Obesity in children and adolescents: the relation between metabolic syndrome and non-alcoholic fatty-liver disease

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Obesidade em crianças e adolescentes: relações com a síndrome metabólica e doença hepática gordurosa não alcoólica

Abstract

This article aims to review clinical and diagnostic aspects of non-alcoholic fatty liver disease associated with obesity and its relation to metabolic syndrome in children and adolescents. An on-line search was carried out of original articles in the Medical Literature Analysis and Retrieval System Online (MEDLINE), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) and Scientific Eletronic Library Online (SciELO) databases, using the following key words: "hepatic steatosis", "non-alcoholic fatty liver diseases", "overweight", "obesity", "children", "adolescents", "ultrasound" and "metabolic syndrome" in English and Portuguese. Two hundred and seventy-five articles were initially selected, all published between 1993 and 2008. After reading this was narrowed down to 67. The literature consulted revealed no consensus regarding the need to screen for metabolic syndrome and non-alcoholic fatty liver disease, especially in obese children and adolescents and those who have excess fat in the abdominal region. An ultrasound examination of the liver is typically used for screening and, in the case of children who present alterations in aminotransferases in addition to fatty infiltration of the liver, a strict clinical follow-up and a liver biopsy are recommended if these symptoms do not disappear on treatment.

Key words *Obesity, Metabolic diseases, Liver diseases, Child, Adolescent, Review*

Resumo

O objetivo deste artigo é revisar os aspectos clínicos e diagnósticos da doença hepática gordurosa não alcoólica associada à obesidade e sua relação com a síndrome metabólica em crianças e adolescentes. Realizou-se busca eletrônica de artigos originais nas bases de dados Medical Literature Analysis and Retrieval System Online (MEDLINE), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e Scientific Eletronic Library Online (SciELO), empregando as seguintes palavras-chave: "esteatose hepática", "doença hepática gordurosa não alcoólica", "sobrepeso", "obesidade", "crianças", "adolescentes", "ultrassonografia" e "síndrome metabólica" e seus correspondentes em inglês "fat liver", "non-alcoholic fatty liver disease", "overweight", "obesity", "children", "adolescents", "ultrasound" and "metabolic syndrome". Inicialmente foram pré-selecionados 275 artigos, publicados no período de 1993 a 2008, e após leitura foram selecionados 67 artigos. Observou-se na literatura consultada que há consenso no tocante à necessidade de rastrear a síndrome metabólica e a doença hepática gordurosa não alcoólica, principalmente nas crianças e adolescentes com obesidade e que apresentm excesso de gordura na região abdominal. A ultrassonografia hepática é considerada como exame de triagem e, naquelas crianças onde se observa além da infiltração gordurosa do fígado, alterações nas aminotransferases, o acompanhamento clínico deve ser rigoroso e a biopsia hepática deve ser indicada se não houver reversão das alterações hepáticas com as medidas terapêuticas adotadas.

Palavras-chave *Obesidade, Doenças metabólicas, Hepatopatias, Criança, Adolescente, Revisão*

Introduction

Obesity is currently acknowledged to be a public health issue and its occurrence in children and adolescents is a cause for concern. Obesity has serious consequences for health, including low self-esteem, depression, disorders of the bones and joints, sleep apnea and precocious sexual development.[1,2] When obesity is visceral, in addition to these complications, it is associated with dyslipidemia, type 2 diabetes and arterial hypertension, which are characteristics of metabolic syndrome.[3]

In recent years it has been found that peripheral resistance to insulin may be the etiopathogenic basis of various clinical manifestations that are common in the obese population, including non-alcoholic fatty-liver disease.[2,3]

Non-alcoholic fatty-liver disease (NAFLD), an emerging clinical problem among obese patients,[1,2] is a common clinical-pathological condition, characterized by impairment of liver function, with tissue damage similar to that observed in alcoholic liver disease, but present in individuals to are non-drinkers or moderate drinkers. The disease ranges from simple macrovesicular steatosis, which can be identified using ultrasound and by alterations in clinical and laboratory parameters, to steatohepatitis, advanced fibrosis and cirrhosis.[2,3]

The great interest in diagnosing obesity and intervening as early as possible in children and adolescents derives from the fact that, in this age-group, different from adults, the evolution of NAFLD and metabolic syndrome can be prevented or even slowed down, since the repair processes in young people may be more active than in adults.[3] Hence, there is a need for professionals who care for children and adolescents, especially pediatricians, nurses and nutritionists to have up-to-date knowledge of the issue.

The principal aim of this article is to review the clinical and diagnostic aspects of non-alcoholic fatty-liver disease associated with obesity and its relation to metabolic syndrome in children and adolescents.

Methods

An on-line search was carried out of original articles in the Medical Literature Analysis and Retrieval System Online (MEDLINE), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) and Scientific Eletronic Library Online (SciELO) databases, using the following key words: "hepatic steatosis", "non-alcoholic fatty liver diseases", "overweight", "obesity", "children", "adolescents", "ultrasound" and "metabolic syndrome" in English and Portuguese. Two hundred and seventy-five articles were initially selected, all published between 1993 and 2008. After reading this was narrowed down to 67 that appeared best to suit the purposes of this review. To provide a basis for the reading the basic physiological and physio-pathological features of adipose tissue are briefly outlined.

Results

Adipose tissue: a complex and active tissue

Adipose tissue can be classified in physiological, anatomical and metabolic terms. Physiologically, there are two types of adipose tissue: white and brown. The brown tissue specializes in thermogenesis; it is common in fetuses and new-borns and practically non-existent in adults.[4] White adipose tissue acts as a complex, active, secretory organ, which both sends and receives signals to modulate energy expenditure, appetite, sensitivity to insulin, and endocrine and reproductive functions, in addition to inflammatory and immunological processes.[5]

The classification of white adipose tissue into subcutaneous and visceral is carried out using anatomical and metabolic criteria that determine the physio-pathology of fat deposits in cases of obesity. Subcutaneous tissue, located underneath the skin in the abdominal, gluteal and femoral regions is less sensitive to the action of insulin.[4] Visceral adipose tissue, which is deposited in the abdominal cavity, forming mesenteric, omental and retroperitoneal fat is most susceptible to the action of insulin. For this reason, visceral adiposity is more often associated with non-alcoholic fatty-liver disease and metabolic syndrom.[6] In visceral adipose tissue there is also greater expression of inflammatory markers, in comparison with subcutaneous adipose tissue, a factor which seems to affect the metabolic impact of intra-abdominal adiposity.[7] In visceral adipocytes, the lipolytic effect of catecholamines is stronger and the antilipolytic effect of insulin weaker, which leads to greater mobilization of free fatty-acids for lipolysis, using intra-abdominal fatty deposits rather than subcutaneous gluteal and femoral subcutaneous fatty deposits.[4]

Adipose tissue constitutes the organism's main reserve of energy and its cells, adipocytes, are the only ones specialized in storing lipids in cytoplasm, in the form of triglycerides, without impairing their functional integrity. Pre-adipocytes (which have not

yet been filled with lipids) become metabolically competent, or, adapt themselves to capture and release energy in the form of fatty acids. Anatomically, the association with adjacent tissues is lost and they are retained in collagen compartment (stroma) containing stromal vascular cells of fibroblastic conjunctive tissue, leucocytes, macrophages, with an increase in blood circulation.[6]

Adipose tissue is the only organ with unlimited growth potential at any stage in life. The size of the adipose tissue mass is a function of the number and the size of adipocytes. It can expand by way of hyperplastic growth (increase in number) and hypertrophic growth (increase in the size of adipocytes). Hypertrophy occurs mainly through the accumulation of lipids in the cell and is reversible, while hyperplasia is irreversible and persists for life.[6,8] The main feature of adipocytes is their capacity for physiological accumulation of triglycerides, without damaging cells. During periods of fasting, these triglycerides undergo lipolysis and release free fatty acides and glycerol into the circulation for liver metabolization, because the oxidation of these acids provides more energy than the oxidation of proteins and carbohydrates. In the immediate post-prandial period, the pancreas releases insulin, augmenting the synthesis of lipids through metabolization of fatty acids and reducing lipolysis and mitocondrial oxidation of fatty acids.[5,9]

Triglycerides derive from two sources: food transported from the intestines to the liver (via kilomicrons), and hepatic synthesis of fatty acids and glycerol under the influence of insulin in the post-prandial period.[8] The liver's fatty acids may also derive from hydrolysis of the fat of peripheral adipose tissues, by way of the action of a hormone-sensitive lipase, stimulated by adrenalin, corticosteroids and other hormones; the transformation of amino acids, or, more frequently, of carbohydrates within the liver itself.[10]

Once inside the hepatocytes, the non-esterified fatty acids (NEFA) and the free fatty acids can undergo two types of transformation. The first occurs at the level of the mitocondria and the peroxisomes and involves β-oxidation of fatty acids to provide alternative energy, resulting in the formation of tri-phosphate adenosine (TPA), carbon dioxide, water and cetonic bodies. Alternatively, they may undergo neolipogenesis, which consists of esterification of the fatty acids to form triglycerides, which, along with cholesterol, phospholipids and apolipoproteins will form very low density lipoproteins (VLDLs). These VLDLs are secreted into the blood stream, giving rise to low density lipoproteins (LDLs), which, after metabolization in the liver, will form high density lipoproteins (HDLs), rich in cholesterol.[8,10]

Thus, under normal conditions, there is no accumulation of fat inside the hepatocytes, although, under pathological conditions, the excess triglycerides may be stored as lipid droplets in the hepatocytes, giving rise to hepatic steatosis.[11,12] The surcharge of lipids in the cytoplasm of other cells that are not adipocytes, such skeletal muscle, liver and Islets of Langerhans, deriving from the afflux of fatty acids in quantities that exceed the oxidative needs of these tissues, increases the metabolic flow to harmful routes of non-oxidative metabolism, thereby causing resistance to insulin, hepatic steatosis and type 2 diabetes.[5,13]

The pathogenic bases of metabolic syndrome

Metabolic syndrome is characterized by the presence of arterial hypertension, dyslipidemia, diabetes and abdominal obesity. The syndrome is accompanied by peripheral resistance to insulin, which is responsible for the appearance of hemodynamic, inflammatory and endotelial alterations, which may occur at any age, increasing the risk of cardiovascular disease.[3,8]

Insulin resistance may be defined as a metabolic alteration, in which higher concentrations of insulin than normal are necessary to set off normal metabolism or normal concentrations of insulin fail to provoke the normal metabolic response. The condition manifests itself as a reduced ability of insulin to inhibit hepatic glycogenesis and to stimulate the use of glucose by the skeletal muscles and adipose tissue.[9,14] It may be central (in the liver) or peripheral (in the muscles or adipose tissue), depending on the primary site of involvement. Peripheral insulin resistance compromises the ability of blood to capture sugar for the skeletal muscles and adipose tissues and manifests itself as an increase in the release of free fatty acids by adipose tissue, secondary to the blocking of the antilipolytic action of insulin on lipoprotein-lipase.[7,8,11]

The most recent studies indicate that peripheral insulin resistance may be the initial process to which the onset or exacerbation of hepatic insulin resistance leads. Organ-specific fat deposition is a strong predictor of hyperinsulinemia and insulin resistance. The increase of triglycerides in myocytes is strongly correlated with muscular insulin resistance. The highly increased availability of NEFAs reduces the use of glucose by the muscles, which constitute the largest consumer of this molecule in the body. The resulting hyperglycemia enables the secretion of

insulin-stimulated glucose, deriving from the increase in glycemia, whose chronic glycotoxicity destroys beta cells. This explains the relation between obesity, insulin resistance and the development of type 2 diabetes.[6,7] Hepatic insulin resistance manifests itself in unregulated synthesis of hepatic glucose resulting from the alteration of glycogenic synthesis and the failure of insulin to suppress glyconeogenesis. Hepatic insulin resistance may also be caused by the accumulation of fat in the hepatocytes.[3]

The genesis of metabolic syndrome – the intrauterine environment

Studies of the phylogenetic and ontogenetic aspects of this syndrome have provided better understanding of the problem. Special attention has been paid by researchers to understanding the adaptive response of the fetus when exposed to an adverse intrauterine environment. The long-term consequences of retarded intrauterine growth (RIUG) and its association with a higher risk of developing obesity and its complications in adult life have already been well described.[15]

Epidemiological studies have shown that there is a close relation between low birth weight and the occurrence of arterial hypertension, hyperglycemia and type-2 diabetes in adult life. One of the explanations of these relations is Barker's theory or the intrauterine programming theory (thrifty phenotype hypothesis), which consists of an adaptation to intrauterine stress during fetal life (intrauterine growth retardation) leading to a permanent alteration in metabolism, body composition and growth (metabolic imprinting), and eventually to future diseases.[16-18]

The thrifty phenotype hypothesis suggests that the nutritional environment of the fetus has a programming effect on the metabolism of glucose and lipids and on blood pressure and, consequently, on adult health. The combination of a relatively poor intrauterine environment and a nutritionally rich post-partum environment will allegedly increase the risk of developing type 2 diabetes and other related diseases. However, it should be borne in mind that it is not the adult disease *per se* that is programmed but the tendency to develop the disease. It is thus important to consider impaired early growth as a risk factor and not as a causal factor. These early risk factors may be exacerbated by biological and social factors during infancy and adult life.[17,18]

The adaptive response to such intrauterine adversities may predispose children to obesity, metabolic diseases and cardiovascular diseases in adult life.

On the other hand, most studies that have analyzed the long-term consequences of fetal and early post-natal growth and which suggest that rapid growth in infancy may have consequences that are harmful to adult health do not separate early from late catch-up. Many of these studies suggest that children who were small at birth and then catch up appear to be particularly at risk. The compensatory growth is desirable because, in the short term, it reduces mortality. However, on the other hand, it may lead to obesity in infancy and adult life.[19-21]

In the womb, the developing organism may undergo a series of environmental influences and this alters the form of expression of some genes (the epigenetic mechanism) as well as the metabolic profile, with repercussions for the rest of the individual's life. This plasticity during a period of rapid development makes this phase of life especially sensitive to the influence of nutrition and other environmental factors.[17,18,22,23]

Metabolic syndrome: clinical and diagnostic features

Screening should be carried out for metabolic syndrome in children and adolescents, as its prevalence in this sector of the population is already well established and has been described in the literature (Table 1).

Various criteria have been proposed for diagnosis of metabolic syndrome in pediatric medicine. All the combinations include glycemia, the lipid profile, obesity and arterial pressure and vary only with regard to the cut off point for normal values, as shown in the notes to Table 1. Although the cut-off point for abdominal circumference remained the 90th percentile, for age and sex, the concentration of glucose on fasting was reduced from 110 mg/dL to 100 mg/dL and the cut-off point for arterial pressure was moved to the 95th percentile, adjusted for age, sex, and stature.[24-27]

In 2007, the International Diabetes Federation (IDF)[28] proposed a criterion for pediatric medicine, as a way of providing some uniformity to the various ways in which metabolic syndrome in children and adolescents has been conceived, and providing a simple, easy to use and universally accepted criterion that enables comparison of prevalence in various countries. It is considered that, in children aged between six and ten years, with an abdominal circumference equal to or greater than the 90th percentile, adjusted for age and sex, metabolic syndrome may be considered to be a hypothetical diagnosis, especially where there is a family history of metabolic syndrome, arterial hypertension,

Table 1

Prevalence of metabolic syndrome in children and adolescents.

Author(s)	Year	Number of cases	Diagnostic criterion	Prevalence of metabolic syndrome
Cook *et al*.[24]	2003	2430	Modified ATP III criterion*	28.7%
Cruz *et al*.[25]	2004	1960	Modified NHANES III criterion**	30.0%
Agirbasli *et al*.[26]	2006	1385	Modified ATP III criterion ***	21.0%
Kim *et al*.[27]	2007	1317 in 1998 848 in 2001	Modified ATP III criterion *	6.8%, in 1998, and 9.2%, in 2001

*Modified TPA criterion III, allowing three or more of the following criteria: triglycerides ≥110 mg/dL, HDL cholesterol ≤40 mg/dL, systolic or diastolic pressure ≥ 90th percentile, fasting glycemia ≥110 mg/dL and abdominal circumference ≥ 90th percentile; **Modified NHANES criterion III, allowing three or more of the following criteria: triglycerides ≥90th percentile, HDL cholesterol ≤10th percentile, systolic or diastolic pressure ≥90th percentile, concentration of glycemia on fasting ≥110 mg/dL and abdominal circumference ≥90th percentile; ***Modified TPA criterion III, allowing three or more of the following criteria: triglygerides ≥90th percentile, HDL cholesterol ≤40 mg/dL or ≤10th percentile, systolic or diastolic pressure > 95th percentile, fasting glygemia >100 mg/dL and abdominal circumference ≥90th percentile.
ATP = adenosine triphosphate; NHANES = National Health and Nutrition Examination Survey; HDL = high density lipoproteins.

cardiovascular disease or obesity. For the ten to fifteen years age group, the criterion is the association of an abdominal circumference equal to or greater than the 90th percentile, adjusted for sex and age, with one or two of the following criteria: an increase in triglyceridemia (≥150 mg/dL), a reduction in HDL cholesterolemia (<40 mg/dL), systolic pressure equal to or greater than 130 mmHg and diastolic pressure equal to or greater than 85 mmHg, and hyperglyceremia (≥ 100 mg/dL). For adolescents aged sixteen and over, the diagnostic criteria have the same cut-off points as those for adults.

Hepatic steatosis: a component of metabolic syndrome?

The evolution of hepatic steatosis into steatohepatitis, progressive hepatic fibrosis and cirrhosis is the result of multiple metabolic abnormalities that can occur in a favorable genetic environment. Although the metabolic routes are not known exactly, the sequence of events for which there is consensus is as follows: obesity, increase in free fatty acids associated with genetic predisposition, resistance to insulin, accumulation of fat, cell damage characteristic of steatohepatitis, and the progression of hepatic histological alterations to inflammation, portal fibrosis and cirrhosis.[5]

The process begins with the development of obesity, which acts as a pro-inflammatory state, since it causes an increase in acute phase mediators, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). The increase in macronutrients and obesity activate the inflammatory signalling paths in cells, as the increase in fat and glucose intake induces inflammation through the rise in oxidative stress.[29] With the accumulation of lipids in the adipocytes and the expansion of adipose tissue, pro-inflammatory cytokins are released.[9,30] The inflammatory signaling involves endotelial cells, adipocytes and macrophages resident in the adipose tissue, which together contribute to the production of pro-inflammatory cytokins and bring on a state of local and systemic resistance to insulin. In this process, the accumulation of lipids in the adipocytes triggers the inflammatory signal and the resident macrophages amplify this.[9]

Once insulin resistance has developed, there is an accumulation of free fatty acids, whose concentration tends to rise as a result of the increase in hepatic neolipogenesis and fatty acids in the diet, which enter the liver through plasma, derived from intestinal absorption of kilomicrons. This increase generates cellular lipotoxicity and leads to hepatic steatosis.[31,32] In recent years, there has been an increasingly frequent association between insulin resistance and non-fatty liver disease. The resulting hyperinsulemia leads not only to hepatic steatosis, but is also associated with progression of the disease to steatohepatitis and cirrhosis.[33-35] Experimental clinical studies suggest that high levels of insulin and glucose in serum may stimulate the expression of growth factor in conjunctive tissue, which could

lead to hepatic fibrosis in genetically obese animals with non-alcoholic hepatic steatosis.[36]

The increase in the number of cases of non-alcoholic hepatic steatosis corroborates the possibility that genetic factors interfere with and determine whether an individual is prone to develop liver damage. It is thus possible that some patients subject to the same stimulus simply develop steatosis, while others, for reason of their genetic make-up, show a pattern of development associating necro-inflammatory phenomena with steatosis.[37,38]

Non-alcoholic fatty liver disease in children and adolescents

NAFLD has been given various names, such as fatty liver hepatitis, Laennec's disease, and diabetic hepatitis, but, since the 2003 Conference of the American Association for the Study of Liver Diseases, it has been conceived histologically as the accumulation of lipids in the liver in excess of 5% to 10% of its weight or with more than 5% of hepatocytes showing lipid deposits that can be identified using an optical microscope in the clear field.[39] Liver damage ranges from simple macrovesicular steatosis to steatohepatitis, advanced fibrosis and cirrhosis. The histopathology is similar to that induced by alcohol, but occurs in individuals who do not drink.[39-41] However, in children and adolescents, the histology differs from the typical spectrum of NAFLD in adults.[42]

In adults, classical histological findings are similar to those present in cases of alcoholic hepatitis and include balloon-shaped degeneration, focal destruction of hepatocytes, Mallory bodies and an inflammatory infiltrate consisting of polymorphonuclear leucocytes, which, typically, surround the damaged hepatocytes, in a process that is known as satellitosis. Inflammation of the perivenular zone and pericellular fibrosis are the most serious.[6] In children and adolescents, the histological changes are different, as shown in Table 2.

Table 2

Comparison of histological alterations in liver biopsies carried out on children and adolescents with those in the adult population.

Histological alterations	Children and adolescents	Adults
Steatosis	Pronounced	Slight
Balonization of hepatocytes	Absent	Present
Mallory's hyaline bodies	Absent	Present
Inflammatory infiltrate	Portal (moderate to severe)	Lobular (slight)
Pericellular fibrosis	Absent or portal alone	Perisinusoidal or pericentral

Source: Adapted from Papandreou *et al*.[42]

NAFLD in children and adolescents is classified histologically into to types: type 1 and type 2, according to the intensity of balloon-shaped degeneration, perisinusoidal fibrois, steatosis, inflammation and portal fibrosis. Type I is characterized by the presence of steatosis with balloon-shaped degeneration of hepatocytes or perisinusoidal fibrosis, but with no portal changes, while, in type 2, steatosis, is associated with inflammation or portal fibrosis, in the absence of perisinusoidal fibrosis and balloon-shaped degeneration (Table 3).[43]

The two types of NAFLD in children are epidemiologically different. Type 2 is more common in younger children, where very severe obesity is present and predominantly in males, Asians, Americans and Hispanics.[6,42] In females, when this type is present, it is most frequently during Tanner's pre-pubertal stage, while type 2 occurs more in the postmenarchal phase. However, type 2 is not exclusive to children, as it has also been found in morbidly obese adults.[44,45]

The first description of NAFLD in children was carried out by Moran *et al*.,[46] in 1983, when they reported three cases of pediatric patients where there was evidence of altered liver functioning, obesity and fatty infiltration of the liver associated with early hepatic fibrosis. From 1984 onwards, large case series studies began to be carried out.[47,48] Most

studies of prevalence conducted before 2000 were in overweight or obese children and many reported NAFLD as a result of the evolution of obesity.[38,47,49,50] Since 2000, the prevalence of NAFLD has been reported to vary between 8% to 80%, as shown in Table 4.

Table 3

Criteria for classification of histological alterations in liver biopsies carried out on children and adolescents.

Differential characteristics	Type 1	Type 2
Balloon-shaped liver degeneration	Present or absent	Absent
Perisinusoidal fibrosis	Present or absent	Absent
Steatosis	Present	Present
Portal inflammation	Absent	Present or absent
Portal fibrosis	Absent	Present or absent

Source: Adapted from Schwimmer *et al*.[43]

Table 4

Prevalence of non-alcholhic fatty-liver disease in overweight and obese children.

Author(s)	Location	Year	Number of cases	Diagnostic criterion	Prevalence of hepatic steatosis
Guzzalonni *et al*.[51]	Italy	2000	375	Ultrasound	42,0%
Chan *et al*.[52]	China	2004	84	Increase in ALT	24,0%
Zou *et al*.[53]	China	2005	113	Increase in ALT	55,7%
Louthan *et al*.[54]	United States	2005	181	Increase in ALT	8,0%
Schwimmer *et al*.[45]	United States	2005b	127	Increase in ALT	23,0%
Flores-Calderon *et al*.[55]	Mexico	2005	80	Increase in ALT	42,0%
Sartorio *et al*.[56]	Italy	2006	268	ALT Level	44,0%
Papandreou *et al*.[57]	Greece	2006	43	Ultrasound	41,8%
Fu *et al*.[58]	China	2006	123	Increase in ALT	44,0%
Schwimmer *et al*.[59]	United States	2006	320	Histopathology	81,0%

ALT = alanin aminotransferase.

This enormous variation in the estimates of prevalence has attributed, in part, to the difficult in determining the presence or absence of a fatty liver using non-invasive methods.[42,59] Schwimmer *et al*.,[59] using histological criteria to diagnose NAFLD to review hepatic tissue obtained by way of necropsy from 742 children and young people aged between 2 and 19 years, report an overall prevalence of 9.6%, rising to 16% in overweight children and 38% in those who were obese. The authors conclude that overweight or obese children and young people account for 81% of cases of NAFLD.

Clinical and diagnostic aspects of non-alcoholic fatty-liver disease

Most children display no symptoms, but may experience abdominal pains, with prevalence of this varying from 42% to 59%.[6,33,41,50] Hepatomegalia may be detected during a physical examination, but, in the initial stages, may go unnoticed by the physician.[60] The presence of acanthosis nigricans, hyperpigmentation of the skin of the neck and the armpits, is associated with the presence of hyperinsulinemia, which is found in many cases of NAFLD in children.[50] In Rashid & Roberts's review[38] of 36

children and adolescents with steatohepatitis, 30 were obese (83%). Sixteen patients had hepatomegalia with the liver palpable under the right side of the back and one had hepatoesplenomegalia. Thirteen patients had acanthosis nigricans around the neck and/or in the armpits. A family history of NAFLD is relevant, as the disease commonly affects members of the same family.[45]

Most published case series find that NAFLD occurs predominantly in boys. This has been observed in a study using the aspartate aminotransferase enzyme as a serological marker (47% of boys were affected, compared to 7% of girls).[61] San Diego's study, which was based on autopsies, showed 10.5% of boys to have NAFLD, compared with 7.4%, of girls.[59] Various publish studies claim that the mean age for the appearance of NAFLD varies from 11.6 to 13.5 years, although the condition can be diagnosed in children as young as two years of age. Age, or more specifically stage of development, is an important variable for the appearance of liver fat. Sex hormones and insulin resistance in puberty may help to cause NAFLD.[14,33,50]

In clinical practice, the diagnosis of NAFLD in childhood is frequently proposed in cases of overweight or obesity associated with evidence of insulin resistance with an increase in aminotransferases or with the presence of liver fat, confirmed by radiology.[14] A diagnosis of NAFLD requires that other chronic forms of liver disease be excluded, including hepatitis B and C, Wilson's disease, alpha1-antitrypsin deficiency, autoimmune hepatitis, the use of hepatotoxic drugs (tetracycline, amiodarone, valproate, methotrexate, prednisone) and total parenteral nutrition.[4,14,41]

The "gold standard" for diagnosis of NAFLD is a liver biopsy, although this is not always the first choice, as it is an invasive procedure that may lead to a series of complications. In children and adolescents, therefore, laboratory examinations and imaging are frequently used to diagnose NAFLD.[14,41] In a recent study involving [84] Chinese children, the presence of NAFLD was suggested by ultrasound in 77%, and 24% displayed an increase in serum concentration of aminotransferases associated with alterations in hepatic ultrasound.[52] Two Italian studies show the presence of NAFLD in obese children in ultrasonography of the liver. The first, involving 72 children, found hepatic echogenicity in 53% of children and 25% presented an increase in transferases and alterations in hepatic echogenicity.[62] In the second study, involving 375 children, the prevalence of hepatic alterations on ultrasound was 42% in the pre-pubescent and pubescent age brackets.[51]

Ultrasonography of the liver should be the first imaging method used to identify a fatty liver. Diffuse hyperechogenicity is found, which has commonly been described as a shiny liver. Focal accumulations of fat can be visualized as geometrical images without a mass effect. The parameters used to test for fatty infiltration of the liver are: an increase in the echogenicity of the hepatic parenchyma in relation to the renal cortex, reduced visibility of the hepatic vessels and intensity of penetration of the echo into the parenchyma.[63] The sensitivity of a liver ultrasound in detecting steatosis ranges from 60% to 100% and its specificity from 66% to 100%.[64]

The ultrasound findings, when characteristic, dispense with the need for computerized tomograghy or magnetic resonance imaging, although a liver biopsy is indispensible for a confirmed diagnosis.[41] Tominaga *et al*.,[48] using liver ultrasound, report the presence of liver fat in approximately 22% of obese children aged between four and twelve years. Computerized tomography (CT) of the abdomen showed a lower degree of density in the hepatic parenchyma compared to the spleen and this may reveal the presence of focal accumulations of fat. Magnetic resonance imaging (MRI) also revealed localized fat deposits, with some areas showing up more brightly. Comparison of these three methods shows that ultrasound is most sensitive for detection of diffuse fatty changes, while, for localized fat, CT and MRI perform better than ultrasound.[6,49]

It should be pointed out that none of the imaging examinations succeeded in distinguishing simple steatosis from steatohepatitis and cirrhosis, and these should therefore be used judiciously. If alterations persist and do not respond to measures taken to treat the condition, a liver biopsy should be considered to provide clear diagnosis and staging.[65] The exclusion of other secondary causes of steatosis is important, so as to enable a primary diagnosis of NAFLD to be arrived at safely. Viral forms of hepatitis and alcoholic liver disease are particular important factors contributing to the high prevalence of these two hepatoxic agents. Serological tests, to exclude the hypothesis of viral hepatitis and the absence of excessive alcohol consumption are prerequisites for diagnosis. The scale of alterations in levels of aminotransferases in serum is not sufficient for differential diagnosis between steatohepatitis, steatohepatitis with cirrhosis and steatosis in isolation.[66] Although the test is not ideal, no other laboratory test has proved to be better than determining the number of aminotransferases in serum for identifying patients with NAFLD.[41]

The alanine aminotransferase test (ALT) is the laboratory test that is most commonly used for investigation of NAFLD.[66] Kinugasa *et al*.,[47] in a study of 299 obese Japanese children, found alterations in levels of transferases in 12% of cases. Strauss *et al*.,[67] in a study of 2450 adolescents aged between 12 and 18 years, found alterations in ALT in 6% of overweight and 10% of obese adolescents.

Final considerations

NAFLD associated with obesity is acknowledged to be the most common cause of chronic liver disease in children and adolescents and is being identified at an increasingly early age. As it is potentially reversible, if diagnosed early, there is an urgent need to raise awareness among pediatricians regarding the need to screen for non-alcoholic fatty-liver disease and metabolic syndrome using simple methods, including measurement of the abdominal circumference and liver ultrasound.

Early diagnosis may also motivate patients to change their lifestyle, as they see that this has benefits which go beyond mere reduction in body weight. The prevention of obesity in childhood should be based on primary health care, which is primarily carried out by a pediatrician, and should involve monitoring of height and weight from the beginning of gestation onwards, thereby allowing more effective preventive measures to be adopted. Intrauterine factors are important determinants of the components of metabolic syndrome and there is also evidence that they affect the development and functioning of the liver. According to the fetal programming hypothesis, malnutrition in the mid- to final stages of gestation result in development of the brain being maintained at the expense of the trunk and the liver, which results in permanent changes in liver functioning.

Knowledge of the etiopathogenesis of non-alcoholic fatty-liver disease and metabolic syndrome and the diagnostic criteria associated with them in children and adolescence may alert pediatricians to the need for early diagnosis and prevention of this disease, so that, by way of adequate intervention, it may be possible to halt the evolution of the disease to more serious future stages, thereby providing patients with a better quality of life.

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