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Review paper

The influence of NAFLD on the risk of atherosclerosis and cardiovascular diseases

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in developed countries and is associated with obesity, dyslipidaemia, diabetes, and metabolic syndrome. Atherosclerosis and cardiovascular diseases are also highly prevalent in this group of patients, due to the presence of shared risk factors. The incidences of coronary artery calcification, hypertension, aortic valve sclerosis, diastolic dysfunction, atherosclerotic plaques, and increased carotid intima-media thickness were more common in patients with NAFLD than in those without. The present paper reviews the medical literature concerning the association between NAFLD and cardiovascular events.

Key words: non-alcoholic fatty liver disease, ischaemic heart disease, atherosclerosis.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in developed countries, with a prevalence ranging from 20% to 30% of the population of Europe. However, experts estimate that NAFLD affects from 25% to 90% of obese patients and 70% of patients with diabetes mellitus [1, 2]. The histologic spectrum of NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis (NASH) with the presence of fibrosis. Simple steatosis tends to be a stable condition, but steatohepatitis may progress to liver cirrhosis [3]. Liver failure in the course of NAFLD is the second most common indication for liver transplantation in the USA [4].

NAFLD is diagnosed mostly in patients between the ages of 40 and 60 years. Although the prevalence of NAFLD is higher in men, faster progression to cirrhosis is noted in women [5]. NAFLD is regarded as an isolated disease or as a spectrum of metabolic syndrome, and is associated with diabetes, obesity, dyslipidaemia, and hypertension [6]. NAFLD is found in 30% to 75% of patients with type 2 diabetes, depending on age and ethnicity [7]. Types of dyslipidaemia have a significant impact on the prevalence of NAFLD. Mixed hyperlipidaemia is reported in 50% of patients with NAFLD. Isolated hypertriglyceridaemia is reported in 27% of subjects with NAFLD, and hypercholesterolaemia in 17% [8]. An analysis of lipid fractions in patients with NAFLD revealed a tendency towards elevated triglyceride levels and low HDL levels in the atherogenic lipid profile [9].

Insulin resistance contributes to the development of NAFLD. Subclinical inflammation plays also an important role in the pathogenesis of NAFLD. High-sensitivity C-reactive protein (Hs-CRP) is elevated in patients suffering with NAFLD, even in young age; hs-CRP may be a marker of NAFLD [10-12]. Hs-CRP is not associated with severity of NAFLD or NASH [11, 12]. Subclinical inflammation also plays the principal role in the pathophysiology of atherosclerosis. Hs-CRP is a stronger cardiovascular risk predictor than LDL-C (low-density lipoprotein) [13]. However, many other studies have shown that oxidant stress and chronic inflammation associated with the production of cytokines including interleukin (IL) 6, tumour necrosis factor α

(TNF-α), pro-coagulant factors, and adipocytokines are also involved in NAFLD pathogenesis [14, 15]. These risk factors are also strongly related to atherosclerosis. Patients with NAFLD exhibit a range of non-traditional risk factors of cardiovascular disease, including hyperuricaemia and hypovitaminosis D [16]. In addition, shared genetic factors exist between NAFLD and coronary artery heart disease, for instance: gene polymorphisms of adiponectin-encoding gene (ADIPOQ), leptin receptor (LEPR), apolipoprotein C3 (APOC3), peroxisome proliferator-activated receptors (PPAR), sterol regulatory element binding proteins (SREBP), transmembrane 6 superfamily member 2 (TM6SF2), microsomal triglyceride transfer protein (MTTP), TNF-α, and manganese superoxide dismutase (MnSOD) [17].

Association between cardiovascular risk and NAFLD

The individuals with NAFLD had a higher risk of 10-year cardiovascular events than healthy individuals. In subjects with and without NAFLD, the mean respective cardiovascular risks according to Framingham scoring were 16.0% and 12.7% in men and 6.7% and 4.6%, in women [18].

A meta-analysis of 34 studies (164,494 participants) published between 1965 and 2015 indicates an increased risk of cardiovascular disease in NAFLD patients, although the prevalence of NAFLD was not associated with mortality from cardiovascular events in this group. The results of this study suggest that NAFLD was an independent risk factor for the incidence of cardiovascular events [19]. However, Hamaguchi *et al.* report that NAFLD is strongly related to metabolic syndrome. Because it is important to note that it is extremely difficult to separate the components of metabolic syndrome in statistical analysis, Hamaguchi *et al.* suggest that high cardiovascular risk in patients with NAFLD is not a consequence of liver disease but of metabolic syndrome [20].

Association between NAFLD, type 2 diabetes, and cardiovascular risk

NAFLD is hepatic manifestation of metabolic syndrome and may predict the development of type 2 diabetes independently of obesity and age [21]. Insulin resistance is a key pathogenic factor for NAFLD and type 2 diabetes. The presence of NAFLD increases twofold the risk of developing type 2 diabetes over a median period of five years [21]. Ekstedt *et al.* found that 78% of patients with NAFLD develop type 2 diabetes or impaired glucose tolerance [22]. Patients with NAFLD and diabetes have a 2-4-fold increased risk of cardiovascular diseases [23]. Of note, the meta-analysis published by Ballestri shows that NAFLD is also associated with an approximately twofold increased risk of incident of metabolic syndrome [24]. Again, Gami *et al.* in a meta-analysis of 37 studies comprising 172,573 patients with metabolic syndrome, found 1.78-fold higher relative risk of cardiovascular events in patients with metabolic syndrome compared to healthy subjects [25]. In another meta-analysis that incorporated 16 observational studies with 34,043 patients with NAFLD, the authors concluded that the presence of NAFLD conferred an OR of 1.64 for fatal and non-fatal incidence of cardiovascular events, and the risk appeared to increase with greater severity of NAFLD [26]. A large number of studies confirm the relationship between NAFLD and incidence of cardiovascular events and death (Table 1).

NAFLD and coronary artery disease

An increasing number of studies suggest the presence of a relationship between NAFLD and coronary artery heart disease [34, 35]. It is estimated that cancers and cardiovascular disease are the leading causes of death in patients with NAFLD [36]. NAFLD is observed in 51% of patients with mild and insignificant coronary stenosis and in as much as 100% of patients with three affected coronary arteries [37]. Perera *et al.* note the presence of NAFLD in 46.7% of patients with acute coronary syndrome [38]. Patients with NAFLD show a significantly higher prevalence of calcified and non-calcified coronary plaques than healthy subjects, independent of the incidence of metabolic syndrome [39]. Again, the coronary flow reserve (CFR), measured as the maximum increase in blood flow through the coronary arteries above the normal resting volume, is significantly lower in patients with NAFLD than in healthy subjects [40].

NAFLD and arrhythmias

NAFLD is associated with an increased risk of the incidence of arrhythmias, especially the atrial fibrillation or ventricular tachyarrhythmias typically observed in the course of left ventricular diastolic dysfunction [41].

NAFLD and hypertension

Hypertension is diagnosed in about 50% of patients with NAFLD [42]. Hypertension predisposes to the development of left ventricular hypertrophy and increases the risk of plaque rupture.

Table 1. Selected observational studies exploring the risk of cardiovascular disease in patients with non-alcoholic fatty liver disease (NAFLD)

Authors, year [ref.]	Study population	Follow-up length	NAFLD diagnosis	Main findings
Söderberg *et al.*, 2010 [27]	Retrospective cohort of 118 Swedish patients with NAFLD and raised serum liver enzymes	24 years	Histology	Patients with NASH, but not those with simple steatosis, had twofold higher rate of cardiovascular disease than the matched general population.
Ekstedt *et al.*, 2015 [28]	Retrospective cohort of 229 Swedish patients with biopsy-proven NAFLD	26.4 ± 5.6 years	Histology	Patients with NAFLD have increased overall mortality (HR 1.29, 95%CI: 1.04-1.59), with a high risk of death from cardiovascular diseases (HR 1.55, 95% CI: 1.11-2.15) and liver-related disease. Stage of fibrosis rather than presence of NASH predicted both overall and disease specific mortality.
Fracanzani *et al.*, 2016 [29]	Prospective case-control study of 125 Italian patients with NAFLD and 250 age-matched and sex-matched control individuals without known liver diseases	10 years	Histology and ultrasound	NAFLD was independently associated with incident non-fatal coronary heart disease (HR 1.99, 95% CI: 1.01-3.91).
Targher *et al.*, 2007 [30]	Prospective cohort of 2103 Italian individuals with type 2 diabetes without baseline viral hepatitis and cardiovascular disease	6.5 years	Ultrasound	NAFLD was independently associated with increased risk of fatal and non-fatal cardiovascular disease events (HR 1.87, 95% CI: 1.2-2.6).
Wong *et al.*, 2016 [31]	612 consecutive Chinese patients undergoing coronary angiograms without knowing liver disease	6 years	Ultrasound	Patients with NAFLD, compared to those without, were more likely to have > 50% stenosis in one or more coronary arteries. NAFLD was not significantly associated with fatal and non-fatal cardiovascular disease events.
Treeprasertsuk *et al.*, 2012 [32]	Community-based cohort of 309 US patients with NAFLD	11.5 ± 4.1 years	Ultrasound and computer tomography	Patients with NAFLD have a higher 10-year cardiovascular disease risk than general population of the same age and sex.
Zeb *et al.*, 2016 [33]	Prospective cohort study of 4119 US adult participants who were free of cardiovascular disease and known liver disease at baseline (The Multi-Ethnic Study of Atherosclerosis)	7.6 years	Computer tomography	NAFLD was independently associated with incident of coronary heart disease events (HR 1.42, 95% CI: 1.00-2.03).

NAFLD and atherosclerosis

The greater intima-media thickness (IMT) of carotid arteries represents a marker of endothelial dysfunction, and subclinical atherosclerosis was found in patients with NAFLD [43]. NAFLD is associated with a high coronary artery calcification score, irrespective of the presence of traditional cardiovascular risk factors and metabolic syndrome [44]. Lower flow-mediated dilation (FMD)-indicated endothelial dysfunction is found in patients with NAFLD and is associated with an elevated risk of acute coronary syndrome and ischaemic stroke [45, 46].

Increased arterial stiffness, as a marker of cardiac hypertrophy and early atherosclerotic changes, was reported in patients with NAFLD [47]. Brachial-ankle pulse wave velocity is used as a simple index of assessing arterial stiffness [48]. Lee *et al.* reported elevated brachial-ankle pulse wave velocity in patients with NAFLD, independent of conventional cardiovascular risk factors and the presence of metabolic syndrome [49]. The increased arterial stiffness results from the degeneration of the extracellular matrix of elastic arteries, apoptosis of endothelial cells, and diffusion of macromolecules into the arterial wall [50]. The decrease in vascular susceptibility leads to an increase in cardiac afterload output and insufficient coronary flow [51].

NAFLD and ischaemic stroke

NAFLD was found in 42.7% of ischaemic stroke patients and 22.7% of controls in a population from Iran. It is estimated that the risk of ischaemic stroke in NAFLD sufferers is 1.68-times higher than in the general population and is associated with the incidence of traditional cardiovascular risk factors [52].

NAFLD and left ventricular systolic and diastolic dysfunction

Morphological and functional changes in cardiac myocytes are observed in cases of NAFLD [53]. Myo-

cardial steatosis is a well-known predictor of diastolic heart failure [54]. Diastolic dysfunction is three times more common in patients with NAFLD than in the general population, especially left ventricular relaxation correlating with NAFLD Activity Score (NAS) [55, 56]. Trovato *et al*. reported a higher left ventricular mass index in patients with NAFLD [57]. In these patients, there is a significantly greater left ventricular filling pressure (E/e' ratio: mitral filling velocity [E]/ early diastolic mitral annular velocity [E/e'] ratio) [55]. However, NAFLD patients with obesity, hypertension, or diabetes also display impaired left ventricular systolic function [58].

NAFLD patients tend to demonstrate the presence of epicardial adipose tissue [59], which acts as a source of pro-inflammatory cytokines and increases the risk of cardiovascular diseases [60]. In addition, NAFLD is strongly associated with an increased risk of aortic valve sclerosis, which is an independent indicator of atherosclerosis [61]. Aortic stenosis is the most common valvular heart disease and increases the risk of cardiovascular death [62].

Histological severity of NAFLD and incidence of cardiovascular diseases

Byrne *et al*. reported a correlation between the risk for cardiovascular mortality and the progression of NAFLD [63]. Many studies found the stage of liver fibrosis and steatosis in NAFLD to be related to the incidence of cardiovascular diseases [64]. Targher *et al*. identified increased carotid IMT levels in advanced stages of hepatic steatosis, necroinflammation, and fibrosis in NAFLD, independent of the presence of traditional risk factors, insulin resistance, and metabolic syndrome [65]. Individuals with NAFLD and advanced fibrosis had a 3.5-fold greater risk of left ventricular hypertrophy [66]. In patients with NAFLD, increased arterial stiffness and epicardial fat thickness, impaired left ventricular function, and higher coronary calcification score correlate with the progression of fibrosis in NAFLD [67].

Treatment of NAFLD could decrease cardiovascular risk

Statin therapy in patients with NAFLD decreases fat accumulation in the liver and even decreases fibrosis in some NAFLD patients [68]. It has been known for many years that statins decrease coronary heart disease risk [69]. This cardiovascular disease benefit is significantly greater in patients with elevated liver enzymes due to NAFLD than it is in patients with normal liver tests [70]. We could explain an excellent protection of statin treatment against cardiovascular risk in NAFLD patients not only with reduction of fat accumulation in atheromatous plaques but also with reduction of subclinical inflammation and with decrease of pro-coagulant factors production in the cardiovascular system, especially in coronary arteries [71]. Statin hepatotoxicity is minimal in patients with elevated liver tests [70]. Study published by Ruscica *et al*. showed that liver fat accumulation is associated with increased circulating PCSK9 (proprotein convertase subtilisin/ kexin type 9) [72]. PCSK9 inhibitors have significant cardiovascular benefit in high-risk patients, but the effect of PCSK9 inhibition on liver fat accumulation and liver fibrosis is still unknown [73]. The cardiovascular benefit of other promising NAFLD treatment options must also be studied in the future.

Patients with NAFLD possess a high risk of developing acute or chronic cardiovascular diseases with shared pathogenic factors. Therefore, it is necessary to estimate the cardiovascular risk in patients with NAFLD and to determine the potential benefits of early cardiovascular prevention strategies.

Disclosure

Authors report no conflict of interest.

References

1. Bellentani S, Scaglioni F, Marino M, et al. Epidemiology of non-alcoholic fatty liver disease. Dig Dis 2010; 28: 155-161.
2. Scorletti E, Calder PC, Byrne CD. Non-alcoholic fatty liver disease and cardiovascular risk: metabolic aspects and novel treatments. Endocrine 2011; 40: 332-343.
3. Hyogo H, Chayama K, Yamagishi S.˙Nonalcoholic fatty liver disease and cardiovascular disease. Curr Pharm Des 2014; 20: 2403-2411.
4. Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol 2013; 10: 686-690.
5. Bacon BR, Farahvash MJ, Janney CG, et al. Nonalcoholic steatohepatitis: an expanded clinical entity. Gastroenterology 1994; 107: 1103-1109.
6. Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatitis steatosis in Northern Italy. Ann Intern Med 2000; 18: 112-117.
7. Lonardo A, Ballestri S, Marchesini G, et al. Nonalcoholic fatty liver disease: a precusor of the metabolic syndrome. Dig Liver Dis 2015; 47: 181-190.
8. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. Hepatology 1990; 12: 1106-1110.
9. DeFilippis AP, Blaha MJ, Martin SS, et al. Nonalcoholic fatty liver disease and serum lipoprotens: the Multi-Ethnic Study of Atherosclerosis 2013; 227: 429-436.
10. Jarcuska P, Janicko M, Drazilova S, et al. Gamma-glutamyl transpeptidase level associated with metabolic syndrome and proinflammatory parameters in the young Roma population in

eastern Slovakia: a population-based study. Cent Eur J Public Health 2014; 22: 43-50.
11. Yeniova AO, Kucukazman M, Ata N, et al. High-sensitivity C-reactive protein is a strong predictor of non-alcoholic fatty liver disease. Hepatogastroenterology 2014; 61: 422-425.
12. Zimmermann E, Anty R, Tordjman J, et al. C-reactive protein levels in relation to various features of non-alcoholic fatty liver disease among obese patients. J Hepatol 2011; 55: 660-665.
13. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342: 836-843.
14. Assy N, Bekirov I, Mejritsky Y, et al. Association between thrombotic risk factors and extent of fibrosis in patients with non-alcoholic fatty liver diseases. World J Gastroenterol 2005; 7: 5834-5855.
15. Takaki A, Kawai D, Yamamoto K. Multiple hits, including oxidative stress, as pathogenesis and treatment target in non-alcoholic steatohepatitis (NASH). Int J Mol Sci 2013; 15: 20704-20728.
16. Targher G, Bertolini L, Scala L, et al. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2007; 17: 517-524.
17. Li XL, Sui JQ, Lu LL, et al. Gene polymorphisms associated with non-alcoholic fatty liver disease and coronary artery disease: a concise review. Lipids Health Dis 2016; 10: 53.
18. Motamed N, Rabiee B, Poustchi H, et al. Non-alcoholic fatty liver disease (NAFLD) and 10-year risk of cardiovascular diseases. Clin Res Hepatol Gastroenterol 2017; 41: 31-38.
19. Wu S, Wu F, Ding Y, et al. Association of non-alcoholic fatty liver disease with major adverse cardiovascular events: A systematic review and meta-analysis. Sci Rep 2016; 16: 33386.
20. Hamaguchi M, Takeda N, Kojima T, et al. Identification of individuals with non-alcoholic fatty liver disease by the diagnostic criteria for the metabolic syndrome. World J Gastroenterol 2012; 7: 1508-1516.
21. Lallukka S, Yki-Jarvinen H. Non-alcoholic fatty liver disease and risk of type 2 diabetes. Best Pract Res Clin Endocrinol Metab 2016; 30: 385-395.
22. Ekstedt M, Franzén LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006; 44: 865-873.
23. Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993; 16: 434-444.
24. Ballestri S, Zona S, Targher G, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. J Gastroenterol Hepatol 2016; 31: 936-944.
25. Gami A, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: A systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007; 49: 403-414.
26. Targher G, Byrne CD, Lonardo A, et al. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol 2016; 65: 589-600.
27. Söderberg C, Stål P, Askling J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. Hepatology 2010; 51: 595-602.
28. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015; 61: 1547-1554.
29. Fracanzani AL, Tiraboschi S, Pisano G, et al. Progression of carotid vascular damage and cardiovascular events in non-alcoholic fatty liver disease patients compared to the general population during 10 years of follow-up. Atherosclerosis 2016; 246: 208-213.
30. Targher G, Bertolini L, Padovani R, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007; 30: 1212-1218.
31. Wong VW, Wong GL, Yeung JC, et al. Long-term clinical outcomes after fatty liver screening in patients undergoing coronary angiogram: A prospective cohort study. Hepatology 2016; 63: 754-763.
32. Treeprasertsuk S, Leverage S, Adams LA, et al. The Framingham risk score and heart disease in nonalcoholic fatty liver disease. Liver Int 2012; 32: 945-950.
33. Zeb I, Li D, Budoff MJ, Katz R, et al. Nonalcoholic Fatty Liver Disease and Incident Cardiac Events: The Multi-Ethnic Study of Atherosclerosis. Am Coll Cardiol 2016; 26: 1965-1966.
34. Baharvand-Ahmadi B, Sharifi K, Namdari M. Prevalence of non-alcoholic fatty liver disease in patients with coronary artery disease. ARYA Atherosclerosis 2016; 12: 201-205.
35. Ajmal MR, Yaccha M, Malik MA, et al. Prevalence of nonalcoholic fatty liver disease (NAFLD) in patients of cardiovascular diseases and its association with hs-CRP and TNF-α. Indian Heart J 2014; 66: 574-579.
36. Armstrong MJ, Adams LA, Canbay A, et al. Extrahepatic complications of nonalcoholic fatty liver disease. Hepatology 2014; 59: 1174-1197.
37. Choi DH, Lee SJ, Kang CD, et al. Nonalcoholic fatty liver disease is associated with coronary artery disease in Koreans. World J Gastroenterol 2013; 19: 6453-6457.
38. Perera N, Indrakumar J, Abeysinghe WV, et al. Non alcoholic fatty liver disease increases the mortality from acute coronary syndrome: an observational study from Sri Lanka. BMC Cardiovasc Disord 2016; 16: 37.
39. Assy N, Djibre A, Farah R, et al. Presence of coronary plaques in patients with nonalcoholic fatty liver disease. Radiology 2010; 254: 393-400.
40. Pinarbaşi B, Demır K, Oflaz H, et al. Measurement of the coronary flow velocity reserve in patients with non-alcoholic fatty liver disease. Turk J Gastroenterol 2012; 23: 720-726.
41. Käräjämäki AJ, Pätsi OP, Savolainen M, et al. Non-Alcoholic Fatty Liver Disease as a Predictor of Atrial Fibrillation in Middle-Aged Population (OPERA Study). PLoS One 2015; 16: e0142937.
42. Tsang SW, Ng WF, Wu BP, et al. Predictors of fibrosis in Asian patients with non-alcoholic steatohepatitis. J Gastroenterol Hepatol 2006; 21: 116-121.
43. Kim HC, Kim DJ, Huh KB. Association between nonalcoholic fatty liver disease and carotid intima-media thickness according to the presence of metabolic syndrome. Atherosclerosis 2009; 204: 521-525.
44. Jaruvongvanich V, Wirunsawanya K, Sanguankeo A, et al. Nonalcoholic fatty liver disease is associated with coronary artery calcification: A systematic review and meta-analysis. Dig Liver Dis 2016; 48: 1410-1417.
45. Colak Y, Senates E, Yesil A, et al. Assessment of endothelial function in patients with nonalcoholic fatty liver disaease. Endocrine 2013; 43: 100-107.
46. Brevetti G, Silvestro A, Schiano V, et al. Endothelial dysfunction and cardiovascular risk prediction in peripheral arterial disease: additive value of flow-mediative delation to ankle-brachial pressure index. Circulation 2003; 28: 2093-2098.

47. Salvi P, Ruffini R, Agnoletti D, et al. Increased arterial stiffness in nonalcoholic fatty liver disease: the Cardio-GOOSE study. J Hypertens 2010; 28: 1699-1707.
48. Shiotani A, Motoyama M, Matsuda T, et al. Brachial-ankle pulse wave velocity in Japanese university students. Intern Med 2005; 44: 696-701.
49. Lee YJ, Shim JY, Moon BS, et al. The relationship between arterial stiffness and nonalcoholic fatty liver disease. Dig Dis Sci 2012; 57: 196-203.
50. Laurent S, Boutouyrie P, Lacolley P. Structural and genetic bases of arterial stiffness. Hypertension 2005; 45: 1050-1055.
51. Quinn U, Tomlinson LA, Cockcroft JR. Arterial stiffness. JRSM Cardiovasc Dis 2012; 30: 1.
52. Moshayedi H, Ahrabi R, Mardani A, et al. Association between non-alcoholic fatty liver disease and ischemic stroke. Iran J Neurol 2014; 4: 144-148.
53. Iacobellis G, Barbarini G, Letizia C, et al. Epicardial fat thickness and nonalcoholic fatty liver disease in obese subjects. Obesity (Silver Spring) 2014; 22: 332-336.
54. Peterson LR, Herrero P, Schechtman KB, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. Circulation 2004; 11: 2191-2196.
55. Mantovani A, Pernigo M, Bergamini C, et al. Nonalcoholic Fatty Liver Disease Is Independently Associated with Early Left Ventricular Diastolic Dysfunction in Patients with Type 2 Diabetes. PLoS One 2015; 7: 0135329.
56. Goland S, Shimoni S, Zornitzki T, et al. Cardiac abnormalities as a new manifestation of nonalcoholic fatty liver disease: echocardiographic and tissue Doppler imaging assessment. J Clin Gastroenterol 2006; 40: 949-955.
57. Trovato FM, Martines GF, Catalano D, et al. Echocardiography and NAFLD (non-alcoholic fatty liver disease). Int J Cardiol 2016; 15: 275-279.
58. Rijzewijk LJ, van der Meer RW, Smit JW, et al. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. J Am Coll Cardiol 2008; 25: 1793-1799.
59. Pisto P, Santaniemi M, Bloigu R, et al. Fatty liver predicts the risk for cardiovascular events in middle-aged population: a population-based cohort study. BMJ Open 2014; 20: e004973.
60. Iacobellis G, Pistilli D, Gucciardo M, et al. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. Cytokine 2005; 21: 251-255.
61. Bonapace S, Valbusa F, Bertolini L, et al. Nonalcoholic fatty liver disease is associated with aortic valve sclerosis in patients with type 2 diabetes mellitus. PLoS One 2014; 5: e88371.
62. Gorczyca-Michta I, Pietrzyk E, Michta K, et al. Zwężenie zastawki aortalnej o etiologii degeneracyjnej – choroba leczona operacyjnie niezależnie od wieku. Prezentacja dwóch przypadków. Choroby Serca i Naczyń 2013; 10: 224-228.
63. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol 2015; 62: 47-64.
64. Domanski JP, Park SJ, Harrison SA. Cardiovascular disease and nonalcoholic fatty liver disease: does histologic severity matter? J Clin Gastroenterol 2012; 46: 427-430.
65. Targher G, Bertolini L, Padovani R, et al. Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care 2006; 29: 1325-1330.
66. Sesti G, Sciacqua A, Fiorentino TV, et al. Association between noninvasive fibrosis markers and cardio-vascular organ damage among adults with hepatic steatosis. PLoS One 2014; 11: e104941.
67. Sunbul M, Agirbasli M, Durmus E, 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: 490-349.
68. Ekstedt M, Franzen LE, Mathiesen UL, et al. Statins in non-alcoholic fatty liver disease and chronically elevated liver enzymes: a histopathological follow-up study. J Hepatol 2007; 47: 135-141.
69. Kjekshus J, Pedersen TR. Reducing the risk of coronary events: evidence from the Scandinavian Simvastatin Survival Study (4S). Am J Cardiol 1995; 76: 64-68.
70. Athyros VG, Tziomalos K, Gossios TD, et al. 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.
71. Janicko M, Drazilova S, Pella D, et al. Pleiotropic effects of statins in the diseases of the liver. World J Gastroenterol 2016; 22: 6201-6213.
72. Ruscica M, Ferri N, Macchi C, et al. Liver fat accumulation is associated with circulating PCSK9. Ann Med 2016; 48: 384-391.
73. Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. N Engl J Med 2017; 376: 1527-1539.