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Clinical observation paper: Fatty liver and metabolic syndrome: is it a burden for the future generations?

Valerio Nobili[a,*], Carlo Agostoni[b]

[a]Liver Unit, Paediatric Hospital Bambino Gesù and Research Institute, 00165 Rome, Italy
[b]Department of Maternal and Pediatric Sciences, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena 20122, Milan, Italy

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Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease from asymptomatic steatosis, with or without elevated aminotransferases, to cirrhosis with complications of liver failure and hepatocellular carcinoma [1]. The histologic appearance ranges from simple steatosis to hepatocellular damage coupled with inflammation (ie, nonalcoholic steatohepatitis) and/or fibrosis [2,3]. The emergence of NAFLD and nonalcoholic steatohepatitis as clinically relevant entities has paralleled the increasing attention on the metabolic syndrome (MS) associated or not with obesity and the central role of insulin resistance, known for a long time to be related to chronic liver disease [4].

In this issue of *Metabolism*, Angelika Mohn and coworkers [5] conducted an interesting study describing the prevalence of the MS among obese prepubertal children. The additional factor added is the presence of NAFLD, which is proposed, based on their findings, to be an additional element of the diagnosis. Before getting into details of this new pediatrics burden, a word about the so-called MS.

First described by Gerald Reaven, *MS* has been defined as "a link between insulin resistance, hypertension, dyslipidemia, impaired glucose tolerance, and other metabolic abnormalities associated with an increased risk of atherosclerotic cardiovascular diseases in adults" [6].

The worldwide epidemic of childhood obesity in the last decades is responsible for the occurrence also in pediatrics of disorders such as the MS [7].

Although there is no complete agreement on the definition of MS in youth, given the limitations described above, the cornerstones of its definition still remain and need to be identified by pediatricians.

By contrast, there is agreement in considering that, because of the high prevalence of fatty liver in association with obesity, insulin resistance, and alterations in glucose and lipid metabolism, NAFLD may be considered the hepatic manifestation of MS [8].

The association between NAFLD and MS has been clearly and repeatedly demonstrated in the literature.

Furthermore, paralleling the severity of fatty liver, there was a significant increase in the prevalence of MS, suggesting that hepatic steatosis may probably be a predictive marker of MS in children.

Recent studies have shown that patterns of fat partitioning are probably one major link between insulin resistance, NAFLD, and MS in obese children.

In addition, low birth weight has been associated with increased risk of developing MS or one of its components (insulin resistance, dyslipidemia, impaired glucose tolerance, type 2 diabetes mellitus [DM2], and hypertension) and cardiovascular disease in adulthood [9]. Persistent metabolic dysfunction may also increase the risk of other diseases, including NAFLD, osteoporosis, schizophrenia, breast cancer, and polycystic ovary syndrome.

The association between low birth weight (primarily term, small-for-gestational-age [SGA] subjects) condition and MS is thought to be the consequence of intrauterine "programming." Fetal programming theory has been proposed to explain how stimuli or insults during critical or sensitive periods of early life can have lifetime consequences [10,11]. In particular, it has been hypothesized that subjects exposed to an adverse environment develop compensatory responses that may become maladaptive if the environment for which they were developed is not that expected or predicted by the intrauterine environment. Fetal malnutrition can be one important programming factor in SGA children. In fact,

* Corresponding author. Tel.: +390668592243; fax: +390668592192.
E-mail address: nobili66@yahoo.it (V. Nobili).

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intrauterine growth restriction, mainly due to a reduced uteroplacental blood flow or to maternal undernutrition or even unbalanced nutrition, may be associated with low insulin secretion and a delayed development of the insulin-producing B-cells. These perinatal alterations might induce a deficient adaptation of the endocrine pancreas and insulin resistance in later life, further emphasized by the exposure to diets unbalanced as far as energy and macronutrient composition [12]. The idea that maternal undernutrition during early to midgestation is able to increase body weight and fat deposition during adolescence and dysregulated glucose uptake is also supported by studies in animal models where an overall 50% lifespan decrease has been observed when intrauterine malnutrition is associated with an excessive postnatal catch-up growth [13].

Among the metabolic abnormalities, insulin resistance has been demonstrated to be an early and consistent finding; and it is likely that insulin resistance plays a primary role in the pathogenesis of the metabolic complications [14]. The mechanism of insulin resistance in SGA subjects is very complex and includes multiple minor genetic effects and complex interactions with the fetal and postnatal environment. In fact, besides environmental and nutritional factors during fetal life, genetic factors also may promote survival and growth of the fetus, favoring insulin resistance in a predisposing postnatal environment. Two genes/pathways have been studied with some frequency in relation with insulin resistance in SGA: the first are genes encoding insulin itself and molecules of insulin resistance signaling, whereas the second pathways are those regulating insulin-like growth factor–I levels [15]. Although insulin resistance has been well documented in children born SGA who achieved later ages, the real mechanism is still unknown. Interestingly, some studies demonstrated that body composition may contribute to the clinical manifestation of insulin resistance and the MS in SGA and premature subjects [16,17]. Furthermore, several evidences support an active role of adipose tissue in the emergence of insulin resistance. Small-for-gestational-age individuals, after a period of undernutrition, are subjected to a catch-up growth under renutrition, which determines important modifications in adipose tissue, with long-term consequences, such as a high risk of early development of insulin resistance [18], so confirming the data reported from the animal studies already mentioned.

Until now, on the basis of numerous evidences demonstrating that early improvement in growth appears beneficial for relevant outcomes, those involved in neonatal follow-up clinics have been encouraged to promote early catch-up growth for SGA subjects [19,20]. Interestingly, starting from 2003, several controversial studies have forwarded the hypothesis that avoiding postnatal catch-up growth could prevent later metabolic abnormalities, at least in selected populations [21,22].

Thus, although caution should still be used in suggesting restricting catch-up growth given the association of early postnatal growth to later neurocognitive outcome [23], an optimal nutritional management needs to achieve individually tailored growth variables and a normal body composition without increasing risk of MS in adulthood, supporting an optimal neurodevelopmental outcome. Indeed, SGA individuals who experienced greater catch-up not always develop MS or its associated disorders, suggesting that other factors, including genetic determinants, environment, and in utero undernutrition, could have an active contribution. Accordingly, as already mentioned, adipose tissue could also modulate the metabolic outcome of SGA subjects [18].

These observations suggest that a routine health surveillance of all adults born SGA should be recommended in normal clinical practice. The challenge is optimizing growth and development while preventing deficiencies and excesses on both quantitative and qualitative standpoints. Whether it will be possible to alter the early metabolic programming by improving specific macro- or micronutrient deficiencies in the neonatal period should be the goal of future research that should help in switching the concept of "catch-up growth" to the concept of "healthy catch-up growth."

Because of its recent discovery, there are no long-term follow-up studies yet on the MS in children. Despite this, there is agreement that MS may develop in obese children so as to produce effects in terms of morbidity and mortality not only in adulthood but also in youth [24].

To date, however, the knowledge of the natural history of disease in childhood is limited; and consequently also, the therapeutic tools are still inadequate to combat the disease. Now, the pediatric use of medications to treat obesity and/or its complications, such as insulin resistance, hypercholesterolemia, hypertension, or DM2, is spreading, although not without risk. The combination of diet and exercise is still the most powerful and useful weapon to combat obesity and its metabolic complications. There are now global efforts directed toward the genetic/molecular study of childhood obesity, insulin resistance, and DM2. Most of these studies are oriented toward the search for possible genes and their polymorphisms that may be associated with MS and related diseases. We hope that, soon, the results from both the clinical and molecular studies will help us to identify new potential therapeutic targets to effectively treat these diseases.

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