PEDIATRICOBESITY
REVIEWARTICLE
doi:10.1111/j.2047-6310.2012.00089.x

The potential role of fatty liver in paediatric metabolic syndrome: a distinct phenotype with high metabolic risk?

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Received 6 March 2012; revised 14 June 2012; accepted 17 July 2012

Summary

Background: The prevalence of obesity and its metabolic consequences has dramatically increased in the last two decades urging physicians to find a reliable definition for early detection, treatment and possibly prevention of metabolic syndrome (MS). MS could be diagnosed in adult patients in the presence of a large waist circumference and ≥2 of the following features: high serum triglycerides, low serum high-density lipoprotein cholesterol, high blood pressure and high fasting glucose. The definition of MS in children is more problematic, and the potential role of its single components on metabolic risk remains largely undefined. Recent evidence strongly suggests not only a relationship between non-alcoholic fatty liver disease (NAFLD) and MS in obese children, adolescents and adults, but also the key role exerted by liver fat deposition in the pathogenesis of MS.

Conclusion: We propose that NAFLD should be routinely checked in obese subjects because early lifestyle changes may be effective in reducing the overall risk of MS.

Keywords: Insulin resistance metabolic syndrome, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis.

Introduction

According to the International Diabetes Federation (IDF), metabolic syndrome (MS) could be diagnosed in adult patients in the presence of a large waist circumference and ≥2 of the following features: high serum triglycerides, low serum high-density lipoprotein (HDL) cholesterol, high blood pressure and high fasting glucose (1). Large waist circumference was also considered as one of the features necessary to establish the diagnosis of MS (2). A definition of MS similar to that adopted for adults has been suggested by IDF for children, but its use is limited because of the lack of population-specific reference values (3). The problem is pressing considering the increasing prevalence of the single components of MS (4–6).

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western countries and includes a spectrum of alterations ranging from steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and liver cirrhosis (7,8). It is associated with dyslipidaemia, obesity and insulin resistance (IR), which are the main features of MS (9).

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Statement of financial support: Any financial assistance was received in support of this study.

A common feature of MS and NAFLD is the underlying IR condition. The liver fat content is increased in subjects with MS and IR, independent of age, gender and body fat distribution (7).

Association of metabolic syndrome, insulin resistance and non-alcoholic fatty liver disease

IR/MS and NAFLD are often associated. There is increasing evidence suggesting that liver plays a major role in the development of IR (10), but it is still unclear whether the presence of liver involvement could worse the metabolic risk in a patient with MS or with IR alone (9). NAFLD is a predictor of the risk of type 2 diabetes mellitus (10) and the insulin-mediated suppression of hepatic glucose production is impaired in children with NAFLD (11). In the first stages of IR, insulin may continue to inhibit the hepatic secretion of very-low density lipoproteins (VLDLs) but, once the liver has become infiltrated with fat, the overproduction of VLDL produces high triglyceride and low HDL levels (12). Fatty liver is thus a strong predictor of IR, as paradigmatically shown in subjects with congenital or acquired lipodystrophies, who are characterized by a redistribution of body fat with concomitant liver steatosis and hypertriglyceridemia (13). Weaker and less convincing evidence links NAFLD to cardiovascular disease (14). According to IDF, abdominal adiposity as detected by a large waist circumference is needed to define MS (1). This is done on the presumption that abdominal adiposity plays a prominent role in the pathogenesis of MS but the available evidence is far from being conclusive in this respect (5). Whatever the case, waist circumference allows an indirect estimate of visceral fat depots and it is noteworthy that an increased waist circumference has been found to be associated with paediatric NASH (15–17). Through the release of free fatty acids (FFAs) and adipocytokines into portal circulation, visceral fat may be responsible for some of the metabolic abnormalities associated with fatty liver and obesity (18). In a recent study, the quantity of diacylglycerol contained in lipid droplets extracted from human livers was the strongest predictor of IR, explaining 64% of its variability (19). Insulin binding to the high-affinity insulin receptor (INSR) in hepatocytes leads to receptor autophosphorylation and activation of INSR substrate-1 (IRS-1), IRS substrate-2 (IRS-2) and downstream kinase AKT, which in turn phosphorylates the transcription factor FOXO1 leading to decreased glucose production and apoptosis (20,21). Liver-specific deletion of INSR in mice causes hyperglycaemia and liver failure (22), suggesting that hepatic IR promotes liver damage not only by inducing metabolic alterations but also by determining hepatocellular apoptosis, which is crucial in NASH progression (23). Insulin may increase availability and oxidation of FFA leading to hepatic steatosis by different mechanisms as summarized in Fig. 1: (i) decreasing adipose tissue lipolysis with consequent increase of FFA flux into the liver; (ii) changing DNA-binding activity of sterol regulatory element-binding protein 1c (SREBP-1c) and peroxisome proliferator-activated receptor α (PPAR-α) thus favouring lipogenesis as a consequence of n-3 long-chain polyunsaturated fatty acid (LCPUFA) depletion; and (iii) hyperinsulinaemia-induced activation of lipogenic factor peroxisome proliferator-activated receptor γ (PPAR-γ) (24). Interestingly, supplementation of n-3 LCPUFA reduces hepatic steatosis and IR in adults and children (25,26).

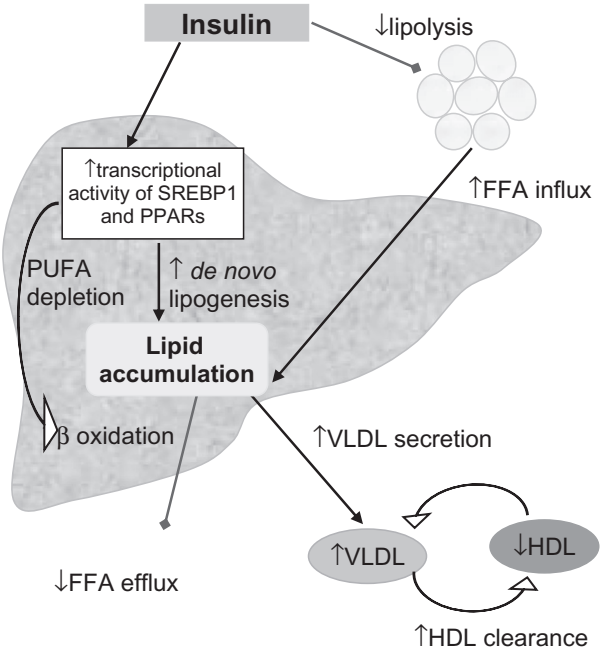

Figure 1 Peripheral insulin resistance may induce non-alcoholic fatty liver disease by different mechanisms as reported in the text. Insulin promotes intrahepatic lipid accumulation by up-regulation of free fatty acid (FFA) influx from adipocytes to hepatocytes, sterol regulatory element-binding protein 1 (SREBP1) and peroxisome proliferator-activated receptor (PPAR) transcriptional activity, β oxidation and very-low density lipoprotein (VLDL) secretion. HDL, high-density lipoprotein; PUFA, polyunsaturated fatty acid.

Activation of SREBP-1c increases the expression of lipogenic genes such as acetyl-CoA carboxylase 1, fatty acid synthase and stearoyl-CoA desaturase 1 (27).

Moreover, PPAR-γ co-activator (PGC)-1β, induced in response to dietary intake of saturated fatty acids, co-activates SREBP-1c to up-regulate *de novo* lipogenesis. Liver PPAR-γ expression is increased in animal models of fatty liver, and a liver-specific knockout of PPAR-γ prevents hepatic fat storage. Adenovirus delivery of PPAR-γ in hepatocytes results in fatty liver, and PPAR-γ interfering RNA reduces liver triacylglycerol content. Moreover, increased expression of liver fatty acid translocase/CD36, a target gene of PPAR-γ, is associated with the development of fatty liver. Finally, over-expression of adipose differentiation-related protein, another target gene of PPAR-γ, increases triglyceride accumulation in rat hepatocytes.

However, the IR/NAFLD association is not so clear-cut as it may appear at first sight. For instance, subjects with familial hypobetalipoproteinaemia have high levels of intrahepatic triglycerides but their hepatic and muscle sensitivities to insulin are similar to those of healthy controls (28). Similar observations have been reported in genetically obtained animal models of fatty liver where neither the glucose nor the insulin tolerance curves were altered despite the high fat content of the liver (29). These findings indicate that liver steatosis *per se* may not be causally linked to IR, representing a marker rather than the cause of metabolic dysfunctions (30).

Lipolysis of visceral fat produces an overload of FFA in the portal system, which is considered the key driver of hepatic IR and NAFLD (24). FFA and other agents may lead to fatty liver and MS in different ways according to the genetic and epigenetic background. Recently, endoplasmic factors have been identified to play a major role in impairing hepatic metabolism after a nutritional overload (31). N-3 LCPUFA acids, and especially docosahexaenoic acid, may interact with cytoplasmic and transcriptional factors regulating triglyceride accumulation and lipid catabolism (26).

The role of adipose tissue in insulin resistance, metabolic syndrome and non-alcoholic fatty liver disease

IR is also closely associated with dys-regulated production adipose tissue-derived circulating factors called adipocytokines. Levels of adipokines guarantee homeostasis of glucose and lipid metabolism, but visceral obesity and excess of adipose tissue greatly alter the adipocytokines balance, thus playing a crucial role in the development of IR, MS and NAFLD. Several adipocytokines, including leptin, adiponectin, resistin, tumour necrosis factor (TNF)-alpha and interleukin (IL)-6, have been involved in the metabolic derangements that characterize MS and in the histological damage observed in NAFLD (32,33). Moreover, interestingly, in obese children the elevation of some adipocytokines (e.g. leptin, TNF-alpha and IL-6) and hypoadiponectinemia may coexist as markers of fat low-grade systemic inflammation (34,35).

Hyperleptinaemia or leptin resistance has been found associated with triglyceride accumulation in liver, muscle and pancreas, resulting in the lipotoxicity phenomenon that causes IR and steatosis and in hyperinsulinaemic profile distinctive of MS in children (36,37). Furthermore, according to the potential role of leptin in inducing fibrosis (38), recently serum levels of leptin have been reported, together with caspase-cleaved CK18 fragments, as a good predictor of NASH and fibrosis in paediatric patients with NAFLD (39).

Adiponectin, an antilipogenic and insulin-sensitizing factor that is in contrast to other adipokines, is expressed at low levels in serum in obese subjects and in a variety of IR states, and it is considered as potential biomarker of MS in paediatric population (37,40,41). In obese children, the reduction of circulating levels of adiponectin is considered an early event in NAFLD that emerges also as a stronger predictor of advanced liver steatosis (42,43).

Although potential mechanisms involved in decrease of adiponectin levels in subjects with IR remain unclear, TNF-alpha could be a good candidate. In fact, the increase levels of TNF-alpha in obese children could be responsible for the associated hypoadiponectinemia (44). A recent cross-sectional study conducted on 137 healthy prepubertal children has highlighted that there is no correlation between circulating levels of TNF-alpha and IL-6 and the risk of cardiometabolic syndrome (45). However, circulating TNF-alpha and IL-6 in combination with the serum levels of endotoxin, plasminogen activator inhibitor-1 results significantly associated with severity of NAFLD in children (46). Interestingly, recently it has been demonstrated that the hepatic progenitor-dependent altered expression of adiponectin, as well as that of resistin and glucagon-like peptide 1, is strongly associated with the severity of NAFLD in children (47).

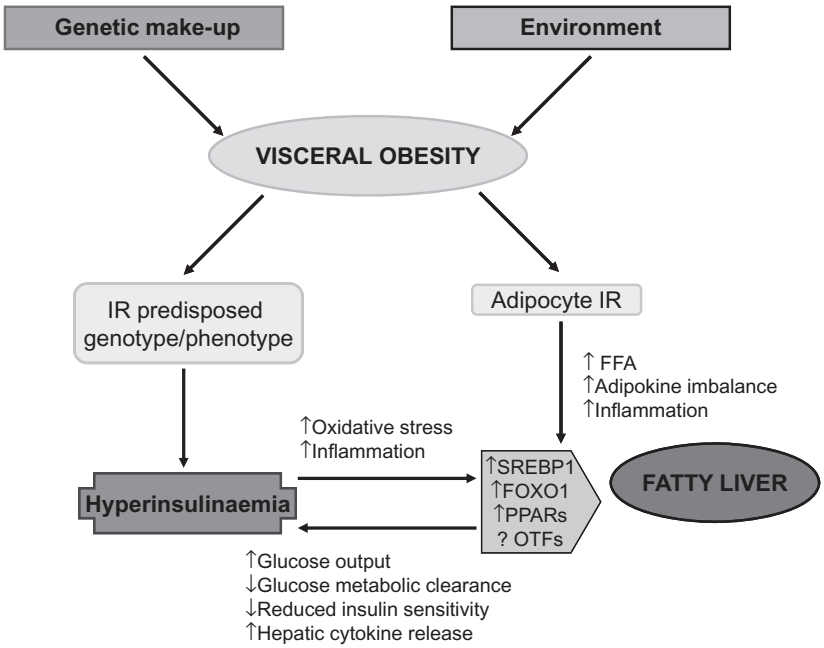

Figure 2 Proposed flow chart that explains the possible pathogenetic correlation between some features of metabolic syndrome and non-alcoholic fatty liver disease. FFA, free fatty acid; IR, insulin resistance; OTFs, other transcription factors; PPARs, peroxisome proliferator-activated receptors; SREBP1, sterol regulatory element-binding protein 1.

The role of the liver

Independent of a cause–effect relationship, liver function and IR are closely related. Most of the biochemical pathways involved in the pathogenesis of MS are located in the liver, which can be considered the 'metabolic factory' of MS (48,49). Once ectopic fat accumulates in the liver, impaired glucose tolerance and hypertriglyceridemia will ensue, with increased risk of type 2 diabetes (50). On the other hand, the causal association between NAFLD and cardiovascular disorders is much weaker (14). Recently, Fabbrini *et al*. (51) studied obese subjects categorized for high or low liver and visceral fat. They found that high fat liver group was at higher risk of developing metabolic deregulation. The authors' conclusion was that intrahepatic triglyceride rather than increased visceral adipose tissue (VAT) leads to metabolic dysfunction in obese subjects. The same group evaluated whether reducing VAT mass by surgical removal of the omentum improves insulin sensitivity and metabolic function in obese patients (52), demonstrating that decreasing VAT through omentectomy does not improve metabolic function in obese patients. Overall, these observations suggest that subjects able to displace fat from the liver would be at lower risk of developing MS. Unfortunately, because of the complex and still poor known pathogenetic mechanisms leading to NAFLD, to date it is very difficult to extrapolate data regarding possible differences between the presence of simple steatosis or NASH and the risk of MS (53). However, a recent study conducted by the Non-alcoholic Steatohepatitis Clinical Research Network demonstrates that some features of MS (particularly central obesity and IR) associate with the histological patterns that define NASH, including steatosis, ballooning and advanced fibrosis, suggesting that MS traits should help identify subjects with more advanced disease or vice versa NASH children could be more prone to develop MS (54).

Within this context, the liver represents the metabolic factor responsible, under certain conditions, for many alterations associated with MS, and it is conceivable that switching off this polluting factory may interrupt some detrimental metabolic loops. Taken together, these findings suggest that genetic factors, epigenetic changes and unhealthy lifestyles may contribute to liver susceptibility to fat accumulation (49) (Fig. 2). It is conceivable that there are many causes and types of fatty liver and that overnutrition triggers most of them (55,56). Accordingly, NAFLD may be the cause or effect of IR/MS on an individual basis and, when NAFLD is the main cause of IR/MS, it can be expected that therapies targeted at reducing liver fat storage may be successful in reducing IR/MS (15). This can explain why the restoration of insulin sensitivity does not always reverse NAFLD (57). Longitudinal studies and randomized controlled trials are needed to determine whether fatty liver is an independent predictor of cardiometabolic risk and whether its treatment could reduce the risk of cardiometabolic disease. Because it is reasonable to speculate that the sooner the intervention is, the

better the outcome would be, we believe that intervention strategies in children and adolescents will elucidate whether an 'hepatometabolic syndrome' really exists and the role of fatty liver as predictor of cardiometabolic disease.

Conflict of Interest Statement

No conflict of interest was declared.

Acknowledgements

The authors wish to thank Dr M. Goran for his suggestions and editorial assistance.

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