



## EDITORIAL COMMENT

# Fat intake and cardiac autonomic dysfunction in obese children: What is the relationship?☆



## Lípidos da dieta e disfunção autonómica cardíaca na obesidade em idade pediátrica: qual a associação?

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Cardiovascular disease in children is becoming ever more common, in parallel with the increasing prevalence of childhood obesity. Tracking of childhood obesity to adulthood increases the risk of developing cardiovascular disease, and by 2035, the number of excess cardiovascular events attributable to adolescent overweight in the USA is expected to exceed 100 000 a year.<sup>1,2</sup> There is thus an urgent need to focus on this problem, in order to prevent cardiovascular disease from affecting children at ever younger ages.

The article by Gulgun et al.<sup>3</sup> in this issue of the *Journal* on the relationship between the levels of different types of erythrocyte membrane fatty acids and cardiac autonomic dysfunction in pubertal children is thus of considerable interest, especially as it deals with the effects of obesity on the autonomic nervous system rather than with the more commonly discussed impact on premature development and accelerated cardiovascular atherosclerosis,<sup>4</sup> including in childhood.

The authors of this case-control study, which included 48 obese and 32 healthy pubertal children aged  $11.95 \pm 2.42$  and  $12.48 \pm 2.27$  years, respectively, conclude that the differences they found between these groups in levels of omega-6

essential fatty acids may play a role in impairment of autonomic cardiac function in obese children.

It has been known for over twenty years that dietary fat intake can influence the fatty acid composition of cell membranes,<sup>5</sup> changes in which can affect the membranes' structural characteristics, particularly the function of membrane proteins, and this in turn can have important effects on cell metabolism and other physiological processes.<sup>6</sup> Escriba et al.<sup>7</sup> showed that changes in the lipid composition of cell membranes in hypertensive patients affected signaling proteins involved in control of blood pressure. At the same time, obesity itself causes a highly pro-oxidant metabolic state that can also contribute to structural and functional alterations in the cell membrane through lipid peroxidation.<sup>8</sup>

It is generally accepted that measurement of plasma fatty acid levels merely reflects the quality of recent dietary fat intake and is also subject to various other influences from diet. Since the fatty acid composition of the erythrocyte membrane appears to remain constant throughout the life of the cell (around 120 days), measuring this will give a more consistent result, and thus a better indication of medium- to long-term intake. This was the approach adopted by Gulgun et al.<sup>3</sup>

As an illustration of the complexity of this subject, as well as being ingested in food, fatty acids can also be synthesized endogenously, through a process known as *de novo* lipogenesis. This is an adaptive mechanism in situations of

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excessive dietary intake of carbohydrate, which is converted into fatty acids and triglycerides, especially in obese individuals. In de novo lipogenesis, endogenous acetyl-CoA is used to produce saturated fatty acids, which are then elongated and/or desaturated to varying degrees.<sup>9</sup>

The erythrocyte membrane lipid profile in obese adolescents is characterized by a high cholesterol/phospholipid ratio, increased saturated fatty acid levels and lower levels of mono- and polyunsaturated fatty acids, leading to a significantly reduced unsaturation index.<sup>6,10</sup> As pointed out above, it is thus logical that such alterations would directly affect flow properties and lipid peroxidation conditions in these membranes, and this has in fact been demonstrated experimentally. Several studies have also shown that low omega-3 fatty acid levels exacerbate the low-level inflammatory state found in adolescent obesity, and that erythrocyte membrane eicosapentaenoic acid levels are inversely correlated with insulin resistance.<sup>11</sup> Various mechanisms have been put forward to explain this association, including competition between glucose and fatty acids as oxidation substrates, inhibition of glucose transport and/or phosphorylation, and release of fatty acids into the portal circulation as a result of lipolytic activity by visceral adipose tissue and release of hormones and cytokines,<sup>9</sup> as also noted by Gulgun et al., although this was not reflected in their results because their study population did not include insulin-resistant obese subjects.

In recent years, several epidemiological studies have produced evidence of impaired cardiac autonomic modulation (CAM) in obese children. Autonomic activity in humans has a circadian rhythm, with predominantly parasympathetic activity at night and predominantly sympathetic activity during the day.<sup>12</sup> CAM reflects the balance between the sympathetic and parasympathetic systems, but in obese children, reduced parasympathetic activity may be seen compared to normal weight children.<sup>13</sup> However, other studies have shown impairment of CAM not only through reduced parasympathetic activity, but also through absolute or relative sympathetic hyperactivity or preponderance in obese children.<sup>14</sup>

The cardiac autonomic nervous system can be assessed non-invasively, simply and reproducibly through analysis of heart rate variability (HRV), which measures the extent of variation between heartbeats. This reflects the balance between sympathetic and parasympathetic activity, which in turn modulates the way cardiac function responds to differing levels of metabolic activity in the body.<sup>15</sup> CAM can thus be assessed by analyzing HRV, which appears to be reduced in obese children and adolescents.<sup>16</sup>

There are associations between the sympathetic nervous system (SNS) and energy balance and metabolic syndrome, and between SNS activity and diet.<sup>17</sup> Sympathetic activation reduces food intake regulated by the hypothalamus and inhibits leptin secretion. Leptin in turn inhibits ectopic lipid accumulation, prevents pancreatic beta cell dysfunction and protects beta cells from apoptosis induced by cytokines and fatty acids. Adiponectin, another adipokine, also promotes fatty acid oxidation and glucose uptake.<sup>18,19</sup> Together, these effects increase insulin sensitivity and reduce serum lipid levels. In obesity and type 2 diabetes, circulating adiponectin levels fall, and a state of peripheral resistance to hyperleptinemia develops; this appears to play an impor-

tant role in SNS activation.<sup>20</sup> A study of 32 obese children showed that HRV was reduced through decreased parasympathetic activity and predominance of sympathetic activity, but that these changes were much more marked in children with insulin resistance than in those without.<sup>21</sup> The study by Gulgun et al.<sup>3</sup> also shows parasympathetic impairment in obese pubertal children compared to controls, and aims to establish a relation between this impairment and omega-3 and -6 fatty acid levels in the two groups.

Low HRV is associated with cardiovascular morbidity and mortality, and is therefore a powerful parameter to be assessed and monitored for the early identification of cardiovascular risk in childhood obesity.<sup>13,14</sup>

At the same time, the question remains whether the alterations in CAM associated with obesity precede and contribute to the etiopathogenesis of cardiac autonomic dysfunction, or are merely a consequence of obesity. Which is cause and which is effect?

The article by Gulgun et al.<sup>3</sup> is a contribution to the accumulating evidence on this subject, which points to disruptions in cell metabolism resulting from long-standing dietary imbalances that lead to organ dysfunction and the development of comorbidities, including impairment of cardiac autonomic control.

The article highlights how important it is for nutritional counseling to focus not only on calorie counts but also on quality and balance in dietary constituents, in view of their value in cardiovascular prevention. Clinical monitoring of obese individuals could include assessment of the erythrocyte membrane lipid profile as a dietary biomarker, as well as HRV analysis as a means for detecting cardiac autonomic dysfunction in obese children.

## Conflicts of interest

The author has no conflicts of interest to declare.

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