

# Obesity and metabolic syndrome in children: what's new?

## Mini review

Obesity is increasing worldwide and has emerged as an epidemic affecting all ages and young people are not an exception.<sup>1-4</sup> The childhood obesity has become a major health concern in recent decades, in particular regarding to future cardiovascular disease and certain types of cancer.<sup>5</sup> Its rising prevalence has led to a parallel rise of the so-called metabolic syndrome.<sup>6,7</sup> That's well established that the nowadays lifestyle accounts for a serious part of this burden, but there are still some doubts about the role of genetic imprinting, adipokines, 25-hydroxyvitamin D (25[OH] D), hepatic fat infiltration and puberty.

The increase of visceral adipose tissue and its secretory products (adipokines) are believed to play a major role in the determination of insulin resistance.<sup>8</sup> Recent evidence suggests a relationship between leptin levels and energy balance in obese children.<sup>9-11</sup> Adiponectin is related to obesity and insulin resistance and appears to be the strongest predictor for metabolic syndrome, even in children, but its role still remains controversial.<sup>12,13</sup> Ghrelin, a somatotropic and orexigenic hormone has also been recognized as an important regulator of energy metabolism.<sup>14</sup> It's important to notice that the amount of brown- (BAT) and white adipose tissue (WAT) has to be considered, as well as their ability to transdifferentiate. They present two opposite functions both essential for survival: white adipocytes store energy released between meals and the brown ones burn lipids to maintain thermogenesis.<sup>15</sup> Some genes are specific for each cell type; UCP1 is restricted to BAT<sup>16</sup> and leptin is absent from classic multilocular brown adipocytes.<sup>17</sup> Over the last decades, the adipose organ has gained particular interest as an endocrine organ and a potential target to new therapeutic strategies, as browning could be harnessed to tackle obesity and metabolic syndrome.<sup>18,19</sup>

Another hot topic is about the 25[OH] D.<sup>20-22</sup> Poor vitamin D status has been associated with future risk of type 2 diabetes and metabolic syndrome in the obese.<sup>23,24</sup> This relationship may be explained by vitamin D's preferred deposition in body fat, making it unavailable for use by other tissues.<sup>25</sup> However, these findings must be interpreted in a surface including effects of pubertal status, presence of nonalcoholic fatty liver disease (NAFLD), PTH status and magnesium levels.<sup>26-29</sup> NAFLD is defined by hepatic fat infiltration in the absence of other excessive alcohol intake, viral, autoimmune and drug-induced liver disease.<sup>30,31</sup> Its prevalence has been reported about 53% in obese children.<sup>32</sup> It's interesting to notice that Pirgon et al.,<sup>33</sup> found that vitamin D status was negatively correlated with HOMA-IR in those with NAFLD but not in those without it, suggesting that there's a crosstalk between several pathways. Adipocytokines seem also to play a role about the vitamin D status Walker et al.<sup>34</sup>

Identified adiponectin as a key regulatory protein in the link between vitamin D deficiency and pediatric obesity but the mechanism they interact has not been elucidated. By contrast, Belenchia et al.,<sup>35</sup> did not find any changes in adiponectin in obese adolescents supplemented with vitamin D but observed a significant decrease in leptin to adiponectin ratio and that correcting vitamin D

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**Menezes Nunes J,<sup>1</sup> Medina JL,<sup>2</sup> Santos AC,<sup>3</sup> Barros H<sup>3</sup>**<sup>1</sup>Luz Saude Private Hospitals, Institute of Public Health of the University of Porto (ISPUP), Portugal<sup>2</sup>Faculty of Medicine, Porto University, Portugal<sup>3</sup>Instituto de Investigacao e Inovacao em Saude, Portugal

**Correspondence:** Joana Menezes Nunes, Luz Saude Private Hospitals, Institute of Public Health of the University of Porto (ISPUP), Portugal, Rua Alberto Serpa nr 150/152, 4100-010 Porto, Tel +351 91 646 22 94, Email joana.maria.menezes@gmail.com

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status of obese adolescents improved insulin sensitivity with results being similar to metformin. It is important to underline that calcitriol is a strong immunomodulator and improves systemic inflammation, which usually accompanies obesity, hyperinsulinemia and eventually beta-cell dysfunction.<sup>23</sup>

Excess adiposity may also influence various aspects of pubertal development and be influenced by pubertal timing. Some studies are inconclusive<sup>36-38</sup> while others found age at menarche to be inversely associated with adiposity in childhood.<sup>39-41</sup> Recent papers suggested that a history of early menarche may help to identify women at risk for metabolic syndrome<sup>42</sup> and that it may play a role in the development of prediabetes and diabetes independently of body mass index.<sup>43</sup> However, little is known about the underlying genetics of pubertal timing, childhood obesity and metabolic syndrome. Five loci are associated with pubertal timing (near MAPK3, PXMP3, VGLL3, ADCY3-POMC and LIN28B), all impacting multiple aspects of growth.<sup>44</sup> A novel variant was found to correlate with the expression of MAPK3 and to be associated with increased prepubertal growth and earlier menarche.<sup>44</sup> Another variant near ADCY3-POMC has been implicated in childhood<sup>45</sup> and adulthood obesity,<sup>46</sup> reduced pubertal growth and earlier puberty.<sup>44,45</sup> Also, rare recurrent copy number variations near MAPK3 on chromosome 16 p11.2 have been shown to be associated with early onset obesity.<sup>47,48</sup>

Recently, the concept of metabolic endotoxaemia (an increase in plasma lipopolysaccharide levels, caused by changes in the composition of the gut-microbiota and gut barrier dysfunctions) has gained attention as one of the triggering factors responsible for the development of insulin resistance, obesity, metabolic dysfunction and low-grade chronic inflammation<sup>49,50</sup> and some authors believe that there's a crosstalk between numerous organs (gut, adipose tissue, muscles, liver, bone and brain),<sup>49</sup> all acting together in a genetic background susceptibility.

A better understanding of the possible biological mechanisms related to the occurrence of metabolic syndrome in children is of major interest as they are usually treatment naïve and otherwise relatively free of co-morbidities, allowing studying the sequence of events of obesity-related pathology. Therefore, efforts to identify children and adolescents at risk earlier in life are very important in order to target them for anti obesity strategies and provide benefit from preventive interventions.

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## Conflicts of interest

The author declares there is no conflict of interest.

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