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REVIEW

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Development of insulin resistance and its relation to diet in the obese child

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Abstract The incidence rate of obesity in youth has continued to increase worldwide and about 30% of obese children display insulin resistance (IR) and other metabolic abnormalities. The present study reviews the mechanisms for development of IR in the obese child and possible links between IR and dietary factors in childhood and adolescence. Although increased concentrations of plasma free fatty acids (FFA) and their counter part at intracellular level, long-chain acyl-coenzyme A (LC acyl-CoA), have been related to the early onset of IR in childhood obesity, a new endocrine paradigm states that adipose tissue secretes a wide variety of hormones and cytokines that regulate lipid energy metabolism. These hormonal changes precede any changes in metabolites such as FFA and glucose and appear to be associated with early IR in childhood. Excessive caloric intake increases IR in children; opposite, substantial reduction of overweight achieved by a hypocaloric diet decreases it. Elevated consumption of animal protein, particularly in early life, as well as diets rich in saturated, *trans*, and *n*-6 polyunsaturated fatty acids, and diets with a high carbohydrate to fat ratio, besides a high glycaemic and low-fiber diet also appear to exacerbate adiposity and IR.

Key words adipocytokines – childhood obesity – diet – free fatty acids – insulin resistance

Introduction

Excess body weight is the sixth most important risk factor contributing to the overall burden of disease worldwide and about 110 million of children are now classified as overweight or obese [15, 44].

IR is usually induced by fat deposited intracellularly, mainly in adipose and muscular tissues [3, 39]. Recent research indicates that inflammation and oxidative stress could be underlying mechanisms at the centre for the development of IR [32]. IR is associated with a number of metabolic abnormalities and clinical manifestations typically known as metabolic syndrome (MS). Recently, Reaven has suggested that the term MS should be replaced with that of Insulin Resistance Syndrome (IRS), which represents a pathophysiological construct under which those abnormalities and clinical syndromes occur more likely in hyperinsulinaemic/IR individuals that do not develop type 2 diabetes [32].

It has been claimed that at least 30% of obese children under 12 years of age display the IRS [46, 48]. IR correlates far more strongly with trunk obesity than with BMI alone, due to visceral fat accumulation

[15, 44, 47] and it has been suggested that IR may be the initial factor triggering the metabolic cascade leading to MS [39].

IR may be modulated by different environmental factors including dietary habits [36]. However, there are scant data on how nutrients and other dietary components affect IR in children. Thus, the aim of the present work is to review the factors involved in the early-onset on IR in childhood and to evaluate the relationship between the amount and composition of diet with IR in obese children.

Development of insulin resistance

Insulin is the major hormone responsible for maintaining energy homeostasis, by coordinating the use of fat depots in adipose tissue, liver and muscle. During fasting, insulin levels fall, glycogen is mobilized, FFA are released and glucose use is limited to certain tissues such as the central nervous system (CNS), whilst others start to oxidise fatty acids released from adipose tissue; at the same time, some hormones, namely glucagon, growth hormone and glucocorticoids act synergically to the low concentration of insulin. This stimulates the release of FFA, which also inhibits insulin signals [26].

Free fatty acids hypotheses for obesity-induced insulin resistance

The "portal theory" links visceral adipose tissue to IR and is based on the direct effects of FFA on the liver [10]. However, the role of portal vein FFA remains somewhat speculative since a lot of facts come from animal studies and need confirmations in humans, specially in obese children in which controversial results have been found; plasma FFA concentrations reported by some authors remained unchanged in children or were not associated with IR [1, 12, 47], whereas others documented alterations of the insulin sensitivity index related to FFA metabolism [33]. Intra-abdominal tissue adipocytes are much more insulin resistant than their subcutaneous counterparts, suggesting that FFA delivery to the liver via the portal vein is increased when visceral tricylglycerol (TG) stores are increased [7]. In children, a number of studies support a link between body fat, visceral fat, and metabolic factors associated with IR [9, 39, 48]. Elevated portal FFA levels might increase hepatic gluconeogenesis, inhibit glycogenolysis and lower glucose uptake, prompting a further increase in the secretion of insulin [7]. Increased levels of TG are well known to occur in children with IR [48] together with intramyocellular and intraabdominal lipid accumulation closely linked to peripheral IR [3, 47]. FFA inhibits the degradation, but not the synthesis, of hepatic glycogen, and stimulate gluconeogenesis. Moreover, FFA also inhibit LPL, thus reducing plasma clearance of TG and VLDL [30]. Hyperinsulinaemia and IR in obese children display a significant direct correlation with FFA levels [33]. Nevertheless, the regulatory role of FFA in context with insulin actions requires more detailed studies in humans and particularly in children since the existing data do not consider sufficiently the dynamic and competitive processes of postprandial versus interdigestive phases.

Elevated levels of long-chain acyl-CoA (LC acyl-CoA) in muscle cells are positively associated with IR, and these compounds are known as the equivalent of FFA at intracellular level [37]. Intramyocellular lipid has been shown to be a major determinant of IR in both obese adults and adolescents [3, 41, 47]. Based on the muscle lipid accumulation occurring in obese children [47], it can be assumed that those mechanisms may be extrapolated to the development to IR in childhood obesity.

In children, an association between an IR state and liver lipid accumulation (non-alcoholic fatty liver disease) has been found [9, 38]. In addition, small dense LDL in obese children have been reported to be associated with plasma TG and IR [27, 43]. Figure 1 shows a summary of major metabolic changes associated to increased mass adiposity and IR mediated by increased levels of FFA.

The endocrine paradigm, an alternative hypothesis to the development of IR

Ravussin and Smith have put forward an alternative to the classical paradigm or portal/visceral FFA hypotheses [31]. The "endocrine" paradigm posits that adipose tissue secretes a wide variety of endocrine hormones and adipocytokines that regulate lipid and energy metabolism [13, 14]. Hormone changes may thus precede any change in metabolites such as FFA or plasma glucose [31]. Figure 2 depicts a summary of the endocrine hypotheses of IR.

A recent study in obese children with and without impaired glucose tolerance has shown a strong relationship between inability to compensate glycaemia (by increased insulin secretion) and severe peripheral IR, as well as low adiponectin plasma levels [47]. However, the ability of insulin to suppress systemic lypolisis was similar in the two groups. Moreover, plasma FFA and glycerol turnover remained unchanged [47]. In a recent study, carried out by our research group in prepubertal obese children, we also

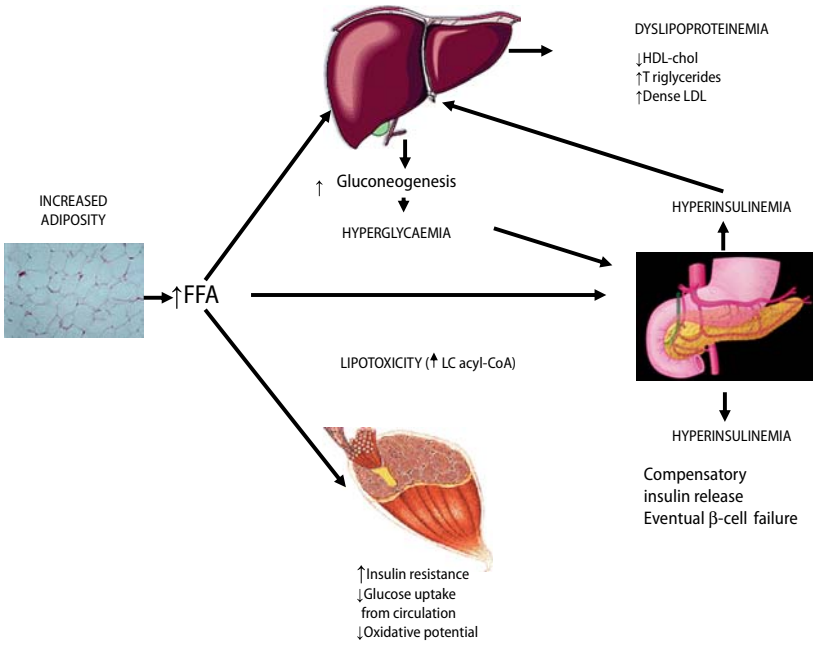

Fig. 1 Free fatty acid hypotheses for obesity-induced insulin resistance. FFA: Free fatty acids; HDL-chol: High density lipoprotein cholesterol; LDL: Low density lipoprotein

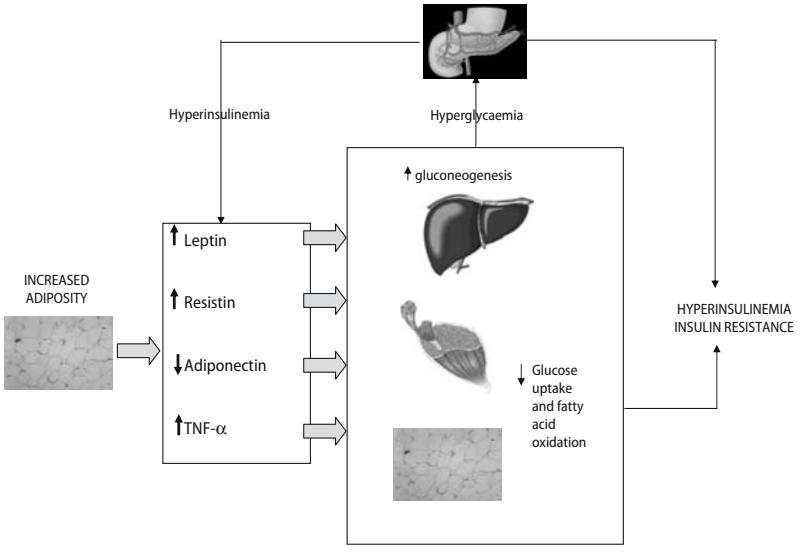

Fig. 2 Endocrine hypotheses for obesity-induced insulin resistance. TNF-α: Tumor necrosis factor alpha

have observed increased levels of TG associated with IR and low levels of adiponectin [12], while FFA levels remain fairly similar to lean subjects, both in fasting and postprandial conditions [12]. Thus, increased levels of FFA do not seem to be the primary cause of IR and expansion of fat mass and secretion of specific adipocytokines e.g. adiponectin, appear to have a main role on that process [13, 14].

In vitro cell studies have documented that low levels of adiponectin and elevated levels of TNF-α inhibit AMP kinase (AMPK), which results into low acyl-fatty acid oxidation [50]. Both facts might have also a role in the development of IR through AMPK [13, 14]. Although these and other recent studies highlight the importance of adipocytokines in obesity, further research is required to determine the factors involved in the complications associated with early-onset of IR in childhood.

Developmental aspects of insulin resistance

In early life it seems to be a metabolic "programming" dependent on environmental and genetics factors that have been associated with metabolic and body composition disorders in adult life [4]. Low

birth weight and children born premature or small for gestational age with a rapid postnatal weight gain have been related to risk factors for the development of IR, type 2 diabetes mellitus and cardiovascular disease in childhood [4].

Insulin resistance as related to foods and nutrients in childhood and adolescence

Recent reviews have documented the role of the diet in inducing IR in animal and human adult studies [20, 25]. However, data on how specific nutrients may affect the development of IR are scarce. Figure 3 summarises the hypothesized effects of diet on the development of IR in children.

Energy dense food

In children and adolescents, the continuing increase in the incidence of type 2 diabetes mellitus and obesity is attributable to excessive caloric intake [17] and particularly to a dramatic rise of consumption of fast food [16, 30]. This is characterised by high contents of saturated and *trans* fatty acid content and simple sugars, as well as low content of fiber [16, 25]. However, the relationship between energy-dense food consumption and IR is based on observational studies. As yet it remains unclear whether this is an effect of the food per se or whether it is due to higher body weight and fat mass.

Although nutritional surveys in the general population do not indicate a significant increase in caloric intake in children and adolescents over the last three decades in Japan and USA, except in adolescent females in the latter [17], dietary intake in some obese children intake is significantly higher than in normal weight children [15, 25]. Nevertheless, nutritional surveys must be considered cautiously since all energy and macronutrient data are obtained in retrospective questionnaires and 24 h or 72 h food recalls.

On the contrary, the substantial reduction of overweight in children achieved by a high carbohydrate and low-fat diet during 1 year results in a significant decrease of IR, associated with and increase in plasma adiponectin and decreased levels of ghrelin and leptin [34]. However, any successful body weight reduction can be expected to improve IR and this finding is not necessarily attributable to the high carbohydrate content of the diet.

Fat

Changes in dietary and tissue fatty acid composition, which might be expected to reduce IR are relatively easily achieved by using the appropriate oils, margarines, oily fish, grains, seeds and nuts, and consuming fewer high-fat dairy products, convenience and confectionary foods, which are high in saturated and *trans* unsaturated fatty acids [24]. Although there is an obesogenic potential in high fat diets that may promote IR, there are no conclusive studies in adults about differences in insulin sensitivity on the high and low fat diets [25]. Also, the extent to which those changes in dietary fat of children can influence IR remains to be established.

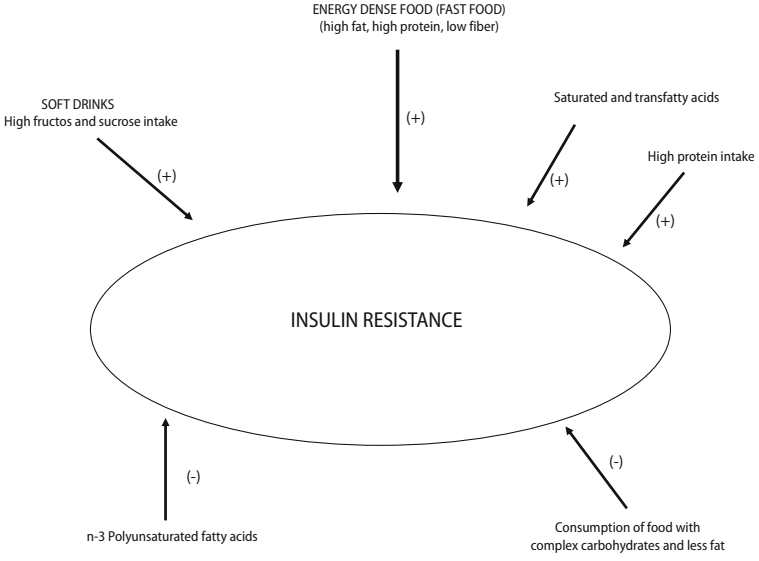

Fig. 3 Role of diet in the development of insulin resistance and other metabolic abnormalitites in children. HDL-chol: High density lipoprotein cholesterol; LDL: Low density lipoprotein; TG: Triacylglycerols

Diets rich in fatty acids mainly saturated and *trans* fatty acids, as well as carbohydrate-rich diets, favor an acute increase in IR independent of adiposity [25]. *Trans* fatty acids are found in the greatest concentrations in liver and adipose tissue, and—like saturated fatty acids—act to reduce cholesterol absorption, enhance formation of abnormal eicosanoids, replace other fatty acids in the cell membrane, increase lipoprotein (a) and LDL levels, lower HDL levels and alter the metabolism of PUFA, which are essential to intellectual development in childhood [22]. However, in a recent study reported by us, Spanish prepubertal obese children had hyperinsulinaemia and IR but they were not correlated with either *trans* fatty acid intake or plasma concentration [21].

Linoleic acid (18:2 *n*-6) and its long-chain derivatives, namely arachidonic acid (20:4 *n*-6), are consumed in relative high amounts in Western diets [35] and it has been suggested that IR may be influenced by dietary linoleic acid in adults [40]. In contrast, IR as measured by HOMA, was not significantly associated with plasma phospholipids and cholesterol ester FA composition in preteen adolescents [18]. However, it has been proposed that the less unsaturated muscle membranes in children whose mothers have higher fasting insulin and triglyceride levels may reflect a genetic reluctance to incorporate PUFA into membranes, thus predisposing them to IR [6].

Efforts to link the *n*-3 PUFA in childhood and adolescents to the development of IR in adulthood are hampered by a lack of supportive epidemiologic and clinical data. However, it has been shown that muscle membrane FA profile in breast-fed infants is similar to that of insulin-sensitive adults, whereas formula-fed infants have a muscle membrane FA profile similar to that of insulin-resistant adults [5]. These results are in keeping with the known differences between human milk rich in long-chain PUFA, namely 20: 4*n*-6 and 22: 6*n*-3, and usual infant formulas lacking those FA [11]. It could be assumed that dietary *n*-3 PUFA due to their anti-inflammatory and anti-atherogenic properties would act in children in a similar fashion to that of the adult [25]. In the next future it would be important to specifically address the influence of those fatty acids on regulation of metabolism in children and how they may contribute to prevent onset of IR.

Carbohydrates

Carbohydrate intake has increased in USA and other developed countries as a result of the decrease in dietary fat and indirect evidence indicates that the quality of carbohydrate has been changing, so that American children are eating high amount of carbohydrates with a higher glycaemic index [30]. Thus, it is proposed that high-glycaemic-index diets lead to excessive weight gain as a consequence of postprandial hyperinsulinaemia and low-glycaemic-index diets lower postprandial insulin levels and IR. In addition, the higher consumption of sweet drinks rich in fructose may also contribute to IR since it is metabolised in the liver mainly to triacylglycerols [23].

In obese adolescents who received either a high carbohydrate/low fat or a low carbohydrate/high fat diet, insulin secretion demands were increased regardless of diet, and failure to increase insulin sensitivity while receiving a high-carbohydrate diet required a further increase in insulin secretion, which may lead to earlier β-cell failure. Moreover, the low-carbohydrate/high-fat diet has resulted in increased gluconeogenesis, which may be a prelude to the increased glucose production and hyperglycaemia observed in type 2 diabetics [45].

On the other hand, differences in the genetic background may also influence the development of IR. African-American (AA) children are hyperinsulinaemic and insulin resistant compared with American White (AW) children. Nevertheless, it has been reported that both insulin clearance and insulin sensitivity correlated inversely with dietary fat/carbohydrate ratio, which was higher in AA than in AW children. This suggests that increased insulin secretion in AA children is not merely a compensatory response to lower insulin sensitivity and that dietary factors may have a role [2].

Postprandial insulin can be reduced either by reducing the amount of carbohydrate in the diet, or by reducing the rate of absorption using low-glycaemic-index foods, but further works needs to be done before a firm conclusion can be drawn as to the optimal amount and type of dietary carbohydrate [49]. However, it seems likely that diets restricted in sweetened sodas and non-citrus juices and containing ample whole grains, vegetables, and fruit could have a major impact on the prevalence of paediatric obesity [9, 15] and indeed in the early onset of IR.

The intake of dietary fiber has been shown to be inversely associated with the probability of having IR in adults [25]. In children and adolescents, dietary supplementation with psyllium (the husk of the seeds *Plantago ovata*) improves glucose homeostasis [28] and whole grain intake is associated with greater insulin sensitivity among adolescents [42]. Moreover, it has been reported that overweight children placed on a high fiber, low-fat diet in a 2 weeks residential program where food was provided ad libitum and daily aerobic exercise was performed, improved IR significantly, despite only modest improvements in body fat [8]. Thus, the

intake of a high fiber diet together with changes in lifestyle habits may contribute to a better glucose homeostasis in children.

Protein

Protein intake per kg bodyweight is some 55–80% higher in formula fed than in breast fed infants and it has been related to increased adiposity due to higher levels of insulin [19]. In fact, long breast feeding seems to prevent obesity in later ages [29, 36] and the "early protein hypothesis" refers that high early protein intakes in excess of metabolic requirements enhance weight gain in infancy and increase later obesity risk [19].

Conclusion

High energy intake as well as increased consumption of dietary fat with a relative high content of saturated and *trans* fatty acids and *n*–6 PUFA, besides a high glycaemic and low-fiber diet, seem to have a role in the early appearance and development of IR in childhood. However, controlled studies are needed to ascertain until what extent the diet may have a causative role in the development of IR in children.

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