NAFLD compared with control (31). Although the plasma ADMA levels were similar in patients with NAFLD and healthy control subjects, it was higher in patients with definitive NASH than in patients with simple steatosis and borderline NASH, but there was no significant difference between the groups (31).

It has been suggested that repair of endothelial cell damage is modulated by circulating bone marrow–derived endothelial progenitor cells (EPCs) and levels of EPCs reflect endothelial repair capacity (32). EPC numbers and migratory capacity are impaired in patients with CAD, and this impairment relates to the number of risk factors for cardiovascular artery disease. The patients with NAFLD have decreased circulating EPC numbers and impaired adhesive function and migration than those without NAFLD. These findings suggest that attenuated endothelial repair capacity may contribute to atherosclerotic disease progression and increased risk of cardiovascular events in NAFLD patients.

Non-alcoholic fatty liver disease and arterial stiffness

It has been shown that arterial stiffness is an independent indicator of symptomatic cardiovascular disease and events, as well as a measure of vascular health. Brachial-ankle pulse wave velocity (ba-PWV) is widely used as a simple index of assessing arterial stiffness and early atherosclerotic change (33). Several studies, made especially in Asia, investigate connection between ba-PWV and NAFLD. Huang et al. (27) has shown in a population-based study on 8632 subjects that NAFLD is associated with elevated ba-PWV, independent of conventional cardiovascular risk factors and the presence of metabolic syndrome. Young and middle-aged subjects without hypertension, diabetes, and obesity were included in an observational study that showed that NAFLD is independently associated with arterial stiffness (34). On 100 biopsy-proven NAFLD patients, Sün-

bül et al. (35) have investigated the relationships between arterial stiffness and the histological severity of NAFLD. They have demonstrated that increased arterial stiffness in NAFLD could reflect both the severity of the underlying hepatic disease and the extent of ectopic fat deposition (not only in the liver but also in the pericardium).

Non-alcoholic fatty liver disease and the pro-coagulant status

The presence of a hypercoagulability status linking NAFLD with a high risk of developing cardiovascular disease has been suggested based on the inflammatory status associated with this pathology and on epidemiological studies (1). Highly sensitive C-reactive protein (hs-CRP) levels were greater in patients with hepatic steatosis than in those without, regardless of metabolic changes (17). Another study, which evaluated 2388 patients diagnosed with NAFLD by echography, concluded that elevated levels of hs-CRP are associated with hepatic steatosis independent of obesity, metabolic syndrome, and other cardiovascular risk factors (36). Many other cross-sectional studies have shown that the serum levels of certain inflammatory markers, such as interleukin-6 and tumor necrosis factor, are elevated in NAFLD patients, average in those with simple steatosis, and low in non-steatosis, control subjects, and that these differences are independent of obesity and other factors (3).

However, a direct link between NAFLD and a pro-coagulant status has not been established yet, probably because of lack of an appropriate set of tests to explore in vivo coagulation. One study including 44 NAFLD patients has established that the thrombotic risk factors (the most frequent being resistance to activated protein C and protein S) are present in at least half of NAFLD patients, and that the presence of one or more thrombotic risk factors is associated with marked fibrosis (36). Another study including 60 patients with NAFLD diagnosed by liver biopsy has shown that thrombotic risk factors are present in more than a third of NAFLD patients, the most frequent risk factor being anti-cardiolipin antibodies (37). Tripodi et al. (38) have established that the plasma of the studied patients presents with a pro-coagulant imbalance that progresses from the initial phases of the disease to the most severe cirrhosis. The pro-coagulant unbalance seems to stem from the combined effect of an increase in factor VIII and a reduction in protein C levels and may cause an increase in thrombosis risk and/or hepatic fibrosis.

In a recent study (39), a wide array of pro-coagulant factors was investigated on a large sample of patients with NAFLD diagnosed by liver biopsy, and compared with a sample lacking in histological anomalies. It was determined that after correcting for metabolic risk factors, the plasma levels of the activated plasminogen inhibitor 1—a major inhibitor of the fibrinolytic system—were significantly elevated. These levels strongly correlated with the severity of the disease. Moreover, substantial epidemiologic clues point towards the fact that increased levels of activated plasminogen inhibitor 1 contribute to developing ischemic heart disease in the general population (39).

Anatol J Cardiol 2016; 16: 534-41

Sîrbu et al.
Non-alcoholic fatty liver disease   **539**

It has also been established that an increased platelet volume is associated with higher platelet activation. The average platelet volume (APV), which influences platelet activation, is a risk factor for atherothrombosis. An increase in APV is associated with acute myocardial ischemia (40), with an unfavorable prognosis for acute cerebrovascular ischemic events, independent of other clinical factors (41). A study conducted on 100 patients with NAFLD diagnosed by hepatic biopsy has concluded that the histological severity of the hepatic injury and inflammation is strongly associated with high levels of APV and therefore represents a potential increase in cardiovascular risk (42). Conversely, Kılçıler et al. (43) did not find any APV modifications in NAFLD patients compared to those without.

Non-alcoholic fatty liver disease and cardiac structure and functions

It seems that NAFLD could affect both left ventricular systolic and diastolic function (44,45). Even though some of these studies included fewer than 100 patients, it is very important that the results remained significant after adjustment for cardiometabolic risk factors. These outcomes are sustained by other subsequent studies; one of these studies underlined the changes of structures related to left ventricular diastolic function, such as left atrium deformation parameters and presence a subclinical myocardial dysfunction by speckle-tracking techniques (46,47). In these patients, there are consequences even on right ventricular diastolic and systolic functions (48). In addition, NAFLD could affect cardiac valves and is strongly associated with an increased risk of prevalent aortic valve sclerosis (49). Therefore, we could talk about an increased rate of congestive heart failure in this patient population (50). Obviously, due to these changes in cardiac and valvular function, there is also a high risk of arrhythmias, especially atrial fibrillation (50).

Conclusions

This narrative review underlined the association between NAFLD and cardiovascular disease. Many studies have shown that patients diagnosed with non-alcoholic fatty liver disease show a high incidence of cardiovascular events, independent of other risk factors. There is a strong association between NAFLD and endothelial dysfunction, arterial stiffness, hypercoagulability status, coronary and carotid artery atherosclerosis, cardiac and valvular functions, congestive heart failure, and arrhythmias (especially atrial fibrillation). The most important characteristic of this association is the rise in mortality and morbidity. Therefore non-alcoholic fatty liver disease diagnosis should become a red flag for the presence of high cardiovascular risk. Lifestyle modifications and drug therapy need to be initiated in an individualized manner for this group of patients, as well as the institution of periodic screening, in order to decrease the cardiovascular risk. Future studies may be necessary to determine the potential benefits of screening for the non-alcoholic fatty liver disease diag-

nosis and, implicitly, to highlight a category of high cardiovascular risk patients who may benefit from aggressive cardiovascular prevention strategies.

References

1. Fargion S, Porzio M, Fracanzani AL. Non-alcoholic fatty liver disease and vascular disease: state of art. World J Gastroenterol 2014; 20: 13306-24. **[Crossref]**
2. Trivedi I, Rinella ME. NAFLD and cardiovascular disease: can the real association be determined? Curr Hepatology Rep 2014; 13: 130-41. **[Crossref]**
3. Scorletti E, Calder PC, Byrne CD. Non-alcoholic fatty liver disease and cardiovascular risk: metabolic aspects and novel treatments. Endocrine 2011; 40: 332-43. **[Crossref]**
4. Dongiovanni P, Romeo S, Valenti L. Genetic factors in the pathogenesis of nonalcoholic fatty liver and steatohepatitis. Biomed Res Int 2015; 2015: 460190. **[Crossref]**
5. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. J Hepatol 2009; 51: 433-45. **[Crossref]**
6. Permutt Z, Le TA, Peterson MR, Seki E, Brenner DA, Sirlin C, et al. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non-alcoholic fatty liver disease - MRI accurately quantifies hepatic steatosis in NAFLD. Aliment Pharmacol Ther 2012; 36: 22-9. **[Crossref]**
7. Ahmed M. Non-alcoholic fatty liver disease in 2015. World J Hepatol 2015; 7: 1450-9. **[Crossref]**
8. Ratziu V, Giral P, Charlotte F, Bruckert E, Thibault V, Theodorou I, et al. Liver fibrosis in overweight patients. Gastroenterology 2000; 118: 1117-23. **[Crossref]**
9. Anty R, Iannelli A, Patouraux S, Bonnafous S, Lavallard VJ, Senni-Burattiet M, et al. A new composite model including metabolic syndrome, alanine aminotransferase and cytokeratin-18 for the diagnosis of non-alcoholic steatohepatitis in morbidly obese patients. Aliment Pharmacol Ther 2010; 32: 1315-22. **[Crossref]**
10. Ulitsky A, Ananthakrishnan AN, Komorowski R, Wallace J, Surapaneni SN, Franco J, et al. A noninvasive clinical scoring model predicts risk of nonalcoholic steatohepatitis in morbidly obese patients. Obes Surg 2010; 20: 685-91. **[Crossref]**
11. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006 ;6: 33. **[Crossref]**
12. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? Eur Heart J 2012; 33: 1190-200. **[Crossref]**
13. Choi DH, Lee SJ, Kang CD, Park MO, Choi DW, Kim TS. Nonalcoholic fatty liver disease is associated with coronary artery disease in

540 Sîrbu et al.
Non-alcoholic fatty liver disease

Anatol J Cardiol 2016; 16: 534-41

Koreans. World J Gastroenterol 2013; 19: 6453-7. **[Crossref]**

14. Chen CH, Nien CK, Yang CC, Yeh YH. Association between non-alcoholic fatty liver disease and coronary artery calcification. Dig Dis Sci 2010; 55: 1752-60. **[Crossref]**

15. Van Wagner LB, Ning H, Lewis CE, Shay CM, Wilkins J, Carr JJ, et al. Association between non-alcoholic fatty liver disease and subclinical atherosclerosis in middle-aged adults: The Coronary Artery Risk Development in Young Adults Study. Atherosclerosis 2014; 235: 599-605. **[Crossref]**

16. Fracanzani AL, Burdick L, Raselli S, Pedotti P, Grigore L Santorelly G, et al. Carotid artery intima-media thickness in non-alcoholic fatty liver disease. Am J Med 2008; 121: 72-8. **[Crossref]**

17. Ampuero J, Gallego-Duran R, Romero-Gomez M. Association of NAFLD with subclinical atherosclerosis and coronary artery disease: Meta-analysis. Rev Esp Enferm Dig 2015; 107: 10-6

18. Volzke H, Robinson DM, Kleine V, Deutscher R, Hoffmann W, Ludemann J, et al. Hepatic steatosis is associated with an increased risk of carotid atherosclerosis. World J Gastroenterol 2005; 11: 1848-53. **[Crossref]**

19. Gastaldelli A, Kozakova M, Hojlund K, Flyvbjerg A, Favuzzi A, Mitrakou A, et al. Fatty liver is associated with insulin resistance, risk of coronary heart disease and early atherosclerosis in a large European population. Hepatology 2009; 49: 1537-44. **[Crossref]**

20. Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Zenari L, et al. Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care 2006; 29: 1325-30. **[Crossref]**

21. Sesti G, Sciacqua A, Fiorentino TV, Perticone M, Succurro E, Perticone F. Association between noninvasive fibrosis markers and cardiovascular organ damage among adults with hepatic steatosis. PLoS One 2014; 9: e104941. **[Crossref]**

22. Mohammadi A, Sedani HH, Ghasemi-Ras M. Evaluation of carotid intima-media thickness and flow-mediated dilatation in middle-aged patients with nonalcoholic fatty liver disease. Vasc Health Risk Manag 2011; 7: 661-5.

23. Neri S, Signorelli SS, Scuderi R, Bruno M, Bertino G, Clementi A, et al. Carotid intima-media thickness and liver histology in hemodialysis patients with nonalcoholic fatty liver disease. Int J Angiol 2011; 20: 149-56. **[Crossref]**

24. Kang JH, Cho KI, Kim SM, Lee JY, Kim JJ, Goo JJ, et al. Relationship between non-alcoholic fatty liver disease and carotid artery Atherosclerosis beyond metabolic disorders in non-diabetic patients J Cardiovasc Ultrasound 2012; 20: 126-33. **[Crossref]**

25. Kim KS, OH HJ, Kim DJ, Kim SK, Park SW, Cho YW, et al. The association between nonalcoholic fatty liver disease and carotid atherosclerosis in subjects with within-reference range alanine aminotransferase levels. Endocr J 2013; 60: 1295-301. **[Crossref]**

26. Lankarani KB, Mahmoodi M, Lotfi M, Zamiri N, Heydari ST, Ghaffarpasand F, et al. Common carotid intima-media thickness in patients with non-alcoholic fatty liver disease: a population-based case-control study. Korean J Gastroenterol 2013; 62: 344-51. **[Crossref]**

27. Huang Y, Bi Y, Xu M, Ma Z, Xu Y, Wang T, et al. Non-alcoholic fatty liver disease is associated with atherosclerosis in middle-aged and elderly Chinese. Atherioscler Thromb Vasc Biol 2012; 32: 2321-6. **[Crossref]**

28. Çolak Y, Senates E, Yeşil A, Yılmaz Y, Öztürk O, Doğanay L, et al. Assessment of endothelial function in patients with nonalcoholic fatty liver disease. Endocrine 2013; 43: 100-7. **[Crossref]**

29. Thakur ML, Sharma S, Kumar A, Bhatt SP, Luthra K, Guleria R, et al. Nonalcoholic fatty liver disease is associated with subclinical atherosclerosis independent of obesity and metabolic syndrome in Asian Indians. Atherosclerosis 2012; 223: 507-11. **[Crossref]**

30. Vlachopoulos C, Manesis E, Baou K, Papatheodoridis G, Koskinas J, Tiniakos D, et al. Increased arterial stiffness and impaired endothelial function in non-alcoholic fatty liver disease: a pilot study. Am J Hypertens 2010; 23: 1183-9. **[Crossref]**

31. Boger RH, Bode-Boger SM, Szuba A, Tsao PS, Chan JR, Tangphao O, et al. Asymmetric Dimethylarginine (ADMA): A Novel risk factor for endothelial dysfunction: Its role in hypercholesterolemia. Circulation 1998; 98: 1842-7. **[Crossref]**

32. Werner N, Priller J, Laufs U, Endres M, Böhm M, Dirnagl U, et al. Bone marrow–derived progenitor cells modulate vascular reendothelialization and neointimal formation: effect of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition. Arterioscler Thromb Vasc Biol 2002; 22: 1567-72. **[Crossref]**

33. Yu XY, Zhao Y, Song XX, Song ZY. Association between non-alcoholic fatty liver disease and arterial stiffness in the non-obese, non-hypertensive, and non-diabetic young and middle-aged Chinese population. J Zhejiang Univ Sci B 2014; 15: 879-87. **[Crossref]**

34. Shiotani A, Motoyama M, Matsuda T, Miyanishi T. Brachial-ankle pulse wave velocity in Japanese university students. Intern Med 2005; 44: 696-701. **[Crossref]**

35. Sünbül M, Ağırbaşlı M, Durmuş E, Kikrak T, Akın H, Aydın Y, et al. Arterial stiffness in patients with non-alcoholic fatty liver disease is related to fibrosis stage and epicardial adipose tissue thickness. Atherosclerosis 2014; 237: 490-3. **[Crossref]**

36. Ndumele CE, Nasir K, Conceicao RD, Carvalhi JA, Blumenthal RS, Santos RD. Hepatic steatosis, obesity and the metabolic syndrome are independently and additively associated with increases systemic inflammation arteriosclerosis. Thromb Vasc Biol 2011; 31: 1927-32. **[Crossref]**

37. Assy N, Bekirov I, Mejritsky Y, Solomon L, Szvalb S, Hussein O. Association between thrombotic risk factors and extent of fibrosis in patients with non-alcoholic fatty liver diseases. World J Gastroenterol 2005; 11: 5834-9. **[Crossref]**

38. Tripodi A, Fracanzani AL, Primigani M, Chantarangkul V, Clerici M, Mannucci PM, et al. Procoagulant imbalance in patients with non-alcoholic fatty liver disease. J Hepatol 2014; 61: 148-54. **[Crossref]**

39. Hugenholtz GC, Northup PG, Porte RJ, Lisman T. Is there a rationale for treatment of chronic liver disease with antithrombotic therapy? Blood Rev 2015; 29: 127-36. **[Crossref]**

40. Pizzulli L, Yang A, Martin GF, Luderitz B. Changes in platelet size and count in unstable angina compared to stable angina or non-cardiac chest pain. Eur Heart J 1998; 19: 80-4. **[Crossref]**

41. Greisenegger S, Endler G, Hsieh K, Tentschert S, Mannhalter C, Lalouschek W. Is elevated mean platelet volume associated with a worse outcome in patients with acute ischemic cerebrovascular events? Stroke 2004; 35: 1688-91. **[Crossref]**

42. Alkhouri N, Kistangari G, Campbell C, Lopez Rzein NN, Feldstein AE. Mean platelet volume as a marker of increased cardiovascular risk in patients with nonalcoholic steatohepatitis. Hepatology 2012; 55: 331. **[Crossref]**

43. Kılçıler G, Genç H, Tapan S, Ors F, Kara M, Karadurmuş N, et al. Mean platelet volume and its relationship with carotid atherosclerosis in subjects with non-alcoholic fatty liver disease. Ups J Med Sci 2010; 115: 253-9. **[Crossref]**

44. Bonapace S, Perseghin G, Molon G, Canali G, Bertolini L, Zoppini G, et al. Nonalcoholic fatty liver disease is associated with left ventricular diastolic dysfunction in patients with type 2 diabetes. Diabetes Care 2012; 35: 389-95. **[Crossref]**

Anatol J Cardiol 2016; 16: 534-41

Sirbu et al.
Non-alcoholic fatty liver disease   *541*

45. Fotbolcu H, Yakar T, Duman D, Karaahmet T, Tigen K, Çevik C, et al. Impairment of the left ventricular systolic and diastolic function in patients with non-alcoholic fatty liver disease. Cardiol J 2010; 17: 457-63.

46. Baktır AO, Şarlı B, Altekin RE, Karaman A, Arınç H, Sağlam H, et al. Non-alcoholic steatohepatitis is associated with subclinical impairment in left ventricular function measured by speckle tracking echocardiography. Anatol J Cardiol 2015; 15: 137-42. **[Crossref]**

47. Karabay CY, Kocabay G, Kalaycı A, Çolak Y, Oduncu V, Akgün T, et al. Impaired left ventricular mechanics in nonalcoholic fatty liver disease: a speckle-tracking echocardiography study. Eur J Gastroenterol Hepatol 2014; 26: 325-31. **[Crossref]**

48. Bekler A, Gazi E, Erbağ G, Binnetoğlu E, Barutçu A, Şen H, et al. Right ventricular function and its relationship with grade of hepatosteatosis in non-alcoholic fatty liver disease. Cardiovasc J Afr 2015; 26: 109-13. **[Crossref]**

49. Bonapace S, Valbusa F, Bertolini L, Pichiri I, Mantovani A, Rossi A, et al. Nonalcoholic fatty liver disease is associated with aortic valve sclerosis in patients with type 2 diabetes mellitus. PloS One 2014; 9: e88371. **[Crossref]**

50. Ballestri S, Lonardo A, Bonapace S, Byrne CD, Loria P, Targher G. Risk of cardiovascular, cardiac and arrhythmic complications in patients with non-alcoholic fatty liver disease. World J Gastroenterol 2014; 20: 1724-45. **[Crossref]**