Obesity and Air Pollution: Global Risk Factors for Pediatric Non-alcoholic Fatty Liver Disease

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Non-alcoholic fatty liver disease (NAFLD) is becoming as an important health problem in the pediatric age group. In addition to the well-documented role of obesity on the fatty changes in liver, there is a growing body of evidence about the role of environmental factors, such as smoking and air pollution, in NAFLD. Given that excess body fat and exposure to air pollutants is accompanied by systemic low-grade inflammation, oxidative stress, as well as alterations in insulin/insulin-like growth factor and insulin resistance, all of which are etiological factors related to NAFLD, an escalating trend in the incidence of pediatric NAFLD can be expected in the near future. This review focuses on the current knowledge regarding the epidemiology, diagnosis and pathogenesis of pediatric NAFLD. The review also highlights the importance of studying the underlying mechanisms of pediatric NAFLD and the need for broadening efforts in prevention and control of the main risk factors. The two main universal risk factors for NAFLD, obesity and air pollution, have broad adverse health effects, and reducing their prevalence will help abate the serious health problems associated with pediatric NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is considered the most common liver disease in various age groups. Its development is strongly linked to obesity (1), as well as to the relative changes in body mass index in each individual, which may be related to the onset of fatty liver (2). Even though liver steatosis has various causes in the pediatric age group, such as inherited metabolic disorders, malnutrition, infections, and drug toxicity, fatty liver disease is often seen in children in the absence of an apparent inherited metabolic defect or a specific cause. The vast majority of children with fatty liver disease are found to be obese and insulin resistant (1, 2). Low- and middle-income countries face the double burden of nutritional disorders, with an increasing prevalence of childhood obesity (3), and therefore, an increasing number of reports of NAFLD in the pediatric age group (4-7). An increasing number of studies have proposed an association between environmental factors, namely air pollution, and fatty changes in the liver. This review will focus on the current knowledge regarding the epidemiology,
diagnosis, and pathogenesis of pediatric NAFLD, as well as the possible associations with obesity and air pollution, which are the adverse effects of urbanization and globalization of lifestyle.

2. Global Trends in Childhood Obesity

The World Health Organization states “An escalating global epidemic of overweight and obesity—“globesity”—is taking over many parts of the world” (8). Of special concern in the context of this epidemic is the escalating trend in the prevalence of childhood overweight and obesity on a global scale. There are several reports on the increasing prevalence of childhood obesity in industrialized countries (9-14); however, this is an emerging health problem in low- and middle-income countries as well (15-18). An analysis of 450 nationally representative cross-sectional surveys of preschool-aged children from 144 countries indicated that in 2010, 43 million children, 35 million of them in developing countries, were estimated to be overweight and obese, and 92 million were at risk of becoming overweight. The global prevalence of childhood overweight and obesity increased from 4.2% (95% CI: 3.2%, 5.2%) in 1990 to 6.7% (95% CI: 5.6%, 7.7%) in 2010. This trend is expected to reach 9.1% (95% CI: 7.3%, 10.9%), or ~60 million, in 2020 (19). It is noteworthy that in many cases, the excess weight of children in developing countries is because of their stunting (15, 20, 21). These findings highlight the need for determining the barriers to healthy lifestyle (22) and promoting healthy living in their current obesogenic environments to reverse the anticipated health and social consequences of childhood overweight, namely NAFLD.

3. Histological Appearance of Pediatric NAFLD

The spectrum of NAFLD ranges from pure fatty infiltration (steatosis) to inflammation non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis (23). It accounts for up to 20% of abnormal liver function test results in most developed countries (24). The histological appearance of NAFLD differs significantly in children and adults; it might represent a physiological response to environmental factors in children and a long-standing adaptation in adults. The histological criteria for distinguishing between adult (type 1) and pediatric (type 2) NASH have been proposed. Prominently, the histological features of liver injury seem to be associated with gender- and age-specific prevalence, i.e., type 2 NASH is more prevalent in younger children, and significantly more boys are affected by type 2 NASH than girls (25). Among obese children, the severity of steatosis is found to be associated with increased visceral fat mass, insulin resistance, lower adiponectin levels, and higher blood pressure (26).

4. Diagnosis of Pediatric NAFLD

4.1. Biochemical Tests

Liver biopsy is the gold standard for diagnosis, but given that it is not feasible in large epidemiological studies, surrogate markers such as serum alanine/aspartate aminotransferases (ALT/AST) or ultrasonography are usually used to detect NAFLD (27). The normal range of ALT/AST levels varies widely, and biopsy-proven NAFLD has been found in children with normal aminotransferase levels (25, 28, 29). Aminotransferases, including aspartate AST and ALT, are commonly used in evaluating liver pathologies such as NAFLD and hepatitis. Given that AST is produced in different tissues such as the liver, heart, muscle, kidney, and brain, ALT has been generally accepted as a better predictor of liver injury. Usually in a clinical setting, an ALT level of 40 IU/L is considered the upper limit of the normal range (30). However, some studies suggested lower cutoff values in children than in adults (31, 32). Moreover, some researchers have proposed gender differences for these levels, i.e., 19 IU/L and 30 IU/L for girls and boys, respectively (33, 34).

4.2. Radiologic Diagnosis

The image-based diagnosis of NAFLD is usually straightforward, but fat accumulation may be manifested with unusual structural patterns that simulate other conditions. Fat deposition in the liver may be identified non-invasively with ultrasonography, computerized tomography, or magnetic resonance imaging (35, 36). In ultrasonography, the echogenicity of the normal liver nearly equals or slightly exceeds that of the renal cortex or spleen. Intrahepatic vessels are tightly defined, and the posterior parts of the liver are well-illustrated. Fatty liver may be identified if liver echogenicity exceeds that of the renal cortex and spleen, with attenuation of the ultrasound wave, loss of delineation of the diaphragm, and poor demarcation of the intrahepatic architecture (37, 38).

5. Prevalence of Pediatric NAFLD

Determination of the prevalence of NAFLD accurately in children is difficult. Because of the aforementioned limitations and controversies in the diagnosis of NAFLD in children and adolescents, data based on surrogate markers might underestimate or overestimate the current burden of pediatric NAFLD. One of the strongest population-based studies, using the histologic definition for NAFLD, was conducted as a retrospective review of autopsies, performed from 1993 to 2003 on 742 children aged 2 to 19 years. The prevalence of NAFLD was estimated as 9.6%, ranging from 0.7% in children aged 2–4 years, to 17.3% in those aged 15–19 years, with the highest documented rate, as high as 38%, in obese children. It is of note that this study revealed differences in terms of race and ethnicity in the prevalence of pediatric NAFLD, with a prevalence of 11.8% in Hispanics, 10.2% in Asians, 8.6% in Whites, and 1.5% in Blacks (39). Results from the US National Health and Nutrition Examination Survey (NHANES 1999–2004) reported a prevalence of 8% for NAFLD in adolescents, based on elevated serum ALT (40). This prevalence is reported to be much higher among...
### Table. Summary of Studies on the Prevalence of Pediatric Non-alcoholic Fatty Liver Disease

| Location | Population Studied | Aims | Findings |
|----------|--------------------|------|----------|
| Widhalm et al. (2010) (63) | Review | Review article | To provide a detailed review for diagnosis and management of NAFLD and NASH | The prevalence ranges from at least 3% in children overall to about 50% in obese children |
| Liu et al. (2010) (53) | China | 23 obese children and 24 non-obese children as controls | To compare biochemical indicators and carotid intima-media thickness (IMT) | The NAFLD group had greater carotid IMT, hyperlipidemia and hypertension than other groups. IMT correlated with BMI, NAFLD and ALT |
| Lin et al. (2010) (52) | Taiwan | 69 obese children aged 6-17 y | To identify biomarkers for liver steatosis in obese children | Thirty-eight (55.1%) subjects had liver steatosis, with elevated ALT in 27 (71.1%) of them |
| Caserta et al. (2010) (47) | Italy | 642 adolescents aged 11-13 y | To determine the prevalence of NAFLD | NAFLD was found in 12.5% of participants, increasing to 23.0% in overweight ones. Increased IMT was associated with NAFLD |
| Nobili et al. (2010) (54) | Italy | 118 children with biopsy-proven NAFLD | To assess the association of severity of liver injury and lipid profile | The NAFLD activity and fibrosis scores had positive correlation with triglyceride/HDL, total cholesterol/HDL, and LD/L/HDL ratios |
| Patton et al. (2010) (56) | USA | 254 children aged 6-17 y | To determine the association of metabolic syndrome with NAFLD | 65 (26%) had metabolic syndrome with greatest risk among those with severe steatosis; hepatocellular ballooning was associated with metabolic syndrome |
| Shi et al. (2009) (60) | China | 308 obese children aged 9 to 14 y | To determine the prevalence of NAFLD and metabolic syndrome | Among all the obese children, the prevalence of NAFLD, NASH and metabolic syndrome was 65.9%, 20.5% and 24.7% respectively |
| Koebnick et al. (2009) (51) | USA | Hospitalized with NAFLD or obesity in 6-25 y | To investigate trends of NAFLD and obesity among hospitalized patients | Between 1986 to 1988 and 2004 to 2006, hospitalization increased from 0.9 to 4.3/100,000 for NAFLD, and from 35.5 to 114.7/100,000 for obesity |
| Reinehr et al. (2009) (57) | Germany | Obese children followed for 1 y | To determine the course of obesity associated NAFLD | 20.6% of obese children had hypertension, 22.3% had dyslipidemia, 4.9% had impaired fasting glucose, and 29.3% had NAFLD |
| Denzer et al. (2009) (26) | Germany | 532 obese subjects aged 8-19 y | To examine the prevalence and markers associated with NAFLD | Hepatic steatosis was higher in boys (41.1%) than in girls (17.2%) and was highest in postpubertal boys (51.2%) and lowest in postpubertal girls (12.2%) |
| Sharp et al. (2009) (59) | U.S.-Mexico border | 31 patients aged 8-18 y | To describe the physical and metabolic characteristics of children diagnosed with NAFLD | The majority of cases were adolescents (12-17 y) and Mexican American. All subjects were overweight |
| Fu et al. (2009) (48) | Taiwan | 220 students (97 normal, 48 overweight, 75 obese) | To investigate the risk factors for NAFLD among adolescents | NAFLD was detected in 39.8% in total, 16.0% in normal, 50.5% in overweight, and 63.3% among obese adolescents |
| Rocha et al. (2009) (58) | Brazil | 1801 children aged 11 to 18 y | To evaluate the prevalence and clinical characteristics of NAFLD | The prevalence of NAFLD was 2.3%, most of whom were male and white. Insulin resistance (IR) was observed in 22.5% of them |
obese children and adolescents, ranging from 10% to 25% based on elevated ALT, compared with 42% to 77% based on ultrasonography (41-44). Table provides a summary of prevalence studies on pediatric NAFLD (25, 26, 39, 40, 45-63).

6. NAFLD or MAFLD?

Because of the well-documented interrelationships between the risk factors, metabolic alterations, and liver histology of NAFLD and metabolic syndrome, a recent review suggested the term MAFLD (metabolic syndrome-associated fatty liver disease), which might describe both groups of patients with common pathophysiological features more accurately (64). A growing body of evidence proposes that NAFLD and metabolic syndrome are interrelated even from childhood. Many studies revealed that the components of the metabolic syndrome are strong predictors of increased ALT activity in NAFLD among children and adolescents (42, 65-71). It is also documented that the higher levels of components of metabolic syndrome increase the risk of elevated ALT in children and adolescents (50).

7. Pediatric NAFLD and Early Atherosclerosis

NAFLD shares the same causal factors with metabolic syndrome, which are also major cardiovascular risk factors. While there are conflicting results about the association of NAFLD with atherosclerotic cardiovascular diseases (72), a review of some studies confirmed the proatherogenic role of NAFLD, and suggested that among adult populations it can be an independent risk factor for atherosclerotic cardiovascular diseases (73). How-

| Study | Country | Sample | Objective | Findings |
|-------|---------|--------|-----------|---------|
| Graham et al. (2009) (49) | USA | Sample of 12-19 y from the NHANES1999 to 2002 | To determine the association of metabolic syndrome and NAFLD | The metabolic syndrome was associated with ALT > 40 U/L (OR = 16.7, CI 6.2-45.1) |
| Carter-Kent et al. (2009) (46) | USA | 130 children with biopsy-proven NAFLD | To assess clinical and laboratory predictors of NAFLD severity | Fibrosis was present in 87% of patients; of these, stage 3 (bridging fibrosis) was present in 20% |
| Alavian et al. (2009) (45) | Iran | 966 children aged 7-18 y | To investigate the prevalence of NAFLD | Fatty liver was diagnosed by ultrasound in 7.1% of children. The prevalence of elevated ALT was 1.8% |
| Kelishadi et al. (2009) (50) | Iran | 1107 children aged 6-18 y | To compare the prevalence of NAFLD in different BMI categories | Elevated ALT was documented in respectively 4.1% of normal weight, 9.5% in overweight and 16.9% in obese group, respectively |
| Fraser et al. (2007) (40) | USA | NHANES participants, aged 12-19 y (1999–2004) | To determine the prevalence of NAFLD | a prevalence of NAFLD of 8% based on elevated ALT |
| Schwimmer et al. (2006) (39) | USA | 742 children aged 2-19 y with autopsy | To determine the prevalence of biopsy-proven NAFLD | Fatty liver was present in 11% of subjects, ranging from 0.7% for ages 2 to 4 up to 17.3% for ages 15 to 19 y |
| Schwimmer et al. (2005) (25) | USA | 127 obese 12th-grade students | To determine the prevalence of NAFLD | Unexplained ALT elevation was present in 23% of participants, in boys (44%) and in girls (7%) |
| Park et al. (2005) (55) | Korea | 1594 children aged 10-19 y | To investigate the relation of NAFLD and the metabolic syndrome | The prevalence of elevated ALT (> 40 U/L) was 3.6% in boys and 2.8% in girls. The prevalence of metabolic syndrome was 3.3% in both boys and girls |
| Strauss et al. (2000) (61) | USA | 2450 children aged 12-18 y | To determine the prevalence of NAFLD in different BMI categories | 6% of overweight adolescents had elevated ALT levels; about 1% of obese adolescents had ALT levels over twice normal |
| Tominaga et al. (1995) (62) | Japan | 810 students, ages 4-12 y | To determine the prevalence of NAFLD | The overall prevalence of NAFLD was 2.6%, boys (3.4%) and girls (1.8%), (P = 0.15) |
| Sharp et al. (2009) (56) | USA-Mexico | 31 patients aged 8-18 y | To describe the characteristics of children diagnosed with NAFLD | The majority of children were aged 12-17 y and Mexican American. All subjects were overweight |

Abbreviations: ALT, alanine aminotransferase; NAFLD; non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis
8. Dietary and Physical Activity Habits Related to Pediatric NAFLD

There is a growing body of evidence about the significance of environmental background in the establishment and development of NAFLD from the early years of life. Unhealthy dietary habits, such as disproportionately high consumption of saturated fats and refined sugars, may harm adipose tissue architecture and homeostasis. They may also alter the peripheral and hepatic resistance to insulin-stimulated glucose uptake, thus favoring chronic low-grade inflammation. Excess nutrients that cannot be stored in adipose tissue would overflow to muscle tissue and the liver. Fat deposition in both sites increases insulin resistance and promotes further fat deposition (78, 79). Lifestyle, notably dietary habits, is associated with the development of NAFLD (80). The diet most recommended for prevention and control of NAFLD is a low-carbohydrate diet, with a very limited amount of refined carbohydrates (81, 82). In our study of adolescents aged 12-18 years we found significant associations between insulin resistance and NAFLD, and similar risk factors and protective factors for these 2 interrelated disorders. Waist circumference and the ratio of apolipoprotein B to apolipoprotein A-I (ApoB/ApoA-I ratio) had the highest odds ratio (OR) in increasing the risk of insulin resistance and NAFLD, whereas cardiorespiratory fitness, followed by healthy eating index, decreased this risk significantly (50).

9. Environmental Factors Related to NAFLD

9.1. Smoking and NAFLD

A growing body of evidence supports the potential effects of exposure to some environmental factors on liver diseases. Environmental exposure related to toxic waste sites was associated with an increased prevalence of autoimmune liver disease (83, 84). Therefore, increasing attention is being given to the effects of environmental factors on liver diseases, including NAFLD. Many recent studies have also documented the association of smoking with the incidence of and acceleration of disease progression in NAFLD, as well as with advanced fibrosis in this process (85-89).

9.2. Air Pollution and NAFLD

The harmful effects of air pollutants on atherosclerotic cardiovascular diseases are well-documented (88). These effects might be mediated through oxidative stress and insulin resistance (90), which are also known to have pivotal roles in the pathogenesis of fatty liver (91). Hence, it can be assumed that such environmental factors might also be associated with NAFLD. It is well-documented that diesel exhaust particles (DEP), which are major constituents of atmospheric particulate matters (PM) in urban areas, generate reactive oxygen species (ROS) (92). The ROS are generated via enzymatic reactions catalyzed by cytochrome P-450 (93), or by a non-enzymatic route (94). In 2007, two experimental studies examined the effects of exposure to DEP on fatty liver for the first time. One of these studies revealed that exposure to DEP might increase oxidative stress, with concomitant aggravation of fatty changes in the livers of diabetic obese mice. This exposure increases the AST and ALT levels, liver weight, and the degree of fatty change of the liver, as ascertained histologically. This study suggested that ROS, lipid peroxides, or inflammatory cytokines produced in the lungs might reach the liver, or soluble constituents of PM might get transferred from the lung to the liver through systemic circulation. Given that exposure to these particles may decrease the mitochondrial membrane potential, and may increase ROS, followed by cytochrome-c release and inner mitochondrial membrane damage, this study proposed that mitochondrial damage could have an enhancing effect on NAFLD, especially in augmenting the effects of oxidative stress on the liver (95). The other experimental study assessed the effects of oxidative stress elicited by DEP in the aorta, liver, and lungs of dyslipidemic ApoE(-/-) mice, at the age when visual plaques appeared in the aorta. Vascular effects secondary to pulmonary inflammation were omitted by injecting DEP into the peritoneum. Six hours later, the expression of inducible nitric oxide synthase (iNOS) mRNA increased in the liver. Injection of DEP did not induce inflammation or oxidative damage to DNA in the lungs and aorta. Therefore, the study proposed a direct effect of DEP on inflammation and oxidative damage to DNA in the liver of dyslipidemic mice (96). Another study investigated the effects of a 6-week exposure to filtered air, in comparison with ambient air PM at doses mimicking naturally occurring levels, on diet-induced hepatic steatosis in mice fed high-fat diets. Progression of NAFLD was evaluated by histologi-
The prevalence of childhood obesity and air pollution is dramatically increasing on a global scale. Given that both excess body fat and exposure to air pollutants are accompanied by systemic low-grade inflammation, oxidative stress as well as alterations in insulin/insulin-like growth factor and insulin resistance, which contribute to fatty liver, an escalating trend in the incidence of pediatric NAFLD and its related complications can be expected in the near future. Studying the underlying mechanisms and broadening efforts to prevent and control the 2 main universal risk factors, obesity and air pollution, which have broad adverse health effects, will help abate the serious health problems associated with pediatric NAFLD.

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