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Pediatric Nonalcoholic Fatty Liver Disease

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1. Introduction

Paralleling the burgeoning epidemics of childhood obesity, nonalcoholic fatty liver disease (NAFLD) is now recognized as the most common cause of chronic liver disease in children [1,2].

NAFLD is a clinic-pathological condition defined by the accumulation of intrahepatic triglyceride fat (IHTF) content in the absence of alcohol consumption [1,2].

NAFLD encompasses a wide spectrum of liver damage, ranging from asymptomatic steatosis with elevated or normal aminotransferases to steatosis with inflammation, ballooning degeneration and pericellular fibrosis (Nonalcoholic Steatohepatitis, NASH) to cirrhosis [2,3].

Although there are limited long-term data on the natural history of NAFLD in children, NASH is increasingly diagnosed in obese children [4] and it may progress to cirrhosis even in this age group [2,5]. In addition, children with NAFLD have a 13.6-fold higher risk of mortality or requiring a liver transplant as compared to age/sex matched controls [6].

During the last years there has been a growing interest in the relationship between NAFLD and the development of metabolic and cardiovascular diseases [7-9].

Several lines of evidence have shown that in obese children and adolescents excessive accumulation of IHTF is associated with important alterations in glucose, fatty acid (FA), lipoprotein metabolism and inflammation, suggesting that IHTF represents a strong risk factor for the development of the Metabolic Syndrome (MetS) and type 2 diabetes mellitus (T2D) [7-10].

Although a multifactorial pathogenesis of NAFLD has been postulated [12-14], obesity and insulin resistance represent two important players in the development of the early stages of the disease [2,14]. Interestingly, although the insulin resistance state could explain the relationship between NAFLD and the development of metabolic alterations [10,15], the presence of liver steatosis is also an important marker of multiorgan insulin resistance [16], opening a debate as to whether hepatic steatosis is a consequence or cause of insulin resistance.

Therefore, it would be of paramount importance to identify children affected by NAFLD and to better understand the pathogenesis of this condition in order to prevent the development of the associated metabolic complications early in life.

2. Definition and prevalence of NAFLD

Despite fatty liver is becoming one of the most common hepatic alterations in obese children [1,2], the prevalence of pediatric NAFLD is uncertain, mainly due to the methods used to assess fatty liver.

NAFLD is defined as an IHTF content > 5% of liver volume or weight and as a presence ≥5% of hepatocytes containing intracellular triglycerides, in the absence of alcohol consumption [17,18].

The gold standard for diagnosing NAFLD is liver biopsy [19,20]. Liver biopsy allows an accurate assessment of histopatological findings, providing information on the type of NAFLD (simple steatosis or steatohepatitis) and the various degrees of hepatic fibrosis [20]. However, the main limitation of the application of liver biopsy in the pediatric age group is due to the fact that it is an invasive procedure; thus, it is not considered as first line to screen the presence of liver disease [19,20].

Although non-invasive methods, such as computer tomography, MRI, or ultrasonography are unable to distinguish between NASH and other forms of NAFLD [19,21], they have an acceptable sensitivity and specificity for the diagnosis of increased fat accumulation in the liver [21]. Furthermore, ultrasound has been shown to have a good correlation with the histological findings of liver biopsy, particularly macrovescicular steatosis [22].

In clinical practice, combining liver function tests, such as serum aminotransferases [18], with liver ultrasound represents a useful way of identifying the presence of liver steatosis in obese children.

In spite of the method used, it is clear that the prevalence of NAFDL is increasing in children and adolescence. NAFLD affects 2.6% of normal children [23] and up to 77% of obese individuals [24,25]. Pediatric NAFLD extends beyond North America according to centers in Europe, Asia, South America and Australia [2,3]. The prevalence of fatty liver in obese children in China, Italy, Japan, and the United States has been reported to be between 10% and 77% [2,3]. Data derived from the National Health and Nutrition Examination Survey III (1988-1994) suggest that approximately 3% of adolescents present abnormal serum amino-

transferase values [26]. Moreover, studies from autopsies of 742 children (ages 2–19 years) reported fatty liver prevalence at 9.6%, and in obese children this rate increased to an alarming 38% [25].

NAFLD has been also described in obese prepubertal children. In the study by Manco et al. [27] NAFLD was detected in children as young as 3 years old.

The prevalence of NAFLD is around 30% in children with a Tanner pubertal stage I, significantly lower when compared to that found in the pubertal age [28].

Alarming data come from our study population of prepubertal Caucasian obese children [29]. Out of 100 severely obese prepubertal children, liver steatosis was found in 52% and was equally distributed between the two sexes [29].

Thus, NAFLD in an emerging health problem even in very young age groups.

3. Pathogenesis and risk factors of NAFLD

Although the pathogenetic mechanism of NAFLD is not completely understood, in accordance with the "two hit hypothesis", insulin resistance and oxidative stress represent two key factors for the development and progression of NAFLD/NASH [12,17,20].

3.1. Insulin resistance and central obesity

The "two-hit" model proposes that fat accumulation in the hepatocytes is a prerequisite for a second hit that induces fibrosis and inflammation [30].

Fat accumulation in the liver is likely to result from insulin resistance and concomitant impairment of fatty acid (FA) metabolism within liver, skeletal muscle and adipose tissue [31].

Insulin resistance seems to be responsible for abnormalities in lipid storage and lipolysis in insulin-sensitive tissues, leading to an increased fatty acids flux from adipose tissue to the liver and subsequent accumulation of triglycerides in the hepatocytes [31]. In particular, steatosis develops when the rate of FA input (uptake and synthesis with subsequent esterification to triglycerides (TG)) is greater than the rate of FA output (oxidation and secretion) [11]. The amount of TG in the hepatocytes represents a complex interaction among [11,31]: hepatic FA uptake, derived from plasma free fatty acid (FFA) released from hydrolysis of adipose tissue and FFA released from hydrolysis of circulating TG; de novo FA synthesis (de novo lipogenesis [DNL]); fatty acid oxidation (FAO); FA export within very low-density lipoprotein (VLDL)-TG.

Obesity is the most important cause in the development of insulin resistance and it has been demonstrated that the critical determinant of insulin sensitivity is not the degree of obesity *per se* but the distribution of fat partitioning [32,33].

Several studies [32,33] have demonstrated that obese adolescents presenting increased intra-myocellular lipid content (IMCL) [32] and visceral fat and decreased subcutaneous fat deposition are more likely to develop insulin resistance.

There is extensive evidence indicating that central obesity is associated with an impaired insulin action in obese pediatric populations. Although controversy remains regarding the contribution of visceral and subcutaneous fat to the development of insulin resistance [33], a previous study by Cruz et al. [35] showed a direct impact of visceral fat accumulation on insulin sensitivity and secretion, independently of total body adiposity, in obese children with a family history of T2D. Indeed, by stratifying a multiethnic cohort of obese adolescents into tertiles based on the proportion of visceral fat in the abdomen (visceral/subcutaneous fat ratio), insulin resistance (homeostasis model assessment) significantly increased and insulin sensitivity (Matsuda index) decreased in obese adolescents with high proportion of visceral fat and relatively low abdominal subcutaneous fat [33].

These findings suggest that obese children and adolescents at risk for developing metabolic complications are not necessarily the most severely obese, but are characterized by an unfavorable lipid partitioning profile.

3.2. Insulin resistance and fatty liver disease: Which comes first?

Despite the demonstrated relationship between IMCL, visceral fat and metabolic dysfunction, the ectopic fat deposition in the liver is emerging as the most important marker of insulin resistance in adults [15] as well as in obese pediatric population [36].

In healthy nondiabetic humans the correlation between the IHTF content and peripheral insulin resistance was much stronger than the correlation with intramyocellular lipid content, visceral fat content or subcutaneous fat content [37]. The relationship between liver steatosis and insulin resistance has been clearly demonstrated in children [36,29]. In our cross sectional study, we evaluated insulin resistance indexes between obese prepubertal children with and without liver steatosis; furthermore insulin resistance indexes were compared to values of normal weight children. Our results showed that children with NAFLD not only presented severe obesity but also an increased degree of insulin resistance when compared to the sex- and age-matched normal weight children [29].

The relationship between insulin resistance and fatty liver disease is not only related to the presence of liver steatosis, but also to the degree of fatty liver. In a multiethnic cohort of obese adolescents, Calì et al. [36] clearly showed a significant decrease in insulin sensitivity and an imbalance between anti- and pro-inflammatory markers [adiponectin and interleukin 6 (IL-6)] paralleling the severity of hepatic steatosis [36]. In particular, adiponectin, the most abundant secretory protein produced by adipose tissue, is closely related with insulin action. Plasma adiponectin concentrations are inversely associated with hepatic steatosis and metabolic complications [37,38].

Although these findings support the central role of insulin resistance in the development of fatty liver, several studies have demonstrated that the presence of liver steatosis is an important marker of multiorgan insulin resistance, independently of BMI, percent body fat, and

visceral fat mass [11,15,36]. In particular, NAFLD has been found to be associated with insulin resistance in liver (impaired suppression of insulin-mediated glucose production) [39,40], skeletal muscle (reduced insulin stimulated glucose uptake) [40] and adipose tissue (decrease inhibition of lipolysis by insulin) [41] in obese children and adolescents, independently of adiposity.

Recently, Caprio et al. [16] reported that obese adolescents with high liver fat content, independent of visceral and IMCL had an impaired insulin action (as assessed by the hyperinsulinemic-euglycemic clamp) in the liver and in the muscle and early defects in β-cell function [16]. These results suggest that the liver has a central role in the complex phenotype of the insulin resistance state in obese adolescents with fatty liver.

Although it is clear that there is an important correlation between insulin resistance and hepatic steatosis, the mechanisms responsible for the interrelationships between fatty liver disease and insulin resistance are not clearly understood. In fact, it remains unclear whether hepatic steatosis is a consequence or the primary event leading to hepatic and subsequently peripheral insulin resistance.

Petersen et al. [42] showed that the lack of adipose tissue in the congenital lipodystrophy is characterized by extreme insulin resistance associated with massive hepatic fat accumulation; intervention with subcutaneous leptin administration in these patients improved whole-body insulin sensitivity mainly due to the mobilization of the excessive fatty liver content.

Models of patients with liver cirrhosis in which hepatic dysfunction is known to be the primary disturbance provide strong support that insulin resistance in peripheral tissues develops secondary to liver disease [43]. 60-80% of patients with liver cirrhosis are glucose intolerant and in 10-15% diabetes occurs relatively rapidly (over a period of 5 years). Diabetes complicating liver cirrhosis, also known as hepatogenous diabetes, and the common form of T2D are the results of a marked reduction in insulin action and a β-cell secretion defect that is not able to compensate the severity of insulin resistance [43,44]. The important role of peripheral insulin resistance in the glucose tolerance of cirrhosis has been highlighted by the observation that liver transplantation, when the dosage of immunosuppressive agents was reduce and corticosteroids withdrawn, was able to restore normal insulin sensitivity not only in the liver but also at the level of the skeletal muscle and adipose tissue and normalizes glucose tolerance in most patients with diabetes [43,44].

The mechanism by which IHTF has an important systemic consequence to adversely affect insulin sensitivity is unknown. However, it has been proposed that fatty liver might interfere with insulin degradation [45]; the resultant hyperinsulinemia may potentially be able to impair insulin action in peripheral tissues, as shown in benign insulinoma induced hyperinsulinemia [43,44,46]. This hyperinsulinemia-induced mechanism may be justified also based on the finding of the reverse experiment: when the prolonged infusion of octreotide was administered to extremely insulin-resistant cirrhotic individuals, the correlation of hyperinsulinemia was paralleled by the restoration of normal insulin sensitivity [43,47].

Although these data showed a clear possibility that intrahepatic fat accumulation plays a key role in the onset of insulin resistance and insulin resistance syndrome, longitudinal data are needed in order to clarify which abnormality comes first.

3.3. Oxidative stress

In accordance with the "two hit hypothesis", dysfunction of various oxidation pathways within the hepatocytes and subsequent overproduction of reactive oxygen species (ROS), may result in the peroxidation of accumulated lipids, inflammation, hepatocellular apoptosis and fibrogenesis [31].

Obese subjects affected by NAFLD present an impaired oxidant-antioxidant status than subjects without [12,48].

Interestingly, we recently observed [48] that obese prepubertal children affected by liver steatosis had impaired levels of receptors for advanced glycation endproducts (RAGEs), which has been demonstrated to be correlated with the progression of several metabolic and cardiovascular diseases. In particular, obese prepubertal children with liver steatosis presented decreased RAGEs levels compared with children without liver disease, underling that oxidative stress could play a role even in the early stages of the disease [48].

3.4. Genetic and environmental factors associated with fatty liver disease

Several genetic and environmental factors are likely responsible for NAFLD and its progression from simple steatosis to NASH.

In fact, although the development of NAFLD is strongly linked to obesity and insulin resistance, there are obese individuals who do not have NAFLD, and since NAFLD can occur in normal-weight individuals with normal metabolic profile, thus multiple genetic and environmental factors should be involved in its development [49].

Initial evidence for a *genetic component* of NAFLD comes from ethnic variation in NAFLD prevalence [50]. Children from certain ethnicities are predisposed to NAFLD, primarily Hispanics, Asians and Native Americans [25,50].

Furthermore, a familial aggregation study of fatty liver in overweight children with and without NAFLD found that fatty liver is a highly heritable trait. Family members of children with biopsy-proven NAFLD and overweight children without NAFLD were evaluated by magnetic resonance imaging (MRI). Fatty liver was identified in 17% of siblings and 37% of parents of overweight children without NAFLD and in 59% of siblings and 78% of parents of children with NAFLD [51].

Interestingly, Romeo et al. [52] conducted the first genome-wide association scan conducted in a large multiethnic population. The authors demonstrated that the patatin-like phospholipase domain containing protein 3 (also known as adiponutrin) gene was strongly associated with IHTF content in adults [52].

These findings have been recently supported by Santoro et al. [53]. By genotyping the *PNLPA3* SNP in a multiethnic group of 85 obese youths, the authors found that the *PNPLA3* rs738409 SNP gene confers susceptibility to hepatic steatosis.

Nutrition and physical activity are important *environmental factors* that determine risk in NAFLD.

Excess food intake and lack of exercise contribute to weight gain, which has been shown to contribute to the progression of liver fibrosis in patients with NAFLD [54]. Specific dietary factors may also play either protective or antagonistic roles in the development and progression of NAFLD. An increased consumption of meat and soft drinks and low consumption of fish were found to be associated with NAFLD cases compared with controls [49]. Furthermore, low intakes of polyunsaturated fatty acid (PUFA) and high intakes of saturated fat and cholesterol were also shown to be associated with NAFLD [49]. Other studies have shown higher-carbohydrate and lower-fat diets to be associated with more progressive disease [49,55]. Notably, very recent animal data have shown that in both mice [49,56] and non-human primates [49] exposure to a maternal high-fat diet leads to a disturbing development and progression of NAFLD in the offspring.

It has been proposed that increase consumption of fructose in soft drinks and fruit drinks may have a role in the pathogenesis of NAFLD [2]. In one study, children with biopsy-proven NAFLD were shown to have significantly elevated plasma TG levels and oxidative stress levels after consumption of fructose as compared with glucose [57]. However, children without NAFLD were found to have no differences in TG or oxidative stress levels following the consumption of glucose compared with fructose [2].

Small intestinal bacterial overgrowth may be an additional environmental factor involved in NAFLD pathogenesis, and dietary supplements such as probiotics could have a beneficial effect [49]. Evidences from animal studies have shown that small intestinal bacterial overgrowth increases gut permeability leading to portal endotoxaemia and increased circulating inflammatory cytokines, both of which have been implicated in the progression of NAFLD [58,59].

4. NAFLD, metabolic and cardiovascular complications in obese children and adolescents

4.1. NAFLD and metabolic complications

NAFLD is nowadays considered the hepatic manifestation of the MetS in adults as well as in children [60]. This is not surprising since NAFLD is closely associated with obesity, insulin resistance, and alterations in glucose and lipid metabolism [44].

The association between NAFLD and MetS has been clearly demonstrated by Burgert et al. [61,62]. In 392 obese adolescents, elevated alanine aminotransferases (ALT) (>35 U/L) levels were found in 14% of participants, with a predominance of White/Hispanic. After adjusting

for potential confounders, rising ALT levels were associated with deterioration in insulin sensitivity and glucose tolerance, as well as increasing FFA and TG levels. Furthermore, increased hepatic fat accumulation was found in 32% of obese adolescents and was associated with decreased insulin sensitivity and increased lipid levels and visceral fat [61]. These results demonstrate that in obese children and adolescents, hepatic fat accumulation is associated with insulin resistance, dyslipidemia and altered glucose metabolism.

In addition, the Korean National Health and Nutrition Examination Survey found participants aged 10 – 19 years with three or more risk factors for MetS had an odds ratio that of 6.2 (95 % CI 2.3 – 16.8) for an elevated serum ALT, which they used as an indicator of fatty liver [62]. Furthermore, a case – control study of overweight children with biopsy-proven NAFLD and age-, sex-, and obesity-matched controls found that children with NAFLD were significantly more likely to have MetS than obese controls without evidence of fatty liver disease [9].

More recently, in a large histology-based study conducted in children with NAFLD [63], MetS was diagnosed in 25.6 % of the subjects, with central obesity and hypertension being the most common of the MetS features observed. In addition, a diagnosis of MetS was predictive of steatosis severity, NASH, hepatocellular ballooning and NAFLD pattern [63].

In a recent study by our group [64], we assessed the role of liver steatosis in defining MetS in prepubertal children. The prevalence of the MetS was around 14% and increased to 20% when liver steatosis was included as an additional diagnostic criterion. These findings underline not only the relevance of the MetS even among prepubertal children but also emphasize the potential importance of testing for fatty liver as a component of the MetS already in this age group [64] (figure 1).
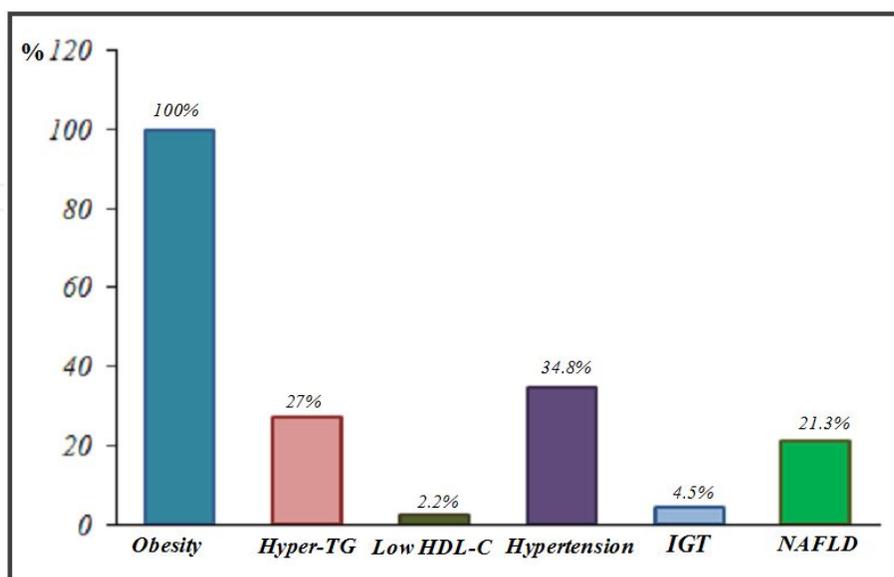

Figure 1. Prevalence of components of the MetS among obese prepubertal children [64].(TG, triglycerides; HDL-C, high density lipoprotein cholesterol; IGT, impaired glucose tolerance; NAFLD, non alcoholic fatty liver disease)

NAFLD in youth may be considered not only a strong risk factor for MetS, but also for T2D [36]. In a cohort of 118 obese adolescents [36] stratifyied according to tertiles of hepatic fat content (as assessed by fat gradient MRI), independently of obesity, the severity of fatty liver was associated with the presence of prediabetes [impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)/IGT]. In fact, paralleling the severity of hepatic steatosis, there was a significant decrease in insulin sensitivity and impairment in β-cell function, as indicated by the fall in the disposition index (DI). Furthermore, paralleling the severity of fatty liver, there was a significant increase in the prevalence of MetS, suggesting that hepatic steatosis may probably be a predictive factor of MetS in children [36].

The important role of intrahepatic fat content in the development of metabolic complications in obese subject has been recently underlined by Fabbrini et al. [15]. The authors showed that in adults with high IHTF insulin action in liver, skeletal muscle and adipose tissue was impaired and hepatic VLDL-TG secretion rate was increased. In contrast, they were not able to observe these metabolic alterations in subjects with high visceral fat volume and matched for IHTF. Therefore, the authors demonstrated that IHTF and not visceral fat is a better marker of metabolic derangements associated with obesity [15,16].

4.2. NAFLD and cardiovascular disease

Recent evidences suggests that individuals with NAFLD are also at high risk for coronary heart disease [3,43]. In adults, elevated serum ALT have been associated with increased risk of cardiovascular and all cause mortality (in addition to liver mortality) [3,65].

A study in Turkish children [66] showed that carotid artery intima-media thickness is significantly higher in obese children with fatty liver than in obese children without fatty liver or normal weight control.

In addition, Pacifico et al. [67] reported that carotid artery intima-media thickness was highest in obese children with echogenic liver and severity of liver fat was an independent predictor of intima-media thickness after adjustment for known cardiovascular factors.

However, given the lack of long-term longitudinal cohort studies in pediatric fatty liver disease, the relationship between the natural history of the disease and the actual risk for future cardiac events is unclear.

5. Conclusions

The prevalence of fatty liver disease is increasing in obese children and adolescence.

Although the exact pathogenetic mechanism is still unclear, there is an urgent need to screen obese children for this pathology. A misdiagnosis of fatty liver could represent a serious risk factor for the development of its associated metabolic and cardiovascular complications during childhood and for exacerbated metabolic abnormalities later in life.

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References

[1] Roberts EA. Pediatric nonalcoholic fatty liver disease (NAFLD): A ''growing'' problem? J Hepatol 2007;46:1133-1142.

[2] Barshop NJ, Francis CS, Schwimmer JB, Lavine JE. Nonalcoholic fatty liver disease as a comorbidity of childhood obesity. Ped Health 2009;3:271-81.

[3] Loomba R, Sirlin CB, Schwimmer JB, Lavine JE. Advances in Pediatric Nonalcoholic Fatty Liver Disease. Hepatology 2009;50:1282-1293.

[4] Hesham A-Kader H. Nonalcoholic fatty liver disease in children living in the obeseogenic society. World J Pediatr 2009;5:245-254.

[5] Molleston JP, White F, Teckman J, Fitzgerald JF. Obese children with steatohepatitis can develop cirrhosis in childhood. Am J Gastroenterol 2002;97:2460-2.

[6] Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of nonalcoholic fatty liver disease in children: a follow-up study for up to 20 years. Hepatology 2008;48(S1):335A.

[7] Pacifico L, Nobili V, Anania C, Verdecchia P, Chiesa C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. World J Gastroenterol 2011; 14;17:3082-91.

[8] Alisi A, Feldstein AE, Villani A, Raponi M, Nobili V. Pediatric nonalcoholic fatty liver disease: a multidisciplinary approach. Nat Rev Gastroenterol Hepatol 2012;9:152-61.

[9] Ryan MC, Wilson AM, Slavin J, Best JD, Jenkins AJ, Desmond PV. Associations between liver histology and severity of the metabolic syndrome in subjects with nonalcoholic fatty liver disease. Diabetes Care 2005;28:1222-1224.

[10] Fabbrini E, deHaseth D, Deivanayagam S, Mohammed BS, Vitola BE, Klein S. Altera‐
tions in fatty acid kinetics in obese adolescents with increased intrahepatic triglycer‐
ide content. Obesity (Silver Spring) 2009;17:25-29.

[11] 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: impor‐
tance of liver and intraabdominal fat accretion. Am J Clin Nutr 2010:92:500-8.

[12] Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. J
Clin Invest. 2004;114:147-52.

[13] Sinatra FR. Nonalcoholic fatty liver disease in pediatric patients. JPEN J Parenter En‐
teral Nutr 2012;36:43S-8S.

[14] Brunt EM. Pathology of nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hep‐
atol 2010;7:195-203.

[15] Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, Oku‐
nade A et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications
of obesity. Proc Natl Acad Sci U S A 2009;106:15430-15435.

[16] D'Adamo E, Cali AMG, Weiss R, Santoro N, Pierpont B, Northrup V, Caprio S. Cen‐
tral Role of Fatty Liver in the Pathogenesis of Insulin Resistance in Obese Adoles‐
cents. Diabetes Care 2012;33:1817–1822.

[17] Manco M. Metabolic syndrome in childhood from impaired carbohydrate metabo‐
lism to nonalcoholic fatty liver disease. J Am Coll Nutr 2011;30(5):295-303.

[18] Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002; 346: 1221-1231.

[19] Pais R, Lupşor M, Poantă L, Silaghi A, Rusu ML, Badea R, Dumitraşcu DL. Liver Bi‐
opsy versus Noninvasive Methods – Fibroscan and Fibrotest in the Diagnosis of
Non-alcoholic Fatty Liver Disease: A Review of the Literature. Rom J Intern Med.
2009;47(4):331-40.

[20] Janczyk W, Socha P. Non-alcoholic fatty liver disease in children. Clin Res Hepatol
Gastroenterol 2012;36:297-300.

[21] Joseph AE, Saverymuttu SH, Al-Sam S, Cook MG, Maxwell JD. Comparison of liver
histology with ultrasonography in assessing diffuse parechymal liver disease. Clin
Radiol 1991: 43:26-31.

[22] Tominaga K, Kurata JH, Chen YK, Fujimoto E, Miyagawa S, Abe I, Kusano Y. Preva‐
lence of fatty liver in Japanese children and relationship to obesity. An epidemiologi‐
cal ultrasonographic survey. Dig Dis Sci 1995;40:2002-2009.

[23] Agawal N, Sharma BC. Insulin resistance and clinical aspects of non-alcoholic steato‐
hepatitis (NASH). Hepatol Res 2005;33:92-96.

[24] Franzese A, Vajro P, Argenziano A, Puzziello A, Iannucci MP, Saviano MC, Brunetti
F, Rubino A. Liver involvement in obese children. Ultrasonography and liver en‐

zymes levels at diagnosis and during follow-up in an Italian population. Dig Dis Sci 1997;42:1428-1432.

[25] 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.

[26] Strauss RS, Barlow SE, Dietz WH. Prevalence of abnormal serum amino transferase values in overweight and obese adolescents. J Pediatr Gastroenterol Nutr 2000;136:727-733.

[27] Manco M, Bedogni G, Marcellini M, Devito R, Ciampalini P, Sartorelli MR, Comparcola D, Piemonte F, Nobili V. Waist circumference correlates with liver fibrosis in children with non-alcoholic steatohepatitis. Gut 2008;57(9):1283-7.

[28] Fishbein MH, Miner M, Mogren C, Chalekson J. The spectrum of fatty liver in obese children and the relationship of serum aminotransferases to severity of steatosis. J Pediatr Gastoenterol Nutr 2003;36:54-61.

[29] D'Adamo E, Impicciatore M, Capanna R, Loredana Marcovecchio M, Masuccio FG, Chiarelli F, Mohn AA. Liver steatosis in obese prepubertal children: a possible role of insulin resistance. Obesity (Silver Spring) 2008;16:677-683.

[30] Day CP, James OFW. Steatohepatitis: a tale of two ''hits''. Gastroenterology 1998;114:842-845.

[31] Tiniakos DG, Vos BM, Brunt EM. Nonalcoholic Fatty Liver Disease: Pathology and Pathogenesis. Annu Rev Patholo Mech Dis 2010:5:145-171.

[32] Weiss R, Dufour S, Taksali SE, Tamborlane WV, Petersen KF, Bonadonna RC, Boselli L, Barbetta G, Allen K, Rife F, Savoye M, Dziura J, Sherwin R, Shulman GI, Caprio S. Prediabetes in obese youth: a syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. Lancet 2003;362:951-957.

[33] Taksali SE, Caprio S, Dziura J, Dufour S, Calí AM, Goodman TR, Papademetris X, Burgert TS, Pierpont BM, Savoye M, Shaw M, Seyal AA, Weiss R. High visceral and low abdominal subcutaneous fat stores in the obese adolescent. Diabetes 2008;57:367-371.

[34] Weiss R, Dufour S, Groszmann A, Petersen K, Dziura J, Taksali SE, Shulman G, Caprio S. Low adiponectin levels in adolescent obesity: a marker of increased intramyocellular lipid accumulation. J Clin Endocrinol Metab 2003;88:2014-2018.

[35] Cruz ML, Bergman RN, Goran MI. Unique effect of visceral fat on insulin sensitivity in obese Hispanic children with a family history of type 2 diabetes. Diabetes Care 2002;25:1631-1636.

[36] Cali A, De Oliveira AM, Kim H, et al. Glucose Dysregulation and Hepatic Steatosis in Obese Adolescents: Is There a Link? Hepatology 2009;49:1896-1903.

[37] Hwang JH, Stein DT, Barzilai N, Cui MH, Tonelli J, Kishore P, Hawkins M. Increased intrahepatic triglyceride is associated with peripheral insulin resistance: in vivo MR imaging and spectroscopy studies. Am J Physiol Endocrinol Metab 2007;293:1663-1669.

[38] Matsuwaka Y. Adiponectin: a key player I obesity related disorders. Curr Pharm Des 2010;16:1896-1901.

[39] Deivanayagam S, Mohammed BS, Vitola BE, Naguib GH, Keshen TH, Kirk EP, Klein S. Nonalcoholic fatty liver disease is associated with hepatic and skeletal muscle in‐ sulin resistance in overweight adolescents. Am J Clin Nutr 2008;88:257-262.

[40] Perseghin G, Bonfanti R, Magni S, Lattuada G, De Cobelli F, Canu T, Esposito A, et al. Insulin resistance and whole body energy homeostasis in obese adolescents with fatty liver disease. Am J Physiol Endocrinol Metab 2006;291:697-703.

[41] Seppälä-Lindroos A, Vehkavaara S, Häkkinen AM, Goto T, Westerbacka J, Sovijärvi A, Halavaara J, Yki-Järvinen H. Fat accumulation in the liver is associated with de‐ fects in insulin suppression of glucose production and serum free fatty acids inde‐ pendent of obesity in normal men. J Clin Endocrinol Metab 2002;87:3023-3028.

[42] Petersen KF, Oral EA, Dufour S, Befroy D, Ariyan C, Yu C, Cline GW, DePaoli AM, Taylor SI, Gorden P, Shulman GI. Leptin reverses insulin resistance and hepatic stea‐ tosis in patients with severe lipodystrophy. J Clin Invest 2002;109:1345-1350.

[43] Perseghin G. Viewpoints on the way to a consensus session: where does insulin re‐ sistance start? The liver. Diabetes Care 2009;32 Suppl 2:S164-167.

[44] Perseghin G, Mazzaferro V, Sereni LP, Regalia E, Benedini S, Bazzigaluppi E, Pulvir‐ enti A, Leão AA, Calori G, Romito R, Baratti D, Luzi L. Contribution of reduced insu‐ lin sensitivity and secretion to the pathogenesis of hepatogenous diabetes: effect of liver transplantation. Hepatology 2000;31:694-703.

[45] Kotronen A, Yki-Järvinen H. Fatty Liver: A Novel Component of the Metabolic Syn‐ drome. Arterioscler Thromb Vasc Biol 2008;28:27-38.

[46] Battezzati A, Terruzzi I, Perseghin G, Bianchi E, Di Carlo V, Pozza G, Luzi L. Defec‐ tive insulin action on protein and glucose metabolism during chronic hyperinsuline‐ mia in subjects with benign insulinoma. Diabetes 1995;44:837-844.

[47] Petrides AS, Stanley T, Matthews DE, Vogt C, Bush AJ, Lambeth H. Insulin resistance in cirrhosis: prolonged reduction of hyperinsulinemia normalizes insulin sensitivity. Hepatology 1998;28:141-149.

[48] de Giorgis T, D'Adamo E, Giannini C, Chiavaroli V, Scarinci A, Verrotti A, Chiarelli F, Mohn A. Could receptors for advanced glycation end products be considered car‐ diovascular risk markers in obese children? Antioxid Redox Signal 2012: 15;17:187-91.

[49]   Moore JB. Non-alcoholic fatty liver disease: the hepatic consequence of obesity and the metabolic syndrome. Proc Nutr Soc 2010; 69: 211-220.

[50]   Louthan MV, Theriot JA, Zimmerman E, Stutts JT, McClain CJ. Decreased prevalence of nonalcoholic fatty liver disease in black obese children. J Pediatr Gastroenterol Nutr 2005;41:426-429.

[51]   Schwimmer JB, Celedon MA, Lavine JE, Salem R, Campbell N, Schork NJ, Shiehmorteza M, Yokoo T, Chavez A, Middleton MS, Sirlin CB.Heritability of nonalcoholic fatty liver disease. Gastroenterology 2009;136:1585-1592.

[52]   Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008;40, 1461-1465.

[53]   Santoro N, Kursawe R, D'Adamo E, Dykas DJ, Zhang CK, Bale AE, Calí AM, Narayan D, Shaw MM, Pierpont B, Savoye M, Lartaud D, Eldrich S, Cushman SW, Zhao H, Shulman GI, Caprio S.A Common Variant in the Patatin-Like Phopholipase 3 Gene (PNPLA3) is Associated with Fatty Liver Disease in Obese Children and Adolescents. Hepatology 2010;52:1281-1290.

[54]   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.

[55]   Solga S, Alkhuraishe AR, Clark JM, Torbenson M, Greenwald A, Diehl AM, Magnuson T.Dietary composition and nonalcoholic fatty liver disease. Dig Dis Sci 2004;49:1578-1583.

[56]   Bruce KD, Cagampang FR, Argenton M, Zhang J, Ethirajan PL, Burdge GC, Bateman AC, Clough GF, Poston L, Hanson MA, McConnell JM, Byrne CD.Maternal high-fat feeding primes steatohepatitis in adult mice offspring, involving mitochondrial dysfunction and altered lipogenesis gene expression. Hepatology 2009;50,1796-1808.

[57]   Vos M, McClain CJ, Jones D. Fructose is associated with increased oxidative stress and elevated plasma triglycerides in children with nonalcoholic fatty liver disease. Hepatology 2008;48 (S1):820A.

[58]   Brun P, Castagliuolo I, Di Leo V, Buda A, Pinzani M, Palù G, Martines D. Increased intestinal permeability in obese mice: new evidence in the pathogenesis of nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol 2007;292:518-525.

[59]   Wigg AJ, Roberts-Thomson IC, Dymock RB, McCarthy PJ, Grose RH, Cummins AG.The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis factor alpha in the pathogenesis of non-alcoholic steatohepatitis. Gut 2001;48,206-211.

[60]   D'Adamo E, Santoro N, Caprio S. Metabolic Syndrome in Pediatrics: Old Concepts Revised, New Concepts Discussed. Endocrinol Metab Clin N Am 2009;38:549-563.

[61] Burgert TS, Taksali SE, Dziura J, Goodman TR, Yeckel CW, Papademetris X, Consta‐ ble RT, Weiss R, Tamborlane WV, Savoye M, Seyal AA, Caprio S.Alanine amino‐ transferase levels and fatty liver in childhood obesity: associations with insulin resistance, adiponectin, and visceral fat. J Clin Endocrinol Metab 2006;91:4287-4294.

[62] Kang H, Greenson JK, Omo JT, Chao C, Peterman D, Anderson L, Foess-Wood L, Sherbondy MA, Conjeevaram HS.Metabolic syndrome is associated with greater his‐ tologic severity, higher carbohydrate, and lower fat diet in patients with NAFLD. Am J Gastroenterol 2006;101:2247-2253.

[63] Patton HM, Yates K, Unalp-Arida A, et al. Association Between Metabolic Syndrome and Liver Histology Among Children With Nonalcoholic Fatty Liver Disease. Am J Gastroenterol 2010; 105:2093-2102.

[64] D'Adamo E, Marcovecchio ML, Giannini C, Capanna R, Impicciatore M, Chiarelli F, Mohn A.The possible role of liver steatosis in defining metabolic syndrome in prepu‐ bertal children. Metabolism 2010;59:671-676.

[65] Lee TH, Kim WR, Benson JT, Therneau TM, Melton LJ 3rd.Serum aminotransferase activity and mortality risk in a United States community. Hepatology 2008; 47: 277-283.

[66] Demircioğlu F, Koçyiğit A, Arslan N, Cakmakçi H, Hizli S, Sedat AT. Intima-media thickness of carotid artery and susceptibility to atherosclerosis in obese children with nonalcoholic fatty liver disease. J Pediatr Gastroenterol Nutr 2008;47:423-427.

[67] Pacifico L, Cantisani V, Ricci P, Osborn JF, Schiavo E, Anania C, Ferrara E, Dvisic G, Chiesa C.Nonalcoholic fatty liver disease and carotid atheroscelrosis in children. Pe‐ diatr Res 2008; 63:423-427.