ENDOCRINOLOGÍA Y NUTRICIÓN
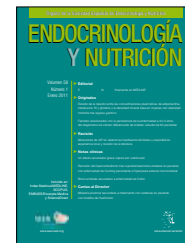
ENDOCRINOLOGÍA Y NUTRICIÓN

REVIEW

Fatty liver and its clinical management in obese adolescents

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Abstract Liver steatosis, also called non-alcoholic fatty liver, is characterized by a pathological fat accumulation in the liver, leading to liver damage in the form of inflammation and fibrosis. These histological features are similar to those in alcoholic hepatitis. Obesity is known to be the most common cause of simple steatosis in the preadolescent and adolescent population with a consequent serious health risk. The aim of this study was to provide an update on the concepts, pathophysiology and clinical management of hepatic steatosis secondary to obesity at an early age.
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Esteatosis hepática y su manejo clínico en el adolescente obeso

Resumen La esteatosis hepática también denominada hígado graso no alcohólico constituye una entidad clínica patológica caracterizada por una acumulación de componente graso a nivel hepático, circunstancia que implicará necesariamente el desarrollo de un deterioro hepático en forma de inflamación y fibrosis, características histológicas éstas similares a las originadas en una hepatitis alcohólica. En la actualidad se sabe que la obesidad constituye la causa más frecuente de esteatosis hepática simple entre la población preadolescente y adolescente con el consiguiente riesgo que ello supone para la salud de nuestra población juvenil. El objetivo de este trabajo es ofrecer una puesta al día de los conceptos, fisiopatología y manejo clínico de una complicación tan grave como es la esteatosis hepática secundaria a estados de obesidad a edades tempranas.
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Historical aspects of non-alcoholic fatty liver

Liver steatosis, also currently known as non-alcoholic fatty liver disease, was first described in 1980 in adult patients by Ludwig et al[1]. Ludwig, a pathologist from the Mayo Clinic, described a clinical and pathological condition whose histological findings were consistent with those of alcoholic

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hepatitis in the absence of alcohol consumption. The first report of this clinical condition in children was published in 1983 by Moran et al[2].

Epidemiology

The current prevalence of fatty liver disease in the young is not well known, and its diagnosis is based on tests which are not routinely done. Geographically, the condition is more prevalent in the United States, and in subjects of a Hispanic origin[3-5]. Recent studies have shown a close relationship between fatty liver and childhood obesity[6-8]. The greater or lower prevalence of fatty liver disease in children will however depend on the population studied. Thus, a 10% prevalence rate has been estimated for the general population, as compared to approximately 70%-75% for obese children. Studies such as the one conducted in Japan on 819 schoolchildren showed a 2.6% prevalence of fatty liver as detected by ultrasound. A clear association was found with higher body mass index (BMI) values. Other studies reported a prevalence ranging from 10% and 77%[9]. A study conducted in our environment reported an 18% prevalence of fatty liver, as detected by ultrasound, in obese children[10]. The condition occurred more frequently in males as compared to females, and mean age at diagnosis ranged from 11 and 13 years[11,12]. The greater prevalence at such age interval appears to be accounted for by the greater insulin resistance resulting from the pubertal period and development at that time[13].

Because of its high prevalence in the pre-adolescent and adolescent populations of developed countries, fatty liver disease has been considered as the main, if not the first, cause of chronic liver disease, always associated to obesity[14,15]. It should be noted, however, that non-alcoholic fatty liver disease is not only associated to obesity, but also occurs in patients diagnosed with chronic malnutrition, lipodystrophy, infection by the human immunodeficiency virus, etc.[16].

Histological and pathophysiological characteristics of the condition

Unlike in adults, histological findings in non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) in pediatric patients include a higher degree of steatosis, portal inflammation and fibrosis, and a lower degree of hepatocyte ballooning and cirrhosis[17]. Pathological lesions are however classified using two study protocols, one of them the classification proposed by the Pathology Committee of the NASH Clinical Research Network[18] that groups all of their characteristics for both adults and children covering the whole spectrum of lesions. The second classification derives from the Schwimmer et al study (2005)[19], where authors described two types of non-alcoholic steatohepatitis. This classification includes type 1 or adult disease, characterized by steatosis, hepatocyte ballooning, and perisinusoidal fibrosis, and type 2 or pediatric disease, in which patients usually have steatosis, inflammation, and portal fibrosis, more common in men than in women and in patients of Asian, native American, and Hispanic origin.

As regards the mechanisms of liver steatosis, the hypothesis most widely accepted today is the one proposed by Day and James in 1998[20]. Rationale for this hypothesis is accumulation of fat in the liver, which will necessarily result in liver impairment occurring as inflammation and fibrosis[21]. From the pathophysiological viewpoint, one of the determinants for the onset and course of this liver impairment will be maintenance of a constant peripheral action to insulin action, as well as oxidative stress caused by lipid peroxidation and activation of certain cytokines,m hormones, and neurotransmitters[21]. According to Day (2002)[20], free fatty acids play a significant role in development of this condition, because once in the hepatocyte they will be oxidized in mitochondria and peroxisomes to produce energy or be again synthesized and transported to the adipocytes, but in this case as very low density lipoproteins (VLDL)[22]. In addition, the ability of hepatocytes to synthesize free fatty acids in conditions of excess carbohydrates derived from dietary provision should not be forgotten. Thus, in clinical conditions of exogenous obesity where fatty acid provision to hepatocytes is increased, in situations of excess carbohydrate provision in diet, in disorders of mitochondrial b-oxidation of fatty acids, and in the event of any disturbance of triglyceride binding to very low density lipoproteins there will be a risk of development of liver steatosis[23]. Figure 1 shows the above discussed process.

Most patients with liver steatosis also have obesity with predominantly central adiposity associated to hyperinsulinism states, resistance to insulin action, and hypertriglyceridemia, all of them factors involved in turn in development of metabolic syndrome[24,25]. Iacobellis et al[26], in their study on pediatric patients undergoing liver biopsy, found a relationship between liver steatosis and percentile values of body mass index, but in this case only for subjects with scores higher than the 85th percentile of such index.

Other molecules have been identified as being involved in the genesis of this disorder, particularly adiponectin, whose plasma levels appear to have an inversely proportional relationship to the occurrence of liver steatosis in obese children[27]. That is, low adiponectin levels are associated to severe necroinflammatory events, thus contributing to development of liver steatosis in children and adolescents[28]. Thus, based on the results of these studies, adiponectin may have a protective role in the occurrence of liver steatosis[29]. However, since steatosis only occurs in some subjects of a given group with similar dietary conditions and lifestyles, it has been suggested that factors additional to those mentioned, such as some intestinal bacterial endotoxins, hormones, and a certain genetic predisposition may be involved in development of liver steatosis[30].

Clinical signs of fatty liver in obese adolescents

Clinical experience with adolescents with fatty liver is limited[31]. However, fatty liver usually occurs during adolescence in obese males showing elevations in some liver enzymes such as alanine aminotransferase (ALT), in addition to hypertriglyceridemia and acanthosis nigricans and with no specific symptoms. The disease is diagnosed in these

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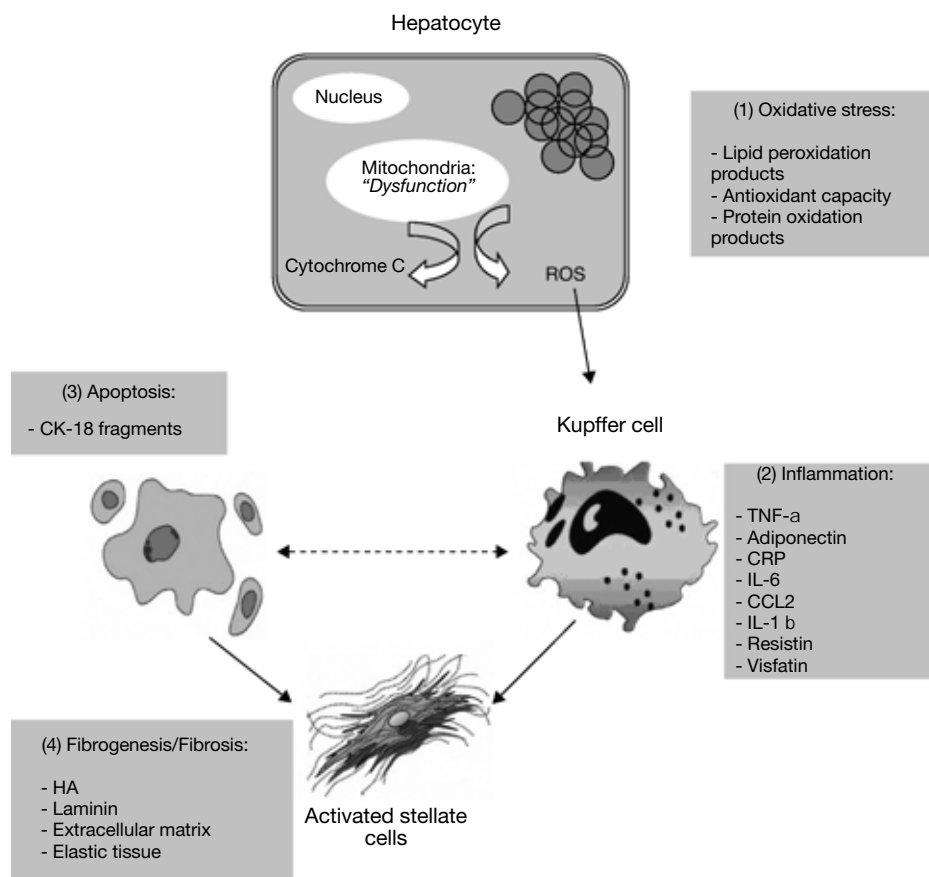
Figure 1 Main biomarkers and processes involved in development of liver steatosis. Adapted from: Wieckowska A et al (reference 36). CCL2: CC-chemokine ligand-2; CK-18: cytokeratin 18; CRP: C-reactive protein; HA: hyaluronic acid; IL-1-b: interleukin-1 beta; IL-6: interleukin-6; ROS: reactive oxygen species; TNF-a: tumor necrosis factor alpha.

subjects by screening or by performing an eventual abdominal ultrasound examination[32]. While the clinical course of disease is often asymptomatic, some patients may report specific symptoms such as diffuse abdominal pain in the right upper quadrant, fatigue, or malaise[33]. Detection of hepatomegaly on physical examination is however uncommon, as excess central and perivisceral fat makes it difficult to detect[34].

Diagnosis

Changes in levels of certain transaminases are among the most obvious clinical signs in adolescents with fatty liver. Serum ALT levels may range from 100 and 200 IU. Serum levels of aspartate aminotransferase (AST) may range from 60 and 100 IU[35,36].

Fishbein et al[37] showed a directly proportional relationship between elevated levels of transaminases and other liver enzymes (AST, ALT, gamma-glutamyl transferase, and alkaline phosphatase) and degree of liver involvement.

Biochemistry tests should also be done to assess the levels of triglycerides, total cholesterol and its fractions, and oral glucose tolerance tests are required to rule out potential changes in carbohydrate metabolism and thus assess the potential existence of insulin resistance[38].

However, the most commonly used diagnostic procedures are imaging tests, mainly abdominal ultrasound. Their diagnostic significance stems from their sensitivity to show the increase in echogenicity induced by fat infiltration at this level[39]. It should however be stated that the efficacy of imaging tests will necessarily depend on the existence of a certain degree of fat infiltration, that is, liver steatosis will only be detected if the infiltrative fat component represents more than 33% of liver parenchyma.

Alternative imaging procedures include magnetic resonance imaging (MRI) and computed tomography (CT). MRI shows a greater precision for detecting fatty liver[40,41]. However, the most precise procedure for diagnosing fatty liver currently available is liver biopsy, because it does not only confirm diagnosis, but also allows for assessing the severity of steatosis and for ruling out any other condition causing liver steatosis[42].

Other procedures currently used to diagnose fatty liver include FibroScan[43] and other noninvasive serum methods such as FibroMax[44], used for screening of fibrosis, steatosis, and steatohepatitis in patients with metabolic risk factors. However, all of these procedures have a poorer diagnostic definition. In the future, procedures based on genomic and

proteomic techniques will probably be used[45], but liver biopsy continues to be the gold standard for diagnosis of liver steatosis[46].

Clinical course in adolescents

Adolescents who suffer simple liver steatosis usually have a favorable course, with no histological progression to severe disease[47]. The course will however greatly depend on the existing degree of liver involvement, so that in patients with more marked fat infiltration the condition may progress to liver cirrhosis[48]. While liver cirrhosis is rare in this age group, it has been reported in some cases[49,50]. As regards potential occurrence of a subsequent hepatocarcinoma, no such cases have been reported in pediatric patients with non-alcoholic steatohepatitis[51].

Current treatment in adolescents

There is currently no consensus about treatment in obese adolescents with fatty liver[52]. Treatment will therefore usually consist of a number of measures aimed at reducing fat accumulation in the liver. Actions to contribute to reduce oxidative stress must also be taken to prevent at this level the development of fibrosis, which could lead to cirrhosis[53]. Weight reduction will necessarily be one of the mainstays of treatment in these patients. To decrease weight, a diet with a low calorie and carbohydrate content should be started to prevent postprandial hyperglycemia[54,55]. Compliance with such diet will ensure a weight decrease by approximately 5% in the first three months, which would in addition result in normalization of transaminase levels[56].

Various drugs have been used for correcting oxidative stress, including ursodeoxycholic acid, which acts as a cytoprotective agent at doses of 10-15 mg/kg. However, no favorable results have been seen in pediatric patients treated with ursodeoxycholic acid[57].

Metformin is another potential treatment and, if applicable, for pediatric patients with exogenous obesity. According to data collected in a clinical trial conducted by Schwimmer et al[58], metformin administered at doses of 500 mg twice daily for 6 months acts by reducing hyperinsulinemia and hepatic resistance to insulin. A marked decrease was also seen in ALT, resulting in a decreased liver involvement, in subjects treated with this drug at the doses and for the period stated above.

Vitamin E is another potent antioxidant agent, as demonstrated in several clinical trials. It is administered at doses of 400-1200 IU/day for periods ranging from 2 and 4 months[59]. Favorable results, including decreases in transaminase levels, have been reported. Use of vitamin E may therefore be considered as an effective therapeutic alternative when dietary management is not successful due to gradual patient noncompliance.

The final step in the therapeutic approach to adolescent patients whose liver steatosis evolves to cirrhosis is liver transplant. Despite the achievements made in liver transplant, its use in pediatric patients with fatty liver is still very limited, not exceeding 1%[55]. It must also be taken into account that some cadaveric liver donors may already show at the time of death a liver steatosis greater than 40%, which may make use of this therapeutic option even more difficult[60].

Based on all of the foregoing, early detection of disease is important to prevent progression of the condition to its complications. It is also important to inform parents about the clinical course of the disease, explaining them the significance and the benefits derived for their children from weight reduction as the most immediate action.

On the other hand, programs for early detection of liver steatosis, particularly in patients with severe obesity, would also have to be implemented at family medicine units, which are the first contact points with patients.

Finally, early lifestyle changes aimed at achieving realistic short and long-term goals should be made in obese subjects with and without liver steatosis.

Conflict of interest

The authors state that they have no conflict of interest.

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