

Pediatric obesity: could metabolomics be a useful tool?

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The doctors of the future will no longer treat the human frame with drugs, but rather will cure and prevent disease with nutrition.

Thomas Edison (1847-1931)

Keywords

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In recent years the literature has shown increasing interest in pediatric obesity, a condition that predisposes towards a higher risk of developing chronic pathologies in adulthood, such as diabetes and cardiovascular diseases. These are important health issues since they are destined to increase owing to the global change to an environment with plentiful food and a sedentary lifestyle. Those who are obese in infancy are more likely to be obese in adulthood. Thus the trend towards pediatric obesity may lead to higher percentages of metabolic syndromes in the coming decades [1]. Progress in the new systems biology methodologies that study the etiological processes at the origin of many pathologies is becoming more and more important thanks to the metabolic alterations that accompany them. In particular, metabolomics, a new analytical technique defined as the study of the complex system of metabolites is capable of describing the biochemical phenotype of a biological system. Despite the progress made in recent years of intense research, unfortunately a large part of the molecular pathogenesis of these complex metabolic diseases remains unknown [2]. Moreover, applications of metabolomics have led to evaluation of responses to the various nutrients (nutrigenomics), in particular to lipids, in diseases such as obesity and diabetes. Recently, attention has concentrated on the identification of biomarkers thanks to metabolomic analyses by means of which it is possible to better define the mechanisms at the base of obesity and prevent its onset [3]. In several metabolomic studies it has been found that the concentration of lactate in urine, blood, or liver tissue is high in obese mice fed a high-fat diet, or in obese Zucker rats lacking the leptin receptor, compared to their

lean controls [4, 5]. Obesity, characterized by deposits of fat in tissues, is normally associated with high plasma levels of free fatty acids (FFA). In agreement with this, the increase in FFA in the serum and liver of obese animals has been observed through metabolomic analysis [6, 7]. A study by Kim KJ et al. [8] investigated the differences in metabolomic profiling between overweight/obese and normal-weight men. Overweight/obese men showed higher levels of triglycerides, total cholesterol, LDL-cholesterol, lower levels of HDL-cholesterol and adiponectin than lean men. Overweight/obese men showed a higher proportion of stearic acid and a lower proportion of oleic acid in serum phospholipids. Additionally, overweight/obese individuals showed higher fat intake and a lower ratio of polyunsaturated fatty acids to saturated fatty acids. Contrary to adults, up to now few studies on metabolomics have been published on animals and humans to evaluate the metabolic condition of obese children (**Tab. 1**). A study by He Q et al. [9] conducted on piglets revealed that HDL, VLDL, lipids, unsaturated lipids, glycoprotein, myo-inositol, pyruvate, threonine, tyrosine and creatine were higher in obese pig serum ($P < .05$), while glycemia and urea were higher in thin pigs ($P < .05$). The results of this work indicate that the obese piglets presented a metabolism different from that of thin ones, as in the case of lipogenesis, lipid oxidation, the metabolism of amino acids and fermentation of gastrointestinal microbes. Another recent metabolomic study [10] revealed a metabolite concentration in the serum of obese children different from that of those of normal weight (between 6 and 15 years of age). Recently, a study was also carried out on adolescents [11]

Table 1. Metabolomics studies that evaluated the metabolic condition in infant obesity.

Author	Year	Type of patient	Sample	Metabolomic analysis	Metabolites results
He Q. et al. [9]	2012	Newborn piglets	Serum	NMR-based metabolomic technology	HDL, VLDL, lipids, unsaturated lipids, glycoprotein, myo-inositol, pyruvate, threonine, tyrosine and creatine > in obese than in lean pigs ($P < .05$). Serum glucose and urea < in obese pigs ($P < .05$)
Wahl S. et al. [10]	2012	Human children	Serum	Mass spectrometry-based metabolomics approach	14 metabolites (glutamine, methionine, proline, nine phospholipids, and two acylcarnitines, $p < 3.8 \times 10^{-4}$) and 69 metabolite ratios ($p < 6.0 \times 10^{-6}$) to be significantly altered in obese children
Mihalik SJ. et al. [11]	2012	Human adolescents	Plasma	Tandem mass spectrometry	Fasting lipolysis and fat oxidation were higher in obese and type 2 diabetes compared with normal weight. Insulin sensitivity was lower in obese and type 2 diabetes

which showed significant metabolic differences between youths of normal weight and obese ones and/or those with type II diabetes. As is known, infantile obesity is one of the most frequent problems in the pediatric age and the risk of an obese child becoming an obese adult increases with age and is directly related to the amount of excess weight. Many researchers have demonstrated that nutrition at an early age and lifestyle have long-term effects on health and the risk of developing chronic diseases in adulthood [12]. Several studies have demonstrated that certain chronic pathologies such as obesity are caused not only by post-natal conditions, but also by exposure to epigenetic factors that may influence and permanently alter fetal “programming” [13, 14]. It appears that in the same way both intrauterine growth retardation (IUGR) and excessive fetal growth (macrosomia), despite the different conditions in the uterus, are associated with an increased risk of becoming obese and the onset of metabolic syndrome in adulthood. The exact mechanism at the root of these long-term effects on growth is still not perfectly clear, but insulin-resistance, which is at the base of both the pathologies, probably plays an important role [15]. By means of metabolomics it was possible to identify some of the relationships among metabolic markers involved in obesity in experimental animals. In particular, an association between a rapid weight increase in early infancy and an increased risk of obesity in adulthood has been found. In a metabolomic study conducted on IUGR rats, the authors assessed the serum metabolic differences between those with rapid post-natal growth and those of slow growth [16]. Their findings suggest that the long-term deregulation in feeding behavior and fatty acid metabolism in IUGR rats depends on postnatal growth velocity. Works in metabolomics have recently appeared in the literature [17, 18] suggesting that the altered glucid metabolism during fetal development in IUGRs may be seen in the increase in extracellular myo-inositol and that this may be considered a valid predictive marker of the development of obesity and type II diabetes in adulthood. Comprehension of changes in metabolic profiles during the lifespan may represent an important reference point in arriving at an understanding of the fundamental mechanisms and their consequent metabolic alterations. It is likely that in the near future by means of metabolomics it will be possible to assess an individual’s nutritional state to understand how single nutrients influence metabolic regulation. It is thus to be hoped that

future progress in connection with this new technique, together with a metabolomic study of mother’s milk and formula milk [19-23], will lead to the creation of better personalized nutritional therapies to prevent infantile obesity and the chronic pathologies of adults connected with it.

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