Chapter 8
Role of the Matrix on the Digestibility of Dairy Fat and Health Consequences

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Abbreviations

AUC	Area under curve
Ca	Calcium
CCK	Cholecystokinin
CLA	Conjugated linoleic acid
CM	Casein micelles
CN	Casein
CRP	C-reactive protein
CVD	Cardiovascular disease
FA	Fatty acids
FG	Fat globule
GGT	Gamma glutamyl transferase
HDL	High density lipoprotein
IL	Interleukin
LAB	Lactic acid bacteria
LCFA	Long chain fatty acids
LDL	Low density lipoprotein
LPS	Lipopolysaccharides
MCFA	Medium chain fatty acids
MCP	Monocyte chemoattractant protein
MF	Milk fat

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MFGM	Milk fat globule membrane
ML	Milk lipids
NA	Not available
NEFA	Non-esterified fatty acids
PC	Phosphatidylcholine
PE	Phosphatidylethanolamine
PI	Phosphatidylinositol
PL	Phospholipid
PS	Phosphatidylserine
RTC	Randomized control trial
SCFA	Short chain fatty acids
FA	Saturated fatty acids
SM	Sphingomyelin
T2D	Type 2 diabetes
TCA	Trichloroacetic acid
TAG	Triacylglycerol
TNF-α	Tumor necrosis factor-α
VLDL	Very low-density lipoprotein
WAT	White adipose tissue
WP	Whey proteins

1 Introduction

Dairy products are basic products largely consumed in the population, from human milk which is the perfect meal for the newborn to a large variety of dairy products from cow and other mammalians. Dairy products consumption has been recommended for its richness in valuable nutrients, but some research some 30 years ago raised concern on dairy lipid possible health impacts. Since then, the scientific community has tried to decipher the intricate parameters of lipid metabolism in response to lipids varying in composition, structure, food source, in a meal, in a diet, etc. In this chapter, the knowledge coming from epidemiologic studies will be first reviewed to reveal the possible factors that should be studied to understand the lipid travel in the food and in the human body after consumption in order to try to understand their physiological role and health impact.

1.1 An Epidemiologic Perspective

After a few decades incriminating dairy products by considering them as a source of saturated fatty acids (SFA) there are new insights on the benefits of dairy products (de Oliveira Otto et al., 2012). Recent detailed reviews and perspectives state

numerous meta-analyses and epidemiological studies about the health impact of different types of dairy products (Drouin-Chartier, Brassard, et al., 2016; Drouin-Chartier, Cote, et al., 2016; Lovegrove & Givens, 2016; Thorning et al., 2016). We will, therefore, summarize endpoints of interest regarding milk fat impact, namely type 2 diabetes (T2D), cardiovascular disease (CVD) risk and hypertension.

A meta-analysis of 22 cohort studies including about 580,000 people describes an inverse correlation between all kinds of dairy products and T2D (Gijsbers et al., 2016). A sub-analysis according to the dairy matrix reveals a similar effect for yogurt only, although the relationship was not linear anymore for the highest yogurt intakes. Notably, no association was found between skimmed fermented products and T2D risk, while a 12% decrease of the risk was observed for a consumption of 40 g of fermented products per day including both skimmed and full-fat products. In this study, skimmed-, half- skimmed- and full-fat milk, cheese, cream and full-fat dairy were not associated with T2D risk.

Regarding CVD risk, several recent meta-analyses conclude that there is either no association or an inverse correlation, between dairy products consumption and CVD risk (Alexander et al., 2016; Chen, Wang, et al., 2016; de Goede, Geleijnse, Ding, & Soedamah-Muthu, 2015; Qin et al., 2015). Looking closer at the type of dairy matrix, cheese consumption was often found inversely correlated with the risk of CVD and stroke. This apparent matrix effect is all the more interesting than cheeses are described as high contributors to salt intake, otherwise known to increase CVD risk. Two cohort studies using a different method show that the plasma concentrations of circulating biomarkers of dairy fat consumption, notably 15 and 17 carbon-chain fatty acids (FA), are not associated with the risk of stroke (Yakoob et al., 2014). Moreover, a recent meta-analysis suggests that the consumption of butter would not be associated with CVD and stroke risks (Pimpin, Wu, Haskelberg, Del Gobbo, & Mozaffarian, 2016). An analysis of three large cohort studies shows that milk fat is not associated with CVD and stroke risks compared to an equivalent carbohydrate intake (Chen, Li, et al., 2016). The authors highlight the need to elucidate whether different dairy products would exert different effects. Finally, nutritional intervention studies test the change in lipid markers of CVD risk. A decrease in low density lipoprotein (LDL)-cholesterol and an increase of high density lipoprotein (HDL)-cholesterol was observed in T2D volunteers after consumption of probiotic yogurts for 8 weeks (Mohamadshahi et al., 2014). Another study shows decreased total cholesterol after 6 weeks of consumption of a probiotic yogurt enriched in *Lactobacillus acidophilus* and *Bifidobacterium lactis* compared to a regular yogurt (Ataie-Jafari, Larijani, Alavi Majd, & Tahbaz, 2009). A meta-analysis confirmed the favorable effects of probiotics (Sun & Buys, 2015) and a review highlights the possible beneficial effects of yogurt consumption on metabolic inflammation and lipid markers of CVD risk in obesity (Pei, Martin, DiMarco, & Bolling, 2017).

The most recent meta-analysis about hypertension shows an inverse linear correlation between hypertension and total dairy products intake, skimmed dairy products intake, and milk (Soedamah-Muthu, Verberne, Ding, Engberink, & Geleijnse, 2012). Regarding lipids, full-fat dairy products were not associated with

hypertension while skimmed products decreased hypertension risk by 4%. A recent review of randomized controlled trials suggests that there is no apparent risk of deleterious effects of dairy products consumption on cardiometabolic risk, regardless of fat content in the dairy products, on a wide panel of risk markers (blood lipids, blood pressure, inflammation, insulin resistance, vascular function) (Drouin-Chartier, Cote, et al., 2016). Authors suggest that the supposed effects of SFA on cardiometabolic risk would be "cancelled" when the latter are consumed as part of a complex matrix such as in cheese and dairy products in general. These authors, as well as a recent expert panel (Thorning et al., 2017), provide incentive to further explore the impact of the "dairy matrix effect" on metabolism.

1.2 Lipid Composition, Structure and Matrices

Lipids consumed in food and meals vary in nature and composition. They are found in foods naturally or through their addition during food formulation or meal preparation. As pointed out in the previous section, the complexity of each food matrix should be considered to better understand metabolic responses, and this also implies considering the transformation of food during digestion and the role of each digestion step on nutrient utilisation.

Milk is the building block of a large variety of dairy products. The complete lipid composition of milk will not be presented in this chapter as it can be found in other chapters of this book. However, some compositional characteristics are recalled as they may impact nutritional and health properties of dairy products. Milk fat is the most concentrated natural source of short-chain fatty acids (SCFA) which are mostly esterified on sn-3 of the triacylglycerol (TAG) (Fig. 8.1). Milk is a rich source of SFA and it contains a rich variety of polar lipids concentrated in the milk fat globule membrane (Jensen & Newburg, 1995). Milk being the first food of newborn mammals, lipids are naturally organized to facilitate digestion and utilization. Fat droplets are excreted by the mammalian cells with a complex membrane, the milk fat globule membrane (MFGM), made of phospholipids, and sphingolipids and containing several proteins and enzymes. Homogenization and pasteurization of milk ensure products stability and safety overtime but induce changes in the fat droplet interface. If milk is first homogenized and then pasteurized, 99% of the absorbed proteins are β- and κ-caseins and the remaining 1% corresponds to MFGM fragments (see reviews, e.g.: Michalski, 2009; Michalski & Januel, 2006). When milk is pasteurized and then homogenized, whey proteins are denatured and interact with casein micelles (mainly κ-caseins) and native proteins of the MFGM. These complexes are then absorbed on the surface of the fat globules upon homogenization.

As shown in Fig. 8.1, several levels of structuration can be considered to describe each dairy product. Each has a specific lipid composition organized in fat droplets with a specific size distribution and interface composition. Any process contributing to change the matrix composition, for example, acid gel formation, cheese making, or butter churning induces a different dairy food structure and lipid organization.

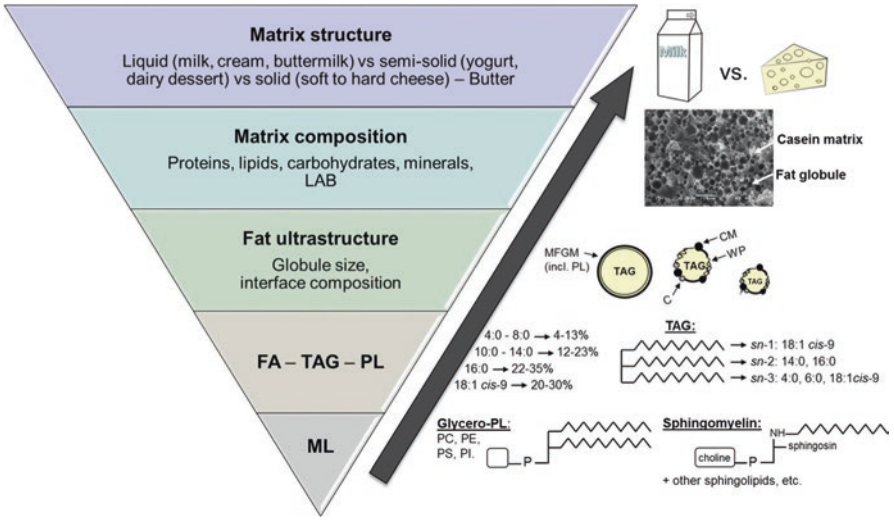


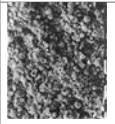
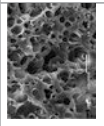
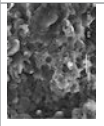
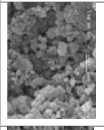
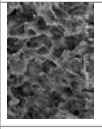
Fig. 8.1 Organization levels of lipids in dairy products. *CM* Casein micelles, *FA* Fatty acids, *LAB* Lactic acid bacteria, *MFGM* Milk fat globule membrane, *ML* Milk lipids, *PC* Phosphatidylcholine, *PE* Phosphatidylethanolamine, *PI* Phosphatidylinositol, *PL* Phospholipid, *PS* Phosphatidylserine, *TAG* Triacylglycerol, *WP* Whey proteins. The NH of sphingosin is shown to visualize the amide bond within sphingomyelin.

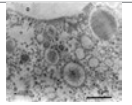
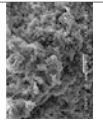
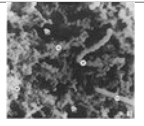
Most dairy products are emulsions, milk and buttermilk are liquid emulsion while cheese is a dispersion of lipid droplets or fat pools in a solid continuous phase. Butter is also an emulsion, but the aqueous droplets are found in a continuous lipid phase containing partially crystallized TAG. Each level of structuration is sometimes referred as microstructure and macrostructure (Barbé et al., 2014) and changes in structures due to different interactions may impact their digestive fate and metabolic outcome as demonstrated later in this chapter.

Natural processes as fermentation have emerged a long time ago to prolong storage time and are at the origin of a wide range of dairy products. From the initial milk composition, an intelligent use of processing tools as pH, enzymes (rennet), concentration, drying, etc. to induce interactions between dairy components are the basis of new dairy food structures (Table 8.1). These products are often a concentrated version of milk nutrients having different matrix organisation.

Table 8.1 classifies dairy products based on their structure and describes their composition in lipid, proteins and calcium, which influences their textural properties. Lipid contents varies from 0% to 90% depending on the dairy products. The emulsified state of milk is kept after its processing into yogurt and cheese in which lipid droplets are embedded in a gelled matrix. The properties of these casein matrices vary from a semi-solid acid gel in yogurt to a solid matrix in cheese. Depending on the cheese making process, the level of mineralization is different resulting in a semi-solid texture for Camembert with a lower calcium content compared to a solid/viscoelastic matrix as Cheddar cheese. Parmesan cheese has a stronger solid

Table 8.1 Dairy matrices composition, structure and digestibility

Dairy products	Proteins[a] (g/100 g)	Lipids[a] (g/100 g)	Ca[a] (mg/100 g)	LAB	Microstructure[b]	Lipid structure[c]	Textural properties	Digestibility[d] (% Gastric MDI)
Butter, salted	0.9	81.1	24	No/ Yes[e]	 Reproduced from[f]	Continuous lipid phase (water in oil emulsion)/ residual traces of MFGM	–	NA
Buttermilk (1% MF)	3.3	0.9	116	No	NA	MFGM fragments, tiny MFG	Liquid	NA
Cheese (Camembert)	19.8	24.3	388	Yes		FG/aggregates/free fat	Semi-solid	66–76%[g]
Cheese (Cheddar)	24.0	33.8	675	Yes		Free fat/aggregates/FG	Solid/ viscoelastic	25–43%[h]
Cheese (Parmesan)	35.8	25.8	1184	Yes		Free fat/aggregates/FG	Solid	NA
Cheese (Cream cheese)	5.9	34.2	98	Yes		Homogenized milk FG/ potential fragments of MFGM	Semi-solid	NA
Cream (35% MF)	2.1	35.0	66	No	NA	Native FG/homogenized milk FG[i]/potential MFGM fragments	Liquid	NA

Milk (whole, 3.25% MF)	3.2	3.3	113	No	 Reproduced from[f]	Native FG/homogenized milk FG/potential MFGM fragments	Liquid	100%[j, k]
Yogurt (greek, plain, 2% MF)	9.7	2.0	283	Yes		Native FG/homogenized milk FG/potential MFGM fragments	Gel/ viscoelastic	100%[j]
Yogurt (plain, 2–3.9% MF)	4.6	2.0	147	Yes	 Reproduced from[l]	Native FG/homogenized milk FG/potential MFGM fragments	Gel/ viscoelastic	100%[i]

Adapted from Turgeon and Brisson (2019)
MFGM Milk fat globule membrane, *FG* Fat globule, *LAB* Lactic acid bacteria, *MF* Milk fat, *NA* Not available
[a]Retrieved from Health Canada (2015)
[b]Authors personal SEM images unless specified
[c]Based on Michalski (2009); Michalski et al. (2013); Lopez et al. (2015)
[d]Matrix degradation index determined at the end of the gastric digestion using an *in vitro* model adapted from Versantvoort et al. (2005)
[e]Based on the processing method used
[f]Heertje (2014)
[g]Fang et al. (2016a); Vallières (2016)
[h]Fang et al. (2016b); Lamothe et al. (2012)
[i]NB: for cream, milk and yogurts, homogenization and its intensity may vary among products/brands
[j]Lamothe et al. (2017)
[k]Milk with 2% MF
[l]Sandoval-Castilla, Lobato-Calleros, Aguirre-Mandujano, and Vernon-Carter (2004). Adapted from Turgeon and Brisson (2019)

character corresponding to a higher calcium content. Electron microscopy allows to see differences in lipid organisation, for example, the continuous lipid phase in butter or the fat globules size, distribution, and aggregation in cheese may be visualized.

In addition to lipid organisation in dairy products, it should also be pointed out that when these dairy products are incorporated in a meal their structure evolves due to cooking, mixing, etc. and this may as well modify their behaviour during digestion. These aspects have not been overlooked until now and most of the nutritional studies were standardized on a nutrient basis without considering a possible effect of the lipid structure and dairy products state on their nutritional properties. For example, how is lipemia changing if lipids come from cheese, butter, or melted cheese? What happens if they are part of a complex meal? How other foods does impact dairy products nutritional properties? Interactions between food and drug absorption has been studied, but not much is known on the relative importance of food interactions on nutritional properties.

1.3 Lipid Digestion

After its ingestion, food undertakes a travel in the digestive tract with several compartments involving mechanical, enzymatic and biochemical reactions aiming to break food into simple components that can pass through the gastrointestinal tract mucosa. The release of a specific component from a food matrix into the digestive juice and being ready to be absorbed is defined as the bioaccessibility. The absorption and passage into the systemic circulation to finally reach its metabolic target is named the bioavailability. Figure 8.2 presents the different steps lipids follow for

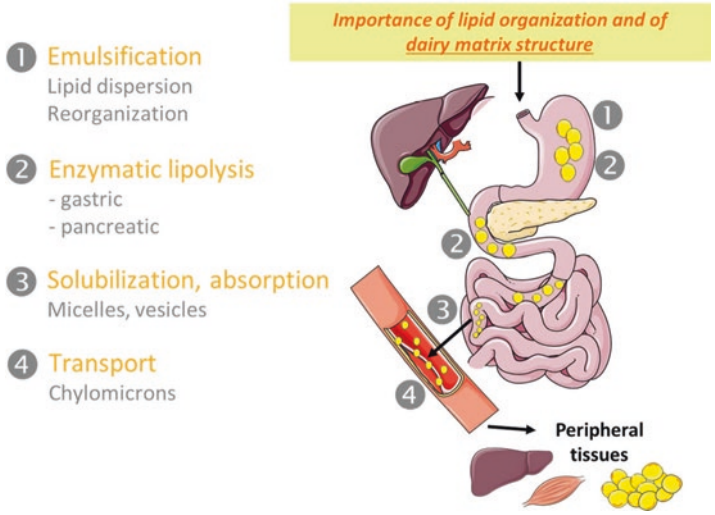


Fig. 8.2 Lipid digestion. Adapted from Michalski et al. (2013)

their digestion and absorption. After swallowing, the bolus formed in the mouth reaches the stomach, a reservoir where food disintegration continues. The physiological temperature increases the proportion of liquid fat, the acidic pH of stomach and the enzymatic attack of the protein network (by pepsin) promotes the release of lipids in the gastric lumen where they can be emulsified by the gastric mechanical movements. Lipids are dispersed and reorganized as oil-in-water emulsified droplets facilitating accessibility for the gastric lipase. Human gastric lipase acts preferentially on position *sn*-3 and generally leads to the hydrolysis of 10–30% of esterified FA, or 5–40% according to different reports (Armand, 2007; Carriere, Barrowman, Verger, & Laugier, 1993; Favé, Coste, & Armand, 2004; Favé, Peyrot, Hamosh, & Armand, 2007). SCFA are preferentially hydrolyzed from TAG than longer ones (German, 2008).

The emulsified chyme exits the stomach into the duodenum. Several factors regulate gastric emptying as the volume contained in the stomach, the degree of the food disintegration and chemical breakdown of the chyme (Stenson, 2006). Fat emptying is delayed compared to the aqueous phase because it floats over it. Furthermore, solid fat may stick to solid particles requiring grinding for their disintegration. Size reduction averaging 1–2 mm is necessary to pass into the small intestine (Kong & Singh, 2008; Stenson, 2006). If lipids are embedded in a solid food matrix, its disintegration is required for lipid release. The physical properties of the matrix may also influence lipid digestion (ex: liquid vs solid foods, emulsified fat or not).

Fat entering the duodenum consists of 70% TAG and a mixture of partially digested hydrolyzed products (Jones & Kubow, 2006). Fat hydrolysis continues with pancreatic lipase acting on lipids emulsified by bile (Favé et al., 2004). The efficiency of lipolysis is dependent on the emulsion droplet size and interface composition (Borel et al., 1994). Nonetheless, the absorption rate of TAG is higher than 95% (Sethi, Gibney, & Williams, 1993). Absorption mechanism is different for SCFA (<12 carbons) and long-chain FA (LCFA >12 carbons). SCFA are more hydrophilic and diffuse directly to the portal vein to be transported to the liver while LCFA requires assembly into mixed micelles to be absorbed (Bernard & Carlier, 1991; Duchateau & Klaffke, 2009; Jones & Kubow, 2006). Regarding LCFA, once they have been taken up by small intestinal enterocytes to be absorbed, FA are re-esterified into TAG and polar lipids and their accretion results in the formation of TAG-rich lipoproteins named chylomicrons. The latter are then secreted into the lymph to reach the bloodstream where they contribute to postprandial lipemia. In peripheral tissues, chylomicrons are hydrolysed by the lipoprotein lipase and released FA are taken up by tissues to be used as an energy source by beta-oxidation. In turn, the white adipose tissue (WAT) stores FA in the form of TAG, and chylomicron remnants remaining in the bloodstream get cleared by the liver (Lambert & Parks, 2012; Mu & Hoy, 2004; Wang, Liu, Portincasa, & Wang, 2013).

1.4 Lipid Metabolism

Lipemia is the amount of lipids present in the bloodstream. During the postprandial phase (i.e., the hours following the consumption of a meal), TAG-rich lipoproteins (firstly chylomicrons produced by the intestine, secondly liver-produced very low density lipoprotein (VLDL)) acutely increase and later decrease due to their hydrolysis by circulating lipases and their further clearance from the bloodstream. If postprandial lipemia is too high for a too long time, arteria are too much exposed to these TAG-rich lipoproteins (Vors, Nazare, Michalski, & Laville, 2014). This is why the kinetics of postprandial lipemia is important, i.e., not only the area under the curve (AUC) of plasma TAG during the postprandial phase, but also the time of appearance of the TAG peak, the maximum concentration reached and also the time for return to baseline lipemia. In fact, humans in Western countries spend most of the day in a postprandial state and it has been clearly established that a too high and too long postprandial lipemia is an independent risk factor to develop cardiovascular diseases (CVD) (Nordestgaard, Benn, Schnohr, & Tybjærg-Hansen, 2007), as observed in subject suffering from metabolic syndrome, obesity or type 2 diabetes (Lopez-Miranda, Williams, & Lairon, 2007). Therefore, studying how to modulate the kinetics of postprandial lipemia, notably by the food matrix, is a subject of growing research interest in the frame of prevention of metabolic diseases (Drouin-Chartier et al., 2017; Grundy, Lapsley, & Ellis, 2016; Keogh et al., 2011; Thorning et al., 2016; Vors et al., 2013).

2 Factors Impacting Lipid Metabolism: In Vivo Studies

2.1 Dairy State (Liquid vs Semi-Solid vs Solid)

Several reviews summarize results on the impact of differently structured dairy products (i.e. different matrixes) on postprandial lipid metabolism and associated metabolic disorders (German et al., 2009; Labonte, Couture, Richard, Desroches, & Lamarche, 2013; Lamarche, 2008; Nestel, 2008).

Acute postprandial studies were performed in vivo. In rats, lymphatic absorption of lipids is slower and lower after gavage with butter < cream cheese < regular or sour cream (Fruekilde & Hoy, 2004). Postprandial studies in humans with metabolic disorders or disease confirm this trend. In T2D subjects, consuming a meal containing 30 g lipid as butter induces a later increase of plasma TAG than using Mozzarella cheese or milk, despite a similar AUC over 6 h (Clemente et al., 2003). This appears consistent with a clinical study where obese men presented a relative delay in the digestion/absorption of spread (unemulsified) vs emulsified milkfat (lower area under the curve of chylomicron-TAG over 5 h), unlike normal-weight men (Vors et al., 2013). Regarding longer-term differences, in a clinical intervention study, 14 healthy men received for 3 weeks a diet containing 20% of daily energy as

milk fat as butter, milk or hard cheese. After 4 days, no differences were observed on postprandial lipid metabolism among groups. However, at the end of the trial, plasma LDL-cholesterol was higher after the butter diet than after the cheese diet (Tholstrup, Hoy, Andersen, Christensen, & Sandstrom, 2004).

Regarding viscosity, structure and gastric emptying modulation human studies showed that ingestion of solid foods slows down gastric emptying compared with liquid foods (Hunt & Knox, 1968), which results in a later appearance of TAG peak in plasma (Dubois et al., 1994). Such phenomenon was also demonstrated using dairy products with different viscosities (Fruekilde & Hoy, 2004; Sanggaard et al., 2004). A study using (1) fresh curd vs cream and (2) fermented milk vs regular milk showed an increase gastric emptying time for viscous matrices. Moreover, fresh curd results in delayed peak of postprandial lipemia vs cream. Of note, a semi-solid or solid texture decreases hunger and induces satiety as observed using semi-solid yogurt and drinkable yogurt compared with a fully liquid dairy drink (Tsuchiya, Almiron-Roig, Lluch, Guyonnet, & Drewnowski, 2006). Moreover, recent studies report that dairy product viscosity or gelation and gel structure (acid, rennet) have an impact on protein digestion and bioavailability, however to date, skimmed milk was used so that the impact on lipid fate was not explored (Barbé et al., 2014; Dupont, Ménard, Le Feunteun, & Rémond, 2014). In humans, full-fat yogurt slows down gastric emptying and induces a slower and prolonged release of proteins in the jejunum compared with whole milk (Gaudichon et al., 1994; Gaudichon et al., 1995). Such approach should thus now be explored regarding the fate of milk lipids; notably homogenization of fat globules can indirectly impact matrix structure (because of decreased globule size and coverage with proteins that interact with the casein network) and possibly the lipid fate (Sect. 2.2) (Michalski & Januel, 2006).

During the digestion of fermented milk, a slower gastric emptying was observed, together with a higher peak of plasma TAG returning faster to baseline than with standard liquid milk (Sanggaard et al., 2004). This can be explained by the higher viscosity of fermented milk, which slows down gastric emptying and ultimately the appearance of plasma TAG. In healthy individuals, consuming a solid meal results in a peak of lipemia appearing 3–4 h after the meal, whereas the TAG peak occurs 2 h after a liquid meal (Dubois et al., 1994). Moreover, in humans, the aqueous phase of a meal empties fast from the stomach, whereas solid and lipid phases empty together after a lag time (Meyer et al., 1986). This is why a more or less solid dairy matrix can impact milk lipid digestion (e.g. hard cheese vs fresh curd). Notably, other components of the dairy matrix such as proteins and calcium can impact postprandial lipid metabolism (see below) (Lorenzen & Astrup, 2011; Mortensen et al., 2009), as well as matrix structure. Regarding hard pressed cheeses (cooked or uncooked), pressing the curd allows to drain the serum. This process disintegrates milk fat globules, notably by inducing coalescence and the formation of “free fat” inclusions, all the more than the pressure is high (Lopez, Cauty, & Guyomarc’h, 2015; Michalski et al., 2004; Michalski et al., 2007). Such structural changes in milk fat inside the product could contribute to cheese properties during digestion but this remains to be elucidated in detail as highlighted in different reviews (Michalski, 2009; Thorning et al., 2017).

2.2 Food Manufacturing Processes

As summarized in Table 8.1 and in Fig. 8.1, dairy processes such as homogenization and cheese press can greatly impact milk fat globule structure and functional properties. Recent research shed the light on a further impact on lipid digestion, absorption and postprandial metabolism. Notably, postprandial lipemia can be greatly modulated by the emulsified structure of fat (Armand et al., 1999; Couedelo et al., 2015; Keogh et al., 2011; Michalski et al., 2013; Vors et al., 2012; Vors et al., 2013). Regarding milk fat, the fat globules homogenized or not, and a milkfat emulsion covered either with proteins or with polar lipids, result in different kinetics of postprandial lipemia in rats (Michalski, Briard, Desage, & Geloen, 2005; Michalski, Soares, et al., 2006). A response of lower amplitude is observed with homogenized vs native globules and for droplets covered with caseins vs soy lecithin. Moreover, still in rats, appearance of absorbed FA in the lymph occurs faster after gavage with homogenized cream than butter, and cumulative absorption over 8 h is greater (Fruekilde & Hoy, 2004). A recent clinical trial shows in healthy men that emulsified milk fat in skimmed milk as part of a breakfast results in a faster and higher plasma TAG peak compared with unemulsified fat, revealing an easier intestinal absorption of lipids (Vors et al., 2013). This demonstrates that the enhancing effect of emulsification on lipolysis and absorption can occur in the frame of a mixed meal in humans. A novel aspect of this work was to elucidate the final metabolic fate of the ingested FA. By a $^{13}CO_2$ breath test, this study demonstrated a higher beta-oxidation of ingested FA when fed in emulsified fat structure (Vors et al., 2013). This was due to a faster influx of dietary non-esterified FA (NEFA) in plasma, thereby used as a priority energy source. In a recent postprandial study, the consumption of soft cream cheese (emulsified dairy fat in a semi-solid matrix), Cheddar cheese and butter (control) as part of a test meal was provided at breakfast to healthy participants in a randomized, crossover and controlled trial (Drouin-Chartier et al., 2017). Of note, the structure of the dairy food was not altered in this study in order to keep their matrix structure. After 2 h, plasma TAGs significantly increase for the cream cheese meal compared to the Cheddar cheese meal. At 6 h, the cream cheese meal induces a lower TAG response compared to the Cheddar cheese meal suggesting different kinetics of postprandial TAG response. In addition, the lower ApoB48 incremental AUC found when consuming cream cheese suggests lower and smaller chylomicron secretion than for cheddar cheese. These results suggest that cream cheese is digested faster than Cheddar cheese confirming that cheese matrix modulates postprandial lipemia.

Combination of homogenization and heat treatment was also studied. In minipigs, gastric lipolysis is lower when milk or fermented milk are pasteurized and homogenized (Timmen & Precht, 1984). In rats, homogenized pasteurized cream modifies fat structure and digestion in the stomach and small intestine compared

with untreated cream (Gallier et al., 2013). In the small intestine, homogenization results in an apparently higher lipolysis and increased appearance of fat crystals in the second half of the small intestine. However, a lower postprandial lipemia was observed in another rat study with homogenized vs native milk fat globules (Michalski, Soares, et al., 2006). To our knowledge, only two clinical trial were performed to date on the impact of milk homogenization on postprandial lipid metabolism. One crossover trial in overweight men consisted in three postprandial tests after the consumption of 900 mL of whole milk unhomogenized, or homogenized, or of 44 g butter with skimmed milk (Masson, 2013). This PhD thesis study reports a lower rise of plasma TAG after homogenized milk than butter, but no difference with unhomogenized milk. The second trial was a pilot study in a small group of 11 healthy volunteers designed to investigate the impact of milk homogenization on gastrointestinal symptoms (Nuora et al., 2018). Milk homogenization did not impact postprandial lipaemia, but after 4 h, authors observed more of the major long-chain SFA (myristic, palmitic and stearic acids) in plasma after homogenized vs unhomogenized milk. Authors report no significant difference in the amount of gastrointestinal symptoms or in the intestinal pressure but point out that further studies in this area are needed with larger group size and longer exposure times to differently processed milk types (Nuora et al., 2018). Of note, another acute trial reports the postprandial response of healthy men to the consumption of a bolus of infant formula differing in fat globule structure: small droplets covered with milk proteins (i.e. similar to homogenized milk fat droplets) vs large droplets coated with phospholipids and proteins (designed to model native milk fat globule structure) (Baumgartner et al., 2013). Here the small droplets covered with proteins resulted in a slower rise in plasma TAG than the large droplets coated with PL and proteins (which is consistent with previous rodent studies; Michalski et al., 2005; Michalski, Soares, et al., 2006). More studies are needed to elucidate in humans the impact of milk homogenization on lipid fate in the body and metabolic consequences. Of note, Tholstrup (2006) used to highlight that the consumption of cheeses made from unhomogenized milk was high in France where coronary mortality was quite low, whereas in Scandinavian countries where milk is rather consumed as homogenized liquid milk, coronary mortality is high (Tholstrup, 2006). However, correlation is not causation and as discussed above, we now know that the specific impact of cheese would rather be due to an overall "matrix effect". Previous reviews on the impact of milk homogenization on health report that to date, no link was established between homogenization and CVD or T2D, but this should be further explored in humans due to the controversial nature of this topic (Michalski, 2007; Michalski & Januel, 2006). This is all the more interesting to explore than homogenization modifies dramatically the size of milk fat globules (see Sect. 1.2) and destroys the native structure of the MFGM (see section MFGM and milk PL content).

2.3 Dairy Matrix Composition

2.3.1 Lipid Content

Lipid Amount One major aspect of dairy matrix composition regarding lipids is the broad range of fat content, from low-fat and so-called/claimed "diet" products to full-fat ones including cheeses. Importantly, dietary guidelines in many countries such as Canada (Health Canada, 2016) or US (US Department of Health and Human Services and US Department of Agriculture, 2015) recommend consuming low fat dairy products. However, recent researches challenge such recommendations.

A study in pigs shows that a regular full-fat cheese results in increased HDL-cholesterol compared with butter after 14 days. However, this beneficial effect was not observed with low-fat cheese (Thorning et al., 2016). In this study though, low-fat cheese was consumed with butter in order to equalize lipid intake. Therefore, observed effects on cholesterol could be due to the presence of the MFGM in full-fat cheese and/or to a "matrix effect" as discussed recently by an expert panel (Thorning et al., 2017). In humans, another team also showed that for a similar consumption of full-fat or low-fat cheese without adjusting lipid and energy intakes, full-fat cheese induced a higher HDL-cholesterol concentration and no difference in LDL-cholesterol (Raziani et al., 2016). Two recent studies show an inverse association or a lack of correlation between the consumption of different dairy products and the appearance of clinical cardiovascular events, and the lack of association between the consumption of low-fat or full-fat dairy products and different metabolic risk factors, notably regarding lipid metabolism and inflammation (Drouin-Chartier, Brassard, et al., 2016; Drouin-Chartier, Cote, et al., 2016). They highlight the importance of studying in more details the metabolic impact of dairy products with different fat contents with an aim to argue on the current dietary guidelines advising to consume low-fat dairy. Long-term nutritional interventions are necessary to elucidate the link between full-fat dairy consumption and metabolic and cardiovascular risks.

FA Composition and Melting Points Milk fat has a relatively solid structure, whose melting point can vary according to its fatty acid profile, notably SFA content. The more or less solid state of TAG at body temperature (37 °C) can also impact their digestibility and absorption. In healthy adults, stearic acid (18:0) in a high melting point fat results in a lower lipid absorption, the latter being in fact inversely correlated with the proportion of solid fat at 37 °C (Berry, Miller, & Sanders, 2007; Berry & Sanders, 2005). Altogether, TAG containing long-chain saturated FA such as palmitate (16:0) and stearate (18:0) melt above 37 °C (e.g. in the range 68–73 °C for homogeneous TAG composed of palmitate and/or stearate only). Solid TAG in the digestive tract results in a limited action of lipases and therefore a lower postprandial lipemia compared with liquid oils (Berry & Sanders, 2005; Sanders, Filippou, Berry, Baumgartner, & Mensink, 2011). The hydrolysis rate by pancreatic lipases of a tripalmitin emulsion that is completely solid is lower

than that of a similar emulsion with liquid tripalmitin (Bonnaire et al., 2008). In humans, vegetable fats of high melting points with a large proportion of solid TAG at 37 °C result in lower postprandial lipemia compared with fats liquid at 37 °C (Berry & Sanders, 2005). Regarding milk fat, Mekki et al. (2002) observed a lower postprandial accumulation of chylomicron triglycerides in plasma after a meal containing spread butter rather that vegetable oil in a sauce. In dairy products, the proportion of solid fat at 37 °C is lower than in high melting point vegetable fats, but still exists. Around 5% of milk TAG can be crystallized at 37 °C (Lopez, 2011) and this proportion can be of 3% in Emmental cheese (Lopez, Briard-Bion, Camier, & Gassi, 2006). In guinea pigs (Asselin et al., 2004) or rats (Lai & Ney, 1998), the plasma TAG concentration or AUC of plasma TAG was lower in animals fed with high melting point milkfat fraction (42–44 °C) compared with a low melting point fraction (13–14 °C). Similarly, rats fed Cheddar-type cheeses manufactured with anhydrous milk fat (AMF) of different melting points showed different postprandial TAG responses (Ayala-Bribiesca, Turgeon, Pilon, Marette, & Britten, 2018). Stearin AMF exhibited the lowest plasma TAG responses compared to the olein AMF. This could be explained by the high proportion of unsaturated saturated LCFA found in the stearin AMF resulting in a melting point higher than body temperature (42.3 vs 37 °C). Also, the mass fraction of the total FA recovered in the animal feces were significantly higher with the stearin AMF diet compared to the olein AMF diet. This was mainly attributed to the higher proportion of palmitic acid (16:0) which is prone to form calcium soap (detailed in the next section). Therefore, FA bioavailability was reduced in the presence of a stearin AMF diet.

MFGM and Milk PL Content Different dairy products can contain different amounts of MFGM and associated components (Fig. 8.1), which is an important structural component of the native MFG and source of bioactive molecules. When incorporated in animal diets, extracts of MFGM or of milk PL were shown to be able to decrease intestinal cholesterol absorption and hepatic lipids. In mice, adding a buttermilk extract rich in milk PL (1.2% PL in the diet) in a diet containing 21% lipid induces a decrease of hepatic total lipids, TAG and cholesterol, and a decrease in plasma lipids (TAG, total cholesterol, phospholipids (PL)). These effects were not observed when the milk PL-rich buttermilk extract was added in a diet containing 4.6% lipids. This suggests a beneficial effect of MFGM or milk PL in a deleterious/obesogenic dietary context (Wat et al., 2009). A hypocholesterolemic effect of the MFGM was also observed in rats with induction of lower hepatic cholesterol and TAG, but higher plasma TAG (Zhou, Hintze, Jimenez-Flores, & Ward, 2012). In mice fed a high-palm oil diet, incorporation of 1.2% of soybean PL induced higher hepatic lipids and higher WAT with larger adipocytes, which is a deleterious feature, compared with the diet devoid of PL. Conversely, when incorporating 1.2% of milk PL in the semi-synthetic high-fat diet, no increase of hepatic nor WAT lipids was observed (Lecomte et al., 2016). Incorporation of 1.6% of milk PL in a chow-based high-fat diet resulted in a lower body weight gain of mice after 8 weeks (Milard, Laugerette, et al., 2019).

A few studies also described a hypolipemic effect of buttermilk consumption in humans (Baumgartner et al., 2013; Conway et al., 2013). Consuming 45 g/day of a chocolate-flavored buttermilk drink during 4 weeks resulted in healthy men and women in decreased fasting plasma concentrations of total cholesterol (−3.1% vs placebo), LDL-cholesterol (−3.1% vs placebo) and TAG (−10.7% vs placebo) in a randomized controlled trial (Conway et al., 2013). Authors discussed the decreased cholesterolemia could be due to sphingomyelin (SM) present in the buttermilk, which could lower cholesterol absorption. Moreover, the decreased plasma TAG could be due to a lower hepatic TAG synthesis when consuming milk PL as observed in mice (Eckhardt, Wang, Donovan, & Carey, 2002; Reis et al., 2013). Baumgartner et al. (2013) studied the impact of the matrix on cholesterol metabolism. To this aim, 97 healthy volunteers were assigned either to the control group, which did not modify its dietary intakes, or to the group consuming one egg per day, or to the group consuming one egg yolk per day incorporated in a buttermilk drink (+215 mg cholesterol/day in women, +97 mg/day in men, in egg groups vs control group). In women consuming 1 egg/day, increased plasma concentrations of total- and LDL-cholesterol were observed vs control group. No increase was observed when the egg was associated with buttermilk (Baumgartner et al., 2013). Here again, authors suggest that the anti-hypercholesterolemic effect could be due to milk PL and notably SM.

A study with 11 healthy volunteers showed that the consumption of a "placebo buttermilk" (fermented skimmed milk) devoid of MFGM for 3 weeks did not modify plasma lipids, which supports the hypothesis that the potential hypolipemic impact of buttermilk could be due to MFGM or some of its components such as milk PL (Thompson et al., 1982). More recently, the impact of two dairy ingredients differing by their MFGM content and emulsified structure was explored on lipid metabolism. Volunteers consumed 40 g of milkfat per day incorporated in a muffin as whipping cream (containing 198 mg of milk PL) or as AMF (containing only 1.3 mg of milk PL) for 8 weeks. AMF-in-muffin diet increased total and LDL- cholesterol plasma concentrations, while whipping-cream-in-muffin diet did not exert such effect (Rosqvist et al., 2015). Authors discussed this could be due to the presence of MFGM in whipping cream. In this study, data indicate no difference in cholesterol absorption or synthesis among groups, suggesting another mechanism not yet elucidated.

Until 2019, clinical nutritional intervention studies led with milk PL or SM did not demonstrate significant effects on fecal excretion and intestinal absorption of cholesterol nor on plasma lipids in healthy volunteers (Ohlsson, Burling, & Nilsson, 2009; Ramprasath, Jones, Buckley, Woollett, & Heubi, 2013). In a parallel group randomized trial, healthy volunteers consumed daily during 4 weeks a dairy drink containing 2.8 g of egg PL or milk PL (by a buttermilk-derived concentrate). Volunteers of the egg PL group increased plasma lipids, while volunteers of the milk PL groups did not (Ohlsson et al., 2009). However, no real hypolipemic effect was observed in the milk PL group (i.e., no decrease of plasma lipids after intervention vs before intervention). Finally, a dietary supplementation with 1 g of milk SM per day for 14 days induced increased HDL-cholesterol but no change in absorption

and synthesis of cholesterol in ten healthy volunteers (Ramprasath et al., 2013). The latter studies could have limited effects due to the low number of volunteers (<30) and/or because volunteers were healthy, without lipid metabolism disorders. In this respect, two recent studies in overweight or obese volunteers show an effect of milk PL consumption on a marker of hepatic steatosis, namely GGT (γ-glutamyl transferase) (Weiland, Bub, Barth, Schrezenmeir, & Pfeuffer, 2016). In the first study, increased GGT observed when consuming a control dairy drink was not observed when the drink was enriched with milk PL. However, no effect of milk PL was observed on plasma lipids and insulin resistance markers. In their second study, authors report a lower GGT concentration with milk PL than with soybean PL, devoid of SM.

Most recently, the first human trial reporting a significant impact of milk PL supplementation on reducing an array of cardiometabolic risk factors in a population at metabolic risk was published by Vors et al. (2020). Overweight postmenopausal women were subjected to a 4 week-dietary intervention with the daily intake of cream cheese either enriched with 3–5 g/day of milk PL via a butter serum concentrate rich in MFGM fragments, or control cream cheese devoid of milk PL (here fat ingredient was butteroil only) (parallel groups). Milk PL incorporated in cream cheese resulted in reduced total and LDL-C (−8.7% in 5 g group after vs before intervention), as well as decreased total/HDL-cholesterol and decreased ApoB/ApoA1 ratio (−6.8% in 5 g group), compared to the control group (no effect). This intervention with milk PL (1) decreased the plasma concentration of cholesterol carried by postprandial chylomicrons and (2) increased the coprostanol/cholesterol ratio in feces, suggesting an increased conversion of cholesterol to coprostanol, a non-absorbable metabolite of cholesterol, by the gut microbiota (Vors et al., 2020). In a complementary crossover clinical trial, four ileostomized subjects consumed these different cream cheeses with varying enrichment of milk PL. Here milk PL decreased intestinal absorption of cholesterol (lower cholesterol tracer concentration AUC in plasma and chylomicrons in the postprandial phase). Additionally, an increased ileal output of both total cholesterol (of dietary + endogenous origin) and of milk SM was observed in ileal efflux after both milk PL-rich meals, confirming previous observations of fecal excretion of milk SM in mice (Milard, Laugerette, et al., 2019). Moreover, these results in humans could have been enhanced by the fact that SM was consumed here as part of a complex milk PL mixture within the cream cheese matrix (from MFGM fragments of the butter serum ingredient), rather than as pure milk SM.

Altogether in animals, MFGM extracts and milk PL were shown to decrease intestinal cholesterol absorption and hepatic lipids in the long term. In humans, few clinical trials report a decrease in fasting lipids (notably cholesterol) or a prevention of increased lipids by consuming buttermilk. Authors suggest this is due to the presence of MFGM in buttermilk. However, to date, most human studies with MFGM extracts of milk PL at around 3 g/day do not show effects on intestinal cholesterol absorption or plasma lipids. Overall, the hypolipidemic effects of milk PL or milk SM observed in rodent studies have been reported in some human studies, although with smaller magnitude of the effects that were often non-significant,

except in the recent trial using a real dairy food matrix and 3–5 g/day of milk PL that resulted in significant favorable effects (Vors et al., 2020). Of note, the small or neutral effects of lower milk PL intakes observed in the 4–12-week trials may contribute to maintaining a relative blood cholesterol homeostasis in the longer term, which would deserve further elucidation. Performing further clinical studies in patients with metabolic syndrome, moderate hypercholesterolemia (as in Vors et al., 2020) or high blood pressure could provide more insight on the potential beneficial effects of milk PL and MFGM and such perspectives are proposed in different articles and reviews (Castro-Gomez, Garcia-Serrano, Visioli, & Fontecha, 2015; Conway, Gauthier, & Pouliot, 2014; Norris, Milard, Michalski, & Blesso, 2019; Ohlsson et al., 2009).

2.3.2 Protein Content

The impact of proteins at the interface of milkfat emulsion droplets has been explained above (Chap. 7). Here we will focus on the impact of the presence of different amounts or quality of proteins in the dairy matrix or in the meal on the metabolic fate of lipids.

In a pilot study, healthy subjects consumed a bolus of dairy cream (30% fat) mixed with water and containing or not 50 g of sodium caseinate (Westphal et al., 2004). Caseinate addition induced a small delay of appearance of plasma TAG and decreased significantly plasma NEFA concentrations. Authors hypothesized this would be due to the increased insulin secretion observed with caseinate. However, another study in adults shows that milk proteins added in a meal do not acutely modify markers of postprandial lipid metabolism (Bortolotti, Schneiter, & Tappy, 2010). This study used complex meals with different types of dairy matrixes, with the control meal containing 19 g of proteins brought by cottage cheese only, while enriched meal brought 56 g of proteins by an additional intake of skimmed milk, buttermilk and cottage cheese. Both meals were isolipidic, 30 g of lipids among which a part was brought by butter in the control meal. Subjects then had a 4 days diet enriched in dairy proteins (by skimmed milk, cottage cheese and yogurts for 1.5 g proteins/kg body weight/day). This short period of protein enrichment of the diet induced increased postprandial chylomicronemia following the same hyperproteic test meal as above, and a lower beta-oxidation (i.e. use as an energy source) of ingested lipids. This suggests that the hyperproteic diet induced a worsening of chylomicron clearance from blood (Bortolotti, Dubuis, Schneiter, & Tappy, 2012). Discrepancies among these two studies could be partly explained by (1) the type of proteins: sodium caseinate vs total dairy proteins, and (2) the type of test meal: simple liquid meal vs realistic mixed meal containing a variety of real dairy products. This provides incentive to further explore the dairy matrix effect on lipemia modulation by different amounts and types of proteins.

The type of proteins presents in a product or a meal appears to be an important modulator of postprandial lipemia. Whey proteins, so-called “fast proteins”, bring amino acids that are readily available in plasma compared to “slow” caseins (Boirie

et al., 1997). Whey proteins also present benefits on some features of the metabolic syndrome, including an improvement of fasting plasma lipid profile (Pal & Radavelli-Bagatini, 2013). Digestion of casein micelles produces caseinomacropeptide, which in turn provokes the secretion of cholecystokinin (CCK), an inhibitor of gastric emptying. This can impact the entire digestion kinetics, as well as the satietogenic ileal brake mechanism (van Avesaat, Troost, Ripken, Hendriks, & Masclee, 2015). Several studies in rodents also describe a beneficial effect of whey proteins on lipid metabolism (Kawase, Hashimoto, Hosoda, Morita, & Hosono, 2000; Sautier et al., 1983; Zhang & Beynen, 1993) such as decreased serum total cholesterol after a supplementation with whey protein concentrate vs caseins (Sautier et al., 1983). Such favourable effects were also explored in humans. Recent clinical trials demonstrated that whey proteins in a meal can decrease postprandial lipemia and chylomicronemia compared to other types of proteins, especially in subjects with abdominal obesity, which can be considered beneficial (Bohl et al., 2015; Holmer-Jensen et al., 2013; Mortensen et al., 2009; Pal, Ellis, & Dhaliwal, 2010). A clinical trial in T2D volunteers compared the impact of a meal containing 100 g of butter (structure: melted in a non-energetic soup), 45 g of carbohydrates (white bread) and containing 45 g of proteins either in the form of calcium caseinate, whey proteins, fish proteins or gluten (altogether proteins in soup). Whey proteins result in a lower postprandial area under curve (AUC) of plasma TAG, NEFA and glucose vs other proteins, and the lipemia peak was delayed. Authors hypothesized a lower production and/or a better clearance of chylomicrons (Mortensen et al., 2009). Another study in non-diabetic obese subjects confirmed an impact of whey proteins on lowering postprandial lipemia compared with fish proteins and gluten (Holmer-Jensen et al., 2013). A 12-week intervention study compared the physiological response to a rich mixed meal including notably different dairy matrixes (butter, cheese, milk) after 4 different diets containing 63 g of milkfat per day (rich or low in short- and medium-chain SFA) and 60 g per day of proteins as whey proteins or caseinate. Regardless of milkfat composition, whey proteins induced a lower number of chylomicrons after a test meal compared to caseinate (Bohl et al., 2015). Here again, a lower production and/or better clearance of chylomicrons could occur, which might be favourable in the long term by limiting CVD risk. This remains to be elucidated with different types of proteins and dairy matrixes. Pal et al. observed in overweight and obese subjects a decrease in fasting plasma total- and LDL-cholesterol after 12 weeks of supplementation with whey proteins vs caseins (Pal et al., 2010). A lower exposition to TAG-rich lipoproteins was also observed in the postprandial phase (AUC of the TAG/ApoB48 ratio, ApoB48 being a marker of chylomicron number). Such decreased exposition of lower arteria to LDL-cholesterol and TAG-rich lipoproteins would be favourable. These studies suggest a hypolipemic effect of whey proteins in the postprandial phase compared with caseinate. Suggested mechanisms included impacts on hepatic de novo cholesterol synthesis, intestinal cholesterol absorption and intestinal FA transport.

However, we must highlight one study leading to different results that can be due to a matrix effect. Mariotti et al. observed an increase of postprandial TAG with total

whey proteins or alpha-lactalbumin in the meal compared with caseins in the meal (Mariotti et al., 2015). Authors proposed a mechanism due to cream droplets being unstable in the casein meal, and to changes in meal viscoelasticity (coalescence and fat phase separation in gastric conditions with caseins, stability of fat droplets in the whey protein meal). We suggest that differences of source and structure of the milk fat in the test meal (cream in the latter study, melted butter in the former studies) could modify the relative impact of whey proteins vs caseins. There again this supports the impact of the food matrix and meal structure on metabolic outcomes.

Altogether, several clinical trials show that the type of dairy proteins can modify postprandial lipemia. Whey proteins would be hypolipemic but this remains to be confirmed using test meals of different protein composition and of different matrix composition and structure. This remains to be explored in detail in humans because an inter-connexion exists between the relative impact of protein amount, type, location at the interface of fat droplets or in the aqueous phase or proteinaceous network, denaturation and consequences relative to viscosity.

2.3.3 Calcium Content

An important aspect of the fate of SFA in the gut consists in their ability to form calcium soaps when they are located at the external positions of TAG and the meal contains calcium, which is naturally the case of most dairy matrixes. Milk fat contains a high proportion of palmitic acid on the sn-2 (internal) position of milk TAG, which ensures a high bioaccessibility of this FA. More generally, milk contains a huge diversity of molecular TAG species that can modify digestion kinetics compared to homogeneous TAG (Mu & Porsgaard, 2005). Notably in milk fat, a proportion of milk SFA are located at the external positions of TAG and can thus, when released by lipases, be associated with dairy calcium, resulting in fecal excretion of calcium soaps (Lorenzen et al., 2007; Lorenzen, Jensen, & Astrup, 2014; Soerensen, Thorning, Astrup, Kristensen, & Lorenzen, 2014). In a crossover clinical trial, 15 healthy men consumed for 2 weeks a control diet low in calcium (devoid of dairy products except butter, 500 mg Ca/day) then two diets enriched in calcium (Ca, 1700 mg/day) by either half-skimmed milk or by semi-hard cheese (Soerensen et al., 2014). The lipid fecal loss increased with the milk diet (5.2 g/day) and the cheese diet (5.7 g/day) compared with the control diet (3.9 g/day). Moreover, consuming both diets enriched in calcium via these dairy products induced a lower increase in fasting plasma concentrations of total- and LDL-cholesterol compared with the control diet. A correlation between lipid fecal loss and plasma cholesterol concentrations was even observed in this study. Such mechanism could contribute do decrease postprandial lipemia as shown in a study where 18 healthy volunteers consumed three isocaloric meals differing in calcium content by dairy products (yogurt and milk): low Ca (68 mg/meal), medium Ca (350 mg/meal) and high Ca (793 mg/meal) (Lorenzen et al., 2007; Lorenzen et al., 2014; Soerensen et al., 2014). Meals with medium and high Ca contents induced a lower AUC of chylomicron TAG compared with the low Ca meal (−17% and −19%, respectively). Most

recently, rats were fed Cheddar-type cheese with regular (50 mg) and higher (66 mg) level of calcium (Ayala-Bribiesca et al., 2018). Higher plasma TAG were found with the high calcium fed group suggesting higher digestive lipolysis. Rat feces were also collected, and significantly higher fat excretion were found for rats fed the high calcium cheese diet. The analysis of the FA profile revealed that the differences were mainly attributed to LCFA that are more prone to precipitate in presence of calcium (detailed in in vitro section).

2.3.4 Lactic Acid Bacteria and Their Metabolites

Endogenous bacteria present in the dairy matrix can be able to metabolize milk lipids and produce more or less bioactive derivatives/molecules. For example, conjugated linoleic acid (CLA) were reported to be formed from linoleic acid (18:2 n−6) in organic yogurts and fermented milks (Florence et al., 2009). Moreover, some bacteria of the host gut microbiota can produce, from dietary lipids present in the intestinal lumen, CLA species that can present beneficial trophic bioactivity in the intestine (Druart et al., 2014; McIntosh, Shingfield, Devillard, Russell, & Wallace, 2009; Russell, Ross, Fitzgerald, & Stanton, 2011). This can be one mechanism explaining why epidemiological studies report overall beneficial health effects of fermented products.

Different reviews of epidemiological studies and meta-analyses of randomized control trials (RCT) highlight that dairy products intake, including fermented and full fat products, is associated with a lower or unaltered inflammatory profile (Labonte et al., 2013; Labonte et al., 2014; Vors, Gayet-Boyer, & Michalski, 2015). A decreased risk of T2D was recently shown with the consumption of total fermented food intake: a meta-analysis of 5 studies showed no association with T2D but a 12% risk reduction was observed when "high fat" products were included for an intake of 40 g/day; cheese intake was not associated with T2D risk (12 studies) and yogurt intake was inversely correlated with T2D risk (−14% for an intake of 80 g/day; 11 studies) (Gijsbers et al., 2016). Other studies report that cheese intake decreases stroke risk and both CHD and CVD risks (Alexander et al., 2016; Chen, Wang, et al., 2016; Qin et al., 2015).

Regarding intervention trials, a recent study demonstrated that milkfat consumed as cheese for 4 weeks reduced more LDL-cholesterol than butter, both products having similar effects on HDL- cholesterol (Brassard et al., 2017). The impact of two diets containing full-fat dairy products including either yogurt and cheese (fermented) or butter, cream and ice cream (not fermented) were compared to a diet containing low fat dairy products (milk and yogurt) in 12 overweight and obese volunteers (Nestel et al., 2013). No significant difference was observed on markers of inflammation and atherosclerosis, despite a tendency of the low fat diet to induce an increase of theses risk markers compared with the diet rich in fermented full-fat dairy products. These results suggest that (1) dairy lipids do not increase inflammation and atherosclerosis, (2) dairy matrix plays a major role in their metabolic effects and (3) fermentation could play a key role in these phenomena. As explained above,

lactic bacteria can generate more or less bioactive lipids in fermented dairy products, but also several other bioactive mediators (Pessione & Cirrincione, 2016). The possible mechanisms for specific effects of fermented dairy products can also be due to fermentation effects notably on the gut microbiota (see below), and also to indirect effects due to matrix structural changes during fermentation and/or ripening.

The impact of fermentation on the digestion, absorption and metabolic impact of milk fat can indeed be due to an array of factors part of the matrix effect. For example, cheese making processes: modify milk fat globule structure by providing more or less aggregation, coalescence, free fat, released MFGM fragments etc.; modify the structure of the proteinaceous phase from gelation to solidification; concentrate more or less calcium and other minerals; and provide bacteria and various fermentation products. Notably, soft cheeses such as Camembert contain native milk fat globules as well as more or less aggregated or coalesced globules (Lopez et al., 2015; Michalski et al., 2003); while Emmental cheese rather contains "free fat" inclusions around which bacteria are located (Lopez et al., 2015; Michalski et al., 2004; Michalski et al., 2007) (see figures in these references). If milk fractions with small or large native milk fat globules collected by microfiltration are used (Michalski, Leconte, et al., 2006), such differences in milk fat globule size are still observed in lipid structures of fermented dairy products made therefrom, which modifies the overall structure of the gel or cheese matrix (Michalski et al., 2003; Michalski et al., 2004; Michalski et al., 2007; Michalski, Cariou, Michel, & Garnier, 2002) and the FA profile of the cheese (Briard & Michalski, 2004).

Importantly, evidence is growing about the impact of bacterial strains on lipid metabolism, notably cholesterolemia-lowering ability of lactic acid bacteria (Ito et al., 2015; Ivanovic et al., 2015; Jo, Choi, Lee, & Chang, 2015; Pan, Zeng, & Yan, 2011; Xie et al., 2011), as reviewed (Pereira & Gibson, 2002). Several studies have been performed in vitro and in rodents, and beneficial prebiotic effects are also documented in humans.

3 Towards a Modulation of Gut Microbiota and Metabolic Inflammation After Dairy Consumption

Beyond alterations of lipid metabolism, obesity and metabolic disorders such as T2D and metabolic syndrome are also characterized by a low-grade chronic inflammatory status named metabolic inflammation (Hotamisligil, 2006; Libby, 2002). Several clinical trials in obese subjects report moderate but chronic increase of proteins involved in inflammation such as C-reactive protein (CRP) or inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). The role of dietary lipids in metabolic inflammation is largely studied (Calder, 2002; Laugerette, Vors, Peretti, & Michalski, 2011; Schwab et al., 2014) as inflammation can be provoked by lipids derived from omega-6 FA for example. Moreover, recent works revealed the role of altered composition of the gut microbiota in metabolic

inflammation. Altogether, the gut microbiota is a key player in health or disease development, notably regarding metabolic diseases including obesity and T2D.

3.1 Gut Microbiota and Associated Endotoxemia

The gut microbiota is now recognized as a major player in the development of obesity and T2D. The bacterial composition of the microbiota impacts energy balance (Turnbaugh et al., 2006), glucose metabolism (Cani et al., 2007) and metabolic inflammation (Cani et al., 2008). The amount and composition of dietary lipids can modulate the composition of the gut microbiota (Murphy, Velazquez, & Herbert, 2015). Lipids from milk, lard, or polyunsaturated FA-rich oil can modulate microbiota composition and inflammation of the adipose tissue (Huang et al., 2013). A recent study in pigs reports that a mixture of vegetable oils and milk fat including MFGM extracts, compared with vegetable oils alone, modifies gut microbiota composition (phylae: increased *Proteobacteria* and *Bacteroidetes*, decreased *Firmicutes*; genus: increased *Parabacteroides*, *Escherichia/Shigella* and *Klebsiella*), intestinal physiology and lymph node secretions (Le Huerou-Luron et al., 2016).

Among possible biomarkers of inflammation associated with the gut microbiota, endotoxemia is a player of particular interest (Laugerette et al., 2011). Bacterial lipopolysaccharides (LPS), so-called endotoxins, are inflammatory molecules naturally present in the digestive tract as endogenous components of the cell wall of Gram-negative bacteria of the gut microbiota. Microbiota is present all along the digestive tract, with an important gradient from 10 bacteria per g of stomach content to 10^{12} bacteria per g of colon content. Recent studies showed that endotoxins can cause a so-called metabolic endotoxemia in plasma after the consumption of unbalanced high-fat meals (Laugerette et al., 2011). Translocation mechanisms from the gut lumen to the blood would be due to (1) intestinal absorption of LPS with dietary lipids in the small intestine on the one hand, (2) paracellular translocation due to altered gut barrier in the colon on the other hand.

Interestingly regarding specific milk fat specificity, mice fed high-fat diets containing 0.25% milk sphingomyelin (SM) presented lower metabolic endotoxemia than after a high-fat diet devoid of milk SM (Norris, Jiang, Ryan, Porter, & Blesso, 2016). This was associated with a lower proportion of Gram-negative bacteria and a higher proportion of *Bifidobacterium* with milk SM. In line with these results, Milard, Laugerette, et al. (2019) recently reported that in mice fed a mixed HF diet, milk PL can limit HF-induced body weight gain and modulate gut physiology and the abundance in microbiota of bacteria of metabolic interest. Namely, mice fed high-fat diet with 1.1% of milk PL had increased *Bifidobacterium animalis* in cecal microbiota compared to control high-fat fed mice devoid of milk PL. Mice fed high-fat diet with 1.1% of milk PL had lower *Lactobacillus reuteri*, which correlated negatively with the fecal loss of milk SM-specific fatty acids. Medium chain fatty acids (MCFA) typical of milk, namely 10:0 and 12:0, and sphingolipids, have also

shown direct bactericidal effects in vitro on *Listeria monocytogenes* and *Campylobacter jejuni*, and lower on *E. coli* O157:H7 and *Salmonella enteritidis* (Sprong, Hulstein, & Van der Meer, 2001; Sprong, Hulstein, & van der Meer, 2002). Therefore, the impact of differential release of milk lipids in the gut do to different structures of dairy matrixes on gut microbiota and endotoxemia regulation would deserve to be investigated in humans.

3.2 Metabolic Inflammation

Dairy product intake would be associated with a lower inflammatory status or would induce no inflammatory effect. As reviewed, dairy products can impact metabolic inflammation with a potential protective effect in normal-weight to obese subjects (Labonte et al., 2013; Labonte et al., 2014; Vors et al., 2015). Plasma markers of inflammation (CRP, IL-6 and TNF-α) were found lower amounts in high- dairy consumers (>14 servings/week) vs low-dairy consumers (<8 servings/week) in an observational study adjusting for confounding factors (Panagiotakos, Pitsavos, Zampelas, Chrysohoou, & Stefanadis, 2010). Moreover, fermented dairy products consumed during 3 weeks by overweight and obese men tended to lower inflammatory status in an intervention trial (Nestel et al., 2013). Yogurt consumption was also reported to reduce metabolic endotoxemia in elderly subjects (Schiffrin et al., 2009).

The presence of more or less MFGM in the dairy matrix might also contribute to impacts on metabolic inflammation. Mice fed diets base on AMF + MFGM and challenged with LPS injection had a lower inflammation (plasma concentrations of IL-6, IL-17, monocyte chemoattractant protein-1 (MCP-1) and TNF-α) than mice fed corn oil and receiving the same proinflammatory challenge; the mechanism would be due to a lower intestinal permeability with AMF+MFGM (Snow, Ward, Olsen, Jimenez-Flores, & Hintze, 2011). However, Zhou and Ward (2019) recently reported, using an ob/ob mice of preexisting obesity, that milk PL may have limited beneficial effects on gut barrier integrity, systemic inflammation, and lipid metabolism in the context of severe obesity. In a study mentioned above where mice were fed a semi-synthetic palm-oil based high fat diet for 8 weeks, or the same diet enriched with 1.2% or either soybean PL or milk PL (Lecomte et al., 2016), the WAT of mice fed with milk PL had a lower expression of markers of macrophage infiltration and of proinflammatory adipokines (MCP-1, IL-6 or TNF-α) compared with mice fed soy PL. This was associated to an increase of the number of goblet cells, that produce mucus in the colon, which could be explained by the presence of fatty acids specific of milk SM in feces (namely 22:0, 24:0) and suggest an improved gut barrier with milk PL. In this respect, Milard, Penhoat, et al., (2019) recently reported that unlike SM within the whole milk PL, pure milk SM can increase the expression of tight junction proteins in vitro in Caco-2 intestinal cells and revealed that IL-8 was a potential mediator of such effect. A modulation of gut barrier function could in the long term exert protective effects against metabolic inflammation

induced notably by the translocation of endotoxins from the gut microbiota (Lecomte et al., 2016), thereby deserving further investigation.

3.3 Newly Revealed Signalling Players: miRNA and Exosomes

Moreover, it would be important to elucidate the fate in the digestive tract and the metabolic impact of complex milk lipid nanostructures after yogurt making or cheesemaking, e.g. lactosomes and exosomes and the mRNA and miRNA they contain (Argov, Lemay, & German, 2008; Argov-Argaman et al., 2010; Bourlieu & Michalski, 2015; Izumi et al., 2015). The metabolic impacts of milk miRNA are a promising emerging research topic (Auerbach, Vyas, Li, Halushka, & Witwer, 2016; Li, Dudemaine, Zhao, Lei, & Ibeagha-Awemu, 2016; Melnik & Schmitz, 2017; Title, Denzler, & Stoffel, 2015).

Altogether, these proofs of concept in rodents support the need to investigate the relative role of the MFGM, milk fat globule structure, and dairy matrix structure, according to different dairy processes, on the gut microbiota, endotoxemia and metabolic inflammation, because the latter can be impacted by dietary lipid fate in the gut through digestion kinetics and rate. New metabolic signalling players should also be taken into account.

4 How In Vitro Models Can Improve Our Understanding of Lipid Metabolism

Several characteristics of the dairy matrices combined with the activity of lactic acid bacteria (LAB) may modulate the cardiometabolic impact of dairy lipid content, but only very little is currently known on this topic. The dairy matrix represents a complex organization of nutrients, each having to first be released during digestion and then transported through the intestine epithelial membrane to be processed and metabolized (Versantvoort, Oomen, Van de Kamp, Rompelberg, & Sips, 2005). The dairy matrix microstructure and macrostructure have been shown to significantly influence kinetics of milk protein digestion in vivo (Barbé et al., 2013). Lipids are differentially incorporated depending on food structure (milk emulsion, cheese, etc.) and little information is available on how lipids behave in the gastric environment and how these behaviors affect digestive processes (Turgeon & Rioux, 2011). In addition, the extent to which dairy product structure and food matrix alter the appearance of FA in the blood circulation, and hence their metabolic fate and cardiometabolic effects, is poorly understood and needs further investigation. In vivo studies are expensive and sometimes difficult to achieve in order to improve our knowledge on dairy lipids mechanism. Notably, exploring lipid digestion in humans requires the use of naso-gastric and naso-duodenal cannulation (Armand et al.,

1999; Carriere et al., 2000), which is a heavy process and does not provide access to the most distal parts of the small intestine. Within the past 10 years, a multiplication of papers using in vitro studies is observed in the literature and standardized in vitro methods were published (Egger et al., 2016; Kopf-Bolanz et al., 2012; Minekus et al., 2014). In vitro models allow to compare food matrices with one another under controlled conditions and to improve our understanding of food behavior during digestion.

4.1 Impact of the Dairy Matrix Structure

Several reviews now suggest that food form and texture of dairy food modulate their nutritional properties (Thorning et al., 2017; Turgeon & Rioux, 2011). Limited number of in vitro studies focused on the impact of different dairy food on lipid bioaccessibility. (Lamothe, Rémillard, Tremblay, & Britten, 2017) evaluated the matrix degradation and FA release for milk, yogurt and cheese. One hour of gastric transit time was selected to compare matrices accurately. Protein hydrolysis was significantly higher in milk and yogurt than for cheese (~35 vs 20%). Milk and yogurt matrix degradation was fast while for cheese, the solid matrix was slowly disintegrated. When nutrients reach the duodenum, protein and lipid hydrolysis is quickly increased for each matrices, and cheese degradation reached values higher than 90% (Lamothe et al., 2017). During gastric digestion, solid matrices require strong shear forces to reduce their particle size to values smaller than 1–2 mm in order to be emptied in the duodenum (Kong & Singh, 2008). In human, the gastric transit time is adjusted based on the composition and the consistency (viscosity, texture) of the chyme (Hunt & Knox, 1968). This is of strong importance in regards to the protective effect of the cheese matrix against saturated FA intake. Indeed, the wide variety of existing cheeses (composition, texture, etc.) suggests potential heterogeneity in their digestive and absorptive processes. Lipid droplets size and their interface organization, TAG structure (position of FA on the TAG glycerol backbone), type and amount of phospholipids, are among the reported factors affecting FA bioavailability (Favé et al., 2004). In addition, fat globules are trapped in the cheese matrix which could delay or gradually release TAG during digestion and subsequently affect postprandial lipemia and also the fate of different lipid species along the gut. Studies investigating the impact of commercial cheeses with different composition and textural properties were performed (Fang, Rioux, Labrie, & Turgeon, 2016a; Fang, Rioux, Labrie, & Turgeon, 2016b; Guinot, Rioux, Labrie, Britten, & Turgeon, 2019; Lamothe, Corbeil, Turgeon, & Britten, 2012). Mild, low fat and aged cheddar along with mozzarella were submitted to an in vitro digestion system (Lamothe et al., 2012). The matrix degradation was investigated and at the end of the gastric digestion, aged cheddar was more disintegrated than low fat cheddar due to its low cohesiveness and elasticity. During the duodenal phase, different kinetics of matrix degradation was observed attributed to the protein matrix density and fat distribution. Mozzarella showed the greatest degradation at the end of the

duodenal digestion due to its porous matrix (large fat pools) and its lower cohesiveness. The disruption of the solid matrix also regulates FA release rate and mozzarella showed the greatest increase in lipolysis within the first 90 min of duodenal digestion. Due to its high degradation, mozzarella lipid content was easily accessible to lipase increasing FA release. The degradation of regular and light cheeses like cheddar and mozzarella was studied using an in vitro model (Fang et al., 2016b). Although lipolysis during duodenal digestion was not the main target of the study, they analyzed the degradation of the matrix over time and cheese disintegration was ranked as followed: cheddar > light cheddar > mozzarella = light mozzarella independently of the digestion step (oral, gastric or duodenal). Using the composition and textural properties data, a prediction model was established to estimate cheese disintegration. Cheese fat content, proteolysis, hardness and chewiness was shown to positively affect the matrix disintegration. In a study including nine commercial cheeses, Guinot et al. (2019) have shown a correlation between texture parameters, cheese disintegration and lipid release from the cheese matrix during in vitro gastric digestion. Elastic and cohesive cheeses as Mozzarella and young Cheddar were disintegrated slowly as compared with cheeses which fractured more easily as aged cheddar. Therefore, the protein network and physicochemical properties of cheese may modulate the kinetics of digestion and lipid absorption.

4.2 Impact of the Dairy Matrix Manufacturing Steps

Dairy processing steps such as heat treatments, homogenization, etc. are required to ensure food safety and stability over time. These operations are known to modify the structure of proteins and lipids which subsequently affect the product composition and texture. For example, the denaturation of whey proteins after heat treatment of milk improve the quality of yogurts. Water retention (Harwalkar & Kalab, 1986) and textural (Cobos, Horne, & Muir, 1995; Rohm & Schmid, 1993) properties of yogurt are improved. The next section explores the possible impact on nutrients digestibility.

4.2.1 The Importance of the Homogenization/Pasteurization Sequence

Early work on the impact processing treatments was mainly focused on dairy proteins. For example, heat treatment promotes whey proteins (β-lactoglobulin) denaturation by increasing their proteolysis by gastric and duodenal enzymes (Mullally, Mehra, & FitzGerald, 1998). Later, the in vitro digestion of protein and lipid from milk products was shown to be affected by the processing treatments (Devle et al., 2014; Tunick et al., 2016; Van Hekken, Tunick, Ren, & Tomasula, 2017; Ye, Cui, Dalgleish, & Singh, 2016a). During digestion, milk proteins namely caseins clots in the gastric environment. This coagulum structure is altered when milk is heated and whey protein is denatured (Ye, Cui, Dalgleish, & Singh, 2016b). The clot was dense

and tightly bound into a homogeneous mass for raw milk while for heated milk, it was more porous and fragmented. In addition, few whey proteins were seen in the clots of raw milk as opposed to the heat treated milk. Proteolysis was also improved with the heat treatment where at the end of the gastric digestion (2 h), no intact casein and whey proteins were visible on an SDS-PAGE as opposed to raw milk. In the presence of whole milk, the fat globules were trapped within these clots but how the structure of these clots affects FA release? In raw whole milk, the clots contained caseins, fat and few whey proteins while in heated milk, caseins, denatured whey protein and fat were fully included in the coagulum (Ye et al., 2016a). Although the coagulum structure was different in both milks, the release of the fat out of the coagulum was similar in both milks. Confocal images taken during gastric digestion revealed that fat globules in both milks were trapped within the coagulum but were not involved in the structure of the clots. This is an agreement with a previous study showing that native fat globules (covered with MFGM) were considered as inactive fillers in rennet gel formed with raw whole milk (Michalski et al., 2002). Therefore, as the clotted proteins are hydrolyzed by pepsin fat is slowly released in the chyme at similar rates in both milks. However, commercial fluid milk is usually homogenized and then pasteurized before its consumption and these treatments affect fat globule structure which could modify the clot structure. Ye, Cui, Dalgleish, and Singh (2017) investigated how these combined processing treatments affected the clot structure, degradation of dairy protein and fat release in the chyme. Raw whole milk was homogenized or homogenized-pasteurized. The degradation of the clot and the release of the fat in the chyme were higher for homogenized-pasteurized milk > homogenized > raw whole milk at the end of the gastric digestion (2 h) and this was mainly attributed to the structure of the clot. In raw whole milk, the coagulum was dense with a smooth cohesive mass while for homogenized-pasteurized milk, the structure was fragmented and brittle. Caseins and whey proteins were almost fully degraded in homogenized-pasteurized milk at the end of the gastric digestion in the clot and in the chyme as opposed to raw whole milk. In homogenized-pasteurized milk, the fat globule can interact with caseins and whey proteins altering the structure of the gel allowing a better diffusion of pepsin. Therefore, proteolysis in increased in homogenized-pasteurized milk promoting clots degradation and fat release. These studies investigated the behavior of milk clotting during gastric digestion and they showed that the processing treatment applied to the milk might affect the kinetics of lipid release.

Other studies have also been made with digestion system mimicking gastric and duodenal steps. (Tunick et al., 2016) proceeded to the digestion of raw whole and skim milks that were subsequently homogenized, pasteurized, homogenized-pasteurized or homogenized-sterilized using an in vitro digestion model. During gastric digestion (last 1 h), only modest differences in protein degradation were observed for milk despite the use of different manufacturing processes. Only homogenized- pasteurized and homogenized-sterilized whole milks showed darker bands in the peptides region (below 5 kDa). During duodenal digestion, the presence of fat in whole milk appears to delay protein digestion independently of the processing treatment. In whole milk, the homogenization treatment showed darker

low molecular weight protein bands (<5 kDa) suggesting possible lipid-peptides associations (Michalski & Januel, 2006) compared to raw skim milk. When whole milks are pasteurized or homogenized-pasteurized, β-lactoglobulin persisted for a longer period of time as shown on SDS-PAGE gels delaying protein digestion compared to pasteurized skim milk. Similar observations were made in another study, where whole homogenized-pasteurized and skim pasteurized milks were digested in vitro using human gastrointestinal enzymes (Devle et al., 2014).

The authors suggested (1) possible FA-β-lactoglobulin associations preventing its hydrolysis or (2) the lack of bile salt secretion in the human duodenal juice. This last hypothesis is plausible since (Kopf-Bolanz et al., 2012) observed that when bile was omitted in their digestion model, β-lactoglobulin was still present and proteolysis was significantly reduced at the end of the duodenal digestion of pasteurized-homogenized whole milk.

Altogether, milk processing treatments clearly have an impact on protein digestion. But what are the consequences on the digestion of lipid? Early work on emulsion have previously shown that the fat droplet size affects their lipolysis by pancreatic lipase (Armand et al., 1992; Benzonana & Desnuelle, 1965). Milk fat homogenization is well known to decrease the fat globule size and an increase in lipolysis is therefore expected (Claeys et al., 2013). Tunick et al. (2016) showed that milks that had undergone a homogenization treatment had higher lipolysis during duodenal digestion due to the increase in free FA content. This was also confirmed by several other studies (Devle et al., 2014; Lamothe et al., 2017; Van Hekken et al., 2017). In addition, the whole homogenized-pasteurized milk exhibited the highest lipolysis at the end of the duodenal digestion (lasted 2 h) (Tunick et al., 2016). Following the homogenization of the milk, the structure of the fat globule is modified, and a new interface is created. The order in which the manufacturing processes (i.e. homogenization before or after the heat treatment) are applied will influence the nature of this new interface (Michalski, 2009). Conversely, whole raw milk that was either pasteurized or pasteurized-homogenized were digested in vitro using human gastrointestinal enzymes showed different protein digestion (Islam et al., 2017). The milk submitted to a homogenization treatment showed increased lipolysis at the end of the duodenal digestion compared to whole raw milk. These results are also in agreement with a previous study which only focused on the duodenal digestion (Ye, Cui, & Singh, 2010). The sequence of the processing step impacts protein hydrolysis kinetics but it is not clear if this has an influence on FA release and on lipemia in human.

Of note, contradictory results were found regarding FA bioaccessibility for homogenized, homogenized-pasteurized and homogenized-UHT milks compared to raw milk (Liang, Qi, Wang, Jin, & McClements, 2017). Raw and homogenized milks have similar FA release at the end of the duodenal digestion as opposed to the other studies (Devle et al., 2014; Lamothe et al., 2017; Tunick et al., 2016; Van Hekken et al., 2017). The authors suggested that the milk sample and the processing steps could be responsible for this discrepancy. However, the milk particle size after processing (raw ~3.6 μm and homogenized- pasteurized ~0.5 μm) were in similar range than the study of (Lamothe et al., 2017) which ruled out these two factors. The

authors also suggest that the different in vitro model could account for these differences but without any further explanation. The selection of the in vitro model, therefore, appears to be of utmost importance and great care should be undertaken to carefully select the enzymes. The utilization of harmonized in vitro model allows better comparison between studies (Mat, Le Feunteun, Michon, & Souchon, 2016; Minekus et al., 2014).

4.2.2 Impact of Gelation/Cheesemaking

During dairy gel formation (acid or rennet), the structure of the dairy protein is altered and several factors such as milk pH, dairy formulation composition, LAB, temperature, etc. are known to influence the matrix structure (Aguilera, 2006). A limited number of studies have looked at the impact of dairy gels processing steps on lipid digestion. Stirred- and Greek-style yogurts were prepared from homogenized and heat treated milk (95 °C × 5 min) (Lamothe et al., 2017). Similar protein and lipid hydrolysis was observed during in vitro digestion. However, Greek-style yogurt tended to have a lower lipolysis attributed to its lower calcium content. Another study investigated how cream homogenization and cheesemaking pH (5.5 and 6.5) during cheddar manufacture will impact cheese nutrients release during digestion (Lamothe et al., 2017). The homogenization had no impact on the matrix degradation during in vitro digestion while the pH showed a significant impact. Cheese made with milk adjusted at pH 6.5 retained a higher proportion of calcium and moisture within the matrix while lower amounts of protein and fat were found when compared to cheese made with milk at pH 5.5. This favored the degradation of cheddar cheese made with milk adjusted to pH 6.5. The pores of the matrix are looser in high moisture cheese promoting enzyme diffusion and increasing protein hydrolysis. Indeed, the percentage of trichloroacetic acid (TCA) soluble proteins at the end of the gastric digestion was higher for cheeses made at pH 6.5. During duodenal digestion, a different behavior was observed. Both cheeses had a constant increase of degradation over time, but it was higher for cheese made at pH 5.5. The higher amount of calcium in cheddar made at pH 6.5 has promoted the contraction of the casein network due to the reduction of electrostatic interactions between casein molecules lowering the matrix degradation during duodenal digestion. This has resulted in a lower protein hydrolysis. Lipolysis was affected by both the homogenization treatment and the cheesemaking pH. FA release is faster for homogenized milk than for non-homogenized milk as expected. In non-homogenized milk, the pH had an important impact on lipolysis. In cheese made at pH 5.5 (low calcium content), the lipolysis rate was significantly lower than for cheese made at 6.5. Calcium ions are known to promote lipolysis due to their capacity to precipitate long-chain FA reducing the steric hindrance around the fat droplet. In homogenized milk, lipolysis was not affected by the milk pH. The smaller fat globules promoted the accessibility of lipases to their action site increasing dairy fat lipolysis. A recent publication investigating fat release and lipolysis of commercial cheeses during in vitro gastric and duodenal digestions (Guinot et al., 2019) revealed differences in

free fatty acids released. The fat globule size (homogenized or not), fat and calcium content were the most influential factors on the lipolysis rate.

Additional research was conducted dairy protein emulsion gels and how their structure impact in vitro lipid digestion, as reviewed in (Guo, Ye, Bellissimo, Singh, & Rousseau, 2017). These studies are important because they allow to gain additional fundamental information on how isolated component of the matrix can impact lipid digestion. For example, gel firmness and protein density were shown to affect the kinetics of lipid release (Guo, Bellissimo, & Rousseau, 2017). Readers are referred to the previous chapter for more information on this topic (Chap. 7).

4.3 Impact of the Dairy Matrix Composition

4.3.1 Protein Content

The amount of dairy protein was shown to have an impact on lipid metabolism (Section 2.3.2). To our knowledge, no study investigated the impact of dairy protein concentration on lipid release as the main outcome. One example was provided in Sect. 4.2.2 where stirred- and Greek-style yogurts containing respectively 5.2 and 9.2% of proteins had no impact on lipolysis (Lamothe et al., 2017) and readers are referred to this section for more details. In addition, (Devle et al., 2014) studied FA bioaccessibility in homogenized-pasteurized whole milk and in milk permeate enriched with dairy fat. At the end of the duodenal step, the degree of lipolysis was low (16%) for ultra-filtered permeate containing milk fat (no protein) compared to full fat milk (37%). This may be due to the ability of milk proteins/peptides to act as emulsifiers in cooperation with bile acids, resulting in smaller fat globules with a larger surface area making them more available for attack by pancreatic lipase (Devle et al., 2014). Additional studies are necessary to confirm this hypothesis.

4.3.2 Fat Globule Size and Interface Composition

Smaller fat droplets improve lipase efficiency which results in vivo, in faster plasma TAG appearance (Vors et al., 2013). The fat globule size as influenced by different homogenization treatment or microfiltration procedure and its impact on FA release was investigated (Berton et al., 2012; Garcia, Antona, Robert, Lopez, & Armand, 2014; Islam et al., 2017). Whole pasteurized milk submitted to two homogenization treatments (5 vs 15 MPa) showed different rate of lipolysis (Islam et al., 2017). For the high pressure treated milk (average size: 0.58 μm), lipolysis reached a plateau after 30 min of duodenal digestion and 78% of FA were released after 120 min. The low pressure homogenized milk (average size: 1.45 μm) did not reach a steady state and only 56% of FA were released at the end of the duodenal digestion. These results suggest different kinetics in FA release.

Another study aimed to investigate the hydrolysis kinetics of pancreatic lipase of milk fat globules with different interface composition (Berton et al., 2012). Raw whole milk (average size: 3.9 μm) was fractionated by microfiltration to obtain milk with small (average size: 1.8 μm) and large (average size: 6.7 μm) native fat globules (Berton et al., 2012). Lipase catalytic efficiency (CE: mL/sec × mg of lipid) was determined based on the fat concentration. Data showed a significantly higher CE for milk with small native fat globules compared to the large native fat globules and raw whole milk. This is in accordance with another study (Garcia et al., 2014). In addition, milk homogenized (altered fat globule interface) at different pressures (HM: 50, 300 and 400 MPa) were studied. Particle size ranging from 1.5 to 0.14 μm for homogenized milks and 3.9 μm for raw whole milk was obtained. Homogenized milk displayed similar CE independently of the pressure used and their values were higher compared to the raw whole milk. Milk homogenized at 50 MPa and milk with the small native fat globule showed similar particle size but showed different behavior. Their data suggests that homogenized milk was hydrolyzed more quickly than milk with native fat globule of similar particle size. Therefore, the size of the fat globule is not the sole factor modulating lipase activity and composition of the interface play an important role. Of note though, in neonatal digestion conditions, it is the interfacial surface area that plays the major role as also pointed out by Bourlieu et al. (2015). Previous works on emulsions in adults' physiological conditions also confirmed the significance of the interface composition on fat digestion and additional information was reviewed in (Golding & Wooster, 2010).

4.3.3 Calcium Content

High calcium concentration in cheese may reduce the bioavailability of specific FA by precipitation as calcium salts (Lamothe et al., 2012). Calcium is known to increase lipase activity during digestion (Hu, Li, Decker, & McClements, 2010), but the formation of insoluble calcium soaps reduces fatty acids absorption and increases faecal fat excretion (Lorenzen & Astrup, 2011). In the duodenal environment, the solubility of calcium soaps decreases with increasing FA chain length and saturation (Graham & Sackman, 1983).

Depending on the calcium concentration in model cheese (cheddar type), lipolysis is increased (Ayala-Bribiesca, Lussier, Chabot, Turgeon, & Britten, 2016) and 4–23% of the fat were insolubilized as calcium soaps in duodenal environment (Ayala-Bribiesca, Turgeon, & Britten, 2017). However, the addition of calcium did not significantly reduce the bioaccessibility of individual long-chain FA in this study as opposed to the in vivo study (Ayala-Bribiesca et al., 2018). In addition, cheeses prepared with AMF having different melting points showed different matrix degradation rates. Indeed, at the end of the gastric digestion the stearin AMF cheese degradation was significantly lower than the control and olein AMF cheeses. As opposed to other studies, this was not associated with the initial texture since cheese hardness was not significantly different at 37 °C. However, the melting points of the AMF could account for these differences. Stearin AMF has a melting point higher

than body temperature (42.3 °C) increasing the resistance to matrix degradation during gastric digestion. Lipolysis and subsequently the overall FA bioaccessibility were also reduced in the presence of stearin AMF due to a lower degradation of the matrix.

The calcium content was shown to promote lipolysis, but the concentration found within the matrix is also important. Casein emulsion gels (mimic cheese analogues) with two calcium concentrations (774 vs 357 mg Ca per 100 g) prepared with AMF were investigated (McIntyre, Osullivan, & Oriordan, 2017). Different kinetics of matrix degradation were found during gastric digestion where the high calcium gel exhibited a faster degradation. At the end of the duodenal digestion, the gels reached the same extent of degradation. However, no differences in lipolysis rate was observed as opposed to the study of (Ayala-Bribiesca et al., 2016) who studied cheeses with different calcium content. The discrepancy between both studies could be attributed to the dose of calcium found in each gel where the control and the high calcium cheeses respectively contained 595 and 1202 mg Ca per 100 g. The comparison of the matrices with the highest calcium levels in both studies shows a difference of 1.6 times lower for emulsified gels. Therefore, the amount of calcium is matrix dependent and further research is needed.

4.3.4 LAB and Cheese Microflora

For most varieties, the cheese microflora has an impact on the cheese FA availability through the action of microbial and/or fungal lipase during the ripening process. This activity is of utmost importance to produce flavour precursors (Collins, McSweeney, & Wilkinson, 2003; Das, Holland, Crow, Bennett, & Manderson, 2005). As an example, *Geotrichum candidum*, a yeast mainly found in washed-rind and mold-ripened cheeses, synthesize two lipase isoforms (GCLI and GCLII) having significant biases toward specific TAG (Baillargeon, Bistline Jr, & Sonnet, 1989; Bertolini et al., 1994; Bertolini et al., 1995). GCLII is more specific for the short-chain FA residues (C8–C14), while GCLI is specific for the C18:1, C18:2 and C18:3 FA residues (Bertolini et al., 1995; Charton & Macrae, 1992; Das, et al., 2005; Jacobsen & Poulsen, 1992, 1995). Moreover, the release of FA from TAG has been reported to be highly species/strain dependent (Collins et al., 2003). All together, this information suggests that the availability of the FA could differ greatly depending on the dairy matrices but to our knowledge, no study has investigated that topic.

5 Examples of Relationship Between In Vitro and In Vivo Models of Dairy Matrix Digestion

In vitro models are important to isolate one or more factors that influence the digestibility of dairy matrices. They are performed to understand the mechanism behind postprandial results or to plan in vivo studies. The literature covered in this chapter

mainly focused on in vitro studies that aimed to understand the impact of the matrix structure, the dairy processing steps, the fat globule size and the calcium content. Correlation between in vitro and in vivo studies allowed to confirm the impact of different kinetics of digestion on postprandial lipemia. As explained previously, the kinetics of plasma TAG release was faster for a cream cheese meal than for a Cheddar meal in healthy volunteers (Drouin-Chartier et al., 2017). Cream cheese is a semi-solid matrix composed of emulsified dairy fat (average size: 0.5 μm) that was shown to easily melt at body temperature increasing fat bioaccessibility (Guinot et al., 2019). For Cheddar cheese, native fat droplets are found (average size: 3.0 μm) and the matrix must be disintegrated to allow dairy fat digestibility. Guinot et al. (2019) studied the matrix disintegration of the cheeses used in breakfast meals of the human clinical trial. The cream cheese was easily disintegrated while Cheddar disintegration was slow and this may have induced different gastric emptying rate and postprandial responses between cheeses. Other in vitro studies, showed that the Cheddar cheese matrix is slowly disintegrated and reached only 25–43% of degradation after 2 h (Fang et al., 2016b; Lamothe et al., 2012). Also, the fat droplet size is significantly lower for cream cheese. Emulsified dairy fat (alteration of the native interface) showed increase lipolysis in in vitro (Islam et al., 2017) and in vivo (Vors et al., 2013) studies. All these studies support the fact that the cheese matrix modulates postprandial lipemia. Another in vitro/in vivo correlation regards the calcium content and FA melting point towards the bioavailability of milk lipids.

Another example of correlation between in vitro and in vivo studies was performed recently with experimental cheese. Cheddar-type cheeses manufactured with different AMF (olein vs stearin) and calcium (regular: 50 mg and high: 66 mg) contents were studied in vitro (Ayala-Bribiesca et al., 2017) and in vivo (Ayala-Bribiesca et al., 2018). In cheddar-type cheese with regular and high calcium content, the stearin AMF exhibited lower plasma TAG responses compared to the olein AMF in the rat model. *In vitro* study revealed that lipolysis and the overall FA bioaccessibility were also reduced in the presence of stearin AMF due to a lower degradation of the matrix. Indeed, stearin AMF has higher melting point than body temperature (42.3 °C) increasing the resistance to gastric digestion. Also, the mass fraction of the total FA recovered in the animal feces were significantly higher with the stearin AMF meal compared to the olein AMF meal independently of the calcium concentration. The *in vitro* study revealed that 23% of the fat was insolubilized as calcium soaps in duodenal environment with the stearin AMF cheese (Ayala-Bribiesca et al., 2017). For the rats fed high calcium cheese, fat excretion was higher and long-chain FA represented 66% of the fat excreted. However, the reduction of the bioaccessibility of individual long-chain FA in the *in vitro* study was not corroborated (Ayala-Bribiesca et al., 2018). Therefore, both studies revealed that dairy fat bioaccessibility and bioavailability were reduced in the presence of a stearin AMF and high calcium concentration diet. This provides incentive to further study *in vivo* and notably in humans, the impact of different combinations of milk FA profiles, calcium content and matrix structures on digestion, absorption and metabolism.

Perspective on the Importance of In Vitro Models In vitro models have traditionally been used to study the survival of probiotic bacteria in food matrices, drug delivery, bioaccessibility of food contaminants and many other application (Adouard et al., 2016; Blanquet et al., 2004; Hernández-Galán et al., 2017; Versantvoort et al., 2005). Nowadays, these in vitro models are now well recognized in the literature since they improve our knowledge about the behavior of food matrices during digestion. Static and dynamic models have been used and each of them possess great advantages and weaknesses (Shani-Levi et al., 2017). Among their strengths, the controlled use of the amount of enzymes, pH, temperature, and stirring speed is reported. On the other hand, it is sometimes difficult to mimic the physiological conditions (children vs. adults vs elderly, fasted vs fed state, etc.), especially gastric emptying being the rate-limiting step of nutrients bioavailability. However, it is always important to keep in mind that for each of in vitro model it is important to perform adequate validation in vivo studies performed in animal model or in humans (Bohn et al., 2017).

In vitro cellular models are also used to understand absorption kinetics of several nutrients (Ex: Caco-2 cell line) and for example, to further understand post-prandial lipid absorption (Vors et al., 2012). The microbiota is also another hot topic since it might impact the host lipid metabolism (Bondia-Pons, Hyötyläinen, & Orešič, 2015). Several in vitro models were created to gain more information on how the host flora is modulated by food, probiotics, drugs, etc. (Aguirre et al., 2016; Fernandez, Savard, & Fliss, 2016; Ramadan et al., 2013). Readers are referred to review papers for more information (Guerra et al., 2012; Payne, Zihler, Chassard, & Lacroix, 2012).

6 Conclusion

Recently gained knowledge of the postprandial phase raises several mechanisms by which the dairy matrix structure can modulate the digestion, metabolic fate and physiological impact of milk lipids (Fig. 8.3), notably by its viscosity, nutrient composition and supramolecular organizations. According to the different types of products and processes, this “dairy matrix effect” has now to be elucidated in more details. Regarding milk processing, more studies are needed to elucidate in humans the impact of milk homogenization on lipid fate in the body and metabolic consequences. To date, reviews report no clear link between milk homogenization and health, but this subject of debate deserves further clinical studies as this process changes dramatically milk fat globule structure. Regarding the fat composition of the dairy matrix, two aspects deserve presently more attention: the amount of fat on the one hand, and the quality of fat regarding PL/MFGM presence and amount.

Different epidemiological studies and meta-analyses of clinical trials highlight the importance of studying in more details the metabolic impact of dairy products with different fat contents with an aim to challenge the current dietary guidelines

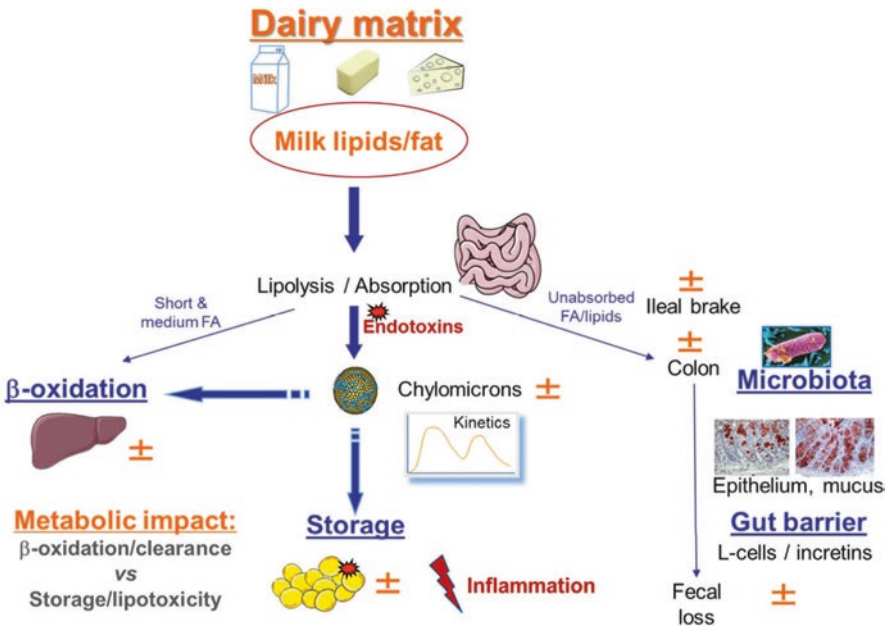


Fig. 8.3 Postprandial lipid metabolism. Intestinal lipid absorption modulates postprandial lipemia and the metabolic fate of absorbed lipids. The coabsorption of endotoxins from the gut microbiota can contribute to metabolic inflammation. Unabsorbed lipids in the gut can trigger satietogenic signals via the ileal brake and via incretin secretion by L-cells, impact gut microbiota and the intestinal barrier notably through a modulation of mucus-producing goblet cells

advising to consume mainly low-fat dairy. Long-term nutritional interventions are now necessary to elucidate the link between full-fat dairy consumption and metabolic and cardiovascular risks, as recent articles suggest a beneficial effect. Regarding the impact of the polar lipid fraction of milk fat, available supplementation studies with MFGM extracts in healthy humans with milk PL at around 3 g/day do not show significant effects on intestinal cholesterol absorption or plasma lipids. Performing studies in patients with metabolic syndrome, moderate hypercholesterolemia or high blood pressure could provide more insight on the potential beneficial effects of milk PL and MFGM, as recently demonstrated in overweight postmenopausal women using 3–5 g/day of milk PL in a cream cheese matrix. Adapted from Michalski (2009), Michalski et al. (2013), Bourlieu & Michalski (2015).

Dairy matrixes can also greatly vary in their protein composition. Several clinical trials show that the type of dairy proteins can modify postprandial lipemia: whey proteins would be hypolipemic but this remains to be confirmed using test meals of different protein composition and of different matrix composition and structure. Moreover, the relative impact of protein amount, type, location at the interface of fat droplets or in the aqueous phase or proteinaceous network, denaturation and consequences relative to viscosity, are related and their consequences should now be

deciphered in humans. This provides incentive to further explore the dairy matrix effect on lipemia modulation by different amounts and types of proteins. Finally, the metabolic importance of the gut barrier and the gut microbiota has recently been revealed. Moreover, metabolic diseases such as obesity and type 2 diabetes are characterized not only by disorders of lipid metabolism but also by metabolic inflammation in which lipid metabolism, gut microbiota and gut barrier play a role. In this respect, the dairy matrix composition and structure can modulate these outcomes in many ways, notably via bioactive metabolites derived from the lactic acid bacteria, by bioactive peptides released during digestion or by components of the MFGM.

Altogether, proofs of concept performed in rodents support the need to investigate the relative role of the MFGM, milk fat globule structure, and dairy matrix structure, according to different dairy processes, on the gut microbiota, endotoxemia and metabolic inflammation. Metabolic inflammation can be impacted by dietary lipid fate in the gut through digestion kinetics. New metabolic signaling players should also be taken into account such as miRNAs. Moreover, the impact of the dairy matrix on other health outcomes such as, e.g., IBD, cancer, cognition, neurological diseases is still an open field of research.

To better screen and understand mechanisms related to matrix disintegration and digestion in the gut, in vitro models will continue to be the first approach as they are performed under controlled conditions, allow comparison between laboratories (when a standardized method is used) and the number of samples studied can be larger than with in vivo trials. Recently, addition of cellular models allows to apprehend absorption kinetics of specific nutrients. However, a validation with in vivo models remains an essential step because some physiological events such as gastric mechanical movements and gastric emptying cannot be mimicked efficiently by in vitro models. Furthermore, the real life feeding pattern is composed of a variety of foods consumed within and between meals. The study of individual foods is only the first step of a more inclusive approach of the digestive fate of meals. It is the variety of experimental approaches used that will permit to gain valuable knowledge on lipid metabolism and continue to explore the complex food-health axis.

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