Postprandial Lipaemia, Haemostasis, Inflammatory Response and other Emerging Risk Factors for Cardiovascular Disease: The Influence of Fatty Meals

S. D. Poppitt*

Human Nutrition Unit, School of Biological Sciences, Department of Medicine, University of Auckland, Auckland, New Zealand

Abstract: Adverse changes in postprandial metabolism may promote the development of cardiovascular disease (CVD) through a range of mechanisms. Since a large proportion of our day is spent in the postprandial state it is important to understand these post meal changes with respect to both the amount and type of nutrient consumed. Of particular importance appear to be the fatty meals, commonly eaten and which can induce significant postprandial lipaemia, accumulation of potentially atherogenic triglyceride-rich lipoprotein (TRL) remnants and formation of highly oxidisable small, dense low-density lipoproteins (LDL). In addition to these relatively well established lipaemic effects there is growing evidence that high-fat foods also have adverse effects on a number of the emerging CVD risk factors including haemostasis, mediators of inflammation and endothelial function. This review will consider the acute effects of high-fat feeding, investigating any differential effects of saturated and unsaturated fatty acids, on postprandial lipaemic profile, haemostatic clotting factors fibrinogen and factor VII, acute phase C-reactive protein (C-RP), inflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), and vascular reactivity.

Keywords: Postprandial, high-fat, lipaemia, haemostasis, C-RP, IL-6, TNF-α, vascular reactivity.

POSTPRANDIAL METABOLISM AND CARDIOVASCULAR DISEASE

Changes in postprandial metabolism are invoked every time we eat a meal. Humans are repeatedly exposed to this non-fasted state and it has become apparent that alongside basal or fasting metabolism, postprandial disturbances may also play an important role in the development and progression of cardiovascular and associated diseases [1-3]. Dietary lipid appears to be important in the control of postprandial metabolism. Significant lipaemia can be induced by as little as 40-50 g of triacylglycerol (TAG) and consecutive fatty meals may enhance the lipaemia, yet we may consume as much as 150g of dietary TAG during a large meal. Exaggerated postprandial lipaemia, characterised by an increase in circulating triacylglycerol-rich lipoproteins (TRL) after eating, was one of the earliest changes to be identified as important to the process of atherogenesis [3] and remains an established feature in the development of cardiovascular disease (CVD) [4-7]. During the lipaemic response TRL and TRL remnants may be deposited into the arterial wall and accumulate in atheromatous plaques [3], there is formation of highly oxidisable small, dense low-density lipoproteins (LDL) and reduced concentration of high-density lipoproteins (HDL) [8], all of which typify the atherogenic lipoprotein phenotype identified by Miesenbock and Patsch in the early 1990s [9].

The regulation of lipaemic response however is not the only critical feature of postprandial metabolism. Large epidemiological trials including the Indian [10] and Lyon [11]. Heart Studies have shown that even in the absence of an improved lipid profile, modulating factors such as diet can improve CVD risk. Other markers of risk which are potentially susceptible to both long-term and acute modification by diet include lipoprotein (a) [Lp (a)], haemostasis, such as plasma fibrinogen and factor VII (FVII), mediators of inflammation including the acute phase C-reactive protein (C-RP) and the cytokines interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), and indicators of endothelial function such as endothelium-dependent vasodilation.

Lp (a) consists of an LDL particle covalently attached to apolipoprotein (a). It is homologous to plasminogen and hence may suppress normal fibrinolytic activity and have a role in atherothrombogenesis [12]. The physiological role of Lp (a) is not yet established but high fasting levels are correlated with markers of inflammation [13] and associated with an increased risk of vascular disease [12, 14, 15]. Whilst fasting Lp (a) was long believed to be predominantly genetically predetermined [16, 17], encouraged by the inability of many lipid-lowering pharmaceutical products to decrease serum levels, there is growing evidence that modulation through diet can alter both fasting and postprandial levels. Interestingly alcohol intake may also modulate fasting levels of Lp (a) [18].

Disorders of both coagulation and fibrinolysis have been shown to contribute to the development of cardiovascular diseases including coronary artery disease, essential hypertension, ischaemic stroke and deep vein thrombosis. Increased plasma fibrinogen and FVII activity have both been identified as independent predictors of cardiovascular mortality in a number of trials [19-21], and whilst this relationship has not been confirmed in all studies [22-25],

*Address correspondence to this author at the Human Nutrition Unit, 18 Carrick Place, Mount Eden, Auckland, New Zealand; Tel: ++ 64 9 36305160; Fax: ++ 64 9 6305764; E-mail: s.poppitt@auckland.ac.nz

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they have been the target of a number of dietary strategies aiming to improve CVD risk. FVII in particular appears to be acutely altered by nutrient intake, including fatty meals [26-28].

Inflammation is critical in all stages of atherosclerosis [29] and C-RP, an acute phase plasma protein expressed principally by the liver, has been shown to predict both cardiovascular events and prognosis post-event [30-34]. There is also a growing body of data that C-RP may actively promote atherogenesis [35-40], causing lesion formation through mechanisms including endothelial dysfunction and leukocyte activation [37, 38, 41] and altering plaque architecture reducing stability and enhancing rupture. Proatherosclerotic effects of C-RP may be caused in part by increased secretion of the endothelium-derived vasoactive factor endothelin-1 (ET-1) and the cytokine IL-6 [40], and there is evidence that IL-6 is necessary for the induction of C-RP [42]. Both epidemiology and intervention trials show that circulating C-RP can be modified through dietary change. Long-term supplementation with n-3 polyunsaturated fatty acids (PUFA) in particular may decrease serum C-RP [43]. Far less is understood about postprandial changes in response to diet.

The cytokines IL-6 and TNF-α are also key mediators of inflammation [44-46] as well as having a role in host defense [47, 48]. IL-6, which appears to have both pro- and anti-inflammatory properties, is produced by immune cells, monocytes, macrophages as well as cardiovascular components such as endothelial cells, vascular smooth muscle cells and ischaemic myocytes [49-51]. Hence it is involved with both inflammation and regulation of cardiac metabolism. Whilst there is evidence that IL-6 is necessary for the induction of C-RP [42] it has also been shown in turn that IL-6 release is stimulated by C-RP [40, 52], although this may be an indirect effect of C-RP down-regulation of an as yet unidentified IL-6 inhibitor such as nitric oxide (NO) [53]. IL-6 has been strongly implicated in the pathogenesis of coronary heart disease [54], severity of left ventricular dysfunction [55] and unfavourable outcome of patients hospitalized for unstable angina [56]. TNF-α also appears to be stimulated by C-RP [52]. Circulating levels are increased in advanced heart failure [57], left ventricular dysfunction, pulmonary edema [58], and cardiomyopathy [59] and predict excess risk of recurrent coronary events [60]. Whilst there is evidence that long-term changes in diet modulate fasting levels of these cytokines [61-63] less is known of their acute postprandial response to meals.

Endothelial dysfunction has also been shown to be a risk factor for CVD [64, 65] and is present in a range of disorders including hypertension, dyslipidaemia, type 2 diabetes (T2DM) and smoking. Endothelial damage may lead to a decreased availability of NO which is a strong endogenous vasodilator [66], and the dysfunction appears to result from a combination of enhanced endothelium activation and impaired endothelium-dependent vasodilation. Conduit vessel endothelial health is commonly determined through measurement of flow-mediated dilation of the brachial artery. As well as being influenced by features of the habitual background diet such as n-3 PUFA marine oils, antioxidants and folic acid, there is growing evidence that endothelium-dependent vasodilation is impaired by acute changes in the postprandial state and that this may be related to the postprandial rise in TAG [67-69].

EFFECT OF HIGH-FAT MEALS ON POSTPRANDIAL RESPONSE

(i) Lipaemia

It has long been established from a range of studies such as those feeding low (0-50g) [70] and high (50-80g) [71] volumes of fat in mixed meals, fat derived from specific high lipid products such as dairy cream [72] and flavoured vegetable oils [73] that there is a strong, dose dependent relationship between the total fat content of a meal and the lipaemic response. The predominant dietary lipid, long chain TAG, is absorbed *via* the enterocytes and secreted as chylomicron particles into circulation. The efficiency with which dietary fat is processed in the small intestine results in almost complete absorption hence chylomicron-TAG can be rapidly influenced by the changes in quantity of lipid eaten. In a recent study carried out by our research group in which a group of lean, healthy men were given a single 59g bolus of dairy-derived lipid at breakfast [74], the characteristic increase in both serum TAG and chylomicron-TAG above baseline occurred as rapidly as 60 minutes after the start of the meal. Whilst the TAG was cleared and levels had returned to the pre-meal baseline 6 hours later, the bolus caused an transient increase of almost 100% above the fasting baseline of 0.8 mmol/L and is a simple example of how a typical fatty meal dramatically impacts on lipaemia on 2 or 3 occasions each day (Fig. **1**).

The mechanisms which link this reoccurring lipaemia with increased CVD risk include poor clearance of the postprandially circulating TRLs, deposition of the lipid onto the arterial wall [75-77] and accumulation into atheromatous plaques [3], and accelerated lipid exchange of cholesteryl esters (CE) and TAG between lipoproteins which leads to generation of CE-enriched particles and transfer into atheromatous plaques. TAG transfer to LDL and HDL increases lipase hydrolysis which in turn decreases lipoprotein size and leads to the formation of both readily oxidized, small HDL and small, dense LDL [78]. In addition to the atherogenic capacity of these lipoproteins [79], they may also be toxic to endothelial cells where they induce endothelial dysfunction [80] possibly through an increase in superoxide ($O_2^{\cdot-}$) and a decrease in NO bioavailability [64, 65].

(ii) Lipoprotein (a)

It has been reported that fasting serum Lp (a) is relatively constant within individuals and not readily altered by events which influence other lipoproteins such as change in body weight, diet or exercise [81]. Numerous long and short-term exercise interventions have failed to elicit a decrease in fasting levels, despite improvements in fitness and other lipoprotein levels in the blood, and only intense load-bearing exercise training, such as distance running or weight lifting, over several months to years has been shown to successfully moderate Lp (a) [81]. However there is growing evidence that both long-term and acute changes in diet may influence Lp (a). High-fat diets consumed over a period of weeks to

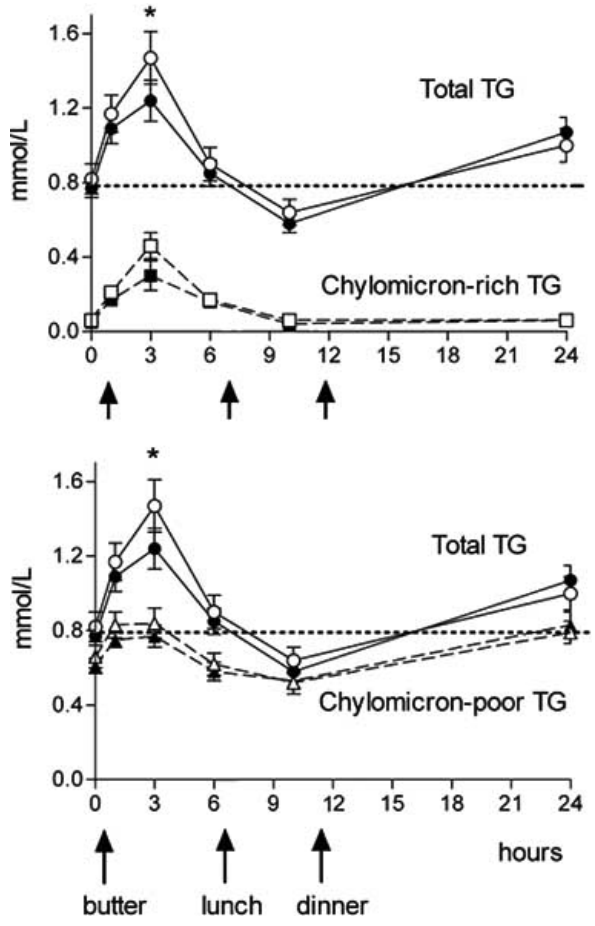

Fig. (1). Postprandial changes in total, chylomicron-rich and chylomicron-poor triacylglycerol (TAG) fractions following consumption of a 3.1 MJ fatty breakfast of which 29% (·) or 45% (o) of the lipid content comprised unsaturated fatty acids (USFA), in a group of 18 lean healthy men. Peak TAG was significantly higher on the high USFA treatment. *P<0.05 (diet x time, ANOVA). Mean ± SEM. From Poppitt *et al.* [74], reprinted by permission from Eur J Clin Nut; 58: 819-827 (2003) Macmillan Publishers Ltd.

months have been shown to increase circulating Lp (a) [82-84], with some suggestion of differential fatty acid effects. The postprandial response of Lp (a) to a single fatty meal also tends to be an increase in serum levels [85-88] although this finding is not universal [89, 90]. In a recent trial by Tholstrup and colleagues [85] a group of young healthy men were given 5 different fatty meals and a rise in postprandial Lp (a) was demonstrated following 4 of the meals, with the peak occurring 4 hours post meal. The accompanying pattern of TRL lipaemia led this group to suggest that postprandial TAG has a role to play in the regulation of Lp (a) [85]. This had previously been noted by Liu *et al.* [88] as part of a study of patients with CHD given an extract of cholestin to decrease serum Lp (a), but the association is yet to be confirmed.

(iii) Haemostasis

Blood coagulation occurs as three basic steps in response to damage to a vessel wall. Prothrombin activator stimulates the conversion of prothrombin to thrombin, which acts as an enzyme to convert fibrinogen to fibrin threads, and then to a formed blood clot [91]. A cascade of coagulation factors initiates the formation of prothrombin activator. FVII, or serum prothrombin conversion accelerator, is a plasma protein which initiates the extrinsic cascade and which upon binding to tissue factor is activated to FVIIa. In the presence of Ca^{++} and phospholipids this in turn activates Factor X to FXa. Similarly, fibrinogen (Factor I) is important in the coagulation cascade as the final substance produced in response to the actions of FVII [92]. There is evidence that FVII and fibrinogen are independent predictors of cardiovascular mortality [19-21], although whether fibrinogen has causal pathology in CVD or whether, as an acute phase protein, it is simply a marker of inflammation has not been resolved [93].

Fasting FVII coagulant activity (FVIIc) is positively associated with serum cholesterol and TAG, and an increase in habitual fat intake has been positively correlated with procoagulant activity in several cross-sectional studies in groups of middle-aged men [94-96], including a significant increase in FVIIc in those on a high-fat diet compared with those avoiding fatty foods [94], and those on mixed diets [95]. There may also be a significant positive association between SFA intake and fasting FVIIc [97]. Intervention studies also show that FVII can be modulated acutely by diet and that an acute change in FVIIc is driven by changes in the concentration of FVIIa [98]. The majority [26, 27, 98-105], but not all [28, 74, 106, 107] postprandial trials have shown that FVIIc and FVIIa increase after a fatty meal (Table **1**). Whether the postprandial lipaemia is causal in the increase of FVIIc and FVIIa however is under debate [108]. The group of Sanders and colleagues [100] have previously suggested that in normotriglyceridaemic subjects as much as 70-90g dietary TAG must be consumed in order to generate a significant increase in postprandial FVIIc. This may help to explain the absence of a change in FVIIc in our trial of healthy men given a bolus of 59g dairy fat [74], a trial by Hunter *et al.* of healthy men given 45g mixed fats [28] and a trial of healthy women by Lindman and colleagues where 90g of fat per day was split into 4 separate test meals [106]. Sanders has also shown that FVIIc may not increase postprandially when the meal is given against a high SFA background diet [107], whilst Larsen found a very weak effect of fatty meals on postprandial FVIIc compared with FVIIa [109]. Interestingly FVIIc did not increase immediately following the meal in a number of these trials in which a positive response is reported, gradually increasing above fasting baseline between 4-8 hours post meal [99, 101].

Far less is known of other components of the coagulation pathway, such as fibrinogen. There is some evidence that whilst fasting levels can be modulated by long-term dietary change [110-112], postprandial fibrinogen levels may or may not be altered following a meal. Freese and Mutanen [26] reported no effect of fat feeding on postprandial fibrinogen when healthy women were given fatty meals containing 1g dietary fat per kg body weight, as did Zahedi *et al.* [113] in a

Table 1. Trials Investigating the Postprandial Effects of High-Fat Meals on Activated Factor VII (FVIIa) and FVII Coagulant Activity (FVIIc)

Author	Subjects	FVIIa/ FVIIc	Fat dose (g)	Outcome
Significant increase in FVIIc				
Salomaa *et al.* 1993 [99]	n=10 male	FVIIc	1g/kg body weight	Significant difference from fat-free meal after 6h
Bladbjerg *et al.* 1994 [105]	n=17	FVIIc	49 en% fat	Significant increase
Freese & Mutanen 1995 [26]	n=12 female	FVIIc	1g/kg body weight	Significant increase P<0.001
Tholstrup *et al.* 1996 [101]	n=10 male	FVIIc	1.2g/kg body weight	Significant increase after 6h
Kapur *et al.* 1996 [103]	n=30	FVIIa	$30g/m^2$	Significant increase P<0.004
Larsen *et al.* 1997 [98]	n=18 male	FVIIa FVIIc	70g	Increased by 60% Increased by 7%
Oakley *et al.* 1998 [100]	n=12 male	FVIIc	95g	Increased by 12.5%
Tholstrup *et al.* 1999 [102]	n=8 subgroup	FVIIc	1.2g/kg body weight	Significant increase P<0.001
Larsen *et al.* 2000 [27]	n=18 male	FVIIa	70g	Significant increase P<0.001
Sanders *et al.* 2003 [104]	n=29 male	FVIIc	67-90g	Increased by 15-17%
No change in FVIIc				
Sanders *et al.* 1997 [107]	n=26 male	FVIIc	80g following (i) high SFA (ii) high n-3/n-6 PUFA	 No change Significant increase P<0.05
Hunter *et al.* 2001 [28]	n=6 male	FVIIa FVIIc	45g	Significant increase P<0.001 No change
Poppitt *et al.* 2003 [74]	n=18 male	FVIIc	59g	No change
Lindman *et al.* 2003 [106]	n=25 female	FVIIc	4 x 23g	No change

more recent study where a 62g fat load was given to a group of healthy men. Our study of lean men given 59g of lipid within a high-fat muffin also showed no evidence of a significant change in fibrinogen [74]. Sanders and colleagues [104] however showed a change in postprandial fibrinogen when between 60-90g dietary fat was given in a 6MJ meal after prolonged high-fat or high-CHO dietary intervention, as did Kozima *et al.* [114] after administration of 100g dairy butter.

(iv) Markers of Inflammation

C-RP

C-RP is an acute-phase reactant which in humans can increase up to 1000 fold through increased hepatocyte synthesis after an acute inflammatory stimulus such as tissue injury or infection [115], and which is one of the most promising emerging risk factor for atherosclerotic disease, independently predicting vascular risk [116, 117]. For example, in a multivariate analysis carried out by Ridker and colleagues [118], once age, smoking, obesity, hypertension, diabetes and family history were accounted for only C-RP and total: HDL cholesterol ratio had independent predictive values. The same research group have noted that more than 20 prospective epidemiologic studies now support fasting levels of C-RP to be an independent predictor of vascular risk, and that 14 cohort studies show prognostic evaluation to be improved for metabolic syndrome, cardiovascular and type 2 diabetes when high sensitivity C-RP is included within the assessment panel [117]. It has been suggested that C-RP levels are strongly related to insulin resistance and that to decrease C-RP insulin sensitivity must be improved [119], and also that C-RP and endothelial function may be interrelated. The relationship between high C-RP and impaired endothelium-dependent vasodilation has however not been supported in studies such as the recent Firefighters And Their Endothelium (FATE) study [120], whose authors conclude that the predictive value of C-RP may be largely independent of abnormalities in endothelial function.

Factors known to modulate C-RP include weight loss and physical activity but less is known of the effects diet.

Epidemiology has shown a high glycaemic diet [121] to be positively and a high cereal diet [122] to be negatively associated with high C-RP levels, suggesting complex CHO to be involved in protection against inflammation. A high-fat predominantly n-3 PUFA diet has also been shown to be negatively associated with C-RP [123]. Interestingly in a recent intervention trial carried out in a group of healthy men, conversion to the Mediterranean diet did not show an improvement in C-RP [124] whereas in subjects with the metabolic syndrome it did decrease C-RP [125]. In a 4 week trial of low-fat and low-CHO diets there was also no evidence of a change in circulating C-RP [126]. There is little evidence however of a significant change in C-RP postprandially. In 32g [127], 50g [128] and 62g [113] fat challenge experiments in healthy subjects there were no postprandial changes in C-RP. In the study of lean men from our laboratory, 59g of dairy-derived lipids given as a high-fat breakfast (71 en% fat) also failed to induce a postprandial change in C-RP over 6 hours despite significant and rapid lipaemia [129]. Only in a group of obese men randomised to placebo treatment within a fish oil supplementation trial has postprandial C-RP been shown to alter significantly in response to a fatty meal [130]. In this trial, 49g of lipid given within a 3MJ milkshake (62 en% fat) decreased circulating C-RP by a small but significant 7% 4 hours after the meal.

***IL-6, TNF*-α**

The pro-inflammatory cytokines IL-6 and TNF-α are increased in obesity, insulin resistance and T2DM [45, 131-133] and while there is evidence of dietary modulation, including an effect of fat quantity [61, 62] and fatty acid composition [63] during long-term supplementation, far less is known about postprandial response. Nappo and colleagues [134] investigated postprandial response of pro-inflammatory cytokines in both healthy subjects and patients with T2DM. The study showed that in T2DM patients both high-fat and high-CHO meals increased IL-6 and TNF-α, although the effect was more sustained following the high-fat meal. In healthy subjects only the fatty meal promoted the transient pro-inflammatory state, with the increase in IL-6 and TNF-α accompanied by an increase in circulating adhesion molecules. Lipaemia was significantly correlated with the increase in TNF-α, IL-6 and vascular cell adhesion molecule-1 (VCAM-1). This led the authors to suggest that inflammatory response as part of endothelial activation was linked to lipaemia in healthy subjects. In the study carried out by Jellema and colleagues [130] in a group of obese men randomised to placebo treatment within a fish oil supplementation trial, a fatty test meal (62 en% fat) significantly increased IL-6 by 118% postprandially but there was no associated postprandial rise in TNF-α. Our study of lean men given a single fatty meal also found a transient but smaller 14% postprandial increase in IL-6 and no associated rise in TNF-α [129].

(v) Endothelial Function

The major functions of the vascular endothelium are maintenance of blood circulation and fluidity, regulation of vascular tone and modulation of leukocyte and platelet adhesion. The endothelium plays a critical role in the prevention of atherosclerosis, and endothelial dysfunction which may be identified in part by impaired endothelium-dependent vasodilation is induced in conditions such as hypercholesterolaemia and considered to be an early marker of CVD [64, 65]. Impaired endothelium-dependent vasodilation in CVD was first reported by Ludmer *et al.* [135] who observed a paradoxical vasoconstriction rather than normal relaxation and vasodilation of the coronary arteries following exogenous administration of acetylcholine. Other studies have since confirmed impaired endothelium-dependent vasodilation in CVD [136-138] and diabetes [139]. Studies commonly measure brachial artery blood flow to assess post-ischaemic vasodilator response to reactive hyperaemia, although it should be noted that the forearm response to reactive hyperaemia may represent not only endothelium-dependent vasodilation but also post-ischaemic vasoreactivity. These endothelial studies however have generated considerable evidence that vasodilation is impaired in the postprandial state [67-69, 140], may be related to postprandial lipaemia and that remnant TRL levels [141], TAG-induced small LDL particles [142] and oxidative stress mechanisms [143] contribute directly to the dysfunction. The generation of reactive oxygen species (ROS) and vaso-active molecules may interfere with the protective endothelium-dependent NO system [144]. Certainly antioxidants have been shown to improve the bioactivity of NO, and attenuate or prevent the decrease in endothelial function associated with the postprandial state [145]. The TRL-remnant particles generated by lipolysis increase the permeability of the endothelium and hence may be cytotoxic for endothelial cells [146] and the postprandial storage of TAG in endothelial cells may also contribute to the endothelial dysfunction [147]. Interestingly, however, a recent study of athletes asked to 'de-train' through abstinence of daily exercise has shown evidence of a disassociation between endothelial function and postprandial TAG [148]. The authors suggest that although fat ingestion does induce transient endothelial dysfunction, interventions that alter postprandial TAG do not always concomitantly alter endothelial function. There is also preliminary evidence in healthy subjects that the postprandial effects of fatty meals may be ameliorated by long-term adaptation to a high-fat background diet [149].

EFFECT OF FATTY ACID COMPOSITION ON POSTPRANDIAL RESPONSE

(i) Lipaemia

Whilst the lipaemic effect of dietary TAG is well established, there is little consensus as to the differential effect of fatty acid classes or individual fatty acids on postprandial TAG metabolism. Whilst trials which modulate diet over a period of weeks consistently show an improvement in fasting lipid profile when unsaturated fatty acids (USFA) are introduced into the diet, postprandial effects of such diets appear to be more complicated. Whilst some trials do show unsaturated fats to preferentially decrease postprandial TAG relative to saturated fatty acids (SFA) [150-155], there are an equal number which do not [85, 156-164]. The postprandial trial carried out in our laboratory measured both total- and chylomicron-TAG and also did not show a lower postprandial response following the USFA-enriched meal. Rather there was a greater lipaemic response when a fatty meal with a higher content of

USFA, predominantly monounsaturated fatty acid (MUFA), was fed (see Fig. **1**) [74]. Several mechanisms have been suggested to explain the greater lipaemic effect of unsaturated fatty acids in these trials. Firstly the physical form of the lipid droplet within the gastric emulsion is such that saturated fats may be less easily lipolysed in the gut, secondly a differential rate of absorption of the lipolysis products, and thirdly differential rates of catabolism of chylomicron remnants [159, 164-167]. When unsaturated fats are considered in more detail there is again conflicting evidence that MUFA may both lower [154] or have no differential effect [168, 169] relative to SFA, whilst PUFA may reduce [150, 152, 153, 170, 171] or increase [164] postprandial TAG relative to SFA.

(ii) Lipoprotein (a)

There are a number of long-term but fewer postprandial trials which have investigated the differential effects of fatty acids on circulating Lp (a). Several long-term trials have found that the increase in fasting Lp (a) that occurs on a high-fat diet is lower when the diet is high in SFA [84, 172, 173], increased on a high MUFA diet [84] and further increased when *trans* fats are introduced into the diet [84]. The postprandial response of Lp (a) also tends to be an increase in response to a fatty meal [85-88], but an early study by Scanu [86] showed that the postprandial response of Lp (a) to high SFA and high n-3 PUFA meals was highly variable, and a more recent study by Tholstrup *et al.* [85] found that the postprandial peak in Lp (a) was decreased following both high MUFA and PUFA meals compared with a high SFA diet, which was the inverse of the response found in the long-term trials. It was also the inverse of the postprandial response of TAG which was increased by USFA, and suggested that plasma TAG may play a role in the regulation of postprandial Lp (a) [85].

(iii) Haemostasis

Several authors have suggested that activation of FVII is driven more by the quantity of dietary fat consumed than the fatty acid composition of the meal [98, 174]. For example, in a study by Miller *et al.* [175] healthy subjects were given isoenergetic meals of fat with a high or low saturated:unsaturated ratio over 7 days and there was no difference in non-fasting FVIIc between the diets on day 7. A number of other trials have been unable to find a significant differential effect of classes or individual fatty acids on circulating postprandial levels of FVIIc [26, 28, 98, 99, 106] including the trial in our laboratory [74], or between *cis* and *trans* acids [104]. Some studies however have found differential postprandial effects. Tholstrup *et al.* [101] showed that the increase in postprandial FVIIc was greater following a high stearate (C18:0) meal compared with a high shorter chain saturate myristic acid (C14:0) meal, and when a diet enriched with MUFA was given compared to a high SFA diet [102], and Oakley *et al.* [100] whilst reporting that the response of FVIIc to various high-fat meals did not differ, also noted that the increase in FVIIc was most clearly seen following a high-oleate diet (C18:1), which supported their previous work [107, 176]. This group have since confirmed that both C18:1 *cis* and C18:1 *trans* differentially increase postprandial FVIIc and FVIIa [177]. In response to the evidence that high MUFA diets may adversely effect FVIIc, Kelly *et al.* [178] further investigated oleic acid but concluded that a background diet high in MUFA has no adverse effect on fasting haemostatic variables and in fact decreased the postprandial activation of FVII in response to a standard fat-containing meal. Williams [179] also showed that postprandial activation of FVII was reduced on a high olive oil diet. The effect of different fatty acids upon FVIIa is also controversial, with trials showing non-fasting peak concentrations to be both lower [109] and higher [177] following an olive oil-enriched meal, higher following 3 weeks on a high- versus low-SFA diet [106], and independent of fatty acid composition [98, 180]. TAG structure also appears to have an effect on postprandial response as shown by Sanders *et al.* [108] in their studies of randomised and non-randomised high-SFA cocoa butter.

There is also conflicting evidence for fibrinogen. Fasting fibrinogen appears to be differentially affected by fatty acid composition. For example, high C18:0 diets increase fasting fibrinogen above both high unsaturated and high C14:0, C16:0 diets [110-112], whilst the Mediterranean diet [124] and a diet high in n-3 PUFA fish oils [181] have been shown to lower fasting levels of fibrinogen. In line with the lack of an acute response of fibrinogen to a high-fat meal there was no evidence that individual fatty acids had a differential effect on postprandial levels of fibrinogen in the trials, including that from our laboratory [74] to [129], where this has been investigated [26].

(iv) Inflammatory Response

C-RP

Whilst a number of trials that have compared a range of SFA and USFA have failed to show an effect of fatty acid composition on fasting C-RP [111, 112, 182], there is a body of evidence to show that α-linolenic acid (ALA, 18:3n-3), a plant-derived n-3 PUFA, may decrease fasting C-RP [43, 183-185]. Given the well established effects of n-3 PUFA on inflammatory cytokine release it might be expected that marine oils would favourably modulate fasting C-RP, but the effects of fish oils remain unclear. Eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) supplementation in T2DM patients [186] and dyslipidaemic obese [187] have resulted in no significant changes in C-RP, whilst non-specific fish oil supplementation significantly decreased this acute phase protein compared to safflower oil in a group of postmenopausal women on HRT [188]. We are not aware of studies that have reported the differential effects of fatty acids on postprandial C-RP, but in light of gathering evidence of the inability of a fat bolus to modulate C-RP, [113, 127, 128] trials on individual fatty acids may also fail to generate a response. Certainly our study showed no differential postprandial changes in C-RP when measured over 6h after a high- and reduced-SFA dairy lipid meal [129].

***IL-6, TNF*-α**

There is a wealth of data from trials investigating the effect of long-term dietary change on fasting cytokine levels. N-6 PUFAs have been shown to be largely [62, 189, 190] although not entirely [63] pro-inflammatory, particularly arachidonic acid (AA, 20:4n-6) which generates eicosanoid derivatives such as prostaglandin E_2, and also linoleic acid

(LA, 18:2n-6) which may also have pro-inflammatory effects *in vivo* [191, 192]. Alternately, marine n-3 PUFA such as EPA can competitively inhibit AA and limit production of TNF-α, IL-6 and IL-1 [61, 193, 194] by mononuclear cells, and plant-derived n-3 PUFAs such as ALA are less effective but may also decrease fasting IL-6 and TNF-α at high doses [184, 193, 195]. There is also evidence that fats rich in MUFA may have an anti-inflammatory role [112, 196-198]. There are few trials as yet which have investigated the postprandial changes that occur in IL-6 or TNF-α. In both of the trials carried out by Nappo [134] and Jellema [130] subjects were given a high-fat test meal but neither group manipulated fatty acid quality. Alteration in the saturated:unsaturated fat ratio in the trial carried out by our laboratory resulted in no differential effect of fatty acid composition on TNF-α, which did not increase postprandially after either meal, or IL-6 which increased on both treatments [129].

(v) Endothelial Function

The influence of fatty acid composition within the habitual background diet on endothelial function has been investigated in a number of long-term trials. An early study of vascular reactivity in a group of T2DM patients showed that a diet high in n-3 PUFA fish oils significantly increased large-artery compliance [199], and this has since been supported by other trials [66, 200, 201]. The Mediterranean diet, which includes a high intake of marine oil n-3 PUFA may also improve endothelial function [66]. Alternately n-6 PUFA, and LA in particular, have been shown to markedly disrupt endothelial barrier function [202]. High SFA lipids appear to have little effect when substituted into the diet longterm [202], but if *trans* fats replace SFAs long-term then vasodilation may be worsened [203]. Whilst it has become established that a large fatty meal transiently increases arterial stiffness, there are as yet few postprandial studies on the differential effects of fatty acids on endothelial function. Of these, high n-3 and n-6 PUFA meals have been shown to improve endothelial function when compared with high MUFA meals [204], there has been no differential effect of a combined high C8:0 + C10:0 + C12:0 SFA meal compared with a high C14:0 + C16:0 SFA meal [205], and no differential effects of SFA compared with high *trans* MUFA/PUFA [206].

CONCLUSIONS

This review has focused on the transient postprandial effects that a lipid-rich diet may impose upon a range of well established and emerging risk factors for CVD. There is clear evidence that adverse changes in postprandial metabolism which result from the ingestion of a fatty meal promote the development and progression of atherosclerosis, but there is as yet little consensus as to the effect of fatty acid classes or individual fatty acids on any of these markers. There is a strong dose dependent relationship between the total fat content of a meal and the lipaemic response, central to which is formation of TRL. Increased postprandial TAG has been related to poor clearance of circulating TRL, deposition of lipid onto the arterial wall and accumulation into plaques, generation and transfer of CE-enriched particles into plaques, decrease in lipoprotein size and formation of highly oxidisable small, dense LDL and HDL. It is also becoming apparent that exaggerated lipaemia is associated with, and may be causal in, adverse changes in factors such as circulating Lp (a), haemostasis and endothelial function. Whether saturated or unsaturated fatty acids preferentially worsen postprandial lipaemia however remains unclear.

High-fat meals acutely increase circulating Lp (a), and TRL have been recently implicated in the response but there is insufficient evidence to conclude any differential effects of fatty acid classes. Haemostasis is adversely affected by consumption of a large fat bolus. Total fat quantity may be more important than type of fat for modulation of FVIIc, and there is preliminary evidence that ingestion of >70g lipid is required to generate a consistent response. FVIIa however may be more sensitive to lower lipid volumes within meals. Whether postprandial lipaemia is causal in the increase of FVIIc and FVIIa remains under debate. Lipaemia may be necessary but not always sufficient for activation of FVIIc. For example, patients with inherited lipoprotein lipase deficiency have massive hypertriacylglycerolaemia but there is no evidence of increased FVIIc [174]. There is little consensus concerning individual fatty acids and FVII, some trials showing no differential effect and others reporting high MUFA meals, specifically high C18:1, to increase FVIIc. Alternately, a diet with a high background oleic acid content has been shown to decrease postprandial activation of FVII in response to a standard fat meal. Lipid-induced postprandial changes in fibrinogen remain unclear with some evidence to show that eating a very large fatty meal may cause a transient change. Whether fat composition is important is also unclear. Several investigations into the effect of acute dietary changes on inflammatory response show an increase in the cytokine IL-6 but not TNF-α and no acute phase response as assessed by changes in C-RP. There are few trials that have as yet investigated diet-induced transient change in these markers however, hence conclusions remain difficult to draw. Consensus shows that vascular reactivity is decreased when a fatty meal is eaten, and there is suggestion that lipaemia may be causal in this acute endothelial dysfunction, possibly mediated via increased $O_2^{\cdot-}$ and suppressed NO bioavailability. There is also evidence however which shows that changes in postprandial TRL do not always concomitantly alter endothelial function. There have been few trials investigating effects of individual fatty acids, although n-3 and n-6 PUFA have been shown to both improve endothelial function above that of high MUFA in a single trial. It has been noted that the actions of n-3 PUFA in cardioprotection are likely to be mediated through changes at vascular endothelium level that improve vascular function, effecting NO and eicosanoids, selective ion channels, and maintaining vascular integrity [207].

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