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Atherogenic dyslipidemia and cardiovascular risk in children with nonalcoholic fatty liver disease

Naim Alkhouri^{1,2}, Christine Carter-Kent¹, Michael Elias¹, and Ariel E Feldstein^{†,1}

¹Pediatric Gastroenterology, Lerner Research Institute Cleveland Clinic College of Medicine of CWRU, OH, USA

²Department of Pediatric Gastroenterology, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Abstract

Nonalcoholic fatty liver disease is now regarded as the most common form of chronic liver disease in adults and children. The close association between nonalcoholic fatty liver disease (NAFLD) and the metabolic syndrome has been extensively described. Moreover, a growing body of evidence suggest that NAFLD by itself confers a substantial cardiovascular risk independent of the other components of the metabolic syndrome. Given the significant potential for morbidity and mortality in these patients, and the large proportion of both pediatric and adult population affected, it is important that we clearly define the overall risk, identify early predictors for cardiovascular disease progression, and establish management strategies. In this article, we will focus on current data linking NAFLD and the severity of liver damage present in children with cardiovascular risk.

Keywords

cardiovascular disease; children; dyslipidemia; metabolic syndrome; nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease in children: epidemiology & pathogenesis

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent chronic liver disease in children in the USA and other parts of the world [1–3]. It is estimated that one in ten children in the USA have NAFLD [4]; however, the real prevalence of NAFLD in children remains largely unknown because of the lack of population-based studies and reliable noninvasive tests for screening.

The full histologic spectrum of NAFLD has been observed in children including simple steatosis with over-accumulation of lipids in the liver mostly in the form of triglycerides (TGs), to nonalcoholic steatohepatitis (NASH), which is characterized by fat accumulation along with hepatocyte injury, inflammation and a variable degree of fibrosis [5,6]. The main source of hepatic lipid loading is free fatty acids (FFAs) that are released into the circulation

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[†]Author for correspondence: Center for Cardiovascular Diagnostics & Prevention, Cleveland Clinic, Cleveland, Ohio, USA, Tel.: +1 216 444 5348, feldsta@ccf.org.

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from adipose tissue. Other sources include FFAs from dietary chylomicrons, *de novo* lipogenesis from glucose, decreased oxidation of FFAs in the mitochondria and alteration of TG export from the liver in the form of VLDL [7,8].

NAFLD & the metabolic syndrome: a new component or an independent risk factor?

The rise in the prevalence of NAFLD corresponds to the epidemic of childhood obesity and the metabolic syndrome (MS). A landmark study by Sonia Caprio and her group demonstrated that the MS was very common among obese children and adolescents with prevalence reaching 50% in severely obese children [9]. Plasma levels of C-reactive protein (CRP) and IL-6, which are potential predictors of adverse cardiovascular (CV) outcomes, correlated significantly with the degree of obesity, whereas adiponectin levels decreased with increasing obesity. More importantly, by using data from the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study, Magnussen *et al.* showed that dichotomous definitions of MS in youth predicted important disease outcomes, such as adult MS, high carotid intima media thickness, and Type 2 diabetes mellitus (DM2) in early-to-middle adulthood [10].

Accumulating new evidence suggests that hepatic steatosis *per se* may confer independent metabolic consequences above and beyond the presence of obesity and MS. Data from the Framingham Heart Study revealed that patients with fatty liver had a higher risk of diabetes, hypertension, MS, higher TGs, and lower HDL and adiponectin levels independent of other fat depots (BMI, waist circumference and visceral adipose tissue) [11]. Moreover, Musso *et al.* found that in nonobese nondiabetic subjects, NAFLD was more tightly associated with insulin resistance (IR) and markers of oxidative stress and endothelial dysfunction than the MS as defined by the Adult Treatment Panel (ATP) III. They suggested that NAFLD should be included in the definition of MS to help identify patients with increased cardiometabolic risk [12]. By using liver steatosis as an additional criterion to define pediatric MS, the prevalence of MS increased from 14 to 20% among white prepubertal obese children referred to an obesity clinic at the University of Chieti in Italy [13]. The same investigators compared two groups of obese adolescents with high hepatic fat fraction (>5.5%) and low hepatic fat fraction measured by fast MRI and showed that fatty liver by itself was associated with impaired insulin sensitivity and early defects in β -cell function [14]. Several experimental studies using different animal models have also provided evidence that lipid accumulation in the liver leads to subacute hepatic inflammation and downstream cytokine production via the NF- κ B pathway, which can cause IR both locally in the liver and systemically leading to the development of DM2 and MS [15]. An elegant animal study using liver insulin receptor knockout mice showed that purely hepatic IR was sufficient to induce a proatherogenic lipid profile and severe atherosclerosis [16].

NAFLD, IR & the adipocyte–hepatocyte crosstalk

Adipose tissue in obese individuals is characterized by a state of low-grade chronic inflammation with accumulation of macrophages and the release of inflammatory cytokines including TNF- α and IL-6 [17–19]. Inflammation plays a central role in inducing IR through the activation of JNK, which inhibits insulin action by serine phosphorylation of insulin receptor substrate-1 [20,21]. IR induced by chronic inflammation is essential for the development of obesity-related complications including NAFLD, DM2, MS and CV disease. In fact, recent trials have evaluated the role of salicylate compounds for the treatment of DM2 through their anti-inflammatory effects [22–24]. High-dose salicylate inhibits the serum kinase IKK- β , which plays a significant role in tissue inflammation and IR through its fatty acid-dependent activation [25]. Hundal *et al.* studied nine patients with DM2 before

and 2 weeks after treatment with high-dose aspirin (7g/day) and showed reduction in fasting plasma glucose, total cholesterol, TG and CRP, independent of body weight [24]. A randomized placebo-controlled trial has shown that salsalate, a pro-drug of salicylate, lowered hemoglobin A1C levels and improved other markers of glycemic control in adult patients with DM2 [26]. Furthermore, salsalate lowered TG levels and increased circulating adiponectin levels, which may predict decreased CV risk. These results should be interpreted with caution due to the relatively small sample size and the short follow-up period. The inhibition of macrophage infiltration into adipose tissue may protect against these complications. Recently, we have shown that adipocyte apoptosis may be an early event during the development of obesity that attracts macrophages to migrate into adipose tissue in both mice and humans [27]. Genetic inhibition of adipocyte apoptosis in a mouse model of obesity leads to a decrease in the number of macrophages in adipose tissue and the protection of these animals from IR, dyslipidemia and hepatic steatosis. Apoptosis can be manipulated by new therapeutic agents including caspase inhibitors and this may represent a new strategy for treating obesity-related complications that predispose to CV disease.

Markers of atherosclerosis & CV complications in NAFLD

The strong association between NAFLD, IR and MS has stimulated an interest in the potential role of NAFLD in the pathogenesis of CV disease. There is a growing body of evidence suggesting an association between NAFLD and CV disease that goes beyond what would be expected by the presence of MS alone [28]. Moreover, patients with the advanced form of NAFLD, NASH, may be at higher risk for atherosclerosis than patients with simple steatosis. This is thought to be due to multiple possible mechanisms including increased oxidative stress and systemic inflammation. CV risk can be assessed by different modalities including the presence of an atherogenic lipid profile, levels of inflammatory markers, markers of endothelial dysfunction and epidemiologic studies evaluating the actual prevalence or incidence of CV disease in patients with NAFLD (Figure 1).

NAFLD & atherogenic dyslipidemia

Atherogenic dyslipidemia characterized by high TGs and low HDL-C concentrations is common in obese children and adolescents. As a matter of fact, the Third National Health and Nutritional Examination Survey (NHANES) III showed that the most common components of the MS in adolescents were high TG and low HDL levels [29]. Plasma lipid levels varied by race and ethnicity, with hypertriglyceridemia and low HDL levels being most common among non-Hispanic white people and least common among non-Hispanic black people. Moreover, increased levels of small dense LDL, another important risk factor for future coronary heart disease mortality and morbidity, appears to be commonly present in obese children [30,31]. The fundamental defect that is thought to lead to this atherogenic lipid profile is the overproduction of larger TG-rich VLDL particles by the liver [32]. Normally, insulin inhibits adipose tissue lipolysis and hepatic VLDL secretion. In obesity-induced IR, there is an increased flux of FFA from adipose tissue to the liver, which can be re-esterified into TG, and increased VLDL secretion by the liver [33]. Other mechanisms of hepatic lipid loading include *de novo* lipogenesis from glucose and decreased FFA oxidation at the level of the mitochondria [34]. Recent studies have suggested a genetic basis for the abnormal lipoprotein metabolism in patients with NAFLD. Genome-wide association studies demonstrated that a genetic variation in adiponutrin/patatin-like phospholipase-3 (PNPLA3) confers susceptibility to NAFLD [35]. Adiponutrin is expressed in the liver and adipose tissue and has lipase activity against TG. The loss of function variant (PNPLA3 rs738409) predisposes a patient to steatosis by decreasing TG hydrolysis in liver cells [36]. Obese patients often have low HDL-C levels even when fasting TG levels are normal, suggesting that other mechanisms in obesity contribute to the low HDL-C levels beyond simply elevation in TG-rich lipoproteins such as increased production of cholesteryl ester

transfer protein by adipose tissue and increased activity of hepatic lipase, as reviewed elsewhere [33].

Ratios of cholesterol ester-rich lipoproteins such as total cholesterol/HDL and LDL/HDL are well established risk factors for CV disease. More recently TG-rich lipoproteins (chylomicrons, chylomicron remnants and VLDL) have been shown to play a role in atherogenesis [37,38]. The TG/HDL ratio correlates inversely with the plasma level of small, dense LDL particles. This ratio is a powerful independent predictor of coronary artery disease development, even stronger than TC/HDL and LDL/HDL ratios [39,40].

Apolipoprotein (Apo)B is the primary protein component of the atherogenic LDL particles, whereas ApoA1 is the primary protein component of the anti-atherogenic HDL particles. The ratio of ApoB to ApoA1 reflects the balance of cholesterol transport and the higher the value of this ratio, the more cholesterol is likely to be deposited in the arterial wall [41,42]. ApoB, ApoA1 and the ApoB:ApoA1 ratio have been reported as better predictors of CV events than LDL-C and they even retain their predictive power in patients receiving lipid-modifying therapy. Measurement of these apolipoproteins could improve CV risk prediction. Moreover, a recent study demonstrated that the ApoB:ApoA1 ratio was strongly associated with the presence of individual MS components, with the MS itself and with IR [43]. However, both ApoB and ApoA1 are produced in the liver and their production might be altered in patients with chronic liver disease including NAFLD [44].

A study of 67 prepubertal children showed that TG/HDL ratio was increased in obese children and it correlated with elevated mean blood pressure and the presence of MS [45]. A TG:HDL ratio ≥ 3 was associated with lower insulin sensitivity and higher visceral fat in another study of 35 overweight adolescents, with a sensitivity of 61% and a specificity of 82% for identifying participants with the greatest degree of IR [46]. This ratio could be a useful tool in identifying children at risk for dyslipidemia, hypertension and the MS [45]. In a case-control study of 150 children with NAFLD and 150 overweight children without NAFLD, Schwimmer *et al.* found that children with biopsy-proven NAFLD had significantly higher total cholesterol, LDL and TG, and lower HDL levels [47]. In a recent study, Cali *et al.* found that hepato-steatosis in adolescents, identified by fast MRI, was associated with a markedly "proatherogenic lipoprotein profile" characterized by small dense LDL, larger VLDL and decreased large HDL concentrations [48]. Although there was no difference in the total number of LDL particles between adolescents with and without hepatosteatosis, those with hepatic steatosis had significantly higher concentrations of small dense LDL. Likewise, total HDL particle concentration was not different between the two groups, but adolescents with hepatosteatosis had significantly higher concentrations of large HDL and lower concentrations of medium HDL particles compared with those without hepatosteatosis. Overall size of the lipoproteins followed a similar trend. This suggests that the ApoB:ApoA1 ratio, which reflects the total number of LDL and HDL particles, may not be a useful marker for CV risk in patients with NAFLD.

We took the previous findings a step further by demonstrating that the histological severity of NAFLD as assessed by NAFLD Activity Score and fibrosis score correlated with higher traditional lipid ratios and a more atherogenic lipid panel in a recent study of 118 children with biopsy-proven NAFLD [49]. This suggests that patients with more advanced disease (NASH and fibrosis) may be at a higher risk for atherosclerosis and CV disease compared with patients with simple steatosis. The ApoB:ApoA1 ratio did not show the same correlation with liver histology as the other lipid ratios. We have shown similar results in another study of a group of adult patients with the full histologic spectrum of NAFLD. NASH was associated with higher lipid ratios independent of obesity, IR and the presence of diabetes [50].

The relative size of HDL and its composition determine its anti-atherogenic properties with large HDL₂ being protective against atherosclerosis and small HDL₃ representing a CV risk factor. Patients with fatty liver have lower circulating levels of HDL₂ and HDL₂:HDL₃ ratio compared with controls suggesting an increased risk for CV disease [51]. The association between liver fat and HDL₂ and HDL₂:HDL₃ ratio remained statistically significant after adjusting for IR and adiponectin levels. HDL size distribution is shifted towards small HDL particles in children with IR, DM2 and the MS [52,53]. Adolescents with hepatic steatosis were found to have decreased levels of the large protective HDL [48]. These data further imply that determination of HDL₂-C, in addition to total HDL-C, may more precisely predict the actual risk for CV events in subjects with fatty liver. Collectively, the previous studies support the presence of an important link between hepatic steatosis/liver injury and the development of an atherogenic lipid profile in children with NAFLD.

NAFLD & systemic inflammation

Nonalcoholic fatty liver disease is associated with a state of chronic inflammation and increased oxidative stress, which may play a role in the pathogenesis of atherosclerosis. Patients with NAFLD have higher levels of high-sensitivity CRP, TNF- α , oxidized LDL and plasma plasminogen activator inhibitor-1 and lower levels of adiponectin than controls [54–58]. Moreover, inflammatory cytokines tend to be higher in patients with NASH compared with patients with simple steatosis. Plasma levels of CRP, which is an indicator of systemic inflammation and a risk factor for atherosclerosis [59], were found to be higher in patients with histologically proven NASH [60]. A large study that included 400 children showed that there was a stepwise increase in high-sensitivity CRP levels from healthy controls to obese children with normal liver to obese children with NAFLD [61]. Data from Nobili and colleagues showed that circulating levels of the inflammatory cytokine TNF- α correlated with histologic liver injury scores in children with NAFLD [62]. Adiponectin is another cytokine secreted from adipose tissue with anti-atherogenic effects [63,64]. Adiponectin levels have been shown to correlate negatively with early markers of atherosclerosis and the MS in obese children [65]. More importantly, adiponectin levels are lower in children with NAFLD compared with lean controls, which may increase their risk for developing atherosclerosis [66]. Bugianesi *et al.* showed that decreased levels of circulating adiponectin in NAFLD is related to hepatic insulin sensitivity and to the amount of hepatic fat content but not to fibrosis or necroinflammation [67].

More recently the neutrophil:lymphocyte (N/L) ratio has emerged as a prognostic marker in patients with CV disease [68]. This ratio integrates information on two different immune pathways, the neutrophils, which are responsible for ongoing inflammation, and the lymphocytes, which represent the regulatory pathway. Thus, a higher N/L ratio is an indicator of the overall inflammatory status of the body. This ratio has been validated as a predictor of outcome in multiple studies in patients with coronary artery disease [68–71]. Nascimento *et al.* demonstrated a significant change in the differential leukocyte count toward neutrophilia in obese patients aged 6–12 years old [72]. We have conducted a study to examine the relationship between N/L ratio and histologic severity of NAFLD in adults and found that this ratio was higher in patients with NASH and advanced fibrosis compared with patients with simple steatosis indicating that the patients with advanced disease may have a higher CV risk [73]. Another validated marker of atherosclerosis that can be easily obtained from routine blood counts is the mean platelet volume (MPV), which reflects platelet activation and aggregation [74,75]. In a study of 128 obese adolescents, MPV was significantly higher in obese patients with NAFLD compared with obese patients without NAFLD or controls. This indicates that children with NAFLD have higher CV risk; however, correlation with liver histology was not examined as the diagnosis of NAFLD was made based on ultrasound findings and the presence of elevated liver enzymes [76].

NAFLD & early vascular changes

Multiple cross-sectional studies have shown a significant increase in carotid intima-media thickness (IMT), as a marker of early atherosclerosis, in patients with NAFLD [77,78]. A recent meta-analysis of seven studies that included 3497 patients showed that NAFLD is strongly associated with carotid IMT and the presence of carotid plaques [79]. Furthermore, the histological severity of NAFLD has been shown to independently predict carotid IMT with significantly higher values in patients with NASH compared with patients with simple steatosis [80]. In a study by Villanova *et al.*, patients with NAFLD had endothelial dysfunction as assessed by brachial artery flow-mediated dilation and the severity of liver disease was associated with more altered endothelial function [81].

Several studies in children have attempted to evaluate the relationship between early atherosclerosis and NAFLD. Pacifico *et al.* found that the severity of fatty liver as assessed by ultrasound was significantly associated with maximum carotid IMT after adjusting for age, gender, Tanner stage and classic CV risk factors [82]. Another study in a pediatric population found carotid IMT to be significantly higher in obese children with hepatosteatosis compared with healthy children or obese children without hepatosteatosis [83]. Kelishadi *et al.* found that carotid IMT was significantly associated with IR and NAFLD in adolescents suggesting that the liver and the vessels share common mediators [84]. The previous findings were confirmed in a large pediatric study assessing the relationship between NAFLD during childhood and CV risk factors [61]. Children with NAFLD (n = 100) had decreased flow-mediated dilation of the brachial artery and increased carotid IMT compared with obese children without fatty liver (n = 150) and healthy controls (n = 150).

Furthermore, autopsy findings in 817 children who died of external causes showed that atherosclerosis was significantly more common in children with fatty liver than those without it (30 vs 19%, respectively) [85]. Multislice computed tomography is another noninvasive method to directly detect and classify plaques in the coronary arteries [86] and to determine which ones are vulnerable to rupture, which can cause acute coronary syndrome. Patients with NAFLD were found to be at higher risk of having vulnerable plaque as detected by multislice computed tomography independent of classic risk factors for CV disease or individual components of the MS [87].

Adhesion molecules such as ICAM-1 and VCAM play an important role in leukocyte interaction with the endothelium and migration into the artery wall as a part of the atherogenic process. Circulating levels of these molecules may reflect endothelial dysfunction and indicate increased risk for CV disease and they have been described to be elevated in patients with the MS [88]. Studies assessing the levels of these adhesion molecules in NAFLD patients have given controversial results. One study in particular showed that NAFLD patients have higher circulating levels of biomarkers of endothelial dysfunction, namely soluble (s)ICAM-1, sCD40 ligand and plasminogen activator inhibitor-1 [89]. In this study, hepatic expression of these molecules by immunostaining correlated with the degree of liver steatosis and necroinflammation. In contrast, a recent study by Lucero *et al.* showed no difference in sICAM or sVCAM levels when comparing patients with the MS with and without fatty liver [90]. Ito *et al.* demonstrated no difference in sICAM-1 between patients with NAFLD and controls; however, there was a marked increase in patients with NASH [91] indicating that the degree of liver injury and inflammation may be a more important factor in the pathogenesis of atherosclerosis than just the mere presence of fatty liver.

Taken together, these studies suggest that NAFLD and the degree of liver damage and inflammation present in both adults and pediatric patients are strongly associated with endothelial dysfunction and early atherosclerosis.

Epidemiologic studies

Numerous epidemiologic studies have clearly demonstrated an increase in the prevalence of CV disease in patients with NAFLD. The mortality rate in patients with NAFLD is higher than the general population, most commonly due to CV disease and malignancy [92,93]. Sanyal *et al.* demonstrated that heart disease contributed disproportionately to mortality in patients with cirrhosis due to NASH compared with those with hepatitis C infection [94]. Diabetic patients with NAFLD diagnosed by ultrasound had an increased incidence of CV events compared with diabetic patients without NAFLD [78]. The notion that hepatic inflammation by itself is atherogenic is supported by the observation that CV disease is strongly associated with elevated alanine aminotransferase and γ -glutamyltransferase, which are surrogate markers of liver necroinflammation [95–97]. Two large pediatric studies showed an association between elevated serum alanine transaminase levels and the prevalence of the MS and IR as markers of CV risk in obese children aged 3–18 years [98,99]. Longitudinal studies are needed to assess the development of adulthood CV disease in these children with abnormal liver enzymes and other risk factors for atherosclerosis.

Future perspective

As we learn more about the associations between NAFLD, dyslipidemia and CV disease, it has become clear that the potential morbidity to adults and children alike is significant. Moving forward, it will be important to determine if abnormal lipid profiles and increased CV inflammatory mediators in children with NAFLD translate into early CV events including myocardial infarction and stroke. The aforementioned studies regarding the detection of increased carotid IMT in patients with NAFLD give some clues as to what lies ahead for children and adolescences diagnosed with NAFLD.

In addition, it will be important to determine if medical treatments that improve hepatic steatosis and reduce hepatic inflammation also impact the course of CV disease in these patients. It has already been shown that lifestyle interventions, if sustained, can have a significant impact on NAFLD. In their 2009 study of 152 adults, St. George *et al.* documented improvement in liver enzymes, insulin levels, total cholesterol and LDL after 3 months of moderate-intensity lifestyle counseling [100]. In one of the only randomized, controlled trials examining the effects of weight loss on NAFLD after intensive lifestyle modification, it was reported that after 48 weeks of intervention, patients who received intensive lifestyle modification lost 9.3% of their body weight as compared with 0.2% loss in control subjects. Importantly, in addition to weight loss, patients experienced improvement in the NAFLD Activity Score as well as reduction in circulating liver enzymes [100]. In children, Nobili *et al.* showed that after 12 months of lifestyle intervention, which included both a tailored diet and increased physical activity, improvement in NAFLD histology, lipid profiles and insulin levels were noted [101]. In the future, it may also be helpful to track serologic indicators of CV risk in response to lifestyle interventions for this cohort of children as well. Thus, we will be able to determine if these types of therapies modify CV risk over time.

Finally, medical therapies targeted at the reduction of mediators of inflammation and/or apoptosis could potentially lead to improvement in the liver damage seen in NASH, but could also lead to the reduction of the CV changes seen in these patients. Potential therapeutic agents of interest might include medications aimed at the reduction of apoptosis, such as caspase inhibitors, the reduction of pro-inflammatory cytokines such as anti-TNF medications or medications that decrease levels of AboB or the ApoB:ApoA1 ratio, thereby leading to a reduction of the formation of atherogenic LDL particles. Thus far, proven effective and safe pharmacological therapies for NAFLD are lacking; however, there is currently ongoing intense research in these areas. The results of the Treatment of

Nonalcoholic Fatty Liver Disease in Children (TONIC) trial, which compares the use of vitamin E or metformin with placebo in the treatment of pediatric NAFLD, have been recently presented at the American Association for the Study of Liver Disease Annual meeting [102]. Neither vitamin E nor metformin demonstrated superiority over placebo for reaching the primary outcome of sustained reduction in alanine aminotransferase. However, vitamin E significantly improved important histological features including hepatocyte ballooning. Other potential therapeutic approaches include omega-3 fatty acids, antioxidants, anti-inflammatory agents such as TNF- α inhibitors, and statins.

Conclusion

It has become clear that NAFLD and the advanced form, NASH, are closely associated with the MS, IR and dyslipidemia in overweight and obese children and adults. This association is due to multiple factors including IR induced by inflammatory pathways and the downstream effects of IR on various organ systems. One of the most important considerations for children with NAFLD and co-existent MS are the potential complications that may develop and become life-threatening including liver fibrosis, end-stage liver disease, hypertensive crises and renal failure. A screening for fatty liver disease, either non-invasively or in selected cases with liver biopsies, should be incorporated into our routine evaluation in children and adolescents who are obese or have the MS. In addition, the risk of CV disease is concerning in these patients as well. Here we have discussed that patients with the MS are at a high risk for CV disease, but patients with NASH may be at an increased risk beyond that which would be expected for patients with the MS alone. Evidence for these findings includes multiple studies documenting the presence of atherogenic dyslipidemia in patients with NAFLD, higher circulating levels of pro-inflammatory cytokines and markers of oxidative stress, as well as evidence that newer prognostic markers of CV risk, such as the N/L ratio and MPV, are higher in patients with NAFLD. We have also detailed epidemio-logical studies showing higher rates of mortality from CV complications in patients with NAFLD.

Taking these findings into consideration, it is important that we continue to identify and refine the tests available to identify patients with NAFLD who are at risk for the development of CV disease so that they may be monitored closely and the proper intervention can take place when problems arise. Also, we continue to stress prevention in obese children before components of the MS or NAFLD arise. Pediatricians and pediatric specialists need to be vigilant in identifying patients who are obese or at risk for becoming obese and initiating early screening and intervention.

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- ▪ of considerable interest

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Executive summary

Nonalcoholic fatty liver disease in children

- Nonalcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease in children and adolescents.
- It is strongly associated with the metabolic syndrome and insulin resistance, which are established risk factors for cardiovascular (CV) disease.

NAFLD & CV risk

- NAFLD confers an increased CV risk independent of the metabolic syndrome and its individual components.
- Patients with the advanced form of NAFLD, nonalcoholic steatohepatitis, may have higher CV risk than patients with simple steatosis.

Atherogenic dyslipidemia & NAFLD

- Liver steatosis is associated with a proatherogenic lipid profile characterized by small dense LDL and larger VLDL.
- Children with NAFLD have higher total cholesterol, LDL and triglycerides, and lower HDL levels.
- The histologic severity of liver injury in children with NAFLD correlates positively with higher traditional lipid ratios and a more atherogenic lipid panel.

Other markers of CV risk in children with NAFLD

- Markers of systemic inflammation such as C-reactive protein, TNF and neutrophil to lymphocyte ratio are increased in nonalcoholic steatohepatitis.
- Endothelial dysfunction is evident in patients with NAFLD as measured by intima-media thickness and circulating levels of adhesion molecules.
- Epidemiological studies have shown an increased prevalence of CV disease in NAFLD patients.

Therapeutic interventions

- Lifestyle interventions with diet and physical activity may lead to improvement in NAFLD and dyslipidemia in children with NAFLD
- Vitamin E, metformin, omega-3 fatty acids and statins may represent efficient novel therapeutic approaches in the treatment of children with NAFLD

Figure 1.

Mechanisms linking obesity, fatty liver and atherosclerosis. Obesity is associated with expansion of adipose tissue and a state of chronic inflammation. This leads to insulin resistance and the release of FFA into the circulation, which results in the development of fatty liver. Further inflammation and oxidative stress are responsible for the progression of fatty liver to NASH, which leads to further insulin resistance, systemic inflammation and an atherogenic lipid profile; all risk factors for cardiovascular disease.

FFA: Free fatty acid; NASH: Nonalcoholic steatohepatitis.