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REVIEW ARTICLE

Non-alcoholic fatty liver disease and metabolic syndrome in adolescents: Pathogenetic role of genetic background and intrauterine environment

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Abstract

In the last three decades the incidence of metabolic syndrome (MetS) has been growing worldwide along with an increase of obesity, type 2 diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD). In children and adolescents such epidemics are particularly worrisome, since the metabolic consequences in adulthood will significantly burden the health care system.

Although the definition of MetS in childhood is still controversial, there is agreement with respect to NAFLD being the hepatic manifestation of MetS. However, the molecular pathogenesis of MetS and its contribution to NAFLD is complex and closely related to the pre- and postnatal environment as well as to genetic predisposing factors. The analysis of the possible relationships between NAFLD and MetS is particularly interesting, not only from an epidemiological point of view, but also to better understand the genetic and environmental factors contributing to the development of both diseases.

We here summarize the most recent epidemiological data on the incidence of both diseases in adolescents, and several aspects linking MetS with NAFLD, discussing the possible role played by genetics and intrauterine environment.

Key words: *Adolescents, life-style, metabolic syndrome, non-alcoholic fatty liver disease*

Introduction

The metabolic syndrome (MetS) is a cluster of metabolic and cardiovascular risk factors including insulin resistance and diabetes, central obesity, elevated cholesterol levels, and high blood pressure (1,2). In particular, the latest worldwide definition of the MetS by the International Diabetes Federation (IDF) includes central obesity defined by increased waist circumference (with ethnicity and sex-specific values) and two or more of the following features: raised triglyceride concentrations ($\geq$150 mg/dL); reduced high-density lipoprotein (HDL) cholesterol (<40 mg/dL in males, <50 mg/ dL in females); elevated blood pressure (systolic blood pressure $\geq$130 and/or diastolic blood pressure $\geq$85 mmHg); and raised fasting glucose ($\geq$100 mg/dL) (3). Although this IDF definition was initially used also for children and adolescents, there is now a new definition of MetS that is more easily applicable in clinical practice. Waist circumference, considered as percentiles rather than absolute values, represents the main component of MetS in children and adolescents (4). As discussed below, MetS in children is defined differently with respect to three age-groups: 6–10 years, 10–16 years, and $\geq$16 years.

Key messages

- Metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) in children and adolescents continue to grow in parallel with the outbreak of obesity.
- Metabolic syndrome and NAFLD present common pathogenetic origins, and their understanding may facilitate the development of long-term, successful preventive strategies and treatment regimens.
- Early identification of children and adolescents at risk (with genetic and/or intrauterine environment predisposition) of metabolic syndrome and NAFLD is required to prevent severe complications in adulthood.

Abbreviations

ATP III	Adult Treatment Panel III
BMI	body mass index
CRP	C-reactive protein
FFAs	free fatty acids
HDL	high-density lipoprotein
IDF	International Diabetes Federation
IL	interleukin
MetS	metabolic syndrome
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NCEP	National Cholesterol Education Program
PNPLA3	patatin-like phospholipase domain-containing-3
ROS	reactive oxygen species
TGF	transforming growth factor
TNF	tumour necrosis factor
VLDL	very-low-density lipoprotein

In the last 20 years, incidence of MetS has increased dramatically in the adult population, and evidence is emerging of wide-spread MetS in children and adolescents (6,7). This escalation is partly due to genetic predisposition and intrauterine events, and partly to over-nutrition and sedentary life-style that characterize the adolescence of urban children (8,9). Unhealthy life-style and consequent obesity during childhood (2–11 years) strongly contribute to making adolescents (12–18 years) prone to develop MetS and related diseases during the teenage period (10).

In addition to the classical components of the MetS, there is increasing alarm regarding the emergence of non-alcoholic fatty liver disease (NAFLD) (11,12), which comprises variable degrees of simple steatosis, non-alcoholic steatohepatitis (NASH), and fibrosis in obese children and adolescents (13). Epidemiological studies support a close association between MetS and NAFLD both in adults and children (14,15). Furthermore, NAFLD, due to its frequent association with obesity, insulin resistance, and alterations of glucose and lipid metabolism, is considered the hepatic 'component' of MetS. Nevertheless, the aetiology of MetS and its contribution to NAFLD is complex and closely related both to genetic predisposing factors and life-style (16–20).

We here review the most recent epidemiological data on the incidence of both diseases in adolescents, and, furthermore, we provide a general idea of several aspects of the link between MetS and NAFLD, discussing the pathogenetic role of genetics and intrauterine environment.

Definition and epidemiology

MetS

In recent years several studies have been performed to achieve a proper definition of MetS in children and adolescents, mainly based on the criteria approved for adults, adjusted for gender and age (18–20). However, some obstacles have been found in applying, to paediatric subjects, the parameters used in adults. For example, the lack of a paediatric central obesity score linked to MetS, the paucity of imbalanced metabolic indicators, the lack of a normal range for insulin levels during childhood, the physiological reduction of insulin sensitivity during puberty, and the ethnic differences in lipid profiles, body composition, and other metabolic features—all limit the application of adult criteria to childhood and adolescence. In a recent systematic review, Ford and Li found 40 different definitions of paediatric MetS in 27 publications (21). These definitions were mainly children-adapted variations of National Cholesterol Education Program (NCEP)/Adult Treatment Panel III (ATP III) criteria (22). A recent IDF consensus has achieved an agreement on the definition of MetS in children older than 6 years and adolescents (5). Two of the NCEP/ATP III-based descriptions of paediatric MetS criteria have been used in large paediatric population studies but, as shown in Table I, different cut-off values for some components of the MetS have been proposed (4,23,24). The use of different definitions to estimate MetS in children and adolescents has provided broadly variable data on the incidence of the disease. Cook et al. (23) in the Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994, estimated that 1 million 12–19-year-old adolescents in the United States had the MetS. In particular, this study reported that the incidence of MetS was 6.8% among overweight adolescents and 28.7% among obese adolescents. However, these results differ from those by de Ferranti

Table I. Diagnostic criteria for MetS in children and adolescents.

Parameters	Cook et al. 2003	de Ferranti et al. 2004
Waist circumference	≥90th percentile (age- and sex-specific)	>75th percentile (age- and sex-specific)
Triglycerides	≥110 mg/dL	≥100 mg/dL
HDL cholesterol	≤40 mg/dL	<50 mg/dL (<45 in boys aged 15–19 years)
Blood pressure	≥90th percentile (age-, sex-, and height-specific)	≥90th percentile (age-, sex-, and height-specific)
Fasting glucose	≥110 mg/dL	≥110 mg/dL

et al. (24), in which the incidence among adolescents was 31.2%. In the last 5 years, the general incidence of 4.2% reported by NHANES III has risen to 6.4% in NHANES 1999–2000, and up to 8.6% in the most recent survey (25,26).

These findings highlight that the cluster of metabolic disorders characterizing MetS in children and adolescents is still under debate, but there is wide consensus on the hypothesis that various components of disease may predispose for an early onset of the cardiovascular diseases in adulthood. In this context, a definition of MetS in the paediatric population may be a useful tool to establish the incidence of disease and also to estimate its potential evolution in adulthood (6). Adolescents, due to their profound changes in body composition, are individuals particularly at risk of developing MetS, with many adverse consequences for health, including greater rates of mortality as young adults. At the same time, these changes may partly explain the difficulty in identifying earlier characterizations of the metabolic syndrome, being still so unstable during and beyond the teenage years.

The incidence of MetS in adolescents increases in parallel to body mass index (BMI), and it appears to be greater in boys than in girls (15,26). Moreover, the ethnic differences in adolescents reflected those observed in adults, with the greatest incidence in Hispanic-Americans, followed by non-Hispanic whites and then Afro-Americans (27).

In the absence of a consensus on the definition of MetS in children and adolescents, the IDF definitions, within their limitations, operatively represent the best diagnostic tool for identifying the condition in young people. The IDF criteria are applicable to three age-groups: 6–9 years, 10–15 years, and 16 years and older (Table II). In all three age-groups central obesity is an essential condition for the diagnosis. In adolescents aged 16 years or more the IDF criteria take also into account the different ethnicities.

NAFLD

The term NAFLD refers to a spectrum of liver diseases that are characterized by the accumulation of excess fat in the liver (>5%–10% by weight) in the absence of significant alcohol consumption or other specific cause of liver disease. The most common form of NAFLD is the simple fatty liver, which is characterized by fat accumulation without liver damage, while the most advanced form of NAFLD is NASH, in which fat accumulation is associated with

Table II. IDF definition for paediatric MetS.

Age	MetS
<6 years	No diagnosis
≥6 to <10 years	Obesity [a]
	Additional measurements are suggested if there is a family history of MetS, type 2 diabetes, dyslipidaemia, cardiovascular disease, hypertension, or obesity
≥10 to <16 years	Obesity [a]
	Adult criteria for:
	Triglycerides ≥1.7 mmol/L
	HDL cholesterol <1.03 mmol/L
	Blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic
	Fasting plasma glucose levels ≥5.6 mmol/L
	Presence of type 2 diabetes
≥16 years	Central obesity [a] with ethnicity-specific values[b]
	Plus two of the following conditions:
	Triglycerides ≥1.7 mmol/L
	HDL cholesterol <1.03 mmol/L in males and <1.29 mmol/L in females
	Blood pressure ≥ 130 mmHg systolic or ≥85 mmHg diastolic
	Fasting plasma glucose levels ≥5.6 mmol/L

[a]Defined as ≥90th percentile of waist circumference.
[b]If BMI is >30 kg/m², central obesity can be assumed and no measurement of waist circumference is required.

liver cell inflammation and different degrees of scarring. Simple fatty liver remains a benign process in most affected children, whereas the presence of necro-inflammation, typical of NASH, may be the driving force for the development of severe fibrosis and cirrhosis. Currently, only the histology discriminates among the different features of NAFLD, hence it appears to be critical for the diagnosis and management of paediatric NAFLD. The histological hall-mark in children with NAFLD is steatosis, but ballooning, inflammation, and fibrosis may be present (28,29). Therefore, liver biopsy is considered the 'gold standard' in establishing the diagnosis of NASH as well as in assessing disease severity (i.e. fibrosis). However, liver biopsy has several limitations particularly in children (i.e. invasiveness), and even though it represents the best methodology for estimating the real incidence of NAFLD in the paediatric population (30). To solve this problem and avoid liver biopsy, numerous non-invasive methods have been proposed as alternative screening/diagnostic tests (31).

Most studies use surrogate markers for NAFLD, such as BMI and serum aminotransferase levels. Alternatively, ultrasound scan can be used, although the diagnostic accuracy of this approach is limited (i.e. the sensitivity drops sharply when the degree of steatosis decreases below 30%, and, in addition, this approach cannot rule out fibrosis), and it is not able to distinguish between simple steatosis and NASH.

In contrast to ultrasound, magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) are able to accurately quantify intrahepatic lipid content, demonstrating a large potential, especially in longitudinal and cross-sectional studies (32).

Even though MRS and MRI today represent the most viable alternative to liver biopsy for evaluating the presence of steatosis, they fail to detect fibrotic tissue. Recent reports indicate the ability of transient elastography to assess liver fibrosis in a large Italian paediatric series with NAFLD (33). Several on-going studies aim to combine different non-invasive tests (i.e. serum markers and imaging) in order to achieve a diagnostic power very close to that obtained with histology.

Nowadays, NAFLD is recognized as the main cause of liver disease worldwide both in adults and children. Greatly variable incidence rates of paediatric NAFLD (from 2% to 10% in all individuals, up to 80% in obese subjects) have been reported in North and South America, Europe, Australia, and Asia (34). This wide variability depends on the type of diagnostic tools but is also influenced by the age, sex, and race of the study population, as well as by the differences in ethnic composition and metabolic risk factors. In particular, hypertriglyceridaemia and/or hypercholesterolaemia, which are frequently associated with both obesity and type 2 diabetes, have been reported in 20%–80% of children with NAFLD. The prevalence of NAFLD rises in hyperglycaemic patients, and insulin resistance is more severe in individuals with NASH than in those with steatosis, thus explaining the significant association of hyperglycaemia with NASH (34,35). The pathogenetic role of these metabolic factors has been demonstrated by several observations, suggesting that NAFLD might be considered the hepatic manifestation of the MetS (36–38). However, recent studies suggest that insulin resistance and MetS might represent a consequence rather than the cause of NAFLD (39).

Risk factors and pathogenetic mechanisms

MetS

Despite a strong correlation between obesity, insulin resistance, and development of MetS, this relationship is nevertheless complex and only partially understood (40). Moreover, besides obesity and insulin resistance, other factors are actively involved in the pathogenesis, including genetic predisposition, adipocytokines, inflammatory molecules, oxidative stress, life-style, and intrauterine events (6,41–44).

Obesity represents the major risk factor for MetS in both children and adolescents. Between 1999 and 2003, the percentage of obese American adolescents increased from 14.8% to 17.4%, implying a higher risk for MetS in young adulthood (6,19,41). Several studies support the importance of insulin resistance in the link between obesity and MetS (45). The pivotal role of insulin resistance in the metabolic syndrome was originally recognized in 1988 by Reaven, with subsequent studies further strengthening this concept (46,47). The relation between insulin resistance, obesity, and MetS is complex, but the presence of visceral obesity and reduced insulin sensitivity seem to be the main mechanisms implicated in the development of the syndrome both in adults and children. A relationship between obesity and insulin resistance, and the prevalence of the MetS has been reported in the paediatric population (6,47,48). The close association of MetS with insulin resistance led investigators to consider these conditions as components of the same syndrome, with a common pathogenetic origin. Insulin resistance is caused by a complex interplay between excess of nutrients, systemic fatty acid, inflammation, hypoadiponectinaemia, and oxidative and endoplasmic reticulum (ER) stress.

The fact that the increasing incidence of MetS results from excess of nutrients secondary to increased food consumption and/or sedentary lifestyle is widely accepted and demonstrated by diet-induced MetS in several animal models (49). Moreover, Westernized diets and high intake of carbohydrate are associated with the increased risk of the MetS in children and adolescents (50–52).

Nevertheless, MetS has a multifactorial aetiology involving genetic background and hormonal balance.

Several lines of evidence have shown that common variants at candidate genes for glucose homeostasis, lipid metabolism, inflammation, and obesity are associated with altered plasma levels of MetS biomarkers (53). Children with at least one parent with MetS are at higher risk of becoming overweight/obese and developing insulin resistance (54). Polymorphisms in the insulin promoter gene have been shown to correlate with the risk of MetS in Italian obese adolescents (55).

In the pathogenesis of MetS, adipose tissue plays a crucial role, particularly determining the excessive release of free fatty acids (FFAs), and pro-inflammatory cytokines that contribute to insulin resistance in muscle and liver (56). Hepatic insulin resistance, in turn, favours the increase of glucose production, very-low-density lipoprotein (VLDL) secretion, and production of pro-inflammatory factors such as C-reactive protein (CRP), and increased production of thrombotic factors such as fibrinogen. Tumour necrosis factor (TNF)-alpha is a well known factor linking obesity, diabetes, and chronic inflammation; however, several other inflammatory mediators and cytokines are over-expressed and involved in the pathogenesis of MetS in children and adolescents (56,57–59).

In the last years there is some experimental and clinical evidence for a causal link between pathogenesis of MetS and oxidative and ER stress and molecules and pathways that regulates these processes (49,60–62). Experimental models have demonstrated that increased oxidative stress is associated with the metabolic pattern of MetS, such as hypertriglyceridaemia, hyperglycaemia, hyperinsulinaemia, and hypertension (60,61). The presence of MetS components in overweight children associates with increased plasma levels of 8-isoprostane, a marker of systemic oxidative stress (62).

Urbanization, unhealthy diet, and sedentary lifestyle increase the risk of MetS for the coming generations. Sedentary behaviour, such as television watching coupled with scarce physical activity, and increased hypercaloric diet regimens (high-fat and/or high-carbohydrate diets) represent today the major risk factors for obesity, MetS, and its co-morbidities in adolescents (6). Thus, an adequate nutritional programme and exercise represent not only the most effective preventive strategy for MetS but also the first-line treatment in obese subjects with metabolic disorders (63).
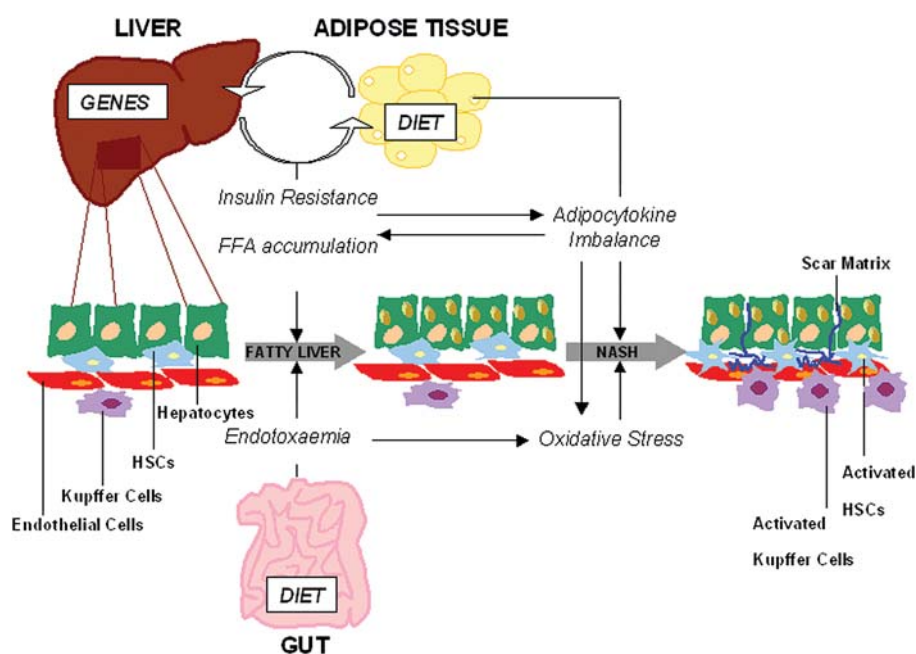

Figure 1. Schematic representation of pathogenetic mechanisms leading to NAFLD. Genetic predisposition and environmental factors (i.e. diet) are determinant in the early events leading to fatty liver, including insulin resistance and fatty liver accumulation. Gut-derived endotoxaemia contributes to the early onset of steatosis as well as to the progression to NASH concomitantly to the oxidative stress and adipocytokines. Cell and tissue-specific alterations that characterize NASH are determined by all these events during NAFLD pathogenesis. Figure supplied by A. Alisi.

NAFLD

The pathogenesis of NAFLD is still unclear. In 1998, Day and James proposed a 'two hit hypothesis', subsequently replaced by the 'multiple hits' hypothesis (64). Accordingly, liver fat accumulation and insulin resistance represent the 'first hits' and lead to fatty liver that is vulnerable to 'second hits' which trigger the progression to NASH (see Figure 1). 'Second hits' include oxidative stress, mitochondrial dysfunction, and imbalance of production/release of hormones derived from adipose tissue (adipocytokines) (65). More recently, the gut/liver hypothesis has been proposed. This suggests that gut bacterial endotoxins activate molecules of innate immune response, acting as possible triggers of the primary fat accumulation in the liver and necro-inflammatory lesions in the progression of steatosis to NASH and severe fibrosis (see Figure 1) (65,66).

The development of fatty liver, occurring when the accumulation of lipids exceeds 5% of the liver tissue, is directly associated to disorders of lipid metabolism that may depend on several factors: excessive consumption of foods enriched in fat and fructose, increased release of free fatty acids (FFAs) from adipocytes (lipolysis), increased endogenous synthesis of lipids (*de novo* lipogenesis) or reduction of FFAs oxidation (mainly due to insulin resistance) (67–69). FFAs introduced by the diet, or released by fat cells, are stored in the liver and for the most part are rapidly incorporated into complex lipids (e.g. triglycerides, phospholipids, glycolipids) and partially oxidized and converted into energy. When the FFAs intake exceeds the storage and oxidative capacity of peripheral tissues, FFAs are diverted to metabolic pathways that cause intracellular accumulation of toxic lipid-derived metabolites, which in turn might induce insulin resistance and activate oxidative stress signalling and inflammatory pathways (69). On the other hand, hepatic insulin resistance, due to systemic factors interfering with insulin signalling, might induce the *de novo* lipogenesis and/or increase the triglyceride export via very-low-density lipoprotein, leading to fatty liver (69–71). Insulin resistance is thought to be a critical factor in the pathogenesis of fatty liver and NASH in children and adolescents (72). Hyperinsulinaemia/insulin resistance associates significantly with elevated levels of ALT and biopsy-proven paediatric NAFLD (73).

Several experimental and clinical studies have highlighted the role played by oxidative stress in the development of NASH from fatty liver (74,75). Saturation of the oxidative processes, due to intrahepatic fat accumulation, induces the release of H_2O_2 and other reactive oxygen species (ROS). When ROS exceed the defensive capacity of intracellular antioxidants, they may induce NASH and fibrosis through lipid peroxidation and induction of adipocytokines (74,76). Lipid peroxidation leads to hepatocyte apoptosis/necrosis and proliferation and activation of hepatic stellate cells triggering intracellular signalling cascade and consequent gene expression of molecules involved in fibrogenesis. Oxidative stress influences the production and release of cytokines and adipokines, such as TNF-alpha, transforming growth factor (TGF)-beta, interleukin (IL)-6, leptin, adiponectin, and resistin, from hepatocytes, Kupffer cells, and adipocytes (77,78). Adipocytokines, that are preferentially secreted by adipose tissue, contribute to the inflammation, apoptosis/necrosis of hepatocytes, and onset of fibrosis, but some of them (TNF-alpha and adiponectin) also play important roles in the associations between obesity, insulin resistance, and liver fat accumulation in the preliminary phases of fatty liver development (69,76).

Increased serum levels of leptin and decreased adiponectin, strongly associated with insulin resistance regulation, have been found in children and adolescents with NAFLD (79,80).

A role of the gut/liver axis has recently been proposed as a critical factor in the pathogenesis of NAFLD. In particular, gut-derived endotoxins may increase in the blood of patients with NAFLD and activate lipopolysaccharide (LPS)-related sensors, such as Toll-like receptor 4, thus contributing to necro-inflammation and oxidative stress (65,66). A key role of systemic endotoxaemia in the pathogenesis of NAFLD has been suggested, and recently an association between endotoxin plasma levels and severity of disease has been demonstrated in paediatric NAFLD (81).

In adolescents, NAFLD appears closely related to several risk factors of the MetS, especially obesity and insulin resistance (12,13). Mechanisms linking NAFLD to insulin resistance and MetS are still largely unknown; however, two main hypotheses have been proposed. Insulin resistance development is extremely complex because it involves both genetic polymorphisms, which influence the synthesis and action of insulin, and the action of environmental factors that promote obesity and NASH. On the other hand, in subjects with a genetic predisposition, environment and life-style interact with thrifty genes, favouring the development of insulin resistance and the inappropriate accumulation of fat in liver and muscle (53,69).

Genetic origins of NAFLD

Genetic predisposition to NAFLD is suggested by documented familial clustering of NAFLD and

NASH and by the racial and ethnic differences in the prevalence of these disorders (82). It has been reported that children from certain ethnicities, including Hispanics, Asians, and indigenous Americans, are more predisposed than others to develop NAFLD/NASH (83). Ethnic/racial disparities might be a predictable effect of the heritability of NAFLD's risk factors (i.e. obesity and insulin resistance), but also a direct consequence of the susceptibility to NAFLD rather than to its risk factors. In this case, family members of children with NAFLD should be considered at high risk for the disease (82).

The search for potential candidate genes associated with NAFLD has been based on data from animal models suggesting the involvement of specific genes, microRNAs, and proteins, and on the selection of *de novo* candidate genes found by genome-wide association (GWA), microarray, and proteomic studies in tissues from patients and animals (82,84,85).

Interestingly, specific gene polymorphisms have been associated with NAFLD. Several polymorphisms have been described in genes that encode for products involved in molecular pathogenesis of NAFLD. In fact, susceptibility to NAFLD/NASH has been associated with genes influencing insulin sensitivity or regulating fatty acid metabolism (i.e. hepatic lipid synthesis, storage, and export), oxidative stress, immune regulation, and fibrosis development (see (82,84,85) for references).

These candidate genes include: TNF-alpha, microsomal triglyceride transfer protein, methylenetetrahydrofolate reductase, adiponectin, peroxisome proliferator-activated receptor gamma coactivator 1alpha, peroxisome proliferator-activated receptor alpha, leptin receptor, and hepatic lipase. Several polymorphisms associated with NAFLD have been related also with MetS, indicating common genetic origins of these diseases (Table III) (86–98).

Romeo et al. have recently described the adiponutrin/patatin-like phospholipase domain-containing-3 (PNPLA3), which could be considered the first NAFLD gene. The variation in PNPLA3 contributes to racial differences in hepatic fat content and influences the susceptibility to NAFLD (99). The hepatic protein expression of adiponutrin is increased by carbohydrate feeding and Western-type diet (100). Moreover, it is may be involved in energy mobilization and storage of lipid droplets (101). The rs738409 PNPLA3 SNP is strongly associated with severe steatosis, NASH, and the progression of liver fibrosis in a large series of Italian and UK patients with NAFLD (102). More recently, the rs738409 PNPLA3 variant has been found to be associated with the severity of steatosis, hepatocellular ballooning, lobular inflammation, and perivenular fibrosis in paediatric NAFLD (103).

Intrauterine environment, early nutrition, MetS, and NAFLD

Epidemiological studies in humans have shown that impaired intrauterine growth is associated with an increased incidence of insulin resistance, type 2 diabetes, and MetS in adulthood (104–106). To explain this association the concept of programming was introduced. Foetal exposure to suboptimal intrauterine conditions, particularly malnutrition, during critical stages of development would lead to adaptive responses that the foetus makes to environmental cues, permanently programming tissue structure and

Table III. Gene polymorphisms found in NAFLD and their correlation with MetS.

Gene	Polymorphism	MetS	Ref.
TNF-alpha	−238 and −308, −1031, −863, −857, −308 and −238	−308 is associated with obesity, hypertension and insulin resistance	(86,87)
microsomal triglyceride transfer protein	-493G/T polymorphism	association with components of MetS	(88)
methylenetetrahydrofolate reductase	C677T and A1298C	no relevant association	–
adiponectin	45G/T and 276G/T	these and other polymorphisms correlate with traits of MetS	(89,90)
peroxisome proliferator-activated receptor gamma coactivator 1alpha,	rs2290602	the association is controversial	(91,92)
peroxisome proliferator-activated receptor alpha	PPARalpha-L162V	association with components of MetS	(93)
leptin receptor	G3057A	other leptin receptor polymorphisms associate with high risk of insulin resistance and MetS	(94)
hepatic lipase	−514C/T	associated to MetS	(95,96)
haemochromatosis (HFE)	C282Y/H63D	no relevant association	–
apolipoprotein A5	APOA5, c.553G/T	association with components of MetS	(97)
adiponutrin/patatin-like phospholipase domain-containing-3	rs738409	adiponutrin polymorphisms associated with obesity but data on MetS are still not available	(98)

functions (107,108). Once the organism is programmed in response to an adverse uterine environment, the exposure to different postnatal environmental conditions, such as over-nutrition, will determine a mismatch between intra- and extrauterine environments, eventually leading to the increased risk of metabolic disease (109).

According to the 'thrifty phenotype hypothesis', when intrauterine foetal under-nutrition occurs during 'critical periods' of embryo–foetal development it permanently modifies the endocrine and metabolic pathways in an attempt to divert the limited nutrient supply to vital organs, such as the brain, at the expense of growth and the development of other organs such as the pancreas and liver. However, this adaptation to an adverse intrauterine environment, orchestrated to improve the chances of survival, may become detrimental if the organism is subsequently exposed to an extrauterine environment characterized by over-nutrition. This *in utero* programming may predispose to insulin resistance and metabolic syndrome, which, combined with the effects of obesity, aging, and physical inactivity, may result in cardiovascular and metabolic diseases (110–112).

Another possible mechanism linking foetal environment with the risk of developing metabolic alterations in childhood and adulthood was proposed by Hattersley and Tooke (113) who introduced the concept of the 'foetal insulin hypothesis', suggesting a strong contribution of genetic factors to the alterations of both insulin secretion and sensitivity. Polymorphisms or mutations in genes associated with insulin sensitivity result in impaired foetal growth, low birth-weight, and subsequent susceptibility to type 2 diabetes and cardiovascular disease in adult life. Mutations in the glucokinase gene determine beta-cell dysfunction, low birth-weight, and type 2 diabetes susceptibility (114).

Furthermore, the structural and functional changes induced by programming may arise from epigenetic alterations of gene expression (115). Animal models of intrauterine growth restriction have confirmed the role of epigenetic mechanisms in the development of long-term consequences for metabolism and blood pressure (115,116). In humans, periconceptional exposure to famine has been associated with persistent epigenetic changes of the insulin-like growth factor- 2 (*IGF2*) gene (117).

A substantial body of evidence indicates that low birth-weight is associated with the components of MetS such as hyperinsulinaemia that may or may not be associated with impaired glucose tolerance and type 2 diabetes, dyslipidaemia, and hypertension (118–123). These alterations may appear as early as in young adulthood, especially in subjects who experienced postnatal catch-up growth in weight (124).

Foetal exposure to the Dutch famine was associated with increased risk of obesity, glucose intolerance, and hypertension in adulthood (125–128).

The effects of *in utero* conditions on adult health and disease also comprise the risk of developing postnatal obesity in foetuses exposed to hyper-nutrition. The excessive weight gain in pregnancy may predispose offspring to altered energy balance and increased adiposity in adulthood (129). Studies in animal models have shown that the hypothalamic systems implicated in the control of appetite may be permanently affected by intrauterine exposure to maternal over-nutrition, eventually leading to a hyperphagic and obese phenotype in adult offspring (130). The metabolic susceptibility to hyper-nutrition extends further into early extrauterine life as rapid weight gain during infancy, often induced by formula feeding, is associated with increased risk of obesity in adulthood (131). Interestingly, it has recently been reported that intrauterine growth restriction (IUGR) is an important risk factor for paediatric NAFLD, whereas breast-feeding is protective for development of NASH and its clinical expression in children (132,133). Within this context, the preventive role of human milk and breast-feeding along with the delayed introduction of solids in the first year of life in preventing childhood obesity (134,135) should always be stressed. Whether the possible causes are related to some environmental conditions or specific human milk biofactors and nutrients (such as protein and fatty acid composition) is still a matter of debate (136). Accordingly, birth-weight (as the main clinical indicator of intrauterine conditions) together with the type of infant feeding should be included in clustering estimation of the metabolic risk in children (137).

Concluding remarks and clinical implications

The definition of MetS in childhood is still controversial. This lack of a consensus on the diagnostic criteria inevitably affects the knowledge of the incidence and the identification of causative factors. In this review we have described the close association between MetS and NAFLD. Increasing evidence suggests that they represent the clinical expression of a common metabolic rearrangement rather than being causally related to each other. In severely obese children with features suggesting MetS, the concomitant presence of NAFLD should be suspected. Unfortunately, there is no reliable clinical, biochemical, or radiological tool to establish the diagnosis of NAFLD which is still based on histological hallmarks, thus limiting the feasibility of early diagnosis. Therefore, the search for non-invasive reliable tests for identifying NAFLD in childhood represents a priority in paediatric research.

In both MetS and NAFLD the interaction between environment and genetic predisposition plays a pivotal role from the early phases of embryo–foetal development. Intrauterine programming, followed by a mismatch between intra- and extrauterine environments, permanently affects tissue structure and function, eventually leading, in genetically predisposed subjects, to the metabolic alterations underlying both MetS and NAFLD. In this context, late interventions such as the promotion of breast-feeding in infancy and a healthy diet and life-style in adolescence and young adulthood may be ineffective in preventing or reversing the metabolic abnormalities. The early identification of 'at-risk' children may lead to nutritional and/or pharmacological interventions aimed at de-programming the organism, taking advantage of the biological plasticity which characterizes the early phases of extrauterine life. Finally, there is increasing evidence indicating that the pre- and periconceptional period represents another critical time window for the metabolic outcome of the offspring, thus suggesting that the optimization of maternal metabolism could represent another target for an effective preventive strategy.

Acknowledgements

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