Role of Dietary Carbohydrates on Metabolic Flexibility in Key Target Tissues: Liver, Adipose Tissue and Skeletal Muscle

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Humans have acquired metabolic adaptations, including enhanced energy storage, to mitigate the effects of famine and starvation. Despite little use in developed, food-rich countries, this adaptive process to a deficit in energy intake persists, at least in part, during weight gain upon refeeding. Energy is directed at accelerating specifically the recovery of the body's adipose tissues rather than other tissues. This preferential 'catch-up' fat is commonly observed in both children and adults after malnutrition, anorexia nervosa, cancer cachexia, diabetes and intentional weight loss.

Carbohydrates help promote these metabolic adaptations in a coordinated way, involving short-term regulatory processes (ie, changes in hormone secretion and signaling pathways), and long-term adaptations (ie, changes in gene expression that sustain the channeling of glucose to fat). The effects of carbohydrates on metabolism, glycemia, insulin and glucagon secretion depend on their glycemic index (GI), saccharide composition, and rates of digestion and absorption in the intestinal tract. Non-digestible carbohydrates can also modulate metabolism following fermentation by the intestinal microbiota to generate short-chain fatty acids and other signaling molecules.

Dietary carbohydrates, depending on their GI, have a strong effect on metabolic flexibility. Metabolic flexibility is the capability of the organism to select fuel oxidation in response to specific nutrient availability.[1] For example, muscle can switch between predominant fat or glucose catabolism to generate energy, depending on the stimulus. This flexibility takes place in normal healthy lean individuals and is hampered in individuals with diabetes and obesity, leading to metabolic inflexibility.

A high glycemic index (HGI) diet leads to increases in serum glucose, insulin, cholesterol and triacylglycerol (TG) levels. These alterations reflect changes in fuel metabolism across key organs and tissues such as liver, muscle and adipose tissue. In liver, a HGI diet increases glycogen and fat deposits, too, since energy is preferentially stored as fat in humans. Fuel selection in muscles of individuals fed HGI diets is biased to glucose consumption instead of fatty acids (FA), which impacts muscle performance during exercise. Finally, a HGI diet increases white adipose tissue mass, which can promote a proinflammatory state in the organism. All these effects are normalized by a low glycemic index (LGI) diet (Fig 1).

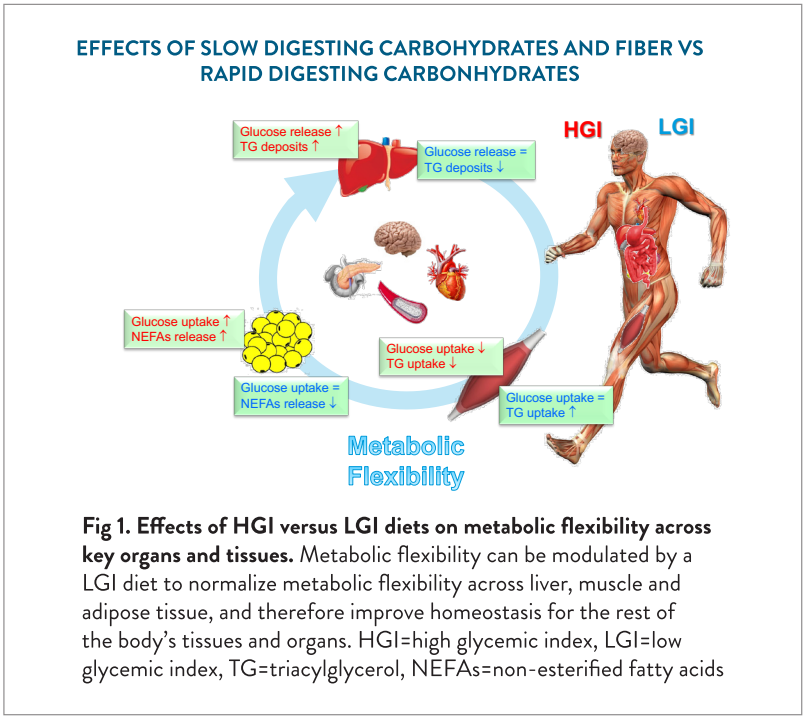

Fig 1. Effects of HGI versus LGI diets on metabolic flexibility across key organs and tissues. Metabolic flexibility can be modulated by a LGI diet to normalize metabolic flexibility across liver, muscle and adipose tissue, and therefore improve homeostasis for the rest of the body's tissues and organs. HGI=high glycemic index, LGI=low glycemic index, TG=triacylglycerol, NEFAs=non-esterified fatty acids

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The liver contributes to homeostasis and metabolic flexibility by helping control the distribution of energy to the rest of the body. Liver has a central role in metabolic flexibility since it can both efficiently use and produce glucose and TG. At the plasma membrane, liver expresses transporters for glucose and FA. Glucose transporter type 2, liver (GLUT2; SLC2A2) is a specialized transporter involved not only in the uptake but also in the export of glucose. Furthermore, GLUT2 can mediate the internalization of other monosaccharides such as fructose, which enter the glycolytic pathway at an unregulated point and thus serves as a quick energy supply when needed (eg, hypercatabolic hospitalized patients, sprinters, weightlifters). However, in a situation of overfeeding, excess of unregulated energy supply such as fructose can promote metabolic inflexibility. In a fasted state, while glycolysis and glycogen synthesis are inhibited in the liver, gluconeogenesis from non-carbohydrate precursors and glycogen breakdown work together in the maintenance of glycemia. Obviously, in a fasted state liver takes advantage of the TG uptake to produce FA and to promote its import by mitochondria through the carnitine palmitoyltransferase 1 (CPT1) transporter. Once FAs are inside the mitochondria, ß-oxidation, Krebs cycle and respiratory chain provide the ATP needed for the liver.

A HGI diet has remarkable effects on liver carbohydrate and lipid metabolism. First, it increases glucose uptake, glycolysis and alters glycogen metabolism. At the same time, it inhibits gluconeogenesis. Under these circumstances, liver is a net glucose consumer rather than a glucose exporter. Regarding lipid metabolism, a HGI diet blocks FA use and enhances the conversion of glucose to TG, promoting a hepatic lipogenic program that leads to an increase in blood TG and cholesterol, enhanced TG transport to adipose tissue, and even worse, hepatic steatosis. Further, a HGI diet raises insulin levels acutely, leading to short-term regulation of liver carbohydrate metabolism. Glycogen synthesis increases, followed by pyruvate dehydrogenase complex (PDC) activation, thus facilitating the synthesis of Krebs cycle intermediates. Nevertheless, a HGI diet exerts its long-term effects in liver through upregulation of several key enzymes. A HGI diet induces the expression of GLUT2 transporter, glycolytic enzymes such as pyruvate kinase (PK), represses expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase 2, mitochondrial (PCK2; PEPCK), and importantly, enhances the amount of lipogenic enzymes such as acetyl-CoA carboxylase (ACAC) and fatty acid synthase (FASN). In parallel, a number of signaling molecules are generated: glucose-6-phosphate (G6P) and xylulose-5-phosphate (X5P).

The long-term regulation of metabolism induced by HGI diets is mediated by specific transcription factors that upregulate expression of genes that encode lipogenic enzymes. For example, carbohydrate-responsive element-binding protein (ChREBP; MLXIPL) contains several phosphorylation sites and a glucose-sensing domain that is activated by G6P.[2] During administration of a LGI diet or fasting, ChREBP is phosphorylated and inactive in the cytosol. A HGI diet increases levels of X5P, which activates protein phosphatase 2A (PP2A; PPP2CA) and promotes de-phosphorylation of ChREBP and its translocation to the nucleus. When G6P binds to the glucose-sensing domain, ChREBP now upregulates expression of genes involved in the conversion of glucose to fat. The effects of a HGI diet can be reverted by the administration of LGI diets that normalize glycemia and insulinemia, and furthermore, decrease liver fat and glycogen levels.[3-4]

Muscle is the main energy consumer of the body. It has the capability to use glucose or FA as metabolic fuels and the potential to switch fuels. This capability to switch fuels is tightly regulated by insulin and insulin sensitivity as well as exercise and training. In a healthy individual, during fasting and low exercise conditions muscle is mainly consuming FA from circulating TG. In a moderate exercise (70% VO_2 max), carbohydrate metabolism supports up to 50% of the muscle energy demand. High intensity exercise makes muscle even more dependent on glucose metabolism.

In muscle, FA are taken up through an inducible fatty acid translocase (FAT; CD36), activated as acyl-CoAs and then transported to the mitochondria by CPT1. After a HGI diet, the enhanced insulin levels promote the translocation of a specific insulin-dependent glucose transporter, GLUT4, to the plasma membrane as well as to block FA transport

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through FAT.[3] This metabolic fuel selection is further conditioned by upregulated glycolysis, induction of PK levels, and even more importantly, by activation of PDC.

PDC constitutes one of the main decision points in muscle fuel selection. PDC is inhibited by phosphorylation by pyruvate dehydrogenase kinases (PDK).[5] In muscle, PDK4 can be regulated acutely and in the long term. It is activated by the FA catabolites ATP, acetyl-CoA and nicotinamide adenine dinucleotide hydrogen (NADH), while pyruvate from glucose metabolism inhibits PDK4. Moreover, HGI diets regulate PDK4 expression through specific transcription factors. In a healthy individual with a LGI diet, and, therefore, low insulin levels, PDK4 amount increases, consequently inhibiting PDC and facilitating the use of FA as fuels. On the contrary, in a healthy individual, a HGI diet enhances insulinemia and lowers PDK4 synthesis. This translates to PDC activation, a preferential use of glucose as the main fuel, and an inhibition in the use of FA.

In a LGI diet, long-term regulation of PDK4 expression is controlled by several transcription factors that include forkhead box O1 (FOXO1) and peroxisome proliferator activated receptors (PPARs). PPARs are activated by FAs and a positive cycle promotes FA as energy source. The switch to a HGI diet blocks FOXO1 in the cytosol by insulin-mediated phosphorylation, and therefore at the nucleus PDK4 transcription is blocked. Furthermore, insulin increases glucose uptake through GLUT4 translocation to the plasma membrane and raises pyruvate levels that depress PDK4 activity, promoting glucose use. This long-term regulation is dependent on insulin-mediated AKT serine/threonine kinase (Akt) intracellular signaling, a key pathway affected by insulin resistance that leads to metabolic inflexibility.[6]

Albeit in the past, adipose tissue has been considered a fat storage organ, this tissue has far more complex metabolism. In a healthy individual, adipose tissue obtains its energy from FA, while glucose is mainly reserved to produce glycerol phosphate needed to re-esterify FA to TG. When the energy provided by the diet is high and the GI is also elevated, a channeling of glucose to TG takes place. The effects of high-energy intake or a HGI diet go beyond the increase in adipose mass. These diets can produce hyperplasia and hypertrophy of adipocytes that lead to inflammation, decrease in insulin sensitivity, increase in non-esterified FA (NEFAs), and altogether diminish muscle glucose uptake and use, as well as promote peripheral insulin resistance.

In a fasted state, adipose tissue mainly uses FA as metabolic fuel. FA from liver are used to provide energy, and the remainder undergoes a re-esterification process that is essential to prevent the generation of circulating NEFAs. Therefore, the control of this TG cycle is important for regulation of metabolic flexibility throughout the body. High fat, HGI diets can promote channeling of glucose to TG, first increasing glucose uptake through a stimulation of GLUT4. Nevertheless, if the situation persists, insulin insensitivity occurs, with a decreased response to beta-adrenergic stimuli and a failure to regulate circulating NEFAs.

The channeling of glucose to TG is also a long-term adaptive process where transcription of lipogenic genes is clearly enhanced. In this process a specific isoform of ChREBP, termed beta, is essential.[2] This isoform is active, permanently located at the nucleus, therefore making and amplifying the effects of a HGI diet in the adipose tissue. A LGI diet can modulate adipose tissue metabolic inflexibility by the activation of PPAR signaling that, together with beta-adrenergic signaling through mitogen-activated protein kinase (MAPK) or 5'-AMP-activated protein kinase (AMPK) pathways, stimulates PDK4 activity, decreases glucose to FA conversion and enhances NEFA esterification.[7] A LGI diet, combined with fiber, also promotes the browning of the adipose tissue, evidenced by the increase of uncoupling mitochondrial proteins (mainly UCP1), which would likely lead to higher basal metabolism.

In conclusion, humans have a program of metabolic adaptations to promote efficient storage and use of fuels that relies on hormonal and transcriptional regulation allowing long- and short-term control of metabolism. Furthermore,

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liver, muscle and adipose tissues crosstalk to finely promote homeostasis. HGI diets might induce long lasting changes in metabolism leading to metabolic inflexibility. These negative effects are enhanced when combined with high fat diets, diabetes or obesity. Current investigations highlight the utility of carefully designed mixtures of slow digesting carbohydrates and fiber for ameliorating metabolic alterations in different physio- and pathological situations.[8]

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