Nonalcoholic Fatty Liver Disease: Cause to Treatment

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INTRODUCTION

Imagine two individuals, both suffering from severe liver damage. With excess fat molecules concentrated in the hepatic cells, their livers are inflamed and scarred. These deteriorating livers are also supplementing the development of chronic obesity, diabetes, cardiovascular diseases, and hyperlipidemia. While one of these individuals is a middle-aged male with a long history of alcohol addiction and abuse, the other is only thirteen years old and has never consumed alcohol. This adolescent is suffering from nonalcoholic fatty liver disease (NAFLD).

The liver is not an isolated organ; it works in conjunction with almost every other system of the body, including the digestive, endocrine, and circulatory system. For instance, the liver regulates blood glucose levels, which is the body’s primary source of energy and fat. The liver metabolizes, i.e. synthesizes and breaks down glucose and fat, depending on the body’s needs, and stores the excess energy temporarily in the form of glycogen and triglycerides (Manco, 2011). In the case of alcohol-induced fatty liver, alcohol disrupts the fat metabolism, causing an influx and accumulation of free fatty acids in the liver (Orman et al., 2013). NAFLD causes the same effect, driven primarily by obesity (Nobili et al., 2009).

In fact, NAFLD prevalence rates parallel the so-called “globesity” (global obesity) rates (Corte et al., 2012). In the United States alone, 17% of children are considered overweight and obese by the Centers for Disease Control and Prevention (CDC); of these, 52% have NAFLD (Oddy et al., 2013). The proportion of children...
Given that children have been exposed to an unhealthy lifestyle for a much shorter period than adults, genetics may play more of a dominant role in pediatric NAFLD prevalence than adult NAFLD; especially considering that in some cases, children have the disease despite optimal dietary and lifestyle habits (Nobili et al., 2014). In fact, one study found that the immediate family members of children with NAFLD had a much higher percentage of liver fat content, with siblings at 9.3% and parents at 14% fat, than the family members of the children without the disease, whose siblings were at 2.7% and parents at 7% (Schwimmer et al., 2009). It is evident that NAFLD is impacted by an individual’s genetics; current research has identified multiple genes that play a role in its development (Dongiovanni et al., 2013).

Since NAFLD is more common amongst Hispanic American than African American populations, 45% versus 24% respectively, there may be a strong genetic predisposition toward developing the disease (Marzuillo et al., 2014). However, besides genetics, other factors can also significantly contribute to the progression of the disease. These are explained in terms of a double hit hypothesis, as shown in Figure 1. The first hit refers to the accumulation of fat in liver cells. This sensitizes the liver to other factors, known collectively as the second hit, which aggravate the liver further, leading to inflammation, scarring, and if left untreated, even cancer (Veena et al., 2014). The majority of pediatric NAFLD patients also show psychological symptoms (St-Jules et al., 2013), reporting a significantly lower quality of life compared to healthy children, 72% versus 83% respectively. Their symptoms include fatigue, depression, insomnia, and poor school performance (Kistler et al., 2010). Children with NAFLD also have a thirteen-fold increased risk of death or of requiring a liver transplant as compared to their healthy counterparts (Feldstein et al., 2009). Undoubtedly, we are letting one preventable and reversible global epidemic, obesity, exacerbate the spread of another preventable disease, advancing both to chronic and fatal conditions. This article examines how NAFLD develops in children and explores preventative measures and treatment options, including lifestyle modifications, in order to present the best interventions for combatting the rapidly increasing rate of pediatric NAFLD.

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Contextual Factors That Favor NAFLD and the Two-Hit Hypothesis

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NAFLD does not refer to one particular disease with a set of symptoms. Rather, it is a spectrum of diseases, with three key stages. The earliest and most prevalent stage of NAFLD is called simple steatosis (Ozgur et al., 2013). This stage involves the accumulation of triglycerides in the liver cells due to an imbalance between the import and export of fatty acids (Nobili et al., 2009), without significant liver inflammation (Roberts, 2007). While simple steatosis is asymptomatic and reversible (Rafeey et al., 2009), if no action is taken to revert the liver’s condition, simple steatosis progresses to nonalcoholic steatohepatitis (NASH). At this stage, liver cells contain harmful amount of fat molecules, and there is significant inflammation with damaged and dead liver cells, which causes scarring (Aqel & Dibaise, 2015). If the liver cells do not regenerate at the same rate as they die, further scarring occurs, leading to cirrhosis (Ozgur et al., 2013), and in some cases, cancer (Boursier & Diehl, 2015). Unlike simple steatosis, NASH is not asymptomatic, although it may be reversible in some cases. However, once the disease has progressed to cirrhosis, the damage is irreversible and fatal (Rafeey et al., 2009).
The most apparent and globally conspicuous genetic relationship of NAFLD is with the gene called PNPLA3, patatin-like phospholipase domain-containing protein 3 (Lim et al., 2010), which is used to make an enzyme called adiponutrin (Park et al., 2015). Adiponutrin is primarily synthesized in liver and adipose (fat) tissue. In a healthy individual, it acts as a triglyceride synthase in adipose cells, and as a triglyceride hydrolase in liver cells. This means it can both synthesize and break down triglycerides, depending on the cell and the environmental factors that it is exposed to (Park et al., 2015). In a NAFLD patient, a single nucleotide mutation, in which cytosine is substituted with guanosine, creates a different version of PNPLA3, a variant called rs738409-G allele, which codes for a modified adiponutrin protein that lacks its hydrolytic function (Marzuillo et al., 2014). This variant is correlated with a diet consisting of highly sweetened beverages and excess carbohydrates (Nobili et al., 2014). This adiponutrin variant continues to synthesize triglycerides in fat tissue, as it would in any healthy individual; however, it does not effectively break down proliferating triglycerides in the liver (Park et al., 2015). The accumulation of these fat particles causes severe steatosis, inflammation, and fibrosis of the liver (Valenti et al., 2010). The PNPLA3-G variant and modified adiponutrin are most commonly found among the Hispanic population, which is also the population with the highest NAFLD prevalence (Marzuillo et al., 2014). Conversely, the population with the lowest rate of NAFLD (African Americans) have been found to carry a different variant of PNPLA3, called rs6006460-T-allele, which is associated with low hepatic fat (Pan & Fallon, 2014).

Marzuillo has hypothesized that there are also relationships between NAFLD and other genes, such as the glucokinase regulatory (GCKR) gene. The GCKR gene codes for a protein called glucokinase regulatory protein. This protein is responsible for mediating a liver enzyme called glucokinase (GCK), which carries out glucose and fat metabolism (Tan et al., 2013). In order to prevent synthesis of excess fatty acids, glucokinase regulatory protein binds to GCK and inhibits its activity. An
NAFLD patient, however, has a different version of the GCKR gene, called rs780094 allele. This variant produces a dysfunctional GCKR, which is unable to inhibit GCK. Consequently, GCK continues to synthesize triglycerides, which accumulate in the liver cells (Petta et al., 2014). The prevalence of both the PNPLA3 and GCKR variants are lowest in the African American population. By contrast, GCKR variant is more prevalent in Han Chinese as compared to high PNPLA3 in Hispanic Americans (Lin et al., 2014).

While such genes predispose an individual to NAFLD, the development of the disease can be described in terms of a two-hit hypothesis. The first hit refers to the factors that lead to the accumulation of fat molecules in the liver, resulting in NAFLD (Nanda, 2004); specifically, obesity, insulin resistance, and hyperinsulinemia (Marzuillo et al., 2015). These factors, along with others like hypertension and glucose regulation, are categorized under metabolic syndrome (Alkhater, 2015). MtS, or metabolic syndrome, is an umbrella term used for a group of risk factors that lead to the development of cardiovascular diseases and type 2 diabetes mellitus (Schwimmer et al., 2008). Considering NAFLD exacerbates the progression of cardiovascular diseases, it is believed to be the hepatic manifestation of metabolic syndrome (Alkhater, 2015). While all children with NAFLD have at least one other disease that is categorized under MtS, obese adolescents are at five times the risk of the syndrome. This link between NAFLD and metabolic syndrome develops in early adolescence due to obesity-driven insulin resistance (Manco, 2011).

Insulin resistance is defined as the body’s inability to lower blood glucose levels in the fasting state, despite the rise in insulin concentration in the blood (Mann et al., 2015). In a healthy body, insulin triggers the muscle, fat, and liver cells to uptake glucose from the bloodstream and either metabolize it for energy or store it as glycogen. Simultaneously, it suppresses the production of free fatty acids in both adipose and liver tissue (Utzschneider & Kahn, 2006). The switch between metabolizing fat or glucose depends on the availability and demand of each macronutrient. In insulin-resistant patients, however, the body loses its ability to make that shift. Neither the adipose tissue nor the liver respond to insulin, glucose does not get absorbed by the cells (Lee et al., 2015), and free fatty acid synthesis continues in adipose and liver cells. Moreover, the adipose cells fail to expand in order to store the excess fat, which consequently gets delivered to the liver (Manco, 2011). Much like NAFLD and metabolic syndrome, fat accumulation and insulin resistance are a cyclical process. That is, the hepatic fat (Marzuillo et al., 2015), as well as the increased rate of triglyceride synthesis (Giorgio et al., 2013), exacerbates insulin
resistance by preventing the activation of insulin receptors (Berardis & Sokal, 2014), worsening hepatic steatosis.

Insulin sensitivity is 55% lower among obese adolescents with NAFLD as compared to healthy children (Lee et al., 2015). Indeed, obesity is a major risk factor for NAFLD (Alkhater, 2015). Studies have shown that while 2–6% of the pediatric population has been diagnosed with the disease, this value significantly increases to 20–50% for obese children. It is especially prevalent in pubertal children and adolescents than in pre-pubertal children (Ackam et al., 2013). At the onset of puberty, children go through hormonal imbalances, fat redistribution throughout the body, and a decrease in insulin sensitivity. Although most of these changes subside as a part of the maturation process (Cruz et al., 2005), the increase in blood insulin levels is sustained throughout adolescence (Loomba et al, 2009). Obesity, insulin levels, and triglyceride synthesis are connected in a cyclical process; an increase in one aggravates another.

These first hit factors then branch into different pathologies, affecting the body as a whole. With proper treatment, the condition is reversible (Lim et al., 2010). The second hit, however, can perpetuate NAFLD and cause further liver damage. This can lead to nonalcoholic steatohepatitis (NASH), which makes reversal of the condition more difficult (Marzuillo et al., 2015). The second hit involves lipid peroxidation and inflammatory cytokine activation, both of which are related to mitochondrial dysfunction (Giorgio et al., 2013). Liver cells are rich in mitochondria, which are cellular organelles that use free fatty acids and oxygen to synthesize energy, carbon dioxide, and water (Basaranoglu et al., 2013). A dysfunctional mitochondrion, however, is unable to efficiently convert most of the oxygen into the required products, instead creating molecules known as reactive oxygen species, or ROS (Nanda, 2004). These ROS negatively affect many cellular processes. They carry out lipid peroxidation (Mylonas & Kouretas, 1999), oxidizing—and thus damaging—fatty acids (necessary for important cellular processes such as intracellular cell signaling and storage). When lipid peroxidation occurs at a high rate, oxidized fatty acids are synthesized at a toxic level. The damage from these molecules overwhelms the repair capacity of the cell, contributing to the fat stored in the liver cells. Moreover, in another cyclic process, lipid peroxidation causes further mitochondrial dysfunction, resulting in overproduction of oxygen species (Takahashi et al., 2010).

ROS also cause an imbalance in cytokine production (Marzuillo et al., 2015) by triggering the release of inflammatory molecules from ectopic fatty tissue (Fitzpatrick et al, 2012), while simultaneously inhibiting the release of anti-inflammatory molecules (Berardis & Sokal, 2014). These inflammatory cytokines include tumor necrosis factor-alpha (TNF-α) and leptin. TNF-α not only enhances insulin resistance (Roberts, 2007), but also activates a protein which binds to the DNA to induce the production of more ROS (Veena et al.,

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**Adipose Tissue**
Body fat, found under the skin

**Cytokine**
Proteins responsible for cellular signaling. They are an active part of the immune system and regulate the maturation, growth, and responsiveness of certain cells

**Hepatic Fat**
Liver fat

**Insulin**
A hormone produced and secreted by pancreas to regulate the synthesis and breakdown of carbohydrates and fats

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Given a high concentration of ROS, TNF-α induces liver inflammation, liver cell death, and fibrosis (Manco et al., 2007). Along with TNF-α, leptin synthesis is also high in obese patients with NAFLD. Leptin is a satiety cytokine, which the brain fails to respond to in cases of chronic obesity (Giorgio et al., 2013). Insensitivity to leptin prevents an individual from recognizing when they are full, and so they continue to eat and gain weight. Note that the damages caused by ROS—the oxidation of lipids, decrease in ATP production, and increase in inflammatory cytokine release—are together categorized under the term oxidative stress. It is due to the collective effects of these events that the liver cells die (Ayala, 2014), thus causing inflammation and scarring of the organ (Basaranoglu et al., 2013).

Along with the aforementioned physiological changes, adolescents also gain increasing freedom to make their own decisions, including those about diet and physical activity. For many, these decisions result in switching to a diet of high calorie foods and a sedentary lifestyle (Giorgio et al., 2013). Therefore, it is important to recognize the type of diet that promotes NAFLD progression. Children with NAFLD tend to eat a diet higher in total saturated fat and refined sugars as compared to both obese and lean children who do not have NAFLD (Mitchel & Lavine, 2014). Fructose, in particular, is associated with NAFLD, as patients with a higher intake of sugar-sweetened beverages are at an increased risk of developing the condition regardless of their age, sex, and BMI (Veena et al., 2014). Fructose is primarily metabolized in the liver, through a mechanism very similar to that of ethanol (Lim et al., 2010), which increases lipid synthesis. It also acts as a pro-inflammatory mediator of NAFLD, contributing to liver inflammation (Alkhater, 2015).

Fructose can also induce bacterial overgrowth and increased bacterial permeability in the small intestine, causing the movement of bacteria from the gut into the blood circulation (Michail et al., 2015). This increase in permeability leads to bacterial toxicity and the conversion of liver cells to myofibroblasts, which release pro-inflammatory molecules such as TNF-α (Alkhater, 2015). The toxins from the gut bacteria also activate the complement system (Zhan et al., 2010), further exposing liver to inflammation (Lim et al., 2010). One of the main bacterial products involved in NAFLD is called lipopolysaccharide (LPS). As an active component of an endotoxin, LPS triggers a cascade of several enzymes involved in the inflammatory pathway (Aqel & DiBaise, 2015).

PREVENTATIVE ACTIONS AND TREATMENT FOR IMPROVING CHILD HEALTH

Before treatment can begin, a diagnosis must be made. According to many studies, this is a fairly difficult process primarily because the early stages of NAFLD are either asymptomatic or the symptoms are unrelated to the liver (Nanda, 2004). There is also a general lack of non-invasive diagnostic tests (Anderson et al., 2015). A physical examination is of no help as it results in a diagnosis of obesity (Roberts, 2007). Consequently, NAFLD diagnosis is based on either elevated levels of aminotransferase...
(ALT), an enzyme that is secreted by damaged liver cells, or by decreased levels of adiponectin. However, even these results are not definitive diagnostic criteria. In fact, there is no proper threshold of ALT with respect to age and sex to indicate NAFLD (Anderson et al., 2015). The only sure way to diagnose NAFLD is to first disprove all other possibilities (Hourigan et al., 2015), then carry out a liver biopsy, especially to distinguish between simple steatosis and NASH (Roberts, 2007).

Once diagnosed, treatment for pediatric NAFLD must occur as soon as possible, with a focus on reversing steatosis and promoting healthy growth and development (Roberts, 2007). The best way known is through weight loss, which decreases the concentration of free fatty acids in liver, increases insulin sensitivity by metabolizing glucose rather than fat, and reduces the synthesis of ROS (Mitchel & Lavine, 2014). Thus, dietary changes and adequate exercise are considered the first line of defense against progression of NAFLD to NASH (Nobili et al., 2009). A low glycemic index (GI) diet is appropriate for weight loss (Loomba et al., 2009), consisting of 50–60% carbohydrates, 23–30% fats, and 15–20% proteins. The intake of high fructose beverages must be reduced as greater amounts of sugar stimulate synthesis of fatty acids in the body, proliferating the fat in the liver (Manco et al., 2008). Since excess fructose is also associated with insulin resistance, steatosis, and oxidative stress, decreasing its consumption will significantly improve liver health (Manco, 2011). Changing to a healthier diet can also significantly decrease the blood levels of ALT (Nobili et al., 2009). Some studies have recorded lower ALT and triglyceride levels after a twelve-month treatment with an omega-3 fatty acid DHA (Berardis & Sokal, 2014). Omega fatty acids, such as DHA and EPA, have been shown to reduce fat deposits by activating certain cellular pathways that induce breakdown of fatty acids and inhibit their synthesis (Manco et al., 2008).

Physicians and researchers agree that proper diet is significant in reversing NAFLD in pediatric patients. However, it is important to cater the lifestyle modifications to each individual; this serves several purposes. First, it improves compliance, which may be a challenge when working with children and adolescent patients. Second, dietary and physical requirements must be continuously reevaluated to account for the child’s developmental rate, changes in body weight, height, etc. (St. Jules et al., 2013). It is extremely important that the child’s needs for growth are met (Berardis & Sokal, 2014), especially during puberty. Physical changes should not be the only aspect accorded importance. During this period, most children and adolescents are already sensitive about their body image and may have low self-esteem. Therefore, overemphasizing the need for weight reduction should be avoided to prevent negative psychological effects (St. Jules et al., 2013). It is in fact harmful to lose a great amount of weight in a short period of time, as this may increase liver injury (Nobili et al., 2009). In order to ensure gradual weight loss, children should begin with moderate exercise like brisk
walking or swimming (Veena et al., 2014). Although forty-five minutes of aerobic exercise per day is recommended (Nobili et al., 2009) for treatment and as positive reinforcement (Roberts, 2007), more studies are required to determine the benefits of exercise on its own, as well as with dietary changes (Deldin & Lee, 2013).

Further research is also required in the pharmacological field, since there is no drug treatment approved specifically for NAFLD (Veena et al., 2014). Pediatric NAFLD treatments are especially difficult because they must account for several factors, such as growth and development, hormonal changes, and rapid lifestyle modifications. Any medication prescribed must be unresponsive towards the changes in an adolescent body (Berardis & Sokal, 2014). For now, given that NAFLD progresses due to the cyclical process involving obesity, diabetes, insulin resistance, and oxidative stress, those are the pathologies targeted by most medicines (Nanda, 2004).

The only weight loss medication approved by the FDA for pediatric use is Orlistat. Although this drug inhibits excess fat absorption, it also interferes with absorption of fat-soluble vitamins. Nonetheless, it may reverse steatosis and insulin resistance (Mitchel & Lavine, 2014). Another medication, metformin, is well documented as a safe and effective treatment for diabetes (Loomba et al., 2009) and insulin resistance (Nanda, 2004), and so is often prescribed to target that aspect of NAFLD. However, many studies have shown that although metformin helps to decrease insulin resistance, it does not improve liver condition any more than lifestyle changes (Manco, 2011).

Another class of insulin sensitizers called thiazolidinediones have been shown to improve insulin sensitivity and reverse steatosis in adults (Nanda, 2004), but are not yet prescribed to children due to the lack of scientific support as well as the known side effects, which include weight gain, cardiovascular disease, and heart failure (Alkhater, 2015).

Antioxidants such as vitamin E supplements are also considered to be a possible treatment option. In some cases, supplements have been shown to decrease the ballooning of the liver cells in NASH (Berardis & Sokal, 2014). However, much like insulin sensitizers, there are either not enough cohort studies on their long term effects (Veena et al., 2014), or the few studies that have been done show no sign that vitamin E is more effective than lifestyle changes (Sarkhy et al., 2014). On the other hand, if vitamin E is administered with UDCA, an acid that deactivates bile to prevent the killing of liver cells, in conjunction with proper diet and exercise, ALT levels show improvement (Cho et al., 2012). In comparison, DHA, an omega-3-fatty acid, results in decreases in both the ALT and triglyceride levels (Alkhater, 2015). Probiotics have been found to have a similar effect (Berardis & Sokal, 2014); in fact, probiotics are being considered as highly valuable anti-inflammatory agents that work by decreasing bacterial translocation (Mitchel & Lavine, 2014).

In extreme chronic cases, and as a last resort, surgery may be considered. Bariatric surgery and transplant is seen as
a treatment option for children whose lifestyle changes were unsuccessful or for those who were diagnosed in the chronic stage. There are not enough studies on the long term safety of pediatric bariatric surgery and its effects on hepatic steatosis and inflammation. However, it has been shown to improve ALT levels (Alkhater, 2015). There are two types of surgeries, gastric banding and Roux-en-Y gastric bypass. Despite variable long-term results, banding is believed to have the least amount of risk and is reversible. The gastric bypass procedure is believed to be more efficient, though it may lead to nutrient deficiencies and protein malnutrition (Mitchel & Lavine, 2014).

Transplantation in NAFLD patients is often complicated by the conditions that come with the disease such as obesity, diabetes, and hyperlipidemia (Nanda, 2004). A condition called post-transplant metabolic syndrome is seen in some children who undergo liver transplants. Moreover, the immunosuppressive therapy that follows a transplant can lead to diabetes, hypertensions, cardiovascular diseases, and steatosis (Nobili & de Ville de Goyet, 2013). Prospective donors, especially those at risk for developing NAFLD themselves, must first undergo liver biopsies (Mathur et al., 2007).

CONCLUSION
Nonalcoholic fatty liver disease (NAFLD) is an increasingly prevalent condition that interferes with the proper growth and development of children. It has a wide array of causative factors, and its effects extend beyond the liver to the whole body. There is a need for discussions about NAFLD at the public level, as fatty liver is mistakenly only associated with alcohol consumption. Obesity, heart disease, and hypertension are rarely associated with the liver, despite being strong contributors to the progression of NAFLD. Since it is imperative that children with NAFLD be diagnosed as soon as possible, increasing knowledge on the disease will allow more cases to be caught in time. In fact, all children—especially those at risk of obesity, and those with a family history of fatty liver—should be screened for NAFLD on a regular basis. This highlights the dire need for further research to develop new diagnostic testing that is noninvasive, accurate, and less expensive.

More long-term research is also needed to determine the efficacy of specific diets, supplements, and medications that are seen as options for NAFLD treatment. Currently, it is extremely important for NAFLD patients to be served by a multidisciplinary healthcare team. Dieticians, hepatologists, psychologists, and cardiologists need to evaluate the cases and be involved with the patient (Nobili et al., 2009). For pediatric patients, family involvement is also necessary to maintain nutritional knowledge and implement physical activity—along with clinical treatment.
REFERENCES


