Review Articles

Cardiovascular Disorders in the Context of Non-Alcoholic Fatty Liver Disease: A Literature Review

Reza Karbasi-Afshar, MD[1, 2], Amin Saburi, MD[3*], Hossein Khedmat, MD[4]

[1]*Atherosclerosis Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.*
[2]*Department of Cardiology, Baqiyatallah University of Medical Sciences, Tehran, Iran.*
[3]*Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.*
[4]*Baqiyatallah Research Center for Gastroenterology and Liver Disease, Tehran, Iran.*

Received 12 March 2013; Accepted 06 December 2013

Abstract

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in the United States and other industrialized countries, and the reported prevalence in the developing countries is also rather high. This disease is associated with a high rate of morbidity and mortality and damage to the other organs. The cardiovascular system is, perhaps, the most vulnerable organ to NAFLD adverse effects to the extent that most mortality associated with this disease is reportedly from the cardiovascular system rather than from the liver itself. In this article, we review the significant aspects of cardiovascular disorders associated with NAFLD, including the epidemiology of cardiovascular diseases in NAFLD patients, factors that interfere in this relationship like hypertension, severity of NAFLD, and age of the patients, and finally preventive strategies whose employment could significantly improve the outcome.

J Teh Univ Heart Ctr 2014;9(1):1-8

This paper should be cited as: Karbasi-Afshar R, Saburi A, Hossein Khedmat H. Cardiovascular Disorders in the Context of Non-Alcoholic Fatty Liver Disease: A Literature Review. J Teh Univ Heart Ctr 2014;9(1):1-8.

Keywords: *Heart • Coronary artery disease • Non-alcoholic fatty liver disease • Review*

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in the industrialized countries. Evidence suggests that it is probably as common in the developing world as it is in the developed world, with a prevalence up to 45% in the general population.[1, 2] NAFLD is a term used to define a large spectrum of conditions, ranging from simple non-symptomatic steatosis to non-alcoholic steatohepatitis, and cirrhosis.[3] Nevertheless, hepatic disorders are not the sole morbidity associated with NAFLD, and several extra-hepatic manifestations of this disease, including malignancies and cardiovascular events, threaten patients' lives.[4, 5]

Cardiovascular disorders constitute major health threats in NAFLD patients. An increased rate of cardiovascular events has been reported in this population,[6] while cardiovascular mortality in these patients has independently increased in those with a prominent metabolic syndrome.[4] Moreover, patients with non-alcoholic steatohepatitis (NASH), a more destructive form of NAFLD, are probably at higher risk of atherosclerosis formation than patients with simple steatosis.[7]

In this article, we review the current literature on the existing data on potential associations between cardiovascular

*Corresponding Author: ***Amin Saburi,*** *Chemical Injuries Research Center, Baqiyatallah University of Medical sciences, Vanak Square, Tehran, Iran. P.O.Box: 14155-3651. Tel: +98-21-81261. Fax: +98 21 88934125. E-mail: dr.saburiamin@gmail.com.*

disorders and NAFLD. The research focuses on most recent articles (especially since 2010) and/or strongest data (prospective and large studies).

Epidemiology of Coronary Atherosclerosis and Non-Alcoholic Fatty Liver Disease Associations

Overwhelming data indicate powerful associations between NAFLD and the risk factors of cardiovascular disorders.[8-11] Compared to the general population with confirmed non-steatotic liver, NAFLD patients have impaired flow-mediated vasodilatation, which is a reliable marker of subclinical atherosclerosis, and this impairment is independent of other established risk factors, including obesity.[12] In a study of 312 consecutive patients undergoing elective coronary angiography, 34 patients with NAFLD diagnosis represented significantly decreased circulating bone marrow-derived endothelial progenitor cells (cEPCs) levels (all p values < 0.05), attenuated EPCs functions, and enhanced systemic inflammation compared to the controls. Multivariate analysis showed that the cEPC level [CD34 + KDR + (cells/105 events)] was an independent reverse predictor of NAFLD (OR: 0.78, 95%CI: 0.69–0.89; p value < 0.001).[13]

Moreover, several studies have shown that NAFLD can result in clinical atherosclerosis as well. In a study of 10153 Korean people participating in an occupational cohort, having fatty liver determined by ultrasonographic evaluation was associated with coronary artery calcification defined by computed tomography, and this association was independent from the conventional risk factors.[13] In another interesting Korean study, 4023 subjects of no known history of either liver or coronary disease were evaluated with the same methodology of the previous one and the authors found that NAFLD was independently associated with coronary artery calcification, and interestingly a higher score of coronary calcification was associated with a higher prevalence of NAFLD.[14] Almost similar to this result, in a study evaluating patients consecutively referred for elective coronary angiography, NAFLD was independently associated with more severe coronary artery disease.[15] A community-based cohort of 2088 male Taiwanese workers showed that the diagnosis of NAFLD by ultrasonography was independently associated with the presence of ischemic changes in electrocardiography.[16] Another study from Taiwan through multivariate analysis showed that the prevalence of NAFLD in asymptomatic patients increased with the severity of the coronary artery calcification score (≤ 100, 38.1%; 101-400, 58.3%; > 400, 64.3%; p value = 0.03).[17] Yilmaz et al.,[18] in their study of coronary flow reserve (CFR) in NAFLD patients found that over 42% of the patients had impaired CFR and this impairment was lowest in patients with more advanced liver fibrosis.

Epidemiology of Coronary Artery Events among Non-Alcoholic Fatty Liver Disease Patients

Several prospective studies have been conducted to examine whether NAFLD and cardiovascular disorders are somehow connected together. Hamaguchi et al.[19] conducted a 5-year prospective cohort study of apparently healthy Japanese people who had come for check-up evaluations and studied them for the availability of NAFLD and the metabolic syndrome. At the end of the follow-up time, the authors found that the incidence of cardiovascular disorders in the NAFLD group was significantly higher than that in the non-NAFLD controls (2.2% vs. 0.3%, respectively; OR: 4.12; 95%CI: 1.58-10.75; p value = 0.004). Another study by the same authors confirmed the previous results; the authors expanded the study with a longer follow-up period (6.5 years) and found a similar relationship between death and cardiovascular disease.[20] Wong et al.[21] showed that NAFLD was an independent predictor of cardiovascular events (adjusted OR: 2.31; 95%CI: 1.46 to 3.64). A more recent prospective cohort study by Lazo et al.[22] on 11371 adults followed for up to 18 years revealed that, compared to the participants without steatosis, those with NAFLD but normal liver enzyme levels had multivariate adjusted hazard ratios (HR) for deaths from cardiovascular disease of 0.86 (0.67 to 1.12). Similar results were obtained when the data were reanalyzed for the NAFLD patients with abnormal liver enzyme levels (OR: 0.59, 95%CI: 0.29-1.20). There are some prominent retrospective cohorts of very long follow-up periods,[23-28] whose data are summarized in Table 1.

Non-Alcoholic Fatty Liver Disease in the Presence of Metabolic Disorders

Metabolic factors are the cornerstone of the pathogenesis of NAFLD,[8] and it is supposed that most ominous events associated with NAFLD are due to the metabolic disorders in this disease. Diabetes mellitus is the main metabolic disorder and can lead to NAFLD or affect its prognosis. In type 2 diabetic patients with known coronary artery disease, Lautamäki et al.[29] found that NAFLD diagnosed by magnetic resonance spectroscopy was independently associated with reduced myocardial perfusion. Targher et al.[30] carried out a 5-year prospective nested case-control study in 2103 type 2 diabetic patients with a diagnosis of cardiovascular disorders at baseline. After adjustment for demographic data as well as conventional risk factors, the presence of NAFLD was significantly associated with an increased risk of cardiovascular events (OR: 1.84, 95%CI:

Table 1. Major retrospective cohort studies on the associations between non-alcoholic fatty liver disease (NAFLD) and cardiovascular events

Study authors	Follow-up (y)	Main results	NAFLD population size
Rafiq et al.[23]	18.5	The most common causes of death were coronary artery disease, malignancy, and liver-related death; with no difference between the NAFLD subtypes.	173 biopsy-proven NAFLD
Ekstedt et al. [24]	13.7	Risk of death from cardiovascular disease was higher by a factor of 2 among 129 patients with non-alcoholic steatohepatitis than in the general population.	129 biopsy-proven NAFLD
Söderberg et al.[25]	28.0	Cardiovascular reasons were the main cause of death in the NAFLD population (30%). Non-alcoholic steatohepatitis (NASH) was associated with increased mortality from all causes and from cardiovascular disease.	118 biopsy-proven NAFLD (20% NASH)
Adams et al. [26]	7.6	There were higher rates of cardiovascular mortality in NASH patients than in the general population.	420 biopsy/imaging diagnosis of NAFLD
Dam-Larsen et al. [27]	20.4	There were higher rates of cardiovascular death in NAFLD patients. Mortality was not associated with histological grading.	170 biopsy-proven NAFLD
Wang et al.[28]	10.0	Risk of cardiovascular disease increased with increasing fatty liver status in both genders. The difference was not only present between individuals with fatty liver vs. non-fatty liver but also between the mild fatty liver and significant fatty liver groups. The odds ratio for every increment of fatty liver severity was 2.3 in the women (95%CI: 1.4-3.5) and 2.7 in the men (95%CI: 1.7-4.1).	462 imaging-diagnosed NAFLD

1.4-2.1; p value < 0.001). In another study by the same authors, involving around 3000 patients with type 2 diabetes, the prevalence of coronary artery disease was independently higher among patients with NAFLD than among those without this disease.[20] Similar findings were also reported by another study on type 1 diabetes.[31] In type 2 diabetic patients with well-controlled metabolic status, even mild elevation in liver enzymes was proved to be independently related to decreased insulin sensitivity and impaired brachial artery flow-mediated vasodilation.[32] In children, NAFLD in overweight individuals has been proven to be associated with multiple cardiovascular risk factors, including higher serum levels of fasting glucose, insulin, total cholesterol, low-density lipoprotein cholesterol, and triglycerides as well as higher systolic and diastolic blood pressure and lower high-density lipoprotein cholesterol, than overweight and obese children without NAFLD (controls).[33] Multivariable analysis in the same study revealed that the children with the metabolic syndrome had 5.0 (95%CI: 2.6-9.7) times the odds of having NAFLD as the controls.

Gamma-glutamyltransferase (g-GT) is a subclinical indicator of insulin resistance,[34] and it has been suggested that its high serum values represent early evidence for oxidative stress. Moreover, hepatic steatosis is characterized by an elevated level of g-GT,[35] which is also a predictor of coronary artery disease.[36] A large population-based study conducted in Germany reported that elevated gamma-glutamyl transpeptidase (GGT) levels in men with hepatic steatosis were strongly associated with higher mortality rates (HR: 1.98; 95%CI: 1.21-3.27).[35] In the same study, when death due to cardiovascular reasons was evaluated, a more than twofold increased risk of cardiovascular disease mortality from elevated GGT levels for both sexes in an age-adjusted model was observed [HR: 2.58 (95%CI: 1.22-5.45) in the males and 3.78 (95%CI: 1.04;-13.73) in the females]. However, in the multiple adjusted model, the association was only preserved for the males [HR: 2.80 (95%CI: 1.24; 6.31) compared to 2.34 (0.61; 8.96) for the females].[35]

Non-Alcoholic Fatty Liver Disease in Patients without Metabolic Syndrome and Cardiovascular Risk Factors

As was mentioned before, overwhelming data suggest that the metabolic syndrome has the strongest relationship with NAFLD.[8] However, there are no extensive data on the cardiovascular risk in NAFLD patients who do not show the metabolic syndrome. Young patients with NAFLD who do not represent the major components of the metabolic syndrome, including diabetes and hypertension, have the echocardiographic features of early left ventricular dysfunction[37] and generally show abnormal left ventricular metabolism.[38] Villanova et al.[39] reported that the brachial artery endothelial flow-mediated vasodilation was decreased in non-diabetic subjects with NAFLD compared with that in control subjects and this decrease was associated with the histological severity of NAFLD independent of age, sex, insulin resistance, and other variables of the metabolic syndrome. Outstandingly, the 10-year possibility of coronary

artery events was moderately increased in these patients.[39]

Non-Alcoholic Fatty Liver Disease and Left Ventricular Disorders

NAFLD has also been reportedly associated with functional and anatomical damage to cardiac ventricles. In a study on Indian adolescents, Singh et al.[40] found that in obese subjects with NAFLD, left ventricular global longitudinal systolic strain and early diastolic strain rates were significantly decreased than lean NAFLD adolescents. Also, the same observation was reported in obese subjects with NAFLD rather than those without NAFLD. In another study on children and adolescents in Turkey, Alp et al.[41] reported increased end-systolic thickness of the interventricular septum as well as larger left ventricular mass and left ventricular index in NAFLD subjects as compared to controls. They also reported that the interventricular septum was statistically different in the study groups. A study on adult NAFLD patients younger than 55 years of age reported increased thickness of the intraventricular septum and posterior wall as well as larger left ventricular mass/height in the NAFLD group. In the same study, left ventricular systolic function was similar in both groups; however, patients with NAFLD had a lower peak velocity of early and early/late ratio diastolic filing in echocardiography.[37] In another study on patients with confirmed diagnosis of essential hypertension, NAFLD was diagnosed in 48 (56%) patients and their data were compared to the 38 reaming patients without NAFLD. The patients with NAFLD had similar prevalence of left ventricular hypertrophy compared to the patients without NAFLD but with higher prevalence of diastolic dysfunction, which remained significant even after multivariate analysis.[42] Another study on patients with essential hypertension, however, showed that NAFLD was associated with insulin resistance but not with increased arterial stiffness.[43]

Non-Alcoholic Fatty Liver Disease and Arterial Hypertension

A population-based prospective longitudinal study in Germany on about 3200 subjects showed that fatty liver was independently associated with increased diastolic blood pressure and hypertension at baseline and with increased systolic blood pressure and hypertension at follow-up. Individuals with fatty liver had a 3-fold higher chance of hypertension at baseline and follow-up (OR: 2.8, 95%CI: 1.3-6.2 and OR: 3.1, 95%CI: 1.7-5.8, respectively) compared to individuals without fatty liver; all the above-mentioned associations were independent to alcohol consumption.[44] Another population-based study from Spain showed that NAFLD was independently associated with prevalent hypertension with an adjusted OR of 1.71 (95%CI: 1.10-2.65).[45] Among non-hypertensive participants, NAFLD was also independently associated with high-normal systolic blood pressure (adjusted OR: 2.13, 95%CI: 1.08-4.20) but not with high-normal diastolic blood pressure. Vasunta et al.,[46] on the other hand, reported higher day-time and night-time measurements of systolic blood pressure as well as day-time measures of diastolic blood pressure in NAFLD patients than in NAFLD-free subjects.

Severity of Fatty Liver and Cardiovascular Diseases

Severity of NAFLD disease and cardiovascular diseases have also been shown to be associated.[47] Choi et al.,[48] in their large study of over 5769 individuals with fatty liver, found that patients with more severe NAFLD were at higher risk for coronary artery disease. In a study in the pediatric context, the authors reported that an increased carotid artery intima-media thickness (IMT), which is a marker of early-generalized atherosclerosis, was associated with higher fatty liver severity.[49] A significant decrease in the brachial artery flow-mediated vasodilation has also been reported to be allied to the severity of NAFLD histology.[47] On the other hand, serum levels of adiponectin, as a marker of cardiovascular disease,[50] have also been reportedly associated with the histological severity of NAFLD.[51] Similarly, the serum levels of plasminogen activator inhibitor-1 (PAI-1), another proven risk factor for cardiovascular disease, have been associated with the histological severity of NAFLD.[52] Consequently, according to the current literature, besides its presence, the severity of NAFLD is also a predictor of more severe cardiovascular disease.

Childhood Fatty Liver

NAFLD is the most common cause of chronic liver disease in children and adolescents in most of the Western world. In the United States, an autopsy study showed that about 10% of the American population aged 2-19 years had NAFLD, with 38% prevalence among obese ones.[53] Similar high figures have been reported among children from Asian countries.[54] The condition in Iran is, albeit better, far from satisfactory.[55] In a recent retrospective study with a 20-year follow-up period, 66 children with NAFLD underwent a total of about 410 person-years follow-up. In this first report of the long-term prognosis of NAFLD in children, the disease was proven to be able to advance to the end-stage liver disease even in children,[56] and the log-rank test showed that observed survival free of liver transplantation was significantly shorter in the NAFLD cohort compared to

the expected survival in the general United States population of the same age and sex (log-rank test; p value < 0.001). The same study showed that children with NAFLD had a 13.6 (95%CI: 3.8 to 34.8; p value < 0.0001) -fold higher mortality rate or liver transplantation requirement than the general population of the same age and sex. This expands our view on the relevance of the issue in children and alerts us to the significance of the prevention and treatment of this population. In a case-control study of 150 children by Schwimmer et al.,[56] having NAFLD was associated with the components of the metabolic syndrome, which are strong predictors of cardiovascular morbidity (discussed before). Another study by the same author involving 817 children having undergone autopsy revealed that the prevalence of coronary heart disease was increased by a factor of 2 among those with NAFLD (Schwimmer JB, Deutsch R, Behling C, Lavine JE. Fatty liver as a determinant of atherosclerosis. Hepatology 2005;42:Suppl:610A. abstract). The same study reported that atherosclerosis was significantly more prevalent in children with fatty liver (30% vs. 19%). An interesting observation was a lack of independent association between the body mass index (BMI) and the presence of atherosclerosis, but there was a significant association between fatty liver status and BMI. On the other hand, the odds of having atherosclerosis in obese children were more than 6 times higher among subjects with fatty liver than those without. Nobili et al.,[57] reporting from the Bogalusa Heart Study in children, demonstrated that the extent of atherosclerotic coverage over the intimal surface was significantly associated with dyslipidemia indices, all of which [total cholesterol/ high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c)/ HDL-c] are well-established predictors of cardiovascular diseases.[58] These data suggest that NAFLD may present as a promoting factor for the cardiovascular threats of overweight and obese children.

Grade of NAFLD has also been reported as a major factor in cardiovascular risk determination of children with NAFLD. Weghuber et al.[59] showed that obese children with simple steatosis rather than steatohepatitis seem to have intact vascular function defined by flow-mediated dilation of the brachial artery measured by ultrasound. In an interesting study from Iran, Kelishadi et al.[60] investigated 100 adolescents and showed that vascular disease in the carotid artery was associated with the ultrasonographic findings of NAFLD. The same findings have been reported in other countries, but because this review article focuses on coronary artery disease and not carotid artery disease, we refer readers to an excellent review article recently published by Pacifico et al.[61]

Prevention and Treatment

NAFLD is a disease of a wide-spectrum pathogenesis with reported high levels of mortality.[62, 63] As a result, the preventive as well as treatment strategies which might have beneficial effects for this disease are also extended, are not applicable to all, and have controversial effectiveness. In our previous studies, we showed that the cardiovascular system is susceptible to insults from seemingly non-associated factors, including hepatic infection by the hepatitis C virus (HCV).[64-66] In a study by Sanyal et al.,[67] investigating differential effects of Pioglitazone, vitamin E, or placebo on non-alcoholic steatohepatitis patients, the authors reported that cardiovascular events occurred with equal frequency in all the three mentioned study groups, although they admitted that their trial might be much too limited to detect meaningful differences in the incidence of cardiovascular events. Several clinical trials have investigated the potential effects of fish oil and/or Omega-3 polyunsaturated fatty acid (n-3 PUFA) consumption on the outcomes of cardiovascular disease. A review on these studies by Wang et al.[68] showed that fish oil significantly reduced myocardial infarction and cardiac and sudden death, and 33 articles reported the preventive effects of it on primary cardiovascular diseases. Be that as it may, the existing literature also contains controversial reports. Another elaborate review article on the potential effects of fatty fish and n-3 PUFA by Mozaffarian and Wu[69] showed their very controversial effects on cardiovascular diseases.[69] In NAFLD patients, Pioglitazone has been proven to have improving effects on the metabolic status.[70] A recent and very extensive review of literature by Musso et al.[71] demonstrated that weight loss through lifestyle modifications was safe and improved cardio-metabolic risk profile; statins and polyunsaturated fatty acids improved steatosis; and Thiazolidinediones improved histological disease activity, glucose, lipid, and inflammatory variables and delayed fibrosis progression. Pioglitazone also improved blood pressure. Vitamin E administration was associated with an increase in insulin resistance and plasma triacylglycerols.[71] Statins are one of the most effective treatment agents in the management of NAFLD.[72] It also has been suggested that statins are the best drugs in the management of cardiovascular disorders in NAFLD patients.[73] The same authors in the prospective GREACE study showed that use of statins, especially Atorvastatin, in NAFLD patients was associated with a significantly lower rate of cardiovascular events (10% vs. 30%).[74] On the other hand, some authors have doubted the effectiveness of statins in reducing cardiovascular risk in NAFLD patients in the absence of dyslipidemia.[75]

Lifestyle interventions such as diet modifications and exercise are fundamental for the treatment of NAFLD. However, like other treatment strategies of NAFLD, they also represent controversial effects on the cardiovascular risk profile. Since a recent review article has assessed this issue thoroughly, we refer readers to this review article by Thoma et al.[76]

Conclusion

NAFLD is an extremely important disease both in the developed and developing countries due to its high prevalence and high rate of morbidity and mortality. This review article addressed cardiovascular disease in the context of NAFLD because of its prominent role in the adverse effects associated with the disease. The ominous effects of NAFLD are not restricted to its components and even in their absence, NAFLD induces morbidity and mortality rates much higher than those in the general population; and often is associated with the severity of liver disease to the extent that NASH is sometimes considered a cardiovascular-dominated manifestation of NAFLD. Not surprisingly, NAFLD-associated morbidity and mortality even affect children. The treatment strategies for NAFLD and cardiovascular disease are similar and are aimed primarily at lifestyle modifications in order to reduce insulin resistance and other cardiometabolic risk factors. Pharmacotherapy for NAFLD is mostly reserved for patients with more severe disease and patients with high-risk factors for cardiovascular disease. Such patients are candidates for early intervention aimed at preventing cardiovascular diseases and controlling the liver disease itself, bearing in mind that most NAFLD patients will ultimately die from cardiovascular events before advanced liver disease develops.

References

1. Liu CJ. Prevalence and risk factors for non-alcoholic fatty liver disease in Asian people who are not obese. J Gastroenterol Hepatol 2012;27:1555-1560.
2. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274-285.
3. Khedmat H, Taheri S. Non-alcoholic steatohepatitis: an update in pathophysiology, diagnosis and therapy. Hepat Mon 2011;11:74-85.
4. Younossi ZM, Otgonsuren M, Venkatesan C, Mishra A. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. Metabolism. 2013;62:352-360.
5. Otgonsuren M, Stepanova M, Gerber L, Younossi ZM. Anthropometric and clinical factors associated with mortality in subjects with nonalcoholic fatty liver disease. Dig Dis Sci 2013;58:1132-1140.
6. Stepanova M, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. Clin Gastroenterol Hepatol 2012;10:646-650.
7. Alkhouri N, Tamimi TA, Yerian L, Lopez R, Zein NN, Feldstein AE. The inflamed liver and atherosclerosis: a link between histologic severity of nonalcoholic fatty liver disease and increased cardiovascular risk. Dig Dis Sci 2010;55:2644-2650.
8. Smits MM, Ioannou GN, Boyko EJ, Utzschneider KM. Non-alcoholic fatty liver disease as an independent manifestation of the metabolic syndrome: results of a US national survey in three ethnic groups. J Gastroenterol Hepatol 2013;28:664-670.
9. Liu J, Young TK, Zinman B, Harris SB, Connelly PW, Hanley AJ. Lifestyle variables, non-traditional cardiovascular risk factors, and the metabolic syndrome in an Aboriginal Canadian population. Obesity (Silver Spring) 2006;14:500-508.
10. Kelly AS, Steinberger J, Jacobs DR, Hong CP, Moran A, Sinaiko AR. Predicting cardiovascular risk in young adulthood from the metabolic syndrome, its component risk factors, and a cluster score in childhood. Int J Pediatr Obes 2011;6:e283-289.
11. Chiang CH, Huang PH, Chung FP, Chen ZY, Leu HB, Huang CC, Wu TC, Chen JW, Lin SJ. Decreased circulating endothelial progenitor cell levels and function in patients with nonalcoholic fatty liver disease. PLoS One 2012;7:e31799.
12. Villanova N, Moscatiello S, Ramilli S, Bugianesi E, Magalotti D, Vanni E, Zoli M, Marchesini G. Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. Hepatology 2005;42:473-480.
13. Sung KC, Wild SH, Kwag HJ, Byrne CD. Fatty liver, insulin resistance, and features of metabolic syndrome: relationships with coronary artery calcium in 10,153 people. Diabetes Care 2012;35:2359-2364.
14. Kim D, Choi SY, Park EH, Lee W, Kang JH, Kim W, Kim YJ, Yoon JH, Jeong SH, Lee DH, Lee HS, Larson J, Therneau TM, Kim WR. Nonalcoholic fatty liver disease is associated with coronary artery calcification. Hepatology 2012;56:605-613.
15. Mirbagheri SA, Rashidi A, Abdi S, Saedi D, Abouzari M. Liver: an alarm for the heart? Liver Int 2007;27:891-894.
16. Lin YC, Lo HM, Chen JD. Sonographic fatty liver, overweight and ischemic heart disease. World J Gastroenterol 2005;11:4838-4842.
17. Chen CH, Nien CK, Yang CC, Yeh YH. Association between nonalcoholic fatty liver disease and coronary artery calcification. Dig Dis Sci 2010;55:1752-1760.
18. Yilmaz Y, Kurt R, Yonal O, Polat N, Celikel CA, Gurdal A, Oflaz H, Ozdogan O, Imeryuz N, Kalayci C, Avsar E. Coronary flow reserve is impaired in patients with nonalcoholic fatty liver disease: association with liver fibrosis. Atherosclerosis 2010;211:182-186.
19. Hamaguchi M, Kojima T, Takeda N, Nagata C, Takeda J, Sarui H, Kawahito Y, Yoshida N, Suetsugu A, Kato T, Okuda J, Ida K, Yoshikawa T. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. World J Gastroenterol 2007;13:1579-1584.
20. Targher G, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G, Arcaro G. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. Diabetes Care 2007;30:2119-2121.
21. Wong VW, Wong GL, Yip GW, Lo AO, Limquiaco J, Chu WC, Chim AM, Yu CM, Yu J, Chan FK, Sung JJ, Chan HL. Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. Gut 2011;60:1721-1727.
22. Lazo M, Hernaez R, Bonekamp S, Kamel IR, Brancati FL, Guallar E, Clark JM. Non-alcoholic fatty liver disease and mortality among US adults: prospective cohort study. BMJ 2011;343:d6891.
23. Rafiq N, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, Younossi ZM. Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol 2009;7:234-238.
24. Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865-873.
25. Söderberg C, Stål P, Askling J, Glaumann H, Lindberg G, Marmur J, Hultcrantz R. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. Hepatology 2010;51:595-602.
26. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129:113-121.
27. Dam-Larsen S, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. Scand J Gastroenterol 2009;44:1236-1243.
28. Wang CC, Tseng TC, Hsieh TC, Hsu CS, Wang PC, Lin HH, Kao

JH. Severity of fatty liver on ultrasound correlates with metabolic and cardiovascular risk. Kaohsiung J Med Sci 2012;28:151-160.
29. Lautamäki R, Borra R, Iozzo P, Komu M, Lehtimäki T, Salmi M, Jalkanen S, Airaksinen KE, Knuuti J, Parkkola R, Nuutila P. Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. Am J Physiol Endocrinol Metab 2006;291:E282-290.
30. Targher G, Bertolini L, Poli F, Rodella S, Scala L, Tessari R, Zenari L, Falezza G. Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. Diabetes 2005;54:3541-3546.
31. Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Pichiri I, Sorgato C, Zenari L, Bonora E. Prevalence of non-alcoholic fatty liver disease and its association with cardiovascular disease in patients with type 1 diabetes. J Hepatol 2010;53:713-718.
32. Schindhelm RK, Diamant M, Bakker SJ, van Dijk RA, Scheffer PG, Teerlink T, Kostense PJ, Heine RJ. Liver alanine aminotransferase, insulin resistance and endothelial dysfunction in normotriglyceridaemic subjects with type 2 diabetes mellitus. Eur J Clin Invest 2005;35:369-374.
33. Schwimmer JB, Pardee PE, Lavine JE, Blumkin AK, Cook S. Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease. Circulation 2008;118:277-283.
34. André P, Balkau B, Vol S, Charles MA, Eschwège E; DESIR Study Group. Gamma-glutamyltransferase activity and development of the metabolic syndrome (International Diabetes Federation Definition) in middle-aged men and women: Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort. Diabetes Care 2007;30:2355-2361.
35. Haring R, Wallaschofski H, Nauck M, Dörr M, Baumeister SE, Völzke H. Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. Hepatology 2009;59:1403-1411.
36. Meisinger C, Döring A, Schneider A, Löwel H; KORA Study Group. Serum gamma-glutamyltransferase is a predictor of incident coronary events in apparently healthy men from the general population. Atherosclerosis 2006;189:297-302.
37. Goland S, Shimoni S, Zornitzki T, Knobler H, Azoulai O, Lutaty G, Melzer E, Orr A, Caspi A, Malnick S. Cardiac abnormalities as a new manifestation of nonalcoholic fatty liver disease: echocardiographic and tissue Doppler imaging assessment. J Clin Gastroenterol 2006;40:949-955.
38. Perseghin G, Lattuada G, De Cobelli F, Esposito A, Belloni E, Ntali G, Ragogna F, Canu T, Scifo P, Del Maschio A, Luzi L. Increased mediastinal fat and impaired left ventricular energy metabolism in young men with newly found fatty liver. Hepatology 2008;47:51-58.
39. Villanova N, Moscatiello S, Ramilli S, Bugianesi E, Magalotti D, Vanni E, Zoli M, Marchesini G. Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. Hepatology 2005;42:473-480.
40. Singh GK, Vitola BE, Holland MR, Sekarski T, Patterson BW, Magkos F, Klein S. Alterations in ventricular structure and function in obese adolescents with nonalcoholic fatty liver disease. J Pediatr 2013;162:1160-1168.
41. Alp H, Karaarslan S, Selver Eklioğlu B, Atabek ME, Altın H, Baysal T. Association between nonalcoholic fatty liver disease and cardiovascular risk in obese children and adolescents. Can J Cardiol 2013;29:1118-1125.
42. Fallo F, Dalla Pozza A, Sonino N, Lupia M, Tona F, Federspil G, Ermani M, Catena C, Soardo G, Di Piazza L, Bernardi S, Bertolotto M, Pinamonti B, Fabris B, Sechi LA. Non-alcoholic fatty liver disease is associated with left ventricular diastolic dysfunction in essential hypertension. Nutr Metab Cardiovasc Dis 2009;19:646-653.
43. Catena C, Bernardi S, Sabato N, Grillo A, Ermani M, Sechi LA, Fabris B, Carretta R, Fallo F. Ambulatory arterial stiffness indices and non-alcoholic fatty liver disease in essential hypertension. Nutr Metab Cardiovasc Dis 2013;23:389-393.
44. Lau K, Lorbeer R, Haring R, Schmidt CO, Wallaschofski H, Nauck M, John U, Baumeister SE, Völzke H. The association between fatty liver disease and blood pressure in a population-based prospective longitudinal study. J Hypertens 2010;28:1829-1835.
45. López-Suárez A, Guerrero JM, Elvira-González J, Beltrán-Robles M, Cañas-Hormigo F, Bascuñana-Quirell A. Nonalcoholic fatty liver disease is associated with blood pressure in hypertensive and nonhypertensive individuals from the general population with normal levels of alanine aminotransferase. Eur J Gastroenterol Hepatol 2011;23:1011-1017.
46. Vasunta RL, Kesäniemi YA, Ylitalo AS, Ukkola OH. High ambulatory blood pressure values associated with non-alcoholic fatty liver in middle-aged adults. J Hypertens 2012;30:2015-2019.
47. Targher G, Marra F, Marchesini G. Increased risk of cardiovascular disease in non-alcoholic fatty liver disease: causal effect or epiphenomenon? Diabetologia 2008;51:1947-1953.
48. Choi SY, Kim D, Kim HJ, Kang JH, Chung SJ, Park MJ, Kim YS, Kim CH, Choi SH, Kim W, Kim YJ, Yoon JH, Lee HS, Cho SH, Sung MW, Oh BH. The relation between non-alcoholic fatty liver disease and the risk of coronary heart disease in Koreans. Am J Gastroenterol 2009;104:1953-1960.
49. Pacifico L, Cantisani V, Ricci P, Osborn JF, Schiavo E, Anania C, Ferrara E, Dvisic G, Chiesa C. Nonalcoholic fatty liver disease and carotid atherosclerosis in children. Pediatr Res 2008;63:423-427.
50. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol 2004;24:29-33.
51. Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? Hepatology 2004;40:46-54.
52. Targher G, Bertolini L, Rodella S, Lippi G, Franchini M, Zoppini G, Muggeo M, Day CP. NASH predicts plasma inflammatory biomarkers independently of visceral fat in men. Obesity (Silver Spring) 2008;16:1394-1399.
53. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. Pediatrics 2006;118:1388-1393.
54. Goh SC, Ho ELM, Goh KL. Prevalence and risk factors of non-alcoholic fatty liver disease in a multiracial suburban Asian population in Malaysia. Hepatol Int 2012;3:1-7.
55. Alavian SM, Mohammad-Alizadeh AH, Esna-Ashari F, Ardalan G, Hajarizadeh B. Non-alcoholic fatty liver disease prevalence among school-aged children and adolescents in Iran and its association with biochemical and anthropometric measures. Liver Int 2009;29:159-163.
56. Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut 2009;58:1538-1544.
57. Nobili V, Alkhouri N, Bartuli A, Manco M, Lopez R, Alisi A, Feldstein AE. Severity of liver injury and atherogenic lipid profile in children with nonalcoholic fatty liver disease. Pediatr Res 2010;67:665-670.
58. Brumbaugh DE, Crume TL, Nadeau K, Scherzinger A, Dabelea D. Intramyocellular lipid is associated with visceral adiposity, markers of insulin resistance, and cardiovascular risk in prepubertal children: the EPOCH study. J Clin Endocrinol Metab 2012;97:E1099-1105.
59. Weghuber D, Roden M, Franz C, Chmelik M, Torabia S, Nowotny P, Gruber S, Waldhäusl W, Klingler A, Bieglmayer C, Bischof M, Wolzt M, Schaller G, Widhalm K. Vascular function in obese children with non-alcoholic fatty liver disease. Int J Pediatr Obes 2011;6:120-127.
60. Kelishadi R, Cook SR, Amra B, Adibi A. Factors associated with insulin resistance and non-alcoholic fatty liver disease among youths. Atherosclerosis 2009;204:538-543.
61. Pacifico L, Nobili V, Anania C, Verdecchia P, Chiesa C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. World J Gastroenterol 2011;17:3082-3091.

62. Salt WB, 2nd. Nonalcoholic fatty liver disease (NAFLD): a comprehensive review. J Insur Med 2004;36:27-41.
63. Sdiri W, Romdhane H, Mbarek D, Ben Abdallah H, Longo S, Abdelli MN, Boujnah MR. Non alcoholic fatty liver disease: a new risk factor for cardiovascular disease?. Tunis Med 2013;91:171-174.
64. Karbasi-Afshar R, Adibi P, Khedmat H, Jalali AR. How Hepatitis C Virus Infection Contributes to Cardiovascular Disease: A Systematic Review. Int J Travel Med Glob Health 2013;1:55-64.
65. Karbasi-Afshar R, Saburi A, Taheri S. Clinical associations between renal dysfunction and vascular events: A literature review. ARYA Atheroscler 2013;9:203-209.
66. Karbasi-Afshar R, Joneidi Jafari N, Velayati AA. Human Immunodeficiency Virus (HIV) and Coronary Atherosclerotic Plaque Formation: A Review. Int J Travel Med Glob Health 2013;1:65-74.
67. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675-1685.
68. Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr 2006;84:5-17.
69. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 2011;58:2047-2067.
70. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297-2307.
71. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomized trials. Diabetologia 2012;55:885-904
72. Ghamar-Chehreh ME, Amini M, Khedmat H, Daraei F, Mohtashami R, Karbasi A, Taheri S. Comparative effectiveness of ezetimibe in improving lipid profile in non-alcoholic fatty liver disease patients: statins still rule. Int J Biol 2012;4:184-190.
73. Athyros VG, Tziomalos K, Daskalopoulos GN, Karagiannis A, Mikhailidis DP. Statin-based treatment for cardiovascular risk and non-alcoholic fatty liver disease. Killing two birds with one stone? Ann Med 2011;43:167-171.
74. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, Pagourelias ED, Theocharidou E, Karagiannis A, Mikhailidis DP; GREACE Study Collaborative Group. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet 2010;376:1916-1922.
75. Dima A, Marinescu AG, Dima AC. Non-alcoholic fatty liver disease and the statins treatment. Rom J Intern Med 2012;50:19-25.
76. Thoma C, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. J Hepatol 2012;56:255-266.