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Elena Inzaghi, Stefano Cianfarani & Valerio Nobili

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Insulin-like growth factors (IGF-I and -II): new actors in the development of non-alcoholic fatty liver disease

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Elena Inzaghi

D.P.U.O. "Bambino Gesù" Children's Hospital – "Tor Vergata" University, Rome, Italy

Stefano Cianfarani

D.P.U.O. "Bambino Gesù" Children's Hospital – "Tor Vergata" University, Rome, Italy and Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

Valerio Nobili

Author for correspondence: Hepato-Metabolic Disease Unit, Bambino Gesù Children's Hospital – IRCCS, Piazza Sant'Onofrio 4, 00165 Rome, Italy
nobili66@yahoo.it

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease worldwide, affecting 20–30% of adults and 3–10% of children in Western countries. The pathogenesis of NAFLD is considered to be multifactorial and factors such as insulin resistance, intrahepatic fat accumulation, oxidative stress, mitochondrial alterations, and stellate cell activation appear to substantially contribute to the development and progression of the disease. In this Editorial, we highlight some evidence suggesting a close link between NAFLD and growth hormone (GH)–IGF (insulin-like growth factor) axis.

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease worldwide, affecting 20–30% of adults and 3–10% of children in Western countries [1]. The increased incidence of NAFLD in childhood has paralleled the progressive increase in the number of overweight or obese children. Indeed, NAFLD is commonly diagnosed in obese patients and is currently considered as the hepatic expression of the metabolic syndrome. NAFLD is a histologically complex alteration encompassing a wide range of conditions, varying from simple steatosis to the necroinflammatory form of non-alcoholic steatohepatitis (NASH). While simple steatosis has a favorable clinical outcome, NASH is a progressive disease characterized by steatosis, inflammatory infiltration, hepatocyte injury, and fibrosis.

The pathogenesis of NAFLD, which is considered to be multifactorial involving both genetic and environmental factors, is not completely understood and it remains unclear why some patients develop necroinflammation whereas others do not. Nevertheless, factors such as insulin resistance, intrahepatic fat accumulation, oxidative stress, mitochondrial alterations, and stellate cell activation appear to substantially contribute to the development and progression of the disease.

The diagnosis of pediatric NAFLD is suggested by elevated aminotransferase levels and hepatic ultrasonography, but liver biopsy is considered as the gold standard for the diagnosis and grading of patients with NAFLD. In fact, only liver histology is able to distinguish between simple non-evolutive steatosis and NASH and determine the severity of liver damage revealing the presence and extent of fibrosis. Furthermore, there are no reliable serum or imaging markers available that may allow physicians to detect the progression of NAFLD from steatosis to fibrosis and eventually cirrhosis.

NAFLD has been reported in several patients with endocrine disorders 2, and increasing evidence suggests a close link between NAFLD and growth hormone (GH)–IGF axis.

GH is the main regulator of postnatal growth and also controls both body composition and metabolism. The growth promoting action of GH is mainly mediated by IGF-I, a component of the insulin-like growth factor system that includes IGF-II, at least six different IGF binding proteins with their specific proteases, and type 1 and type 2 IGF receptors. There is mounting evidence

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suggesting that both IGF-I and IGF-II, besides their mitogenic action, play an active role in the regulation of protein, carbohydrate and lipid metabolism.

The initial evidence suggesting the role of the GH–IGF axis in NAFLD stemmed from the observation that hepatic steatosis is more common in patients with GH deficiency compared to those without GH deficiency [3]. Adults with permanent childhood-onset GH deficiency present several comorbidities, including NAFLD, after discontinuation of GH replacement therapy [4]. GH replacement therapy has been shown to improve body composition, mitochondrial function and NASH in adulthood [5,6]. Interestingly, selective deletion of the GH receptor gene in the liver causes impairment of lipid metabolism leading to steatosis, probably secondary to dysregulation of downstream signaling pathways involving factors such as JAK2 and STAT5 [7]. Patients with GH insensitivity syndrome develop NAFLD in adulthood [8]. The observation that IGF-I replacement therapy does not influence liver status suggests a direct action exerted by GH in the liver, independent of IGF-I.

Patients with liver cirrhosis show a reduction in IGF-I levels that parallels the progression of liver disease [9]. IGF-I levels have also been associated with steatosis, progressively decreasing with liver fat accumulation [10]. IGF-I has been reported to predict the occurrence of liver steatosis and NASH in obese patients [11] and as a marker of both fibrosis and steatosis in patients with NAFLD [12].

The mechanisms underlying the association between IGF-I levels and NAFLD are still largely unknown. The insulin-like activity of IGF-I may account for a positive effect on insulin resistance which is closely associated with metabolic syndrome and NAFLD. Consistently, the abrogation of liver-derived IGF-I induces insulin insensitivity in muscle, liver, and fat tissues [13].

IGF-I may also have an anti-fibrotic effect on the liver. Serum IGF-I levels are significantly lower in patients with moderate-to-severe fibrosis compared with patients with mild or no fibrosis [14]. Furthermore, the levels of a fibrotic marker, such as hyaluronic acid, are inversely related to the IGF-I and IGF-I/IGFBP-3 ratio in patients with NAFLD [12]. In an animal model, an increased expression of IGF-I in hepatic stellate cells reduces fibrogenesis and accelerates liver regeneration, apparently through both upregulation of HGF and downregulation of TGF-β1 [15]. The IGF-I gene transfer to cirrhotic livers reverses fibrosis meanwhile improving liver function [16]. In humans, patients with liver cirrhosis show amelioration of liver damage and increase in albumin levels when supplemented with IGF-I [17].

Mitochondrial dysfunction is assumed to play a key role in the development of NASH. IGF-I administration was reported to prevent the development of NASH by improving mitochondrial function and reducing oxidative stress [7] as observed in both *in vitro* and *in vivo* studies [18,19].

Another intriguing hypothesis refers to the possible anti-inflammatory effect exerted by IGF-I in the liver as suggested by the established relationship between IGF-I and C-reactive protein in obese women [20]. This mechanism has recently been proposed by Hribal *et al.* [21] who have observed a direct regulatory effect of IGF-I on the local expression of inflammatory biomarkers. PPAR-γ activation may represent the link between IGF-I action and the transcriptional activation of inflammatory response genes [22]. Proinflammatory cytokines stimulate the development of NASH and inhibit IGF-I secretion from hepatocytes [12]. Therefore, the local imbalance between IGF-I and cytokines may constitute the favorable ground for the development and progression of NAFLD. These results suggest that IGF-I has GH-independent actions in the liver.

IGF-II stimulates tissue growth and development during intrauterine life. Recently, IGF-II has been increasingly investigated as a metabolic regulator, since several lines of evidence have shown the association of its polymorphism with body weight, insulin sensitivity and lipid profile [23]. The physiological actions of IGF-II in the liver have never been extensively investigated. The recent finding of a close relationship between IGF-II and fibrosis in the lung suggests the existence of a similar mechanism in liver. It is noteworthy that IGF-II levels is lower in cirrhotic patients and correlates with the progression of liver damage [24]. We have recently found an association between IGF-II serum levels and the progression of liver fibrosis in a cohort of obese children with biopsy-proven NAFLD [25]. Alternatively, since more than 60% of circulating IGF-II levels is genetically determined, the secretion rate of IGF-II thus determined may account for the susceptibility of an individual to develop NAFLD/NASH.

In conclusion, several lines of evidence suggest that both IGF-I and IGF-II may play a major role in the development and progression of NAFLD. The mechanisms through which IGFs participate in the pathogenesis have not yet been fully elucidated. The potential clinical implication of these findings is the use of IGFs as serum markers of the severity of liver damage in obese children and adolescents with NAFLD.

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