# Metabolic Impact of the Amount and Type of Dietary Carbohydrates on the Risk of Obesity and Diabetes

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**Abstract:** The relationship between dietary carbohydrates and the current obesity and diabetes epidemic is the subject of intense renewed interest. Since glucose is an essential source of energy, with limited body stores, maintenance of blood levels and changes in its metabolism are strongly determined by the intake of carbohydrates in the diet. Depending on the individual genetic susceptibility and the impact of other risk factors, these metabolic changes can potentially deteriorate into manifest abnormalities with an important disease risk.

In this review we focus on the impact of changing the quantity and quality of dietary carbohydrates on the biochemistry of fat synthesis and storage and on the metabolic abnormalities that can lead to overweight and obesity and to complications such as the metabolic syndrome and type 2 diabetes mellitus.

Using simple illustrations of the metabolic pathways involved, we summarize current research on the following issues:

- Does an increase in dietary carbohydrates induce changes in blood lipids and an increase in body fat?
- Does a diet with a high glycemic index lead to higher energy intakes, obesity and a higher risk of developing type 2 diabetes mellitus?
- Is sucrose more obesigenic than starch?
- Does excessive consumption of food and drinks sweetened with fructose explain the current epidemic of obesity and diabetes?

Despite convincing experimental data explaining the metabolic outcomes of excess consumption of these carbohydrate types, the evidence from dietary intervention studies has been undermined by methodological issues. Clear nomenclature and classification are still needed before this information can be applied to explain metabolic risks in each individual as well as to set up guidelines for the public health authorities and the food industry.

**Keywords:** Obesity, diabetes mellitus**,** sucrose, glycemic index, fructose, lipogenesis.

## INTRODUCTION

### The Obesity Epidemic and Carbohydrates

The current obesity epidemic is becoming a major public health burden both in developed and developing countries. More than ten years ago the World Health Organization estimated that 90% of diabetes mellitus type 2 and 30-40% of cardiovascular disease cases are directly caused by obesity [1]. It also predicts that by 2015 1,5 billion people will be overweight and that 2,6 million people will die every year as a result of being overweight or obese [2].

Even small changes in body weight (5 kg) have an impact on health. In particular, an excess of abdominal (rather than peripheral) fat, as seen, for example, with increases of 5 cm in waist circumference, is associated with increased disease risk [3]. These changes are always the inevitable result of an imbalance between energy intake and expenditure. This imbalance reflects a shift in life habits favoring a diet with a caloric content that is excessive for the often low levels of physical activity [4, 5].

In this review we discuss the potential obesigenic effects of increasing the quantity of carbohydrates both in absolute terms as well as relative to the fat intake. In the second part, we analyze the impact of the type of carbohydrate and summarize the changes induced by added sugars, rapidly digestible and high glycemic index carbohydrates and fructose.

Since 40 to 70% of the phenotypic variability of obesity is determined by more than 200 candidate genes or genomic regions on all chromosomes [6-8], we also mention the genes directly involved in regulating the aspects of carbohydrate metabolism that are relevant to obesity.

The overall aim of this review is to provide evidence that can be used to compile adequate dietary guidelines for the general population and for individuals at risk of diabetes and cardiovascular diseases.

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**Table 1. Classification of Carbohydrates According to their Chemical Structure**

| Class (DP*) | Sub-Group | Components |
|---|---|---|
| Sugars (1-2) | Monosaccharides | Glucose, galactose, fructose, mannose, tagatose |
| | Disaccharides | Sucrose, lactose, trehalose, maltose, isomaltulose |
| | Polyols | Sorbitol, mannitol |
| Oligosaccharides (3-9) | Malto-oligosaccharides | Maltodextrins |
| | Other oligosaccharides | Raffinose, stachyose, fructo-oligosaccharides, galacto-oligosaccharides |
| Polysaccharides (>9) | Starch | Amylose, amylopectin, modified starches, glycogen |
| | Non-starch polysaccharides | Cellulose, hemicellulose, pectins, hydrocolloids |

DP * = Degree of polymerization. Adapted from FAO Corporate Document Repository: Carbohydrates in Nutrition http://www.fao.org/docrep/W8079E/w8079e07.htm

We first give a brief summary of the nomenclature, structure and metabolism of the major dietary carbohydrates.

## Classification of Carbohydrates

Based on their chemical structure, carbohydrates (CHO) are classified according to the degree of polymerization into sugars, oligosaccharides and polysaccharides (Table **1**).

Other nomenclatures refer to metabolic pathways and physiological effects. Carbohydrates that provide the body with monosaccharides for metabolism are defined as glycemic, digestible or available. Metabolizable CHO can be further subdivided according to their capacity to increase blood glucose. This metabolic outcome is dependent on the food matrix and the relative content of complex versus simple sugars, the use of modified or resistant starches, cooking methods and various effects of food processing. Sugars added during the manufacturing processes are classified as added or extrinsic sugars, to distinguish them from those that are naturally present in foodstuffs (intrinsic) and in milk.

However, chemical structure and the above-mentioned characteristics do not wholly explain the nutritional effects of CHO on health. This difficulty together with the lack of consensus on the classification of carbohydrates in different food matrices has compromised the interpretation of results from clinical studies and undermined attempts to establish causal links with metabolic alterations. This lack of solid evidence still hampers the compilation of adequate dietary guidelines. The current trend is to take into account modulation by other nutrients and to view foodstuffs as part of a global nutritional profile with specific functional and health consequences [9].

## The Importance of Carbohydrates and Glucose as Fuel: Implications for Disease Risk

Glucose supplies nearly half of the 150-300 moles of ATP needed daily and, in basal physiological conditions, contributes to 99% of the energy expenditure in the brain. [10]. For these reasons glucose metabolism is exquisitely regulated in the human body and blood glucose levels are maintained within strict limits: lower than 10 mmol/L (180 mg/dL) to avoid the serious toxicity of elevated glucose, as occurs in diabetes mellitus, and higher than 2.2 mmol/L (40 mg/dL), to supply the brain with around the 100-200 gram glucose it needs daily to avoid hypoglycemic complications. This is achieved by a fine balance between on the one hand glucose uptake into the tissues and on the other, entry into the blood stream from either the liver or from the gut (after meals). The liver supplies blood glucose from either its modest stores of glycogen (less than 100 gram) or *via* gluconeogenesis, which can supply up to two-thirds of blood glucose during the post absorptive and fasting states. As regards the supply *via* the gastro-intestinal tract, the major dietary CHO, except for mannose and fructose, are first converted into glucose before further metabolic use (Fig. **1**).

Thus dietary CHO are not in a strict sense essential nutrients. Nevertheless, their intake, by changing blood glucose patterns, affects insulin secretion directly and can thus have an important and immediate impact on diurnal human metabolism. Consequently, glycemic metabolism is especially susceptible to dietary CHO-induced alterations, with potential pathologic consequences that can lead to obesity, diabetes mellitus and cardiovascular disease.

This pathogenic potential periodically attracts renewed interest, which often coincides with the introduction of novel CHO in food. It is also interesting to note that in contrast to substantial differences in the intakes of fats, protein, fibers, vitamin C and sodium, the proportion of energy provided by CHO is only slightly lower (around 35% of the total daily energy intake) in the Paleolithic than the Modern diet (> 40%). The main difference lies in the sources of carbohydrates (fruits and vegetables, with 3% honey in the Paleolithic in contrast to cereal and dairy and 25% energy from added sugars in the Modern diet [11, 12]). Later on in history, the discussions on the role played by CHO compared to fats evolved in parallel to the increase in sugar consumption after its introduction into Europe by Napoleon in 1815 and the subsequent industrial processing of foodstuffs [13]. More recently, the interest has centered on the intensive use of added CHO in foods and sweetened beverages in relation to the current obesity and diabetes epidemic and the emerging evidence on the efficacy of weight-loss diets that are low in CHO [14-16].

In the next two sections, we analyze the following question: "To what extent is obesity and its complications determined by the amount and/or by the type of carbohydrates in the diet?"

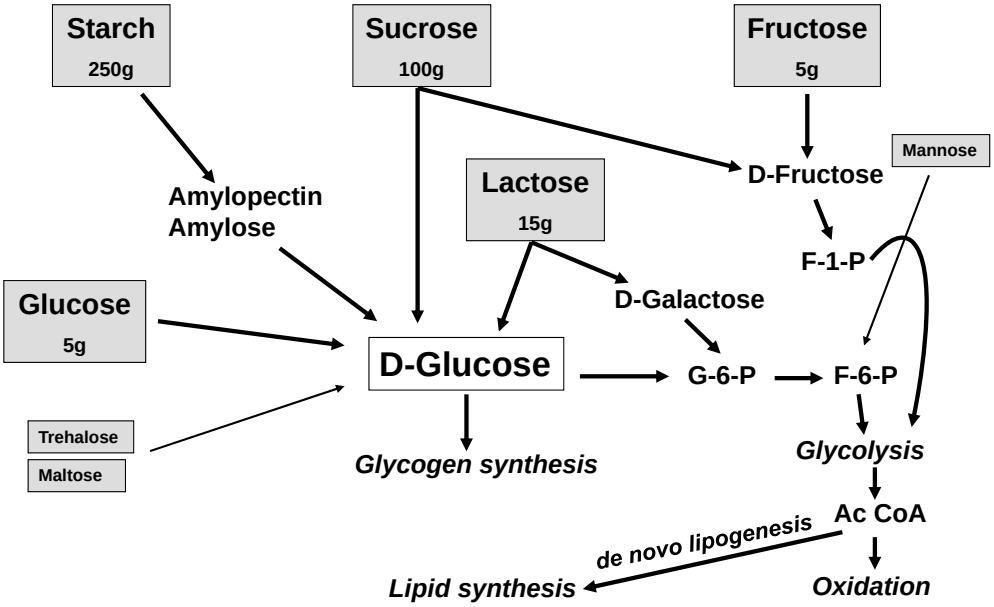


**Fig. (1). Metabolism of Dietary Carbohydrates (CHO).**

Glucose is the key converging molecule and about 300 gram are metabolized each day. In this review we focus on the impact of CHO with different glycemic index and content in sucrose and fructose, on metabolic changes, such as *de novo lipogenesis*, that may result in obesity and its complications. Abbreviations:G-6-P, glucose -6-phosphate; F-1-P fructose-1-phosphate; F-6-P, fructose -6-phosphate; Ac CoA, acetyl coenzyme A.

## QUANTITY OF CARBOHYDRATES IN THE DIET

### *De Novo Lipogenesis* from Carbohydrates?

The first question to ask is if the relative proportion of CHO compared to fat affects accumulation of body lipids. The relevance of this question was highlighted by studies showing that high CHO diets led to increases of serum triacylglycerol in both animals and humans [17, 18]. The "Carbohydrate Induction Theory" postulated that excess dietary CHO (i.e. those not used to generate energy or to replenish glycogen stores) would be converted into lipids via the metabolic pathways of *de novo lipogenesis* that takes place mainly in liver and adipose tissue (Fig. **1**). This, together with a decrease in fat breakdown (lipolysis), would be the direct consequence of the rapid increases of insulin that accompany CHO-rich meals [16]. A few relevant examples of classical studies are summarized here. First, the increase in serum triacylglycerol triggered by a high CHO diet is not permanent as shown by Antonis in a pioneer experiment where a high caloric (3000 Kcal daily), high fat (40% energy) diet was replaced by a high CHO (15% energy from fat) diet with the same total amount of calories. After 5 weeks, serum triacylglycerol had increased, sometimes even doubled. However, in the subsequent 6 months of the same high CHO diet, fasting serum triacylglycerol gradually returned to the initial values. It should be noted that this experiment did not provide any information on diurnal triacylglycerol variations or on changes in body fat [19]. Second, massive CHO feeding (4800 Kcal, 86% energy from CHO) for 7 days first saturated glycogen stores (to a maximum of 15 gram/kg body weight). The extra CHO were oxidized and a limited amount was converted into fats which increased by 150 gram /day [20]. Isotopic studies to trace the incorporation of labeled CHO atoms into VLDL in the liver, demonstrated an increase in VLDL synthesis (from 2 to 10 gram/day) and a mean fat balance of 275 gram after 96 hours of overfeeding (by 50% with CHO). This corresponds to a 2-3-fold increase in *de novo lipogenesis* [21]. More recent studies show that in eucaloric diets with a high proportion of CHO, the increase in serum triacylglycerol is mainly due to its decreased clearance (uptake and oxidation) in peripheral muscle [22]. As regards synthesis, the incorporation of fatty acids arising from *de novo lipogenesis* into VLDL increases in high CHO diets [23]. It is now also recognized that glucose directly regulates the transcription of genes responsible for fatty acid synthesis and oxidation [24]. The net impact of clearance versus synthesis on serum triacylglycerol levels is highly variable and strongly determined by many factors such as duration of the dietary intervention, fed versus fasted, diurnal patterns, type of CHO, as well as baseline conditions such as BMI, insulin levels and sensitivity, triaclyglycerol levels and genetic factors [25].

In conclusion from these studies and based on the metabolic concepts outlined in the last 15 years [4, 5] it can be summarized that the metabolic fate of CHO is determined by both the total caloric content of the diet and the proportion of macronutrients (Fig. **2**: see legends for a more detailed description).

In mixed eucaloric diets (Fig. **2A**) energy is obtained from both CHO and fats. Conversion of CHO to body fat is energetically expensive (12% compared to only 3% in the case of dietary fats) and is limited. In eucaloric diets with high proportions of CHO (Fig. **2B**) both oxidation of glucose and conversion to glycogen are increased and some *de novo lipogenesis* can take place, depending on multiple factors (see above). The inverse situation, a eucaloric diet with a low to very-low content in CHO, usually contains a high proportion of calories from fat since the caloric contribution from protein can seldom rise above 30-35%. After 6 weeks of a very low CHO eucaloric diet (8%energy from CHO

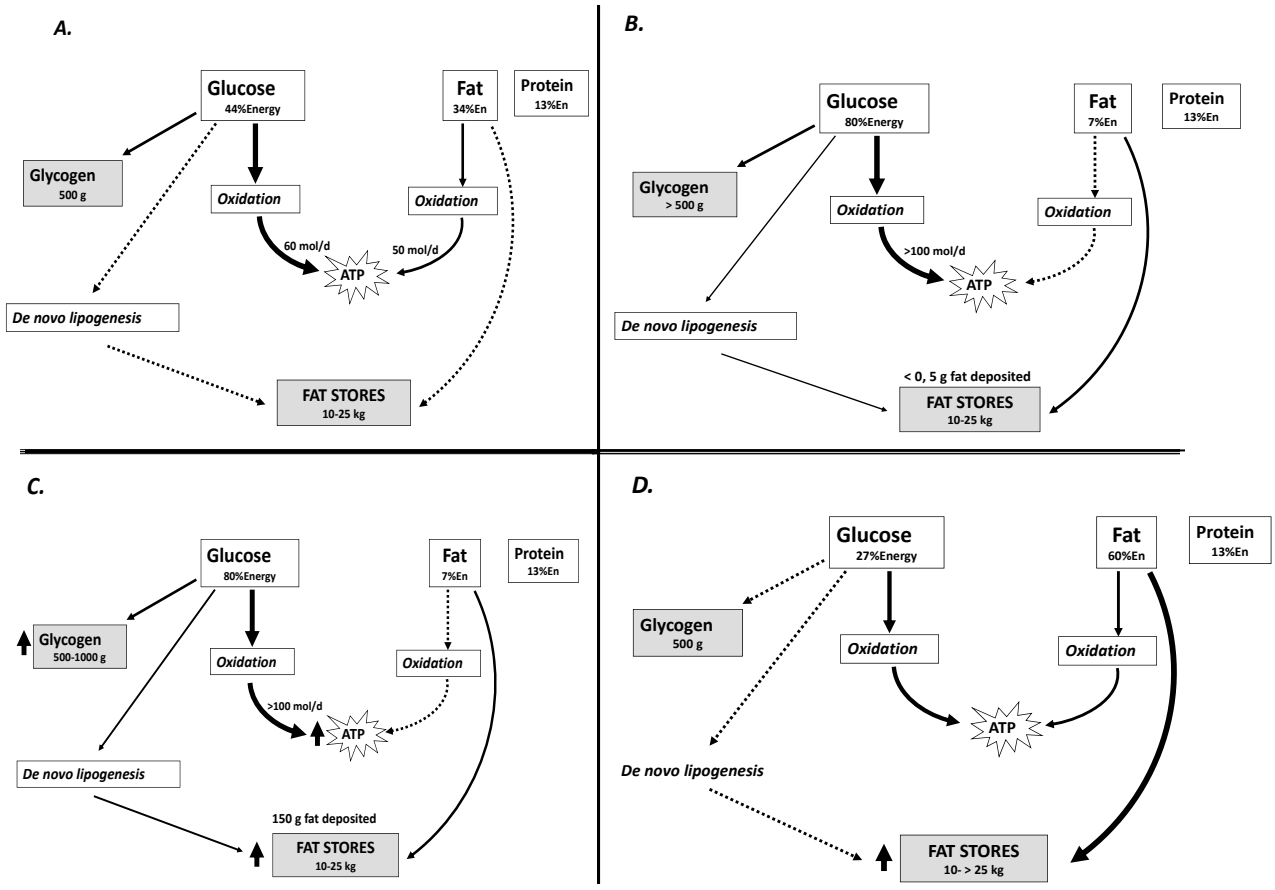


**Fig. (2). Metabolic Fate of Carbohydrates and Fats After Meals.**

***A. Balanced mixed eucaloric diet***. Glucose is preferentially oxidized and produces approximately half of the energy needed. The rest is used for replenishment of glycogen stores. In second place, all the fatty acids from the ingested fat are oxidized to produce the remaining energy needed. Since the ingestion of nutrients is balanced to expenditure, it contains no excess of calories and there is negligible deposition of fat.

***B. Eucaloric diet with a high proportion of carbohydrates.*** Energy expenditure does not change and a higher proportion of the energy is produced by CHO oxidation. The remaining glucose is used to produce glycogen and there is moderate *de novo lipogenesis* but no net deposition of body fats.

***C. Hypercaloric diet with an excess of carbohydrates.*** Energy expenditure and glucose oxidation increase. Excess glucose is used to load glycogen stores to saturation (about 500 gram higher than in normal diets) and the rest converted to fat by *de novo lipogenesis*. Since glucose is preferentially oxidized, less fat will be oxidized, leaving an excess that will be deposited as body fat stores. In this way, dietary fats form the main source of body fat deposition.

***D. Hypercaloric diet with an excess of fat.*** Glucose and fat oxidation rates do not change. The excess in dietary fat is thus wholly converted into body fats.

compared to a habitual 48%) lean men lost an average of 3 kg body fat mass and this loss was mainly determined by the change in insulin levels [26]. The metabolic effects of eucaloric diets differing in the proportion of CHO/fat/protein have often been studied in weight-maintenance or *ad libitum* conditions, often after a hypocaloric weight-loss period. One important conclusion of these studies is that the rate of weight regain was similar but that beneficial changes in insulin sensitivity and serum lipids were determined by the proportion of mono unsaturated fats and protein [27, 28]. The impact of CHO type in weight-maintenanceand other diets is discussed in the following sections.

In hypercaloric diets caused by an excess of CHO (Fig. **2C**), *de novo lipogenesis* will occur after a maximal amount of glucose is oxidized or converted to glycogen. Fat deposition is mainly provided by the relative excess of dietary fats since these are oxidized to a lesser extent. In the hypercaloric diets caused by an excess of fats (Fig. **2D**), fat oxidation rates do not increase immediately and the caloric excess in the form of dietary fat is almost totally converted into body fat, which has an almost limitless storage capacity. Subsequent trafficking of fuels between tissues, for example when the energy balance is negative (between meals), will release fatty acids from adipose tissue and preferentially redistribute this fat fuel to metabolically active tissues such as liver and skeletal muscle for oxidation [29]. Indeed high fat diets have been shown to induce increases in fat oxidation in skeletal muscle during subliminal exercise and consequently, fat loading is a strategy used in endurance training [30]. The situation under pathological conditions such as obesity is discussed in the section "Modifying Factors".

Though this review does not discuss the metabolic consequences of hypocaloric diets with different proportions of CHO, fats and proteins, it should be mentioned here that the

metabolic consequences of changing macronutrient proportion during negative energy balance do not necessarily mirror the four situations of (positive or neutral) energy balance described above. Indeed, hypocaloric diets with very low carbohydrates(12% energy) in obese subjects lead to greater increases in markers of lipolysis (ketones and free fatty acids) together with greater decreases of markers of lipogenesis (incorporation of palmitoic acid in triglycerides) and deposition of body fat (leptin) when compared to low-fat (56%energy as CHO) hypocaloric diets. These effects are accompanied by improvements in insulin sensitivity and a less atherogenic serum lipid profile [16]. However, in this diet the lowering in the proportion energy from carbohydrates is accompanied not only by an increase in energy contribution from fat (from 24 to 59%) but also from protein (from 20 to 28%). It should be noted that low CHO/high protein weight-loss diets, independently of fat, improve body fat mass control [31]. The impact of micronutrient and alcohol content in these diets is also significant and the subject of other reviews.

### Appetite Control and Palatability

In addition to the changes in glucose and fat metabolism outlined above, differences in the proportion of ingested CHO, protein and fat can affect appetite control and thus caloric intake by various pathways. Supplementing a meal with extra calories as CHO suppresses hunger in the first 1 to 3 hours more effectively than when the extra energy is in the form of fat [32]. Several mechanisms have been proposed. In addition to the hormonal responses to stomach filling and to post-meal changes in blood glucose, amino acids and triglycerides, specific glucose sensors in liver and brain are directly involved in the regulation by the hypothalamus of feeding and the sensations of hunger and satiety. Lipid induced dysregulation of glucose sensing would, by disrupting both the secretion of insulin as well as the suppression of glucagon in the fed state, block the signals that are necessary to stop excessive feeding. The ensuing uncontrolled appetite may well be one of the earliest manifestations in the pathogenesis of obesity [33]. It should be stressed that translation of these short-term studies to the free-living habitual situation has so far not been consistent and that it is incorrect to conclude that high carbohydrate diets protect against excessive energy intake in the long-term [34]. Other effects that are inherent to dietary CHO/fat proportion such as bulk, meal matrix and protein and fiber content are primarily determined by the quality of fat or CHO (discussed in the following sections). And finally, the responses of individuals to the pro-obesigenic setting of high food palatability are highly variable.

### Modifying Factors

It should be stressed that the scenarios described above do not apply to pathological situations associated with severe hormonal imbalances such as, for example, acute intravenous glucose re-feeding in malnutrition or in obese patients with different degrees of insulin resistance [4]. For example, trafficking of substrates between tissues differs. In lean subjects preferential delivery of fat to metabolically active tissues such as liver and skeletal muscle favors fat oxidation whereas in obese subjects dietary fat is preferentially delivered to adipose tissue and stored as body fat. Thus sensing of excess energy and coupling to dietary intake are impaired in obesity prone individuals. The failure in liver and muscle to increase fat uptake and oxidation rates in response to increased fat intakes is caused in part by the insulin resistance of the obese phenotype [29, 35].

Moreover, the individual responses to different CHO content of diets are extremely variable. Gene polymorphisms or mutations can affect CHO metabolism in general and/or in response to specific types and quantities of CHO. Recent discovery of linkage between obesity and the PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3) gene and of lower mRNA levels of this enzyme in adipose tissue of obese women, indicates that regulation of glycolysis can play a fundamental role in the susceptibility to the changes in CHO metabolism that promote obesity [36]. The impact of the genotype can also be modulated by the quantity of CHO. For example in women, the Gln27Glu polymorphism of the beta-2 adrenoceptor is associated with a doubled risk of obesity when the diet contains more than 49% energy as CHO [37]. Similarly, the obesity risk associated with the Pro12Ala polymorphism of the PPAR gamma gene differs with the CHO intake [38]. Finally, the rs2297508 polymorphism of the SREBP-1c (sterol regulatory element binding protein-1c) gene modulates the impact of high CHO diets on dyslipidemia and insulin sensitivity [39]. These gene/metabolism relationships are strongly modulated by gender. For example, women differ significantly from men in nutrient handling, fat oxidation/lipolysis rates, lipoprotein turnover and body fat distribution, as reviewed extensively elsewhere [40].

It should be noted that in the above-mentioned studies the increase in dietary CHO was often achieved by adding sugared drinks or not clearly specified CHO, in this way also changing the balance between the different types of CHO in the diet. This distinction was initially not taken into account when analyzing the impact of CHO quantity on body fat deposition but, as seen in the next section, the specific metabolic effects of each type of CHO can have important consequences on the appearance of obesity and its complications [41].

## QUALITY OF CARBOHYDRATES IN THE DIET

Since the functional and metabolic effect of a given CHO cannot be simply extrapolated from its chemical structure, several parameters have been proposed to measure CHO quality based on its effects on glucose absorption and its metabolic use. In this review we concentrate on the capacity to alter blood glucose levels and on the specific effects of added sugars containing sucrose and fructose.

### Glycemic Index and Load

The concept of glycemic index (GI) has been in use for more than 25 years [42, 43] and its validity repeatedly reviewed and questioned [44, 45]. It is defined as the 2-hour incremental area under the glucose response curve after a standard amount (50 g) of available CHO of a test food relative to that of a control food (white bread or glucose). An impressive amount of work has been dedicated to compile tables with the GI of foods, taking into account not only the type of CHO but also the influence of processing, cooking, amount of the servings (glycemic load) and content in fiber and other foodstuffs [46]. The methodology, problems of

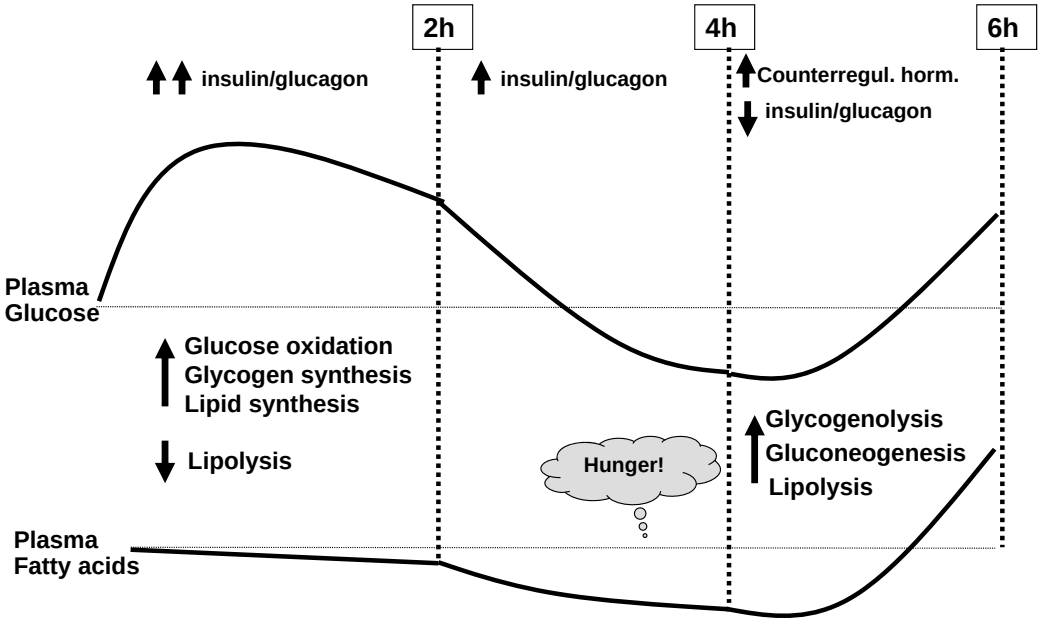


**Fig. (3). Metabolic Events after the Ingestion of a Meal with a High Glycemic Index.**

In the first 2 hours, the excessive and often rapid increase in blood glucose will trigger an abnormal increase of insulin and a decrease of glucagon secretion. The insulin/glucagon imbalance in favor of insulin stimulates the metabolic pathways that utilize glucose (glucose oxidation, glycogen synthesis and lipid synthesis) and inhibits lipolysis. The persistence of this hormonal imbalance causes an excessive decrease of blood glucose and free fatty acids (2-4 hours). This phenomenon of postprandial hypoglycemia is accompanied by a strong sensation of hunger. These alterations also trigger rebound increases of glucagon and other counter regulatory hormones with a reversal of the insulin/glucagon balance and stimulation of glucose-releasing pathways (glycogenolysis and gluconeogenesis) and of lipolysis. As a result, blood glucose and fatty acids again increase abnormally in the late postprandial phase (4- 6 hours). These exaggerated fluctuations thus prolong the duration of hormonal imbalances.

intra- and inter-individual variability, need of standardization and clinical utility in obesity and diabetes have been recently reviewed [47, 48].

In essence, the glycemic index (and its derived parameter the glycemic load) is an attempt to quantify the capacity of a CHO or meal to increase blood glucose. It is widely acknowledged that alterations in the pattern and degree of glucose increase can trigger both acute and chronic metabolic abnormalities that favor obesity and diabetes [44]. The acute changes after a meal with a high GI are outlined in Fig. (**3**).

The abnormally high postprandial blood glucose triggers imbalances between on one hand the insulin and on the other glucagon and eventually also the other counter regulatory hormones. As a result, there are excessive fluctuations and a postprandial fall in the concentration of blood glucose and free fatty acids.This scenario is accompanied by insufficient postprandial satiety and often leads to increased voluntary consumption of high-energy foods. For example, in obese children, increasing the GI of oatmeal without modifying the proportion of macronutrients by using instant instead of steel-cut oats, resulted in a 53% increase in caloric intake [49]. In the long-term, this craving for high-energy foods can become a habit that often results in weight gain. Moreover, the repeated metabolic imbalances lead to a state of hyperinsulinism and insulin resistance with elevated plasma triacylglycerol and deposition of body fat, as well as causing toxic damage in the pancreatic β–and endothelial cells. These chronic changes favor the development of obesity, diabetes and cardiovascular disease, as outlined in Fig. (**4**).

The underlying changes at the sub cellular level are being gradually identified. A recent investigation (FUNGENUT) detected differences in gene expression in subcutaneous fat tissue of patients with metabolic syndrome after 12 weeks of either a low or a high glycemic index diet. Although there were no changes in body weight in either group, in the low GI group 71 genes linked to insulin signaling, such as for example insulin receptor, insulin-like-growth-factor binding protein 5 and hormone sensitive lipase, were down-regulated. In this group there was also an improvement in the insulingenic index (ratio of the increment of insulin /increment of glucose in the first 30 minutes of an oral glucose tolerance test) a measure of early insulin secretion that is altered in the first stages of glucose intolerance [50].

The pathophysiological hypothesis proposing a causal link between a high GI diet and obesity, diabetes and cardiovascular disease has been tested in cross-sectional and longitudinal epidemiological studies. Table **2** shows a summary of prospective cohort studies investigating the risk of developing type 2 diabetes. Except for two studies both conducted on elderly subjects, the multivariate adjusted risk was higher by 21 to 59% when comparing the highest to the lowest quintile of GI.

Meta-analysis of intervention studies examining the impact on markers of metabolic control have confirmed that low-glycemic diets favor a greater weight-loss as well as better lipid and glycemic control [59, 60] and a lower incidence of diabetes [61]. In practical terms, these studies indicate that a two-serving increment in whole-grain consump-

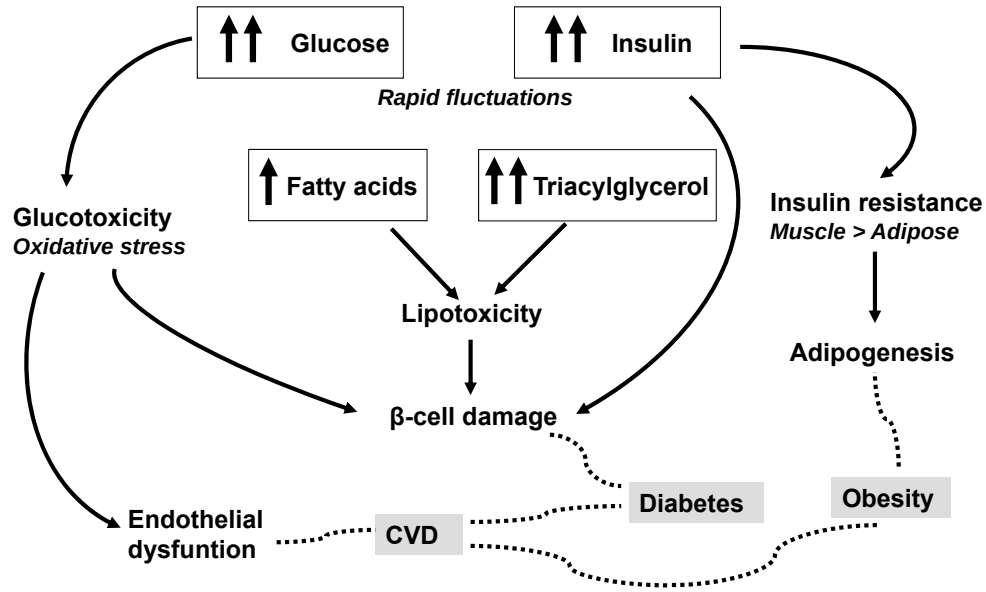


**Fig. (4). Long-Term Metabolic Effects of a Diet with a High Glycemic Index.**

The frequent state of hyperinsulinemia causes a state of insulin resistance that is more pronounced in muscle than in adipose tissue thus favoring a redistribution of metabolites to the adipocyte and deposition of body fat. The rapid fluctuations and increases in glucose and fatty acids are directly toxic to both the β cell in the pancreas and the endothelial cell in the vasculature. These alterations can account for a higher incidence of obesity, diabetes and cardiovascular disease (CVD).

**Table 2. Prospective Cohort Studies on the Relationship Between Dietary Glycemic Index and Incidence of Type 2 Diabetes Mellitus**

| Name of Study | Subjects (age) | Duration (follow-up) | Findings | Reference |
|---|---|---|---|---|
| Nurses Health Study | 65 173 women (40-65 yr) | 6 years | RR of highest/lowest quintile GI = 1.37 [1.09-1.71] Protection by cereal fiber | Salmeron [51] |
| Health Professionals Study | 42 759 men (40-75 yr) | 6 years | RR of highest/lowest quintile GI = 1.37 [1.02-1.83] Protection by cereal fiber | Salmeron [52] |
| Iowa Women's Health | 35 988 women (55-69 yr, postmenopausal) | 6 years | No relation between GI and diabetes risk Protection by whole grains, cereal fiber, magnesium | Meyer [53] |
| Melbourne Collaborative | 36 787 men & women (40-69 yr) | 4 years | OR per 10 GI units = 1.32 [1.05-1.66] Protection by total CHO, sugar, magnesium | Hodge [54] |
| Black Women's Health | 59 000 black women (21-69 yr) | 8 years | IRR of highest/lowest quintile GI = 1.23 [1.05-1.44] Protection by cereal fiber | Krishnan [55] |
| Nurses Health Study II | 91 249 women (24-44 yr) | 8 years | RR of highest/lowest quintile GI = 1.59 [1.21-2.10] Protection by cereal fiber | Schulze [56] |
| Healthy Aging & Body Composition | 1 898 men & women (70-79 yr) | 4 years | 0R of highest/lowest quintile GI = 1.0 [0.5-2.0] | Sahyoun [57] |
| Shanghai Women's Health | 64 227 women (40-70 yr) | 4.6 years | RR of highest/lowest quintile GI = 1.21 [1.03-1.43] Higher risk with rice intake | Villegas [58] |

Some examples of published studies examining the association between a diet with high glycemic index and the incidence of type 2 diabetes mellitus are shown. Results are expressed as multivariable adjusted relative risk (RR), odds ratio (OR), incidence rate ratio (IRR), with 95% confidence intervals between square brackets.

tion is associated with a 21% decrease in the risk of developing type 2 diabetes mellitus [62]. A decrease in glycemic load of 17 gram of glucose equivalents daily is also associated with favorable decreases in fasting triacylglycerol and body weight. It should be noted, however, that the benefit is more pronounced in subjects with impaired baseline metabo-

lism [63] and could not be confirmed in all studies [64]. It is also evident that low GI and glycemic load diets are often achieved by decreasing total CHO intake as evidenced by the positive associations between GI and dietary CHO even after energy adjustment [57]. Thus it was not always possible to differentiate from the beneficial effects of lowering total CHO (see above) and thus increasing the proportion of dietary protein and fat. Moreover, the associated changes in fiber composition, food matrix, fructose content (see below) and in general other nutrient composition have independent metabolic effects that complicate the analysis of those specifically caused by the lowering of GI [45]. In the recently completed European DIOGENES study, where the aforementioned factors were carefully controlled for, the lowering of GI by 4.7 units that was achieved resulted in a significantly lower weight regain [65].

**Sucrose Versus Starch**

In 1972, John Yudkin first published his bestseller "Pure, White and Deadly!" [66]. And the terms "empty calories" (at that time referring mainly to sugar), "added" or "extrinsic" sugars, acquired widespread use in nutritional discussions.

Based on animal studies, Ahrens proposed in 1974 a mechanistic hypothesis to explain the potential pathobiochemical effects of sucrose. The increase in caloric intake and fluid retention would lead to obesity and hypertension as well as to a deterioration of liver function and eventually to the development of a fatty liver. The resulting impairment of mitochondrial respiration and subsequent lowering of the ATP/(ADP+AMP) ratio would lead to an increase in purine conversion to uric acid.The decrease in VLDL clearance by the liver would cause an increase in blood triacylglycerol [17]. These alterations have since been recognized as components of the metabolic syndrome [67].

Subsequent observational epidemiological human studies have, however, been unable to establish a direct association between sugar consumption and obesity. In the MONICA and Scottish Heart Health studies, the median sugar intake was similar across the BMI spectrum of study subjects and there was even an inverse relationship between quintiles of extrinsic sugar consumption and prevalence of obesity [68]. In the Dietary and Nutrition Survey of British Adults the negative relationship between sugar intake and BMI was only found in men but not women [69]. Moreover, cross-country studies have revealed a reciprocal relationship between the intakes of fats and sugars (but not complex carbohydrates) when examining their percent contribution to total energy intake. This observation underscores the natural preference to consume energy-rich foods regardless of their source. In other words, the excess energy is either supplied by sugars when fats are less available or by fats in case of fat oversupply [70].

The available evidence is also insufficient to establish a direct causal link between sugar intake and obesity [71]. Intervention studies, either *ad libitum* or hypocaloric, comparing the impact of substituting sucrose by starch did not detect any significant differences in weight loss [72, 73] despite the fact that starchy diets give better satiety. Prospective and intervention studies also failed to find any association between high sucrose diets and insulin resistance or risk of type 2 diabetes [74, 75]. In non-medicated type 2 diabetic patients on a weight-maintenance diet and receiving the same total amount of CHO in the form of either sucrose or complex CHO for one month, glucose and lipid parameters did not differ, but postprandial insulin was lower in the low sucrose diet [76].

Notwithstanding these observations, there is still not enough evidence to reject the 30-year-old hypotheses of Yudkin and Ahrens on the capacity of added sugars to cause metabolic alterations that may predispose to obesity in case of exposure to a high fat diet. Longer-term and higher-powered studies will be needed in order to reveal the real differences in the obesigenic capacity of "high fat" compared to "high fat sweet foods".

**Sweetened Beverages with High Fructose Corn Syrup and the Diabesity Epidemic**

Two observations re-awakened the debate on CHO quality but shifted the interest from sucrose to other added sweeteners. It was observed that as a result of nutritional campaigns warning about the unhealthy effects of fats, consumption of dietary fat in the USA decreased from >40% in 1965 to ~33% of energy intake in 1995 [77]. Despite this improvement, obesity and type 2 diabetes have continued to increase exponentially during this period. This "diabesity epidemic" has occurred in parallel with the consumption of sweetened soft drinks [78]. A recent meta-analysis has discovered a more than 20% increased risk of metabolic syndrome and type 2 diabetes mellitus in the highest sweetened beverage consumers [79]. Furthermore, dyslipidemia (decrease in HDL cholesterol and increase in triglycerides) is linearly related to the consumption of added sugars [80].

One possible explanation is that CHO in sweet beverages do not induce satiety to the same extent as solid forms of CHO [81]. Interestingly, however, diabesity was not associated with fruit juice consumption [82]. This is in sharp contrast to the strong association with the use of corn syrup as a sweetener, in particular that containing a higher proportion (55%) of free, unbound fructose (high fructose corn syrup, HFCS) [78, 83]. Whereas fructose consumption from natural sources has remained constant or decreased, the proportion of sweeteners consisting of HFCS has doubled in the last 30 years [84].

Apart from differences in the rate of gastro-intestinal absorption, excessive fructose consumption can have several metabolic consequences which are unsurprisingly similar to those proposed so many years ago by Ahrens with regard to sucrose and the metabolic syndrome.

**Metabolic Effects of Fructose: Fructose Index?**

As outlined in Fig. (**5**), fructose metabolism differs from that of glucose in several fundamental aspects. An increase in blood fructose levels does not stimulate insulin secretion and fructose has specific phosphorylating (fructokinase) and aldolase(B)enzymes which allow it to enter the glycolytic pathway by-passing the rate limiting steps of glucose- and fructose-6-phosphate- phosphorylation. Moreover, fructose up-regulates enzymes catalyzing fatty acid synthesis [85]. These peculiarities, together with the increased production of glycerol-3-phosphate, favor conversion of fructose into lipids in the form triacylglycerol in the liver [86].The net increase in serum triacylglycerol is *de facto* higher after acute

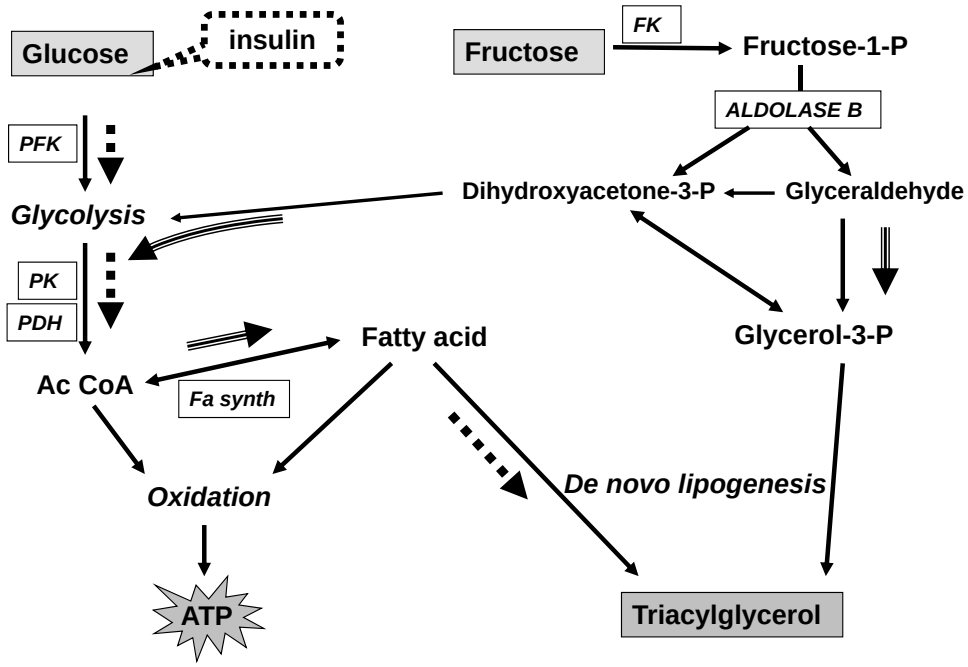


**Fig. (5). Metabolism of Fructose.**

Fructose is specifically metabolized by fructokinase (FK) and aldolase B to form didhydroxyacetone-3-phosphate and glyceraldehyde. These intermediary metabolites either join the glycolytic pathway or are converted to glycerol-3-phosphate. Fructose also specifically activates enzymes that catalyze the synthesis of fatty acids, thus shifting the use of acetyl coenzyme A (Ac CoA) from energy-production to lipid synthesis (empty arrows). When fructose is ingested together with food or drinks containing glucose, insulin secretion will be stimulated and will activate enzymes such as phosphofructokinase (PFK), pyruvate kinase (PK) and pyruvate dehydrogenase (PDH) that enhance glucose utilization and conversion to fatty acids (dotted arrows). Thus, the presence of fructose channels hexose metabolites towards de novo lipogenesis and, as a consequence, increases triglyceride synthesis and body fat deposition.

intake of pure fructose than after equivalent amounts of glucose [87]. Moreover, co-ingestion of glucose together with unbound fructose (as for example in HCFS), will, by triggering a sharp insulin release, promote lipogenesis even further [86].

The increases in serum triacylglycerol can give rise to further alterations in serum lipids. For example, fructose consumption has been shown to predict smaller LDL particle size in normal and overweight children [88]. However, in healthy men exposed for 6 weeks to high dietary fructose, the increase in serum triacylglycerol was not accompanied by any change in the serum concentration of total and HDL cholesterol [89].

Since these events occur mainly in the liver, the increased *de novo lipogenesis* will result not only in higher VLDL production but also in the deposition of excess fat inside the hepatocyte and increased synthesis of lipid-derived signaling molecules such as diacylglycerol. The resulting mitochondrial dysfunction and the stimulation of a novel protein kinase C that disrupts the phosphorylation of insulin response proteins, lie at the basis of the hepatic insulin resistance that is observed after week-long high fructose consumption [90] (Fig. **6**).

In adipose tissue and skeletal muscle, high-fructose affects the gene expression of enzymes that promote lipid synthesis such as stearoyl-CoA desaturase-1 and acetyl-CoA carboxylase-2 as well as those that mark early insulin resistance such as glucose transporter- 4 [91]. This response is tissue and hexose-specific as the magnitude of mRNA change differs in visceral and subcutaneous adipose tissue and in response to isocaloric high-glucose. In these ways, high fructose, compared to glucose, will preferentially promote visceral adiposity and insulin resistance [92].

Other long-term consequences of excessive and unbalanced fructose consumption are alterations in the glucose/insulin fasting and postprandial rhythms that disrupt leptin/ghrelin- dependent hunger signaling in the central nervous system and result in excessive appetite. In combination with fructose-induced lipogenesis, this excessive energy intake will further promote body fat deposition and lead to overweight and obesity [93]. Daily intake of one additional sweet drink for 19 months increased the body mass index by 0.24 $kg/m^2$ in children and adolescents [83].

An additional consequence of fatty liver deposition is increased uric acid production that can, by decreasing nitric oxide bioavailability, inhibit endothelial-dependent vasodilatation and promote hypertension [94, 95]. In summary, these specific pathobiochemical effects of fructose lead to visceral adiposity, impaired glucose tolerance, hyperinsulinemia, hypertriglyceridemia and hypertension, all features of the metabolic syndrome [96].

Other pathogenic properties of fructose are its higher capacity to glycate proteins and thus to form more advanced glycation products both *in vivo* and during cooking and food processing. These and the ensuing glycoxidation products can further worsen the pro-oxidant and inflammatory processes that are especially active in cardiovascular disease and diabetes [97].

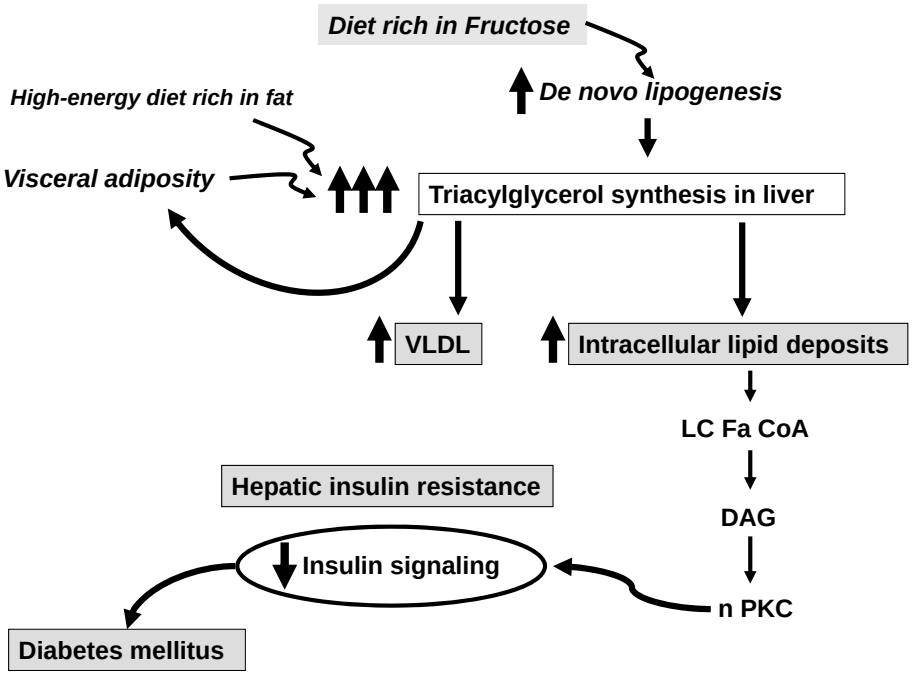


**Fig. (6). Long-Term Metabolic Effects of Fructose.**

Fructose-induced de novo lipogenesis leads to increased triacylglycerol synthesis, with elevated levels of circulating VLDL and deposition of fat in the abdomen (visceral fat) and in the liver cell (fatty liver). These intracellular fat deposits cause dysfunction of mitochondrial respiration and enhanced liberation of long-chain fatty acid metabolites (LC Fa CoA) and diacylglycerol (DAG). These activate novel protein kinases (n PKC) which interfere with insulin signaling in the cell and thus cause hepatic insulin resistance. Persistence of these alterations is conducive to type 2 diabetes mellitus.

Despite this convincing, though as yet incomplete evidence, it is still too early to designate excessive fructose intake as the main culprit of the current obesity epidemic [98]. Human studies have demonstrated changes in serum lipids and insulin sensitivity after short-term (6-day) feeding with fructose but only after consuming amounts (25% of total daily energy) that are much higher than habitual intakes (less than 10% of energy) [99]. Great care should also be taken to identify other risk factors and to evaluate their relative roles within the complex network of metabolic interactions and hunger/satiety signaling. For example, even relatively short (6-7 day) dietary interventions with high fructose reveal gender-related differences, with more marked increases in serum triacylglycerol and hepatic insulin resistance in young males than in females [100], and in offspring from type 2 diabetic patients [101]. Furthermore, in diabetic patients dietary fructose uptake is more rapid due to (fructose-induced) up regulation and higher levels of GLUT 5 in the intestine [102]. In addition, intracellular fructose concentrations can rise substantially by endogenous conversion of glucose into fructose due to the increased flux along the polyol pathway that occurs during hyperglycemia [103, 104]. And finally, the above-mentioned lipogenesis, increased uric acid and advanced glycation products further compromise the already deficient endothelial function in diabetic patients [98, 105].

All these abnormalities seem difficult to reconcile with the fact that fructose itself has a low glycemic index and induces smaller increments in postprandial insulin in both diabetic and non-diabetic subjects [106]. Moreover, it is naturally extracted from fruits and vegetables that are indisputably healthy. Notwithstanding these considerations, it is obvious that processed foods and drinks with added (therefore, more bio-available) fructose differ in both quantity and quality from fruits containing intrinsic sugars. In order to analyze their metabolic impact correctly, more precise and sensitive markers of insulin resistance and dyslipidemia are required [88]. One would also need to report the percent of dietary energy supplied by fructose more accurately (using the recently proposed "fructose index") [107], and to specify the proportion of fructose derived from fruits/vegetables compared to that from sweets and drinks [108].

## DIETARY GUIDELINES FOR TOTAL CARBOHYDRATES, GLYCEMIC INDEX, SUCROSE AND FRUCTOSE: NEED FOR REASSESSMENT?

The 2003 joint WHO/FAO Expert consultation report, that advocated a balanced diet to prevent chronic diseases in general, recommended daily dietary intake ranges of 55-75% of total energy as carbohydrates [109]. The Institute of Medicine (IOM) and the American Diabetes Association (ADA) set these ranges at 45-65% with a minimum of 130 gram daily for adults, including diabetic patients [110, 111]. It should be noted that these recommendations were derived not with the aim of preventing CHO deficiency but rather from the primary decision of setting upper limits of 35% energy for fats, based on the paradigm that high dietary fat predisposes to obesity and its complications. As illustrated in our discussion, these recommendations do not necessarily apply to all individuals and need reassessment.We propose that quantifying % energy from CHO or fat is obsolete and misleading and that the interest should focus on the accurate characterization of the quality of each macronutrient and the means to prevent excessive caloric intake.

As regards the glycemic index or load as a risk factor for obesity there is no consensus or guidelines, although some studies observed beneficial impacts by lowering GI by 4 units or glycemic load by 17 gram [63, 65]. As mentioned in the section on glycemic index, accurate and reproducible quantification is difficult to achieve and strongly confounded by factors such as ripeness, food matrix, processing and inter-individual differences. Notwithstanding these constraints, in both type 1 and type 2 diabetic patients, diets with a low GI effectively result in a significant lowering of glycated hemoglobin thus demonstrating a clinically relevant improvement of glucose homeostasis [112]. Similar, and in some studies even better improvements are obtained after low CHO ketogenic diets [113], suggesting common beneficial effects in diabetes. Future, well-designed trials, testing food products with the same amounts of carbohydrate, fiber, protein and fat but with different GI need to be developed [114, 115].

With respect to "free" or "added" sugars (referring to all mono- and disaccharides naturally present in honey, syrups and fruit juices, plus those added to foods and soft drinks during manufacture and cooking) the upper limits set by the WHO and IOM were < 10% and <25% energy respectively [109, 110]. In 2002, the American Heart Association (AHA) did not find sufficient global evidence to label sugar as detrimental or beneficial. And hence it recommended that "high sugar intakes should be avoided" without specifying amounts [116]. The 2006 AHA Diet and Lifestyle Recommendations mentioned the need to limit beverages with added sugars or caloric sweeteners (namely sucrose, glucose, fructose, maltose, dextrose, corn syrups, concentrated fruit juice and honey) [117]. The most recent AHA recommendations are much more specific, setting as upper limits 100 and 150 kcal of added sugars allowed daily for women and men respectively, stretching this limit up to 300 kcal in the very physically active men. These allowances for added sugars (representing 3 to 9.6% of total energy needs) are notably lower than the above-mentioned (10%) WHO guidelines [118]. Indeed, there is no consensus worldwide, as illustrated by the disparity between the various European countries in terms of recommendations (ranging from 8-15% energy from sugars) and estimated intakes [119, 120].

When deciding on the daily maximum tolerated intakes of fructose it seems reasonable to examine the different target groups separately and to interpret the clinical relevance of the end-point being monitored. For example in healthy young males, intakes of around 50 g/d (about the average intake in the United States) are associated with increased postprandial triacylglycerol and alterations in insulin sensitivity and intakes of > 100g/d with increased fasting triacylglycerol [100]. On the other hand, meta-analyses of intervention studies conclude that intakes up to 90 g/d do not worsen blood glucose regulation and $HbA_{1c}$. It should be noted, however, that these conclusions refer exclusively to studies not involving HFCS [121]. In spite of the lowering effect on blood glucose and $HbA_{1c}$, also demonstrated in diabetic patients [106], the ADA does not promote the use of added fructose as sweetening agent, as opposed to fructose in fruits and vegetables [111]. This decision is based on the differences in intestinal absorption, metabolism and associated cardiovascular risk factors that are present in these patients (see the section on the metabolic effects of fructose).

In view of the evidence on sugars and fructose, an upper limit of 10% energy from "free or added sugars" seems arbitrary since these guidelines fail to distinguish between the various types of sugars, their source and method of food processing, their presence as solid or liquids and the relative composition of free unbound fructose and glucose.

## SUMMARY, CONCLUSIONS AND PERSPECTIVES

In summary, experimental data at the cellular and tissue/organ level demonstrate that surplus calories in the form of various types of CHO cause pathological changes leading to insulin resistance, body fat deposition, dyslipemia and vascular dysfunction, as well as altered appetite control. However, the evidence from dietary intervention studies is still insufficient to establish a causal link, partly due to serious methodological limitations such as the definition and classification of the CHO and the lack of accurate biomarkers of the metabolic outcomes. In order to tackle these methodological difficulties, clear nomenclature and classification guidelines are urgently needed. We need a consensus on the meaning and pathophysiologic relevance of terms such as total, free, extrinsic/intrinsic, added/natural, simple/complex, of high or low glycemic or fructosemic index, cariogenic, milk sugars etc when referring to "sugars". For instance, we need to clearly distinguish between fructose contained in fruits and vegetables and fructose added to beverages or processed foods (currently about two-thirds of total fructose intake) [122]. The next step would be to set up acceptable ranges of intake for each pathophysiologically relevant component, with clear specifications for each group of individuals or disease and distinguishing between short- and long-term effects. And finally, to view dietary intakes in terms of habit and shift the emphasis from discrete nutrients to dietary patterns [123]. These guidelines can then be followed by public health experts, legislators and the food industry in order to ensure correct labeling and information to the consumer.

One possible approach to recognize the important inter-individual variability in the metabolic response to the carbohydrates discussed in this review is to study the genetic susceptibility. Despite impressive advances in the investigation of the genetic background of obesity, the search for screening methods to identify the relevant genetic variants is complicated. This is mainly due to the multifactorial nature of obesity and the involvement of multiple genes scattered all over the genome. Only widespread multinational studies will be capable of unraveling their relevance and the underlying molecular interactions, not only between the genes themselves but with environmental factors such as diet and exercise [124]. Nevertheless, we expect in a foreseeable future, that each individual can adapt the general dietary recommendations according to his/her genetic profile and can thus benefit from personalized changes in the CHO content of their diet [125].

In any case, the guidelines that can be derived from the information summarized in this review are only relevant when considered within the context of the primary goal of achieving and maintaining a healthy body weight by balancing caloric intake and physical activity.

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B.M.K. wrote the paper and has primary responsibility for the final content, L.P.G. provided the project conception and has primary responsibility for the final content. Both authors read and approved the final manuscript.

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