

From the liver to the heart: Cardiac dysfunction in obese children with non-alcoholic fatty liver disease

Anna Di Sessa, Giuseppina Rosaria Umano, Emanuele Miraglia del Giudice, Nicola Santoro

Anna Di Sessa, Giuseppina Rosaria Umano, Emanuele Miraglia del Giudice, Department of Woman and Child and General and Specialized Surgery, Seconda Università degli Studi di Napoli, 80138 Naples, Italy

Anna Di Sessa, Nicola Santoro, Department of Pediatrics, Yale University School of Medicine, New Haven, CT 06520, United States

Author contributions: All the authors conceived and wrote the manuscript.

Supported by The Allen Foundation, the American Heart Association (AHA), No. 13SDG14640038; and the American Heart Association (AHA) to Dr Nicola Santoro, No. 16IRG27390002.

Conflict-of-interest statement: Nothing to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Nicola Santoro, MD, PhD, Department of Pediatrics, Yale University School of Medicine, 330 Cedar Street, PO Box 208064, New Haven, CT 06520, United States. nicola.santoro@yale.edu
Telephone: +1-203-7376356
Fax: +1-203-7856421

Received: August 22, 2016

Peer-review started: August 24, 2016

First decision: September 27, 2016

Revised: October 24, 2016

Accepted: November 21, 2016

Article in press: November 22, 2016

Published online: January 18, 2017

Abstract

In the last decades the prevalence of non-alcoholic fatty liver disease (NAFLD) has increased as a consequence of the childhood obesity world epidemic. The liver damage occurring in NAFLD ranges from simple steatosis to steatohepatitis, fibrosis and cirrhosis. Recent findings reported that fatty liver disease is related to early atherosclerosis and cardiac dysfunction even in the pediatric population. Moreover, some authors have shown an association between liver steatosis and cardiac abnormalities, including rise in left ventricular mass, systolic and diastolic dysfunction and epicardial adipose tissue thickness. In this editorial, we provide a brief overview of the current knowledge concerning the association between NAFLD and cardiac dysfunction.

Key words: Cardiac dysfunction; Non-alcoholic fatty liver disease atherosclerosis; Children; Cardiovascular risk

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Recently, growing scientific evidences suggest that obese children with non-alcoholic fatty liver disease are more predisposed to cardiovascular disease. Interestingly, this association seems to be independent from adiposity. In fact, based on recent findings, it has been proposed that liver steatosis plays an independent role in determining early atherosclerosis and cardiac dysfunction.

Di Sessa A, Umano GR, Miraglia del Giudice E, Santoro N. From the liver to the heart: Cardiac dysfunction in obese children with non-alcoholic fatty liver disease. *World J Hepatol* 2017; 9(2):

INTRODUCTION

Currently, non-alcoholic fatty liver disease (NAFLD) represents the major cause of chronic liver disease in childhood and is considered a multisystem disease that affects many extra-hepatic organs^[1]. Experimental evidence suggests that children with NAFLD have a higher risk of developing end stage liver disease than the general population of United States of same age and gender^[2]. Moreover, NAFLD has emerged as an independent risk factor for cardiovascular diseases (CVD)^[3,4], including coronary artery disease and cardiac dysfunction^[5-8].

The molecular mechanisms linking NAFLD to cardiovascular complications are still poorly understood^[6,8]. Children with NAFLD display increased free fatty acids that may lead to myocardial lipid accumulation with consequent impairments in myocardial substrate metabolism and efficiency and, finally, cardiac dysfunction^[7,8]. Moreover, the presence of a low-grade inflammatory state in these patients contributes to the release of several mediators that amplify this condition^[6,8]. Therefore, it has been hypothesized that intra-hepatic fat might exert a key pathogenetic role in developing cardio-metabolic complications (Figure 1).

In the last 20 years, NAFLD has become the most common liver disease in pediatrics^[1], as result of the increased prevalence of early onset obesity^[2,4]. Although NAFLD develops in the context of insulin resistance related to obesity, it is possible that a parental effect exists. As suggested by experimental studies in rats, in fact, paternal and maternal obesity during preconception could lead to obesity, glucose metabolism abnormalities and liver steatosis in the offspring^[5].

ATHEROSCLEROSIS

NAFLD represents an independent risk factor for CVD as it is associated with dyslipidemia, insulin resistance and alterations of cardiac function independent of the degree of obesity^[3,4].

Recent studies^[2,3,6] have shown that atherosclerosis and alterations of cardiac function may occur already during childhood, as demonstrated by the presence of early onset subclinical atherosclerosis as measured by impaired flow-mediated vasodilation and increased carotid artery intimal medial thickness as well as by the presence of abnormalities in myocardial structure and function in obese children and adolescents^[3,4] (Table 1).

Despite this evidence, the relationship between NAFLD and cardiovascular alterations is still poorly understood. Moreover, it is unclear whether there is a causal relationship between intra-hepatic fat accumulation and alterations of cardiac dynamics or whether the

two phenomena are just independent complications of obesity.

It is possible that intra-hepatic fat accumulation may be a pathogenic determinant of CVD. In fact, NAFLD can lead to atherosclerosis by causing an abundant secretion from the liver of lipoproteins [large very low density lipoproteins (VLDL)]^[7], which, in obese individuals with NAFLD, are abundant in oxidized fatty acids^[8,9]. The higher concentration of large VLDL results in a high concentration in plasma of very small LDL, which in turn are a major contributor to the atherosclerotic plaque^[7], and their accumulation within the plaque would ultimately lead to ischemic events. NAFLD *per se*, in fact, is a hyperlipidemic state in which adipose tissue insulin resistance^[10] and enhanced hepatic *de novo* lipogenesis^[11] lead to an abnormal accumulation of fat in the liver, turning the hepatocytes in a fat producing factory.

It is important to remember that myocardial atherosclerosis occurs very early in life. Seminal studies in the Bogalusa cohort showed that atherosclerosis often begins in pediatric age^[12], as demonstrated by the fact that fatty streaks are detected already in the aorta and the coronary arteries of children^[6,13]. Since NAFLD can begin during childhood in obese children, it is reasonable to think that it can be an important determinant of these early events observed already in the pediatric population.

CARDIAC ABNORMALITIES

While, the association between NAFLD and atherosclerosis could be easily explained by the abundance of circulating lipids present in obese children with NAFLD, it is more difficult to explain the relationship between NAFLD and cardiac function and geometry^[14,15]. It has been reported that adolescents with NAFLD show an impaired systolic and diastolic function and an increased left ventricular mass compared to both healthy controls and age and gender matched obese adolescents without NAFLD^[14,15] (Table 1).

To explain this observation several pathogenic mechanisms have been hypothesized, including the role of the liver as a generator of circulating mediators that could be involved in the cardiac remodeling^[3,11,16,17]. In fact, the presence of a low-grade inflammatory state in patients obese patients with NAFLD and insulin resistance contributes to release of several cytokines and adipokines (*e.g.*, IL-6, TNF-alpha, visfatin, FGF-21, adiponectin, resistin, leptin) that amplify this condition and worsen the metabolic phenotype^[3,11,17]. Whether the trigger for this condition, usually referred to as "sterile inflammation", is NAFLD or insulin resistance *per se* is unclear, but a large body of evidence suggests that inflammatory cytokines may be the link among fatty liver, insulin resistance and myocardial changes^[3,17]. In fact, adiponectin, a strong insulin sensitizer, seems to be

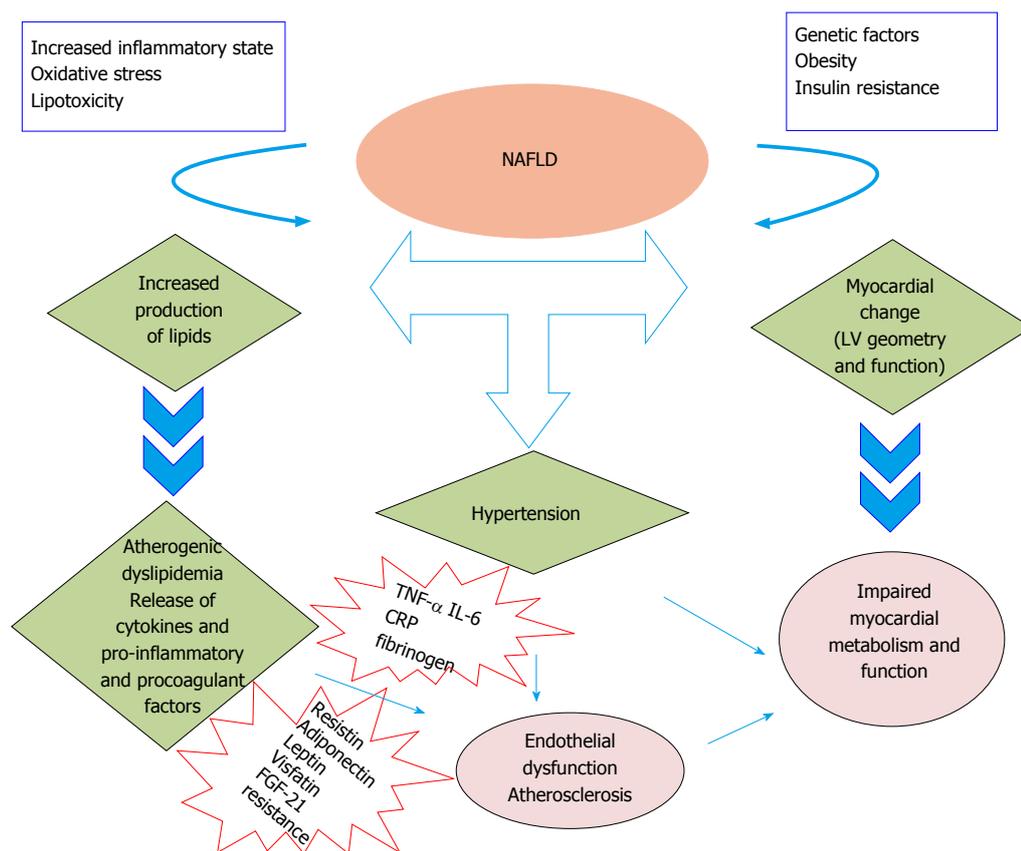


Figure 1 The multifactorial mechanisms leading nonalcoholic fatty liver disease patients to unfavorable cardiac outcomes. CRP: C-reactive protein; IL-6: Interleukin-6; TNF- α : Tumor necrosis factor- α ; FGF-21: Fibroblast growth factor-21; NAFLD: Nonalcoholic fatty liver disease; LV: Left ventricular.

decreased in patients with NAFLD and some studies have suggested that low adiponectin levels may affect cardiac function and atherogenic risk. In contrast, patients with NAFLD experience also an increased production of pro-inflammatory and pro-atherogenic cytokines (IL-6, IL-12, TNF- α), which in turn worsens insulin resistance, mostly through the down-regulation of insulin-receptor-substrate and by affecting gluconeogenesis^[3,17], these compounds could also affect the cardiac morphology and dynamics. More importantly, some data suggest that fibroblast growth factor 21 (FGF-21), a protein synthesized and secreted by the liver in high amounts in obese subjects with fatty liver, might play a role in cardiac hypertrophy^[16]. Some investigators have speculated that FGF-21 resistance occurring in NAFLD could lead to cardiac damage in NAFLD patients^[16].

On the other hand, given that NAFLD is associated with high systolic blood pressure^[18] it could be also argued that changes in myocardial structure might be the consequence of high blood pressure^[18]. Against the latter hypothesis, there is the evidence that changes in cardiac morphology observed in children with NAFLD do not resemble the cardiac adaptation consequence of high blood pressure^[19]. In fact, hypertension increases left ventricular (LV) mass and changes heart morphology as a result of overload. Recent findings reported that

obese children both with and without NAFLD showed no differences in LV mass and posterior wall thickness, while children with NAFLD were more likely to present low LV strain rate - a load - independent parameter that expresses LV elastance and deformation - than those without NAFLD. Therefore, the authors suggested that NAFLD affects myocardial fiber organization leading to systolic and diastolic dysfunction^[19].

CONCLUSION

Besides the large amount of literature suggesting an association between NAFLD and CVD, the pathophysiologic mechanisms underlying these associations are far from being clear, therefore, in the future more studies should be focused on this area of research to unravel those mechanisms and to develop novel therapeutic strategies.

Moreover, we need to establish also whether NAFLD could be considered a marker of subclinical atherosclerosis as well as a cardiovascular risk factor even at a very early age. In fact, because of its strong relationship with CVD, NAFLD diagnosis could represent a red flag for the presence of high cardiovascular risk. In this scenario the prevention and treatment of NAFLD may play a crucial role in avoiding not only end-stage liver disease but also CVD.

Table 1 Principal features and findings of the studies regarding the association between non-alcoholic fatty liver diseases and cardiac dysfunction

Ref.	Study design and methods	Population (n)	Main findings
Bonci <i>et al</i> ^[4]	Systematic review and meta-analysis Systematic literature search for papers from January 2000 to September 2014	12 observational studies: 9 studies based on adult population and 3 studies performed in pediatric population were selected	Children with NAFLD were not different from those without for LV mass Both children with and without NAFLD presented an increased LV mass compared to controls However children with NAFLD presented higher E/e' ratio rather those without NAFLD
D'Adamo <i>et al</i> ^[7]	Cross-sectional study NAFLD diagnosis performed by MRI Evaluation of VAT Lipoprotein particle characterized by MRS	Mean age 14.6 yr Obese African American (33) Obese Hispanic (33)	In multiple regression analyses liver fat accumulation resulted independently and significantly related to large VLDL concentrations
Sert <i>et al</i> ^[14]	Cross-sectional study NAFLD diagnosis performed by ultrasound and elevated serum alanine aminotransferase Pulsed and tissue doppler Echocardiography	Mean age 13.3 yr Healthy (68) Obese with NAFLD and elevated ALT (97)	NAFLD children showed increased CIMT and abnormalities of both LV structure and function LV CIMT and LV mass were positively related to HOMA-IR in obese children with NAFLD
Alp <i>et al</i> ^[15]	Cross-sectional study NAFLD diagnosis performed by liver biopsy Echocardiography	Obese without NAFLD and low ALT (83) Mean age 12 yr Healthy (150) Obese with NAFLD at United States (93)	NAFLD group had increased epicardial fat thickness, end-systolic thickness of the interventricular septum, and larger LV mass, as well as LV systolic and diastolic dysfunction
Pacifico <i>et al</i> ^[18]	Tissue doppler Echocardiography Cross-sectional study NAFLD diagnosis performed by MRI	Obese without NAFLD at United States (307) Mean age 12.5 yr Healthy (18)	Children with NAFLD presented signs of left ventricular dysfunction compared to children without NAFLD Subjects with a more severe NASH had a worse cardiac dysfunction
Singh <i>et al</i> ^[19]	Liver biopsy for NASH in 41 subjects Echocardiography Cross-sectional study NAFLD diagnosis performed by MRS Echocardiography	Obese with NAFLD at MRI (54) Obese without NAFLD at MRI (54) Mean age 15 yr Lean (14) Obese with Intrahepatic triglyceride content (15) Obese with increased Intrahepatic triglyceride content (15)	Obese adolescents with NAFLD show a worse systolic and diastolic functions rather than lean and obese adolescents without NAFLD independent from anthropometric parameters and blood pressure

MRI: Magnetic resonance imaging; NAFLD: Nonalcoholic fatty liver disease; MRS: Magnetic resonance spectrometry; VAT: Visceral adipose tissue; NASH: Non-alcoholic steatohepatitis; LV: Left ventricular; ALT: Alanine transaminase; CIMT: Carotis intima media thickness; VLDL: Very low density lipoproteins.

REFERENCES

- 1 **Loomba R**, Sirlin CB, Schwimmer JB, Lavine JE. Advances in pediatric nonalcoholic fatty liver disease. *Hepatology* 2009; **50**: 1282-1293 [PMID: 19637286 DOI: 10.1002/hep.23119]
- 2 **Feldstein AE**, Charatcharoenwithaya 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 [PMID: 19625277 DOI: 10.1136/gut.2008.171280]
- 3 **Pacifico L**, Chiesa C, Anania C, De Merulis A, Osborn JF, Romaggioli S, Gaudio E. Nonalcoholic fatty liver disease and the heart in children and adolescents. *World J Gastroenterol* 2014; **20**: 9055-9071 [PMID: 25083079 DOI: 10.3748/wjg.v20.i27.9055]
- 4 **Bonci E**, Chiesa C, Versacci P, Anania C, Silvestri L, Pacifico L. Association of Nonalcoholic Fatty Liver Disease with Subclinical Cardiovascular Changes: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2015; **2015**: 213737 [PMID: 26273598 DOI: 10.1155/2015/213737]
- 5 **Ornellas F**, Souza-Mello V, Mandarin-de-Lacerda CA, Aguila MB. Programming of obesity and comorbidities in the progeny: lessons from a model of diet-induced obese parents. *PLoS One* 2015; **10**: e0124737 [PMID: 25880318 DOI: 10.1371/journal.pone.0124737]
- 6 **Pais R**, Giral P, Khan JF, Rosenbaum D, Housset C, Poynard T, Ratziu V. Fatty liver is an independent predictor of early carotid atherosclerosis. *J Hepatol* 2016; **65**: 95-102 [PMID: 27129836 DOI: 10.1016/j.jhep.2016.02.023]
- 7 **D'Adamo E**, Northrup V, Weiss R, Santoro N, Pierpont B, Savoye M, O'Malley G, Caprio S. Ethnic differences in lipoprotein subclasses in obese adolescents: importance of liver and intraabdominal fat accretion. *Am J Clin Nutr* 2010; **92**: 500-508 [PMID: 20573788 DOI: 10.3945/ajcn.2010.29270]
- 8 **Santoro N**, Caprio S, Giannini C, Kim G, Kursawe R, Pierpont B, Shaw MM, Feldstein AE. Oxidized fatty acids: A potential pathogenic link between fatty liver and type 2 diabetes in obese adolescents? *Antioxid Redox Signal* 2014; **20**: 383-389 [PMID: 23815500 DOI: 10.1089/ars.2013.5466]
- 9 **Santoro N**, Caprio S, Feldstein AE. Oxidized metabolites of linoleic acid as biomarkers of liver injury in nonalcoholic steatohepatitis. *Clin Lipidol* 2013; **8**: 411-418 [PMID: 26405460]
- 10 **D'Adamo E**, Cali AM, Weiss R, Santoro N, Pierpont B, Northrup V, Caprio S. Central role of fatty liver in the pathogenesis of insulin resistance in obese adolescents. *Diabetes Care* 2010; **33**: 1817-1822 [PMID: 20668154 DOI: 10.2337/dc10-0284]
- 11 **Santoro N**, Caprio S, Pierpont B, Van Name M, Savoye M, Parks EJ. Hepatic De Novo Lipogenesis in Obese Youth Is Modulated by a Common Variant in the GCKR Gene. *J Clin Endocrinol Metab* 2015; **100**: E1125-E1132 [PMID: 26043229 DOI: 10.1210/jc.2015-1587]

- 12 **Zhang H**, Zhang T, Li S, Li Y, Hussain A, Fernandez C, Harville E, Bazzano LA, He J, Chen W. Long-term Impact of Childhood Adiposity on Adult Metabolic Syndrome Is Modified by Insulin Resistance: The Bogalusa Heart Study. *Sci Rep* 2015; **5**: 17885 [PMID: 26640243 DOI: 10.1038/srep17885]
- 13 **Lamotte C**, Iliescu C, Libersa C, Gottrand F. Increased intima-media thickness of the carotid artery in childhood: a systematic review of observational studies. *Eur J Pediatr* 2011; **170**: 719-729 [PMID: 20978785 DOI: 10.1007/s00431-010-1328-y]
- 14 **Sert A**, Aypar E, Pirgon O, Yilmaz H, Odabas D, Tolu I. Left ventricular function by echocardiography, tissue Doppler imaging, and carotid intima-media thickness in obese adolescents with nonalcoholic fatty liver disease. *Am J Cardiol* 2013; **112**: 436-443 [PMID: 23642511 DOI: 10.1016/j.amjcard.2013.03.056]
- 15 **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 [PMID: 23040432 DOI: 10.1016/j.cjca.2012.07.846]
- 16 **Santoro N**, Caprio S. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis in obese adolescents: a looming marker of cardiac dysfunction. *Hepatology* 2014; **59**: 372-374 [PMID: 23913480 DOI: 10.1002/hep.26663]
- 17 **Abenavoli L**, Peta V. Role of adipokines and cytokines in non-alcoholic fatty liver disease. *Rev Recent Clin Trials* 2014; **9**: 134-140 [PMID: 25514909 DOI: 10.2174/1574887109666141216102458]
- 18 **Pacifico L**, Di Martino M, De Merulis A, Bezzi M, Osborn JF, Catalano C, Chiesa C. Left ventricular dysfunction in obese children and adolescents with nonalcoholic fatty liver disease. *Hepatology* 2014; **59**: 461-470 [PMID: 23843206 DOI: 10.1002/hep.26610]
- 19 **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, 1168.e1 [PMID: 23260104 DOI: 10.1016/j.jpeds.2012.11.024]

P- Reviewer: Abenavoli L, Marchesini GM, Marzuillo P, Rocha R, Souza-Mello V

S- Editor: Kong JX **L- Editor:** A **E- Editor:** Li D





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

