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REVIEWS: CURRENT TOPICS

Digestible and indigestible carbohydrates: interactions with postprandial lipid metabolism

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Abstract

The balance between fats and carbohydrates in the human diet is still a matter of very active debate. Indeed, the processing of ordinary mixed meals involves complex processes within the lumen of the upper digestive tract for digestion, in the small intestine mucosa for absorption and resecretion, and in peripheral tissues and in the circulation for final handling. The purpose of this review is to focus on available knowledge on the interactions of digestible or indigestible carbohydrates with lipid and lipoprotein metabolism in the postprandial state. The observations made in humans after test meals are reported and interpreted in the light of recent findings on the cellular and molecular levels regarding possible interplays between carbohydrates and lipid moieties in some metabolic pathways. Digestible carbohydrates, especially readily digestible starches or fructose, have been shown to exacerbate and/or delay postprandial lipemia, whereas some fiber sources can lower it. While interactions between dietary fibers and the process of lipid digestion and absorption have been studied mainly in the last decades, recent studies have shown that dietary carbohydrate moieties (e.g., glucose) can stimulate the intestinal uptake of cholesterol and lipid resecretion. In addition to the well-known glucose/fructose transporters, a number of transport proteins have recently been involved in intestinal lipid processing, whose implications in such interactions are discussed. The potential importance of postprandial insulinemia in these processes is also evaluated in the light of recent findings. The interactions of carbohydrates and lipid moieties in the postprandial state may result from both acute and chronic effects, both at transcriptional and posttranscriptional levels.

Keywords: Carbohydrate; Fiber; Insulin; Lipids; Lipoproteins; Postprandial state; Intestine

1. Introduction: the importance of postprandial lipemia

Most people in Western countries consume fat-containing meals at regular 4- to 5-h intervals and, frequently, snacks and drinks. Following the consumption of a typical fat-containing meal (30–60 g of fat), circulating triacylglycerols (TGs) show a pronounced increase (i.e., postprandial lipemia) after 1 h and can remain high for 5–8 h [1]. It is therefore likely that the usual state of TG metabolism for most humans is postprandial [2–5].

As illustrated in Fig. 1, the postprandial period is characterized by a physiological transient accumulation of triglyceride-rich lipoprotein (TRL) particles in the circulation, provided both by the liver [in the form of very-low-density lipoproteins (VLDLs) in the fasting state] and by the small intestine (chylomicrons secreted specifically after lipid digestion and absorption). Through this postprandial process, adipose tissue is efficiently filled with lipid moieties, and the resulting accumulated remnant particles in the circulation can be taken up by the arterial wall (atherogenic particles): the remainder is finally cleared from the circulation, mainly by the liver. The capacity of individuals to regulate circulating TG levels

Abbreviations: apo, apolipoprotein; AUC, area under the curve; Cav-1, caveolin-1; CD36, cluster determinant 36; CE, cholesteryl ester; CETP, cholesterol ester transfer protein; ER, endoplasmic reticulum; FA, free fatty acid; FC, free cholesterol; FABPpm, fatty-acid-binding protein plasma membrane; FATP4, fatty acid transport protein 4; GLUT, glucose transporter; HDL, high-density lipoprotein; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; MTP, microsomal triglyceride transfer protein; NPC1L1, Niemann–Pick type C1 like 1 protein; PKC, protein kinase C; SGLT1, sodium glucose transporter 1; SR-BI, scavenger receptor class B type I; TRL, triglyceride-rich lipoprotein; VLDL, very-low-density lipoprotein.

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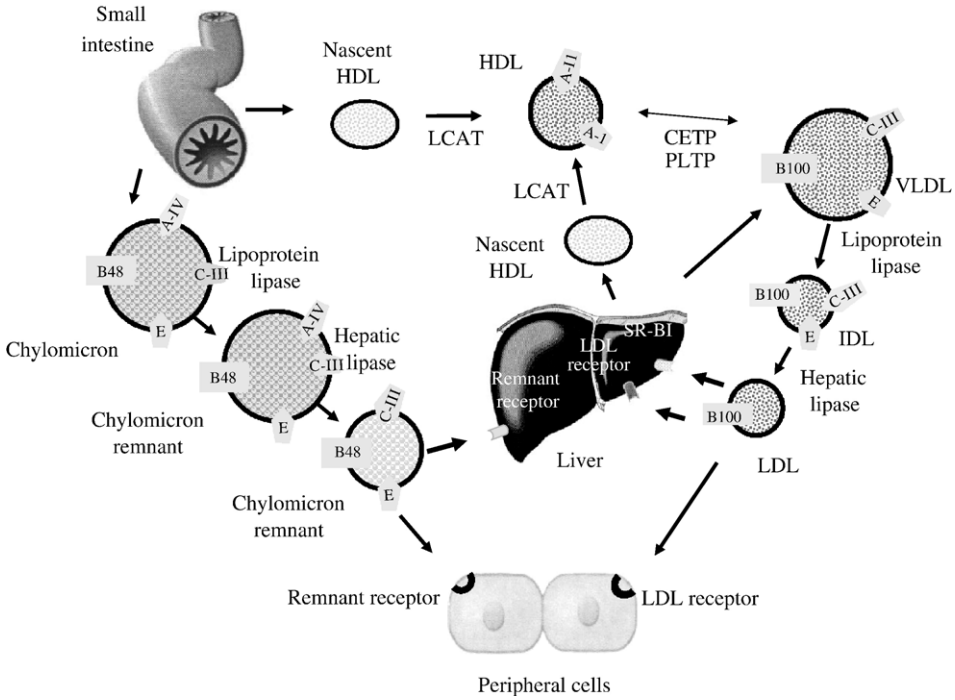

Fig. 1. Lipoprotein-mediated lipid transport in humans. Both TGs and CEs are transported into the core of lipoproteins, while polar lipids and apoproteins at the aqueous interface critically determine interactions with enzymes and cellular receptors that control this complex transport system. Different lipoproteins are represented by gray circles or ellipses. Different arrows indicate different routes that are followed by the lipoproteins. AI, AII, AIV, B48, B100, CII, CIII and E denote apos of the same name. Postprandially, the small intestine delivers chylomicrons that are rapidly transformed into chylomicron remnants by lipoprotein lipase bound to the luminal surface of capillary endothelial cells. Chylomicron remnants are then processed by hepatic lipase (HL) and taken up by liver cells via receptor-mediated endocytosis, equivalent to the mechanism of uptake of LDL. VLDLs secreted by the liver are hydrolysed by LPL, producing smaller particles called intermediate-density lipoproteins (IDLs), which are converted by HL into LDL. The process of HDL maturation begins with the secretion of nascent HDL particles by the liver and the intestine, followed by particles that are more cholesterol-enriched. The lecithin acyl transferase (LCAT) enzyme, which is carried on HDL particles, esterifies FC molecules to form CEs, which migrate to the core of the HDL particle to form mature HDL particles. Cholesterol ester transfer protein (CETP) and phospholipid transfer protein (PLTP) mediate the exchange of CE and PL between TRL and HDL. HDL remnants may bind to putative hepatic receptors that mediate HDL uptake, internalization and degradation. Hepatic SR-BI may also contribute to the modification of circulating HDL particles, promoting their uptake and degradation. Peripheral cells take up LDL and chylomicron remnants by receptor-mediated endocytosis and exit cholesterol through HDL by HDL receptors and scavenger receptors. FABP, fatty acid binding protein; LCFA, long chain fatty acid; MG, monoacylglycerol; TG, triacylglycerol.

and to clear TRLs can be modulated by various gene polymorphisms [6–9]. It is now recognized that high postprandial lipemia is a characteristic metabolic abnormality of a number of lifestyle-related conditions that are associated both with increased morbidity (such as hypertriglyceridemia, metabolic syndrome, obesity and Type 2 diabetes) and mortality, especially from cardiovascular diseases [10–14].

Most daily meals are mixed meals made of various foodstuffs that provide numerous nutrients, including lipids, digestible carbohydrates (starch, sugar, etc.) and indigestible carbohydrates (e.g., mostly fibers). This means that postprandial metabolism resulting from the digestion and absorption of available nutrients is a highly complex process involving numerous potential interactions. This is reinforced by the fact that current diets are especially rich in fats and readily available carbohydrates and are poor in dietary fibers [15], in the context of a sedentary lifestyle [16].

In this review, we will update available knowledge on the interactions between digestible or indigestible carbohydrates and postprandial lipid metabolism in humans. Emphasis will then be placed on mechanisms involved in the alterations observed.

2. Effects of dietary carbohydrates on postprandial lipid metabolism in humans

2.1. Digestible carbohydrates

Clinical studies support the concept that diets rich in highly digestible carbohydrates can lead to high levels of fasting plasma TGs as a result of hepatic VLDL and chylomicron remnant accumulation due to altered lipoprotein secretion and/or clearance, as reviewed [17,18]. Moreover, several studies have shown that the amount or the nature of carbohydrates in an individual meal can alter postprandial lipid metabolism. The addition of glucose (50–100 g) to fatty test meals may or may not increase postprandial lipemia in healthy subjects [19–21], whereas the addition of sucrose [22] or fructose [23,24] markedly increases postprandial triglyceridemia. The addition of 75 g of oligosaccharide mixture to a fatty meal can reduce

(−10%) postprandial triglyceridemia [25]. In healthy subjects, starchy foods (white bread and pasta) do not induce noticeable alterations in the overall postprandial TG response but induce a late accumulation of apolipoprotein (apo) B48-containing chylomicrons [26]. In subjects with insulin resistance, the ingestion of a high-glycemic index mixed meal can, to some extent, raise postprandial hypertriglyceridemia by stimulating the accumulation of apoB100- and apoB48-containing TRLs [27]. Finally, adding various digestible carbohydrates to a test meal can elicit a biphasic response of postprandial lipemia [27,28].

Taken together, these data indicate that readily digestible carbohydrates and, more markedly, fructose have the potential to cause exacerbated postprandial lipemia in response to a fatty meal in humans.

2.2. Dietary fibers

Adding certain dietary fiber sources to mixed test meals [29,30] at the level of 4–10 g/meal can, to some extent, reduce the postprandial triglyceridemia and cholesterolemia generated by a mixed meal. Sources of soluble viscous cholesterol-lowering fibers (i.e., oat bran) or those with hypotriglyceridemic properties (i.e., concentrated wheat fiber or wheat germ) have been shown to display such an effect postprandially. In another study, a high-fiber diet (41 g/day) induced lower plasma glucose and insulin peaks compared with a low-fiber diet (12.4 g/day) at the end of a day-long follow-up, together with a nonsignificant trend to lower diurnal TG levels [31]. A few of the other studies using other sources of dietary fibers (oat fiber, pea fiber, soybean fiber and psyllium) have not shown these alterations of postprandial lipid parameters.

3. Mechanisms involved during processing in the gut

3.1. Gastric emptying

It has been reported that adding a moderate dose of glucose (75 g) to a fatty meal resulted in a 2-h delay in gastric emptying in healthy subjects [21]. The addition of 75 g of digestible oligosaccharides also caused a significant delay in gastric emptying [25]. While the overall effects of various sources of dietary fiber on gastric emptying have been known for a long time [32], a specific effect on dietary lipids has not been reported.

3.2. Lipid digestion

In the gut of humans and monogastric animals, dietary lipids are present in the form of heterogeneous emulsified droplets [33]. TG digestion first occurs in the stomach and is catalyzed by gastric lipase [34], while most fats are further hydrolyzed in the duodenum and jejunum under the action of pancreatic lipase [33]. Lipolytic products that are generated are dispersed in the form of vesicles and mixed micelles [35], which interact with the intestinal mucosa to ensure the uptake of lipid moieties. Several steps in this very complex process can be altered in the presence of digestible or indigestible carbohydrates.

Chronic dietary regimens rich in digestible carbohydrate, unlike fat-rich ones, are known to lower the levels of lipases secreted by the gastric mucosa or the pancreas into the small intestine [36,37]. Conversely, regimens rich in some dietary fiber (wheat bran, pectins and guar gum) have been shown to increase lipase concentration and output into the duodenum, possibly due to a compensatory mechanism to counteract lipase binding [38].

To our knowledge, the ability of digestible carbohydrates to alter some steps in the process of fat digestion has not been thoroughly investigated. In contrast, a number of in vitro studies have shown that dietary fibers can alter the lipolysis process. Two main mechanisms have been recognized. Some soluble fibers forming viscous solutions (range, 0–20 mPa/s) drastically reduce the rate of lipid emulsification, with a resulting noticeable lowering of the extent of fat lipolysis [39,40]. This has been confirmed in laboratory animals with guar gum [41] and in ileostomized subjects with oat bran [30]. Other fibers, such as chitosan, can generate aggregates with lipid globules and consequently lower the extent of lipolysis [42]. Finally, some extractable soluble proteins present in wheat bran and germ can have an inhibitory effect on pancreatic lipase catalytic activity, as shown in vitro [38] and in laboratory animals [43].

3.3. Lipid micellization

It has been shown for a long time in vitro [38,44] and during some animal experiments [45] that various dietary fiber sources can bind bile acids, as well as mixed micelle components such as monoacylglycerols (MGs) and free fatty acids (FAs) or free cholesterol (FC), thus explaining the partial disruption of the micellization process, leading to reduced micellar solubilization of lipid moieties and, finally, to blunted and/or delayed intestinal uptake of lipid moieties and cholesterol [46]. This was confirmed during a study in ileostomized subjects [30] where an oat-bran-enriched meal significantly increased MGs (11.4-fold) and FAs (2.4-fold) present in 24-h ileostomy effluents.

4. Mechanisms involved during intestinal absorption

4.1. Intestinal lipid absorption and intracellular processing

The next step in lipid assimilation is the uptake process occurring at the enterocyte brush border membrane. The intestinal absorption of cholesterol and fatty acids or MGs is a multistep process that is regulated by multiple genes at the enterocyte level, and the mechanisms by which lipid absorption occurs are simple passive diffusion [47,48] and protein-facilitated processes [49–52]: different potential intestinal lipid transporters have recently been identified, as illustrated in Fig. 2. Two of these, belonging to the multiligand scavenger receptor family, regulate the

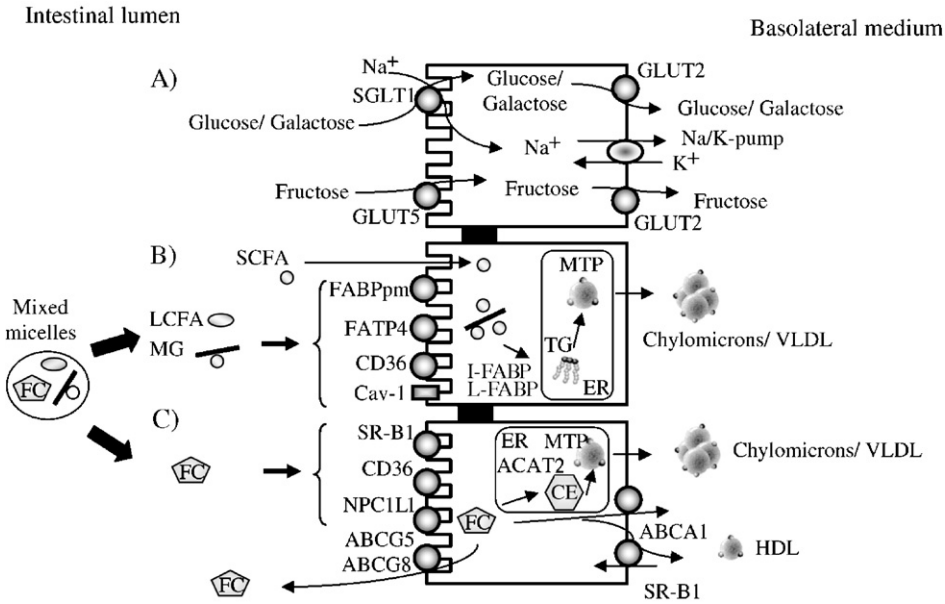

Fig. 2. Mechanisms of the intestinal absorption of sugars and lipid moieties. (A) Glucose and galactose transport across the brush border occurs by a sodium/glucose (galactose) cotransporter (SGLT1), while passive fructose transport is mediated by a uniporter, glucose transporter (GLUT) 5. The exit of all three sugars out of the cell across the basolateral membrane occurs through GLUT2. (B and C) FAs, MGs and FCs are dispersed in the luminal lumen as mixed micelles and are then absorbed through the brush border membrane by enterocytes. (B) Short-chain fatty acids (SCFAs) diffuse passively across the membrane. For LCFA and MG transport, several proteins have been identified and proposed as candidates for transporters. These include FABPpm, FATP4 (a member of a large family of FA transport proteins), CD36 and Cav-1. Within intestinal cells, FAs are bound to the liver FABP (LFABP) and the intestinal FABP (IFABP) and used for the de novo synthesis of TGs and phospholipids. The MTP facilitates the transfer of FAs translocated in the ER lumen into the intestinal chylomicrons (and VLDL). (C) FC absorption is mediated by the facilitated transporters SR-BI, CD36 and NPC1L1. Within intestinal cells, the absorbed FC is esterified, forming CEs, which are catalyzed by the acyl CoA cholesterol acyl transferase 2. MTP facilitates the transfer of CE to intestinal chylomicrons and VLDL, secreted into the basolateral medium space. ABC transporters are involved in cholesterol efflux (ABCG5/ABCG8 transport cholesterol from the cell into the intestinal lumen, and ABCA1 transports cholesterol from the cell to the bloodstream).

absorption of various substrates. Scavenger receptor class B type I (SR-BI) facilitates the intestinal uptake of cholesterol, TGs and other lipid nutrients [53–57], while cluster determinant 36 (CD36)/FAT interacts with MGs or FAs and participates in cholesterol absorption [57–59] with the involvement of caveolin-1 (Cav-1), which mediates vesicular uptake [60].

In addition to these scavenger receptors, more specific intestinal membrane lipid transporters have been identified. It has been suggested that FAs are carried into enterocytes by a fatty-acid-binding protein (FABP) bound to the fatty-acid-binding protein plasma membrane (FABPpm) and by a fatty acid transport protein 4 (FATP4) [60]. The Niemann–Pick type C1 like 1 protein (NPC1L1) transporter has been identified as being critical for the absorption of both cholesterol and plant sterols [61–64], while members of the ATP-binding cassette (ABC) family (ABCG5, ABCG8 and ABCA1) are involved in efflux processes. ABCG5 and ABCG8 represent apical sterol export pumps that promote the active efflux of cholesterol and plant sterols from enterocytes back into the intestinal lumen for excretion [65,66], thus limiting the intestinal absorption of neutral sterols. ABCA1 located in the basolateral membrane of enterocytes is involved in the efflux process of cholesterol towards circulating high-density lipoproteins (HDLs) [67–69].

Once uptake has been achieved, lipid moieties have to be channeled through enterocytes before secretion into the basolateral space. While the processes of intracellular cholesterol transport are largely unknown, fatty acid trafficking has been more extensively studied. Members of the FABP family characterized in enterocytes ensure this function: intestinal FABP is thought to be involved in the intracellular transport of FAs [70,71], while liver FABP more specifically binds long-chain fatty acids (LCFAs) and lysophosphatidylcholines [72,73]. The last intracellular step for FAs and cholesterol is resynthesis into TGs and cholesterol esters (CEs), before assembly and secretion into intestinal triglyceride-rich apoB48-containing lipoproteins. This step is critical for the transport of lipid moieties and requires the microsomal triglyceride transfer protein (MTP) [74,75]. In addition to chylomicron assembly, enterocytes have been shown to transport dietary cholesterol via an apoB-independent pathway [76–78], with the involvement of ABCA1 [69,79].

4.2. Glucose regulates intestinal lipid absorption

Studies undertaken to characterize intestinal lipid absorption are most generally performed through in vitro experiments, where lipids are dispersed in micelles or vesicular structures without consideration for any other nutrients. However, in vitro and in vivo studies have

revealed relationships between glucose levels and lipid uptake. High extracellular glucose concentration significantly increased brush border membrane fluidity and permeability at tight junctions in human intestinal Caco-2 cells [80] and isolated loops of the small intestine [81]. Thus, glucose affects the transepithelial transport of nutrients permeating the cell barrier by paracellular transcellular passive diffusion and facilitated transport [80,82]. It is likely that there is an indirect regulation of intestinal lipid uptake by dietary glucose. This hypothesis has recently been confirmed by several in vivo and in vitro studies. An inverse relationship between glycemic load and HDL cholesterol has been described [83–85]. It has been observed that women who consumed more cholesterol with a low carbohydrate intake had lower concentrations of low-density lipoprotein (LDL) cholesterol than women with a high carbohydrate intake [86]. In vitro, a short-term incubation (3 h) of intestinal Caco-2 TC7 cells with glucose on the apical side induced a significant increase of cholesterol uptake in a dose-dependent manner [87]. The mechanism involved in this glucose-induced regulation of uptake process is not yet fully identified. An alteration of the physical properties of the enterocyte brush border, which in turn regulates the activity of membrane transporters, is probable, but other regulation pathways should also be considered.

Dietary glucose transport initially occurs through sodium glucose transporter 1 (SGLT1) (Fig. 2A), which modulates a protein kinase C (PKC) signaling pathway distinct from the insulin signaling pathway [88–90]. Cell exposure to high glucose leads to the down-regulation of both PKC mRNA [91] and protein activities [92]. Moreover, a PKC pathway affects the different mechanisms of cell lipid metabolism. It regulates both intestinal cholesterol absorption [87] and possibly FA uptake (unpublished observations) and cholesterol uptake from HDL [93]; it also decreases lipid accumulation in human macrophages [94] and is implicated in the expression levels of lipid transporters such as SR-BI [95], ABCA1 [96] and MTP [97]. Thus, a PKC pathway regulates both cholesterol and glucose uptakes and may be a link between the two metabolic processes.

Mechanisms by which the PKC pathway regulates cholesterol uptake remains to be identified. However, there may be two different modes of regulation of the activity of intestinal cholesterol transporter(s). First, a direct interaction with membrane transporter(s) by (de)phosphorylation at its intracellular domain, inducing regulation of protein activity, can be hypothesized. Indeed, intracellular domains of some enterocyte lipid transporters contain conserved potential phosphorylation sites for PKC [98–100]. Secondly, glucose-induced regulation of the lipid transporter expression level at the intestinal brush border is also possible. After a long-term exposure to high glucose concentrations, mRNA levels for ABCA1, SR-BI [101] and CD36/FAT [102] increased. Interestingly, ABCA1 expression was inversely correlated with fasting glucose concentration in normoglycemic men [68]. It is noteworthy that some gene polymorphisms have been associated with different variables of glucose and cholesterol metabolism [103]. The regulation of lipid transporter expression may be due to gene promoter activity being enhanced by high glucose at the transcriptional level [101]. These data are of concern and suggest that dietary patterns resulting in an increase in dietary glucose uptake may have an unfavorable influence on blood lipids.

4.3. Interaction of insulin with cholesterol absorption

After short-term incubation, insulin at postprandial levels was inefficient in regulating lipid absorption in intestinal Caco-2 cells (B. Play et al., unpublished data), indicating that dietary glucose is able to stimulate cholesterol absorption by an insulin-independent mechanism. On the other hand, after long-term cell incubation with high insulin levels or in diabetics, intestinal cholesterol absorption is altered. Cholesterol absorption efficiency is low in Type 2 diabetes [104,105] and high in Type 1 diabetes [106,107], suggesting an insulin-regulated pathway with a possible involvement of ABCG5 and ABCG8 transporters. Indeed, the expression of *abcg5* and *abcg8* genes is down-regulated in Type 1 diabetes [106,107] and in streptozotocin-induced diabetic rats [108]: in the latter case, insulin supplementation partially normalizes the cholesterol absorption level [108]. Thus, a high insulin level is potentially able to induce a high expression of enterocyte ABCG5 and ABCG8, which in turn increases intracellular cholesterol efflux into the intestinal lumen. As a result, intestinal cholesterol absorption decreases and elimination increases.

While ABCG5 and ABCG8 are potential targets for the insulin-regulated absorption process, other lipid transporters are of potential interest, too. However, there is limited information as to whether the expression of these proteins is altered in intestinal tissues. It is noteworthy that FAT/CD36 too is up-regulated at the transcriptional level in obesity and Type 2 diabetes [102,109], and that gene variations modulate glucose homeostasis and contribute to the metabolic syndrome associated with Type 2 diabetes [110]. The hormonal induction of SR-BI has already been established, with protein expression increasing in streptozotocin-induced diabetic rats [111] and decreasing after in vivo insulin treatment [112]. Obviously, insulin is involved in a long-term regulation process that takes place in enterocytes and modulates nutrient absorption. Its mode of action has not yet been fully characterized, but insulin may either act directly on gene promoters or act indirectly by modulating the activity of transcription factors regulating the expression of some lipid transporter genes.

In conclusion, the regulation by glucose of mechanisms involved in intestinal absorption occurs over two distinct time scales: one over minutes and hours (dietary sugars and readily available carbohydrates) and the other over days (glycemia and insulinemia). It appears that dietary glucose may regulate cholesterol absorption by a short-term mechanism that probably involves a PKC pathway. In

contrast, glycemia may regulate cholesterol absorption by a long-term mechanism involving insulin action.

4.4. Overall effect of digestible carbohydrate on intestinal lipid absorption and resecretion

If absorbable monosaccharides stimulate intestinal absorption and/or resecretion of dietary lipids by the small intestine, this should result in an increased output of chylomicrons into the circulation. Indeed, several studies have reported such observations in humans. A recent study in healthy humans provided the very interesting observation that, compared to water, the ingestion of glucose (38 g) 5 h after a fat meal led to less lipid staining in the jejunal mucosa and submucosa and increased postprandial rises in chylomicron TGs and apoB48 [113]. The authors concluded that, after a fat load, fats are partly retained within the jejunal tissues and are released further into the plasma following glucose ingestion.

Adding a moderate dose of glucose (75 g) to a fatty meal in healthy subjects resulted in a noticeable delay in the occurrence of the chylomicron peak in line with a 2-h delay of gastric emptying [21]. Moreover, the addition of an oligosaccharide mixture (75 g) to a fatty meal resulted in a 2-h delay and in reduction (−11%) in postprandial chylomicron response in healthy subjects [25]. Conversely, the addition of fructose (50 g) to a fatty meal (5 or 40 g) resulted in markedly higher postprandial concentrations of TGs in chylomicron fractions, as well as of retinyl palmitate, a marker of chylomicron remnants [23,24]. In the hamster model, it has clearly been shown that fructose enhances the secretion of apoB-containing intestinal lipoproteins during fat feeding [114].

Finally, it has been reported very recently that intestinal Caco-2 cells adapted for 2 weeks to a low glucose concentration (0 and 5 mM glucose in apical and basal compartments, respectively) secrete more TRL (2.1-fold) than cells cultured at a high glucose concentration (25 and 25 mM glucose in apical and basal compartments, respectively) by an increase in the TGs available for lipoprotein assembly in the endoplasmic reticulum (ER) lumen [115].

4.5. Dietary fiber and intestinal lipid absorption and resecretion

Overall, it has been recognized for a long time that a meal or a diet enriched in certain dietary fibers (oat bran, barley fiber, pectins, gums and wheat germ) can significantly increase fecal fat excretion (generally by twofold to fourfold) in humans or experimental animals [30,116].

As shown in vitro and with animal models, increasing the viscosity of the intestinal content to a sufficient extent alters organ motility, potentially decreases intraluminal mixing and increases the thickness of the unstirred water layer at the intestinal mucosa. These combined effects likely explain the observed reduced rates of the intestinal uptake of cholesterol and fatty acids (as well as glucose) in the presence of viscous fibers [46].

To our knowledge, it has not yet been reported that dietary fiber can alter intracellular processes involved in lipid trafficking within enterocytes.

Evidence that intestinal lipid (oleic acid and cholesterol) resecretion can be impaired in the presence of some fibers has been provided by animal studies with lymph cannulation [117], but variable effects have been observed after chronic or acute supplies of fiber sources.

Although this phenomenon is not quantitatively very great, the observations made highlight the interference that some dietary fibers can exert on physicochemical conditions within the intestinal lumen, leading to delayed and/or reduced intestinal uptake and resecretion into the bloodstream.

Indeed, our laboratory has undertaken several studies addressing the question of whether sources of dietary fiber can alter postprandially the chylomicron output from the small intestine into the circulation of healthy subjects. In one study [29], adding 10 g of dietary fiber into a test meal in the form of concentrated wheat fiber significantly reduced (−21%) the chylomicron TG area under the curve (AUC) postprandially and, this source, together with others (wheat germ and oat bran), significantly reduced (−29% to 55%) the chylomicron cholesterol AUC. This was not observed with pea or soybean fibers. In another study [30], adding 10 g of oat bran into a test meal led to a 37%, 43% and 31% lowering of postprandial chylomicron TG, cholesterol or phospholipid responses, respectively. While a few of the other studies performed have not shown such effects with other fiber sources, our data support the concept that some fiber sources can, by altering lipid processing in the gut and probably resecretion, lower the accumulation of intestinally derived chylomicrons in the circulation postprandially. Depending on the study, reduced postprandial glycemia and/or insulinemia was or was not observed concomitantly with changes in postprandial lipemia. This suggests that changes in postprandial fluxes of glucose may alter, directly or indirectly through insulin response, chylomicron secretion from the small intestine, as discussed above.

5. Mechanisms involved in the postabsorptive state

In addition to the mechanisms discussed above, one remaining key question regarding the interaction of carbohydrate with postprandial lipid response relates to the respective role of a direct effect of elevated glycemia or an indirect effect through induced hyperinsulinemia or both on peripheral tissues. While available knowledge is insufficient to allow for a definitive evaluation, we will briefly discuss these aspects, which are illustrated in Fig. 3.

5.1. Effect of postprandial glucose and fructose

It has been known for a long time that lipogenesis can take place in the liver, generating fatty acids from glucose and thus stimulating the synthesis of hepatic TGs, as well as VLDL assembly and secretion. Nevertheless, except under extreme nonphysiological conditions (i.e., chronic

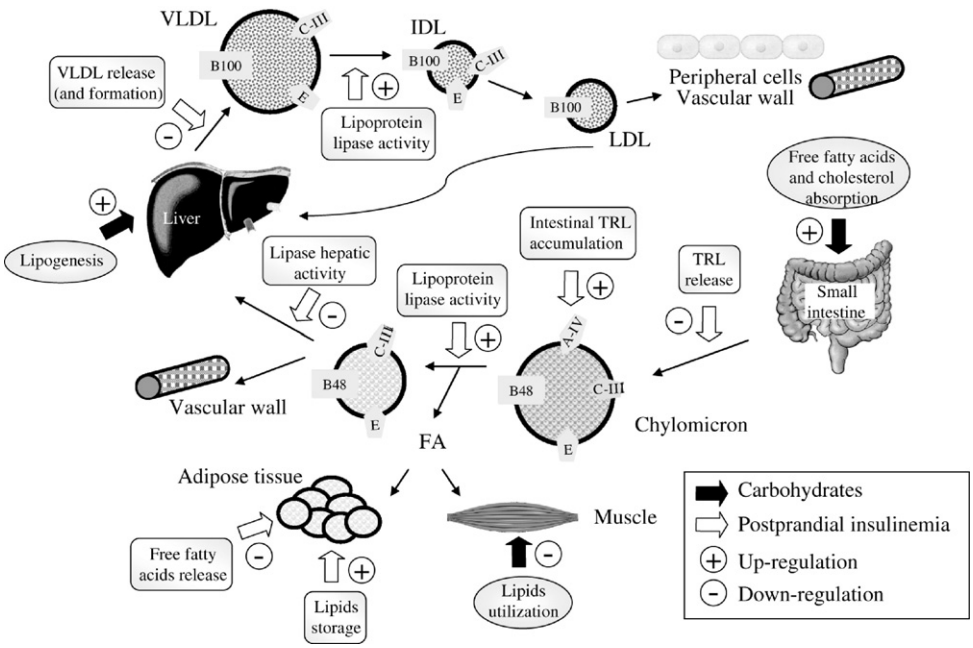

Fig. 3. The interactions of carbohydrates and insulin with the postprandial metabolism of lipoproteins. Different lipoproteins are represented by gray circles. Different arrows indicate the different actions of carbohydrates (black arrows) and insulin (white arrows). AIV, B48, B100, CII, CIII and E denote apos of the same name.

70% carbohydrate diet), lipogenesis only marginally accounts for the de novo synthesis of TGs in humans [118]. It is thus unlikely that glucose plays a key role through this mechanism. Conversely, fructose is a preferred substrate for lipogenesis, and this process is thus expected to play an important role in the fasting TG-raising property of fructose-rich diets in both human and animal models. Clearly, fructose enhances VLDL accumulation and secretion by the liver [114]. Nevertheless, it is not known whether this process can explain the marked postprandial elevation of either VLDL in some studies and/or chylomicrons in others. The fact that fructose or starchy foods generating glucose can both specifically enhance postprandial chylomicron accumulation suggests that other organs (such as the small intestine) are involved, in line with mechanistic observations as reported. The possibility that fructose acutely alters liver capacity to clear chylomicrons remnants, leading to exacerbated accumulation in the circulation, cannot be excluded.

5.2. Effect of postprandial insulin

After the ingestion of a mixed meal containing digestible carbohydrate-generating glucose, the resulting transient postprandial hyperglycemia is accompanied by dose–response hyperinsulinemia. In contrast, fructose only displays a light hyperinsulinic effect (about 20% that of glucose). It is well known that insulin level is an important modulator of several key aspects of lipid homeostasis, especially de novo fatty acid and cholesterol synthesis, hepatic VLDL production and secretion, or lipoprotein lipase expression and activity [119]. Because fructose stimulates postprandial lipemia more markedly than glucose, it is unlikely that the direct effect of insulin is crucial in healthy subjects. In addition, correlations between hyperinsulinemia and hypertriglyceridemia during the cited postprandial studies have not systematically been found. Nevertheless, clamp studies in humans have clearly shown that hyperinsulinemia leads to lower hepatic VLDL concentrations.

Moreover, postprandial hyperinsulinemia (modulated using different mixed test meals generating more or less glucose) has been shown to cause a late postprandial accumulation of intestinally derived apoB48-containing chylomicrons in healthy humans [26]. This phenomenon has also been observed, even more intensely, when a glycemic meal is replaced by a 3-h euglycemic–hyperinsulinic clamp superimposed on a no-carbohydrate meal [26]. Thus, it has been concluded that hyperinsulinism per se is a key determinant of an abnormal pattern based on a late accumulation of intestinally derived chylomicrons and remnants with no alteration in the number of hepatic VLDL (as apoB100). Considering the kinetics obtained, it has also been suggested that hyperinsulinemia may transiently block the secretion of apoB48 particles, leading further to exacerbated release in the late postprandial period. As mentioned above, from our studies using the human intestinal Caco-2 cell line (unpublished observations), hyperinsulinemia does not seem to noticeably alter the level of intestinal lipid uptake and basal lipid secretion.

It is noteworthy that, in subjects with insulin resistance, exacerbated postprandial lipid responses are induced by the addition of carbohydrates. Moreover, ingestion of a high-glycemic index mixed meal, as compared to a low-glycemic index meal, increases the postprandial rise in

glycemia and insulinemia and the accumulation of both apoB100- and apoB48-containing TRLs in these subjects, thus increasing postprandial triglyceridemia and modifying the kinetics of peak occurrence [27]. This suggests that, in the presence of insulin resistance, both hepatic and intestinal TRL patterns are affected by the postprandial hyperinsulinic state.

To summarize, depending on the specific study, concomitant changes in postprandial lipid parameters and insulinemia have been reported or not. This indicates that a direct relationship between postprandial insulin levels and lipoprotein particle accumulation is a complex process requiring further investigation.

6. Conclusion

Based on the worldwide phenomenon of ongoing changes in dietary patterns and reduced physical activity, a key unsolved unanswered question in nutrition science is the respective role of dietary fats and digestible/indigestible carbohydrates in health and emerging diseases. High dietary fat intake, exacerbating postprandial lipemia and altering the overall lipoprotein pattern, has been established and acknowledged as a cardiovascular risk factor. Conversely, digestible and indigestible carbohydrates have been recommended, while a high intake of sugars is generally thought to be detrimental. Nevertheless, setting sound and more conclusive dietary recommendations requires a detailed understanding of how dietary carbohydrates and fats interact and modulate key metabolic pathways in the postprandial state.

In this review, we focus on available knowledge on the interactions of digestible or indigestible carbohydrates with lipid and lipoprotein metabolism in the postprandial state. We report that digestible carbohydrates, especially readily digestible starches or fructose, tend to exacerbate and/or delay postprandial lipemia, whereas some fiber sources can display lowering effects. While interactions between dietary fibers and the process of lipid digestion and absorption have been investigated during the last decades, recent studies have shown that dietary carbohydrate moieties (e.g., glucose) can stimulate both the intestinal uptake of cholesterol and lipid resecretion. It appears that the interactions of carbohydrates and lipid moieties in the postprandial state may result from both acute (dietary sugars and readily available carbohydrates) and chronic effects (hyperglycemia and hyperinsulinemia syndromes) at the transcriptional and posttranscriptional levels. Dietary glucose can regulate cholesterol absorption by a short-term mechanism that probably involves a PKC pathway. In contrast, glycemia may regulate cholesterol absorption by a long-term mechanism involving insulin action. Our scientific knowledge in this area is still limited, and more extensive research, as well as further metabolic consequences, is required to better understand the mechanisms occurring during meal processing.

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