## Review

**Postprandial lipemia and cardiovascular disease risk: Interrelationships between dietary, physiological and genetic determinants**

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### Abstract

Although the independence of the association and causality has not been fully established, non-fasting (postprandial) triglyceride (TG) concentrations have emerged as a clinically significant cardiovascular disease (CVD) risk factor. In the current review, findings from three insightful prospective studies in the area, namely the Women’s Health Study, the Copenhagen City Heart Study and the Norwegian Counties Study, are discussed. An overview is provided as to the likely etiological basis for the association between postprandial TG and CVD, with a focus on both lipid and non-lipid (inflammation, hemostasis and vascular function) risk factors. The impact of various lifestyle and physiological determinants are considered, in particular genetic variation and meal fat composition. Furthermore, although data is limited some information is provided as to the relative and interactive impact of a number of modulators of lipemia. It is evident that relative to age, gender and body mass index (known modulators of postprandial lipemia), the contribution of identified gene variants to the heterogeneity observed in the postprandial response is likely to be relatively small. Finally, we highlight the need for the development of a standardised ‘fat tolerance test’ for use in clinical trials, to allow the integration and comparison of data from individual studies.

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### Contents

1. Introduction ................................. 23
2. Fasting triglycerides, postprandial lipemia and cardiovascular disease risk ................................. 23
3. The independence of triglycerides as a cardiovascular disease risk factor ................................. 23
4. Physiological mechanisms underlying the impact of postprandial lipemia on cardiovascular disease risk ................................. 23
   4.1. Triglyceride-rich lipoprotein remnant infiltration into the arterial wall ................................. 25
   4.2. HDL and LDL concentration and subclass profile ................................. 26
   4.3. Inflammatory and oxidative status ................................. 27
   4.4. Hemostasis ................................. 27
   4.5. Vascular function and reactivity ................................. 27
5. Acute impact of dietary fat amount and composition on the postprandial lipemic response ................................. 27
6. Regulation of postprandial lipemia by genetic factors ................................. 28
7. Relative impact of common gene variants on postprandial lipemia compared to established regulators ................................. 29
8. Regulation of postprandial inflammation, hemostasis, and vascular function by physiological factors ................................. 29
   8.1. Inflammation ................................. 29
   8.2. Hemostasis ................................. 30
9. Vascular function and reactivity ................................. 30
10. Closing remarks ................................. 31

### References

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1. Introduction

Due to the frequency of meal ingestion, individuals spend the majority of the day, approximately 18 h, in the fed (postprandial) state. The term given to the metabolic events that occur following the digestion and absorption of a meal that contains fat is postprandial lipemia. The magnitude and duration of the postprandial triglyceride (TG) response is influenced by a number of metabolic processes, including the rate of secretion of TG from the intestine and the liver, the activity of enzymes involved in the processing of TG-rich lipoproteins (TRLs: lipoprotein lipase (LPL) and hepatic lipase (HL)) and the rate of clearance of TRL remnants by receptor-mediated processes (Fig. 1).

It is now well established that the postprandial lipemic response is influenced by both the amount and type of dietary fat given in a test meal [1]. However, the postprandial TG response to a standardised fat-rich meal has been shown to be highly variable between individuals [2] and there is considerable interest in understanding both physiological and genetic determinants of the lipemic response and the mechanisms that underpin its impact on the progression of cardiovascular disease (CVD).

2. Fasting triglycerides, postprandial lipemia and cardiovascular disease risk

In 2007, Sarwar et al. [3] reported on the association between TG, predominately fasting, and risk of coronary heart disease (CHD), where original data from the EPIC-Norfolk (non-fasting TG) and Reykjavik studies were presented along with an updated meta-analysis which included 27 additional prospective studies. In the Reykjavik cohort, an age and gender adjusted odd ratios (OR) (95% confidence intervals) of 2.04 (1.78–2.32) was evident in those in the top vs. bottom tertile of fasting TG. An equivalent adjusted OR of 1.72 (1.56–1.90) was reported for the combined meta-analysis of all 29 studies. In a more recent output from The Emerging Risk Factor Collaboration (ERFC), which involved 300,000 individuals sourced from 68 separate long term prospective studies, a comparable age and gender adjusted hazard ratio (HR) for CHD was evident across the quartiles of TG concentration. However the association was lost (0.99, 0.94–1.05) following full adjustment of the model [4]. Differences in the strength of association observed between TG and CVD risk in the two-meta-analyses is likely to be attributable to the degree of correction for confounding factors, with full correction for high density lipoprotein-cholesterol (HDL-C) (which is highly metabolically associated with TG, see below) in all studies included in the ERFC analysis likely to over-correct the model and underestimate the actual risk associated with circulating TG levels.

Since Donald Zilversmit highlighted that atherosclerosis was a postprandial phenomenon over 30 years ago, numerous prospective case-control studies have qualitatively established postprandial TG as a risk factor for CVD (as reviewed in [1]). Three large prospective studies, namely the Women’s Health Study (WHS) [5], the Norwegian Counties Study (NCS) [6] and the Copenhagen City Heart Study (CCHS) [7] have confirmed the association and provided quantitative information about the relationship. In the WHS, unadjusted HR for incidence of CVD of 0.90 (0.47–1.72), 1.78 (1.02–3.10), 1.72 (0.99–2.98) and 2.81 (1.68–4.73) were reported across the quintiles (Q) of non-fasting TG levels (Table 1) [5]. In the NCS, comparable HRs for CVD deaths of 1.61 (1.28–2.03), 1.69 (1.35–2.12), 1.95 (1.36–2.43) and 3.27 (2.66–4.03) were observed in women with corresponding values of 1.04 (0.98–1.33), 1.17 (1.05–1.31), 1.39 (1.25–1.55) and 1.78 (1.61–1.98) in men (Table 1) [6]. This observation of an approximate 2-fold greater impact of non-fasting TG on cardiovascular events in women, also evident in the CCHS [7], is consistent with the HR associated with fasting TG in women vs. men [8] (although the above mentioned meta-analysis of 29 prospective studies considering fasting TG failed to show this [3]). At present, the etiological basis of the differential effect of gender on the cardiovascular impact of non-fasting TG concentrations is unknown, as these differences remain following correction for all established CVD risk factors.

Although non-fasting TG levels are in general considered more discriminatory with respect to CHD risk relative to fasting levels (for more extensive review see [9]), the issue remains somewhat controversial. In the WHS, although the minimally adjusted HRs were comparable, only non-fasting TG remained significantly associated with incidence CVD with HRs of 1.09 (0.85–1.41) and 1.98 (1.21–3.25) in tertile 3 of fasting and non-fasting TG, respectively [5]. In contrast, comparing the EPIC Reykjavik and Norfolk cohorts suggests no important differences in the predictive value of non-fasting (Norfolk) vs. fasting (Reykjavik) TG in the group as a whole, although in agreement with the WHS, non-fasting TG were more discriminatory in women [3].

3. The independence of triglycerides as a cardiovascular disease risk factor

Circulating TG is metabolically intimately linked with HDL; with elevated TG levels resulting in increased HL-mediated HDL hydrolysis and decreased HDL-C concentration. There is much ongoing debate regarding the independence of TG as a CVD risk indicator and its causal relevance, with many considering the impact of TG on CVD risk to be largely mediated through HDL-C. Consideration of the output from the three large prospective studies WHS, NCS and CCHS, provides insight into this discussion. In the WHS, a significant impact of non-fasting TG was evident even after full adjustment of the model, with a HR of cardiovascular events of 1.99 (1.05–3.78) in Q5 (Table 1) [5]. Although HDL-C was not included as a covariate in the primary analysis of the NCS and CCHS studies, a secondary analysis was conducted in which no significant impact of non-fasting TG remained in the NCS in either gender following adjustment for HDL-C [6] (Table 2). The output from the CCHS is somewhat more difficult to interpret as no fully adjusted model (including HDL-C and all other risk indicators) was presented. However, adjustment for age plus HDL-C only, had little impact on the HR values. Therefore, although the independence of non-fasting TG remains somewhat equivocal, some independent association is evident, in particular in women, with an attenuation rather than complete loss of risk following adjustment for HDL-C and other established CVD biomarkers. In principle, randomised controlled trials (RCTs) with TG-lowering agents such as fibrates, nicotinic acid or statins should be able to resolve the issue of causality of TG in CVD. However, in practice, this is not possible as such interventions affect other major lipids such as low density lipoprotein-cholesterol (LDL-C) and HDL-C. Although from a risk prediction perspective, the independence of non-fasting TG as a CVD risk marker is important, from a pathophysiological argument it is not. Non-fasting TG is a clinically significant CVD risk factor, which is influenced by, and influences (as will be reviewed in subsequent sections) many elements of the CVD risk phenotype, and therefore represents an important therapeutic target.

4. Physiological mechanisms underlying the impact of postprandial lipemia on cardiovascular disease risk

Although, as discussed, a direct relationship between postprandial TG and CVD risk has now been established, the mechanisms by which TRLs exert their effect on the vascular wall are poorly understood. The sections below detail potential mechanisms of both lipid and non-lipid origin. Consensus is yet to be reached as to the effects
Table 1
Hazard ratios (95% confidence intervals) for cardiovascular events associated with non-fasting triglyceride levels.

<table>
<thead>
<tr>
<th>Quintiles of non-fasting TG</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women’s Health Study [5] (WHS)</strong> (median follow up 11.4 years)</td>
<td></td>
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<tr>
<td>TG, mg/dl (mmol/l) ≤85 (0.96) 86–113 (0.97–1.27) 114–154 (1.28–1.73) 155–214 (1.74–2.40) ≥215 (≥2.41)</td>
<td>1273</td>
<td>1233</td>
<td>1320</td>
<td>1273</td>
<td>1292</td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>18</td>
<td>20</td>
<td>42</td>
<td>47</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>No. of CVD events</td>
<td>1</td>
<td>0.90 (0.47–1.72) 1.78 (1.02–3.10) 1.72 (0.99–2.98) 2.81 (1.68–4.73)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 1a</td>
<td>1</td>
<td>0.83 (0.43–1.61) 1.57 (0.89–2.87) 1.41 (0.79–2.55) 2.09 (1.13–3.86)</td>
<td></td>
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<td>0.003</td>
</tr>
<tr>
<td>Model 2b</td>
<td>1</td>
<td>0.89 (0.45–1.75) 1.63 (0.90–2.96) 1.60 (0.87–2.95) 1.99 (1.05–3.78)</td>
<td></td>
<td></td>
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<td>0.02</td>
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<td><strong>Norwegian Counties Study [6] (NCS)</strong> (mean follow up 27 years)</td>
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<tr>
<td>Women</td>
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<tr>
<td>TG, mean (range), mmol/l ≤85 (0.96) 86–113 (0.97–1.27) 114–154 (1.28–1.73) 155–214 (1.74–2.40) ≥215 (≥2.41)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No. of participants</td>
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<td>8303</td>
<td>8576</td>
<td>8654</td>
<td>8482</td>
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</tr>
<tr>
<td>No. of CVD events</td>
<td>110</td>
<td>204</td>
<td>233</td>
<td>280</td>
<td>469</td>
<td></td>
</tr>
<tr>
<td>Model 4d</td>
<td>1</td>
<td>1.61 (1.28–2.03) 1.69 (1.35–2.12) 1.95 (1.36–2.43) 3.27 (2.66–4.03)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 5e</td>
<td>1</td>
<td>1.57 (1.02–1.61) 1.34 (1.03–1.68) 2.02 (1.45–2.82)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Men</strong></td>
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</tr>
<tr>
<td>TG, mean (range), mmol/l ≤85 (0.96) 86–113 (0.97–1.27) 114–154 (1.28–1.73) 155–214 (1.74–2.40) ≥215 (≥2.41)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
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<td>8477</td>
<td>8553</td>
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</tr>
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<td>No. of CVD events</td>
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<td>582</td>
<td>703</td>
<td>801</td>
<td>1001</td>
<td></td>
</tr>
<tr>
<td>Model 4d</td>
<td>1</td>
<td>1.04 (0.98–1.33) 1.17 (1.05–1.31) 1.39 (1.25–1.55) 1.78 (1.61–1.98)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 5e</td>
<td>1</td>
<td>0.92 (0.82–1.03) 0.96 (0.85–1.08) 1.03 (0.92–1.15) 1.07 (0.96–1.21)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>IHD deaths</strong></td>
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<td></td>
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<tr>
<td>No. of events</td>
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<td>373</td>
<td>474</td>
<td>561</td>
<td>689</td>
<td></td>
</tr>
<tr>
<td>Model 4d</td>
<td>1</td>
<td>1.14 (0.98–1.33) 1.37 (1.18–1.58) 1.68 (1.46–1.93) 2.11 (1.85–2.41)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 5e</td>
<td>1</td>
<td>1.00 (0.86–1.16) 1.09 (0.84–1.69) 1.43 (1.02–2.01) 2.02 (1.45–2.82)</td>
<td></td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Copenhagen City Heart Study [7] (CCHS)</strong> (mean follow up 26 years)</td>
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<tr>
<td>TG (mmol/l) &lt;1.00 1.00–1.99 2.00–2.99 3.00–3.99 4.00–4.99 5.00–5.99</td>
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<tr>
<td>Women</td>
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<tr>
<td>No. of participants</td>
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<td>3948</td>
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<td>237</td>
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<td>MI incidence</td>
<td></td>
<td></td>
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<tr>
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<td>382</td>
<td>141</td>
<td>30</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
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<td>2.2 (1.6–3.2) 4.4 (2.6–6.8) 3.9 (2.0–7.7) 5.1 (2.0–12.9) 16.8 (6.8–41.6)</td>
<td></td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 7f</td>
<td>1</td>
<td>1.7 (1.2–2.5) 2.5 (1.6–3.9) 2.1 (1.0–4.3) 2.4 (0.9–6.2) 5.4 (2.1–13.9)</td>
<td></td>
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<td>&lt;0.001</td>
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<tr>
<td>IHD incidence</td>
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<tr>
<td>No. of events</td>
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<tr>
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<td>1</td>
<td>1.7 (1.4–2.1) 2.8 (2.1–3.6) 3.0 (1.9–4.7) 2.1 (1.0–4.3) 5.9 (2.8–12.4)</td>
<td></td>
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<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Model 7f</td>
<td>1</td>
<td>1.4 (1.1–1.8) 1.8 (1.4–2.5) 1.8 (1.2–2.9) 1.2 (0.6–2.5) 2.6 (1.2–5.5)</td>
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<td>&lt;0.001</td>
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<tr>
<td>Men</td>
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<td>No. of participants</td>
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<td>1366</td>
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<td>477</td>
<td>270</td>
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<td>54</td>
<td>64</td>
</tr>
<tr>
<td>Model 6d</td>
<td>1</td>
<td>1.6 (1.1–2.3) 2.3 (1.5–3.4) 3.6 (2.3–5.7) 3.3 (1.9–5.9) 4.6 (2.7–8.0)</td>
<td></td>
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<td>&lt;0.001</td>
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<tr>
<td>Model 7f</td>
<td>1</td>
<td>1.4 (1.0–2.1) 1.6 (1.1–2.4) 2.3 (1.4–3.7) 1.9 (1.0–3.4) 2.4 (1.3–4.2)</td>
<td></td>
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<td>&lt;0.001</td>
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<tr>
<td>IHD incidence</td>
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<tr>
<td>No. of events</td>
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<td>853</td>
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<td>198</td>
<td>80</td>
<td>98</td>
</tr>
<tr>
<td>Model 6d</td>
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<td>1.3 (1.0–1.7) 1.7 (1.3–2.3) 2.1 (1.5–3.0) 2.0 (1.2–3.1) 2.9 (1.9–4.5)</td>
<td></td>
<td></td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 7f</td>
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<td>1.1 (0.8–1.4) 1.3 (0.9–1.7) 1.3 (0.9–1.9) 1.2 (0.7–1.9) 1.5 (1.0–2.4)</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
</tbody>
</table>

TG, triglycerides; CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction.

a Adjusted for age, blood pressure, and use of hormone therapy.
b Adjusted for covariates in model 1, plus total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C).
c Adjusted for covariates in model 2, plus diabetes mellitus (DM), body mass index (BMI) and high sensitivity C-reactive protein (CRP).
d Adjusted for age.
e Adjusted for age plus TC, systolic blood pressure, smoking, BMI, time since last meal, physical activity (PA), and menopausal status in women.
f Adjusted for age, TC, BMI, hypertension, DM, smoking, alcohol, PA, lipid lowering therapy, and menopausal status and use of hormone therapy in women.
g Composite of nonfatal MI, nonfatal ischemic stroke, coronary revascularisation and/or death due to cardiovascular causes.
h At least two of chest pain, increased cardiac enzymes or electrocardiographic changes indicative of MI.
i Previous MI, symptoms of stable or unstable angina.
of postprandial lipemia on some of these pathways, in particular inflammatory status and hemostasis where response to dietary TG is variable.

4.1. Triglyceride-rich lipoprotein remnant infiltration into the arterial wall

During the postprandial phase, TG is carried in the circulation by chylomicrons, which are synthesised in the intestine and transport fat of dietary origin (exogenous fat), and very low density lipoproteins (VLDLs) which are synthesised and secreted by the liver (endogenous fat). Raised levels of these TRL particles before and after a fat containing meal are associated with an increased CVD risk[10,11]. The development of techniques to distinguish between apolipoprotein (apo)B-48 and apoB-100, found exclusively in chylomicrons and VLDL (and their remnants) respectively, has enabled the impact of diet and disease states (e.g. diabetes, metabolic syndrome and CVD) on pathways of exogenous and endogenous TRL metabolism to be delineated. During the postprandial phase, apoB-100 containing particles account for 80% of the increase in TRL number, with the majority of the increase in TG concentration accounted for by apoB-48 containing lipoproteins[10]. The amount and type of fat given in a meal has been shown to influence the rates of metabolism of chylomicrons and their remnants, which has important consequences on the residence time of liver-derived TRLs (and their remnants) in the circulation, and in turn the potential impact on LDL-C and HDL-C concentration. The European Atherosclerosis Society (EAS) Consensus Panel have recently

Table 2

<table>
<thead>
<tr>
<th>Adjustment level</th>
<th>Women none</th>
<th>Women fulla</th>
<th>Men none</th>
<th>Men fulla</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Norwegian Counties Study [6] (NCS)</strong></td>
<td></td>
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</tr>
<tr>
<td>IHD deaths</td>
<td>1.44 (1.32–1.57)</td>
<td>0.99 (0.88–1.13)</td>
<td>1.24 (1.19–1.29)</td>
<td>1.03 (0.97–1.08)</td>
</tr>
<tr>
<td>Adjustment level</td>
<td>Women age only</td>
<td>Women age plus HDL-C</td>
<td>Women full except HDL-C</td>
<td>Men age only</td>
</tr>
<tr>
<td><strong>Copenhagen City Heart Study [7] (CCHS)</strong></td>
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<td></td>
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<tr>
<td>MI incidence</td>
<td>1.46 (1.34–1.59)</td>
<td>1.41 (1.26–1.57)</td>
<td>1.20 (1.05–1.37)</td>
<td>1.18 (1.13–1.23)</td>
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IHD, ischemic heart disease; MI, myocardial infarction; HDL-C, high density lipoprotein cholesterol.

*a* Adjusted for HDL-C, age, total cholesterol (TC), systolic blood pressure, smoking, body mass index (BMI), time since last meal, physical activity (PA), and menopausal status in women.

*b* Adjusted for age, TC, BMI, hypertension, diabetes mellitus, smoking, alcohol, PA, lipid lowering therapy, and menopausal status and hormone therapy in women.
reviewed the evidence for the contribution of TG and TRLs to the development of CVD and suggested that the association between TG and CVD was potentially driven by the number of TRLs, highlighting the significant contribution that apoB-100 containing TRLs play in driving the pathology of exaggerated lipemia [12]. Although detailed reviews clearly highlight the contribution of liver-derived TRLs in the pathogenesis of atherosclerosis [13–15], the inclusion of apoB-48 measurements in clinical studies has provided new insights into the atherogenicity of intestinally derived TRLs, and a brief overview of the potential mechanisms will be presented.

A recent study has reported that raised plasma apo B-48, but not total apo B was correlated with carotid intima-media thickness (a surrogate marker of the progression of atherosclerosis) in individuals with familial lipid disorders, T2DM and CVD [16]. This finding in plasma confirms earlier associations between the levels of apoB-48 containing lipoproteins in the smaller denser lipoprotein fractions (Sf 20–60) and progression of coronary atherosclerosis [10,11]. In a similar manner to liver-derived TRL, elevated levels of postprandial apoB-48 containing lipoproteins are thought to be implicated directly, and indirectly, with the presence of CVD. Evidence from animal studies have shown that chylomicron remnants can directly infiltrate the arterial wall [17], and the mechanisms whereby chylomicron remnants provide the lipid constituents of arterial lesions are thought to occur by two processes. Firstly, the chylomicron remnants may bind and penetrate the arterial surfaces, with evidence suggesting a similar binding affinity to arterial biglycan (secreted by proliferating smooth muscle cells in the atherosclerotic lesion) as LDL [18]. The second process involves the binding of chylomicrons to glycoprophosphatidylinositol-anchored HDL binding protein (GPIHBP)-1 on the luminal surface of the endothelial cells and degradation to remnants by the action of lipases [19]. In this instance, the uptake of remnants into the arterial wall may occur at sites of endothelial injury. Animal and in vitro studies have suggested that whilst the number of chylomicron remnants bound to biglycan is lower than LDL, there is a greater mass of particle cholesterol associated with the binding of chylomicron remnants [20]. This finding has been further supported by Mangat et al. [21] in which delayed clearance of intestinally derived apoB-48 particles in type 1 diabetics compared with control subjects was proposed to be associated with a 7-fold greater arterial retention, as demonstrated by these researchers in an ex vivo study of remnant particles (and associated cholesterol) in a rodent model of diabetes. Albeit preliminary, these findings highlight the potential contribution of apoB-48 to the atherogenicity of raised postprandial TRL, and suggest that different mechanisms may operate for the intestine and liver derived TRLs.

4.2. HDL and LDL concentration and subclass profile

A delayed clearance of TRLs from the circulation leads to an accumulation of TRL particles carrying acceptor sites for the cholesterol ester transfer protein (CETP) which drives the transfer of TG from TRLs to both LDL and HDL, and cholesterol ester (CE) from HDL to TRL [13] (Fig. 2). The remodelling of the lipid contents...
of the LDL and HDL makes them suitable substrates for lipase action facilitating the formation of smaller denser LDL (LDL3), and HDL (HDL3) particles which are rapidly removed from the circulation, thereby decreasing HDL-C concentrations. Low circulating HDL-C levels and a preponderance of small dense LDL have been reported in men with established CVD and the atherogenic lipoprotein phenotype [13]. The lower binding affinity of smaller denser LDL3 to the LDL-receptor extends their residence time in the circulation which increases their infiltration rate into the arterial wall.

### 4.3. Inflammatory and oxidative status

Chronic inflammation is a key pathogenic event associated with atherosclerosis and CVD. Proinflammatory monocytes/macrophages within the vessel intima accumulate in atherosclerotic plaques producing cytokines, interleukin (IL)-6 and tumour necrosis factor (TNF)-α, whilst T lymphocytes stimulate production of collagen-degrading metalloproteinases (MMPs) and procoagulant tissue factor (TF) [22]. Acute phase reactants including C-reactive protein (CRP) increase and may in turn drive thrombogenesis and decrease clot stability. Endothelial dysfunction, characterised by increased adhesion molecules (such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)), and the chemokine monocyte chemoattractant protein-1 (MCP-1) expression also contribute to monocyte recruitment and a proinflammatory status within the intima. It has been proposed that each meal consumed stimulates a low-intensity and transient inflammatory response, an event which has been termed postprandial metabolic inflammation [23], and that postprandial lipemia may be a causative inflammatory protagonist. In vitro studies of human aortic endothelial cells have led to the proposal that TRLs are central to the inflammatory activation of vascular cells although whether this is a direct effect of TRLs alone or a potentiation of cytokines or associated mediators is unclear [24,25]. In a previous summary of early postprandial clinical studies we showed the inflammatory response to lipemia to be highly variable [26]. Review of recent intervention studies in cohorts of lean healthy individuals confirms this variability. Increased gene expression and/or circulating concentrations of IL-6 have been reported in 4 [27–30] of 8 [31–34] studies, of TNF-α reported in 4 [27,28,31,34] of 8 [29,32,35,36] studies, and of CRP reported in 2 [27,28] of 6 [29,34–36] studies. Adverse changes following a fat-rich meal have also been observed in MMP-1 and MMP-9 [33,34], SOCS-3 [35], ICAM-1 and VCAM-1 [37], and white blood cells (WBC) [33]. Associations between non-fasting TG and a proinflammatory response are yet to be confirmed in large population studies. The response of nuclear factor-κB (NF-κB), a transcription factor that has a key function in integrating intracellular regulation of the immune response and inflammation, is of considerable interest. It has been suggested that the inflammatory response of factors such as TNF-α and CRP are not directly affected by hypertriglyceridaemia but stimulated through oxidative stress and NF-κB activation [36].

### 4.4. Hemostasis

Disorders of both coagulation and fibrinolysis contribute to the development of CVD such that elevated plasma fibrinogen, activated factor XII (FXIIa) and FVII coagulant activity (FVIIc) have long been proposed as predictors of CVD mortality [25]. Blood coagulation occurs as three basic steps in response to damage to a vessel wall. A cascade of coagulation factors initiates prothrombin activator to convert prothrombin to thrombin, which acts as an enzyme to convert fibrinogen to fibrin threads and then to a formed blood clot. FVII, serum prothrombin conversion accelerator, initiates the extrinsic cascade and which, upon binding to TF, is activated to FVIIa. Similarly fibrinogen (Factor I) is important in the response to the actions of FVII. Of importance also is plasminogen activator inhibitor type 1 (PAI-1), the major inhibitor of fibrinolysis, the process whereby fibrin clots produced through coagulation are broken down. We also previously reviewed the early postprandial studies of lipemia and hemostasis [26] and concluded that whilst relationships with the amount of dietary fat were emerging, the relevance of fat type was still unclear. In line with markers of inflammation, the lack of human postprandial data makes it difficult to identify physiologic and genetic determinants of the postprandial hemostatic response. Nevertheless, a picture of acute modulation of FVII is emerging, with the majority of studies showing FVIIa and FVIIc to increase after a fatty meal. It is surmised that postprandial lipemia may activate FVII through direct adherence to the protein fraction of large TRLs. Dose–response relationships, the impact of individual fatty acids and the causality of this relationship remain under debate. Less is known of fibrinogen and other components of coagulation including PAI-1, with some evidence that the former may be unresponsive postprandially [26].

### 4.5. Vascular function and reactivity

The endothelium plays a critical role in the maintenance of vascular tone by releasing a large array of vasoactive substances, the most important being nitric oxide (NO), a potent vasodilator that causes smooth muscle relaxation and arterial dilation [38]. Endothelial dysfunction characterised by an increase in vascular tone and a reduction in vascular reactivity, has been strongly associated with CVD risk and has emerged as a critical early modifiable event in the development of atherosclerosis [39]. Numerous studies have highlighted the prognostic value of in vivo measures of vascular reactivity of both the coronary and peripheral arteries, in predicting future coronary events [39,40]. Over the past decade, there has been considerable interest in the effects of meal fat quantity and quality on postprandial vascular reactivity. The majority of studies conducted in healthy individuals show an impairment in vascular function 2–8 h following ingestion of moderate to high fat meals [36–80 g fat] [41]. This is an important observation as individuals spend the majority of the day in the postprandial state and it is likely that these transient changes repeated on a daily basis, could have implications for long-term vascular health and overall CVD risk.

A potential novel biomarker of vascular function, endothelial progenitor cells, has also been shown to increase in number following ingestion of a high-fat meal [42]. Endothelial progenitor cells originate in the bone marrow and are seen in small numbers in healthy individuals, but tend to increase following vascular injury. Vascular reactivity assessed using flow mediated dilatation (FMD) has been shown to be associated with endothelial cell progenitor number and function [43,44]. However, very little is known about the impact of meal fatty acid composition on circulating levels of endothelial progenitor cells.

### 5. Acute impact of dietary fat amount and composition on the postprandial lipemic response

The postprandial lipemic response has been shown to be influenced by both the amount and type of dietary fat in the test meal [1]. Dose-dependent increases in the postprandial plasma TG response have been observed with single meals containing 30–50 g fat, with little difference in response with meals exceeding 80 g fat. The type of fat given in a meal has been shown to influence the fatty acid composition of chylomicron particles and
of considering cohorts as homogeneous entities with respect to the subsequent postprandial TG response [1]. Although differences in study design, and types of fat and carbohydrate in the test meal make comparisons between studies difficult, meals rich in saturated (SFA) and monounsaturated fatty acids (MUFA) tend to show similar postprandial TG responses, with lower lipemia observed with n−6 polyunsaturated fatty acids (PUFA) [45], butter [46] and high doses of long chain (LC) n−3 PUFA [1]. Although SFA and MUFA show similar plasma TG responses, findings from our group have shown a MUFA-rich meal to result in greater numbers of both large (Svedberg flotation rate (Sₘ) > 400) and small (Sₘ 60−400) chylomicrons, whereas the SFA meal lead to a greater enrichment of TRL particles with apoproteins (apo)C−III and E [47] suggesting that the meal fatty acid composition may impact on many aspects of dietary TG metabolism. At present, the physiological consequences of the effects of the meal fat induced changes in TRL lipid and apolipoprotein composition remain to be elucidated.

6. Regulation of postprandial lipemia by genetic factors

In 2007 [1] and 2008 [48], two expert reviews considered the available literature on lifestyle (acute and chronic composition of the diet, alcohol, exercise, smoking) and physiological determinants (age, gender, genotype, menopausal status, insulin sensitivity status, physical activity, adiposity) of the postprandial lipemic response. In the intervening years, numerous related publications have appeared in the literature, with an updated review published in 2010 [49]. The following discussion is by no means exhaustive but will endeavour to highlight the important recent findings in the field regarding genetic mediators of postprandial TG, and attempt to quantitatively compare their relative impact compared to some traditional modulators such as age, gender and body mass index (BMI), using our DISRUPT database [50]. The DISRUPT Cohort includes 467 individuals, of whom 257 completed the same sequential meal protocol (80 g fat in total), where detailed postprandial assessment was conducted by collecting up to 12 blood samples over an 8 h assessment period [50].

As highlighted by Lopez-Miranda et al., variants in the majority of the apoprotein genes (A1, A4, A5, C3 and E), fatty acid binding protein 2 (FABP2), LPL, HL, microsomal transfer protein and scavenger receptor B1 have been associated with the extent of postprandial lipemia [1], with many of the reported associations not validated in independent cohorts.

ApоА5 is involved in many stages of TRL metabolism, including hepatic VLDL production, receptor-mediated TRL remnant clearance along with regulating LPL activity. In a recent output from the Triglyceride Coronary Disease Genetics Consortium and ERFC, data for 73,252 individuals from 39 studies were used to investigate the impact of the common apoA5−1131T>C single nucleotide polymorphism (SNP), rs662799, in the promoter region of the gene on the impact of the common apoA5−1131T>C single nucleotide polymorphism (SNP), rs662799, in the promoter region of the gene on hepatic VLDL production, receptor-mediated TRL remnant clearance and TG is provided by Perez-Martinez et al. [49]. Although focussed on fasting TG, two further studies have reported on the additive impact of apoE (see later), apoA5 and LPL [55] and apoA5 and apoE [56] variants in predicting hypertriglycerideremia. For the latter study Sousa and co-workers reported ORs of severe hypertriglycerideremia of 4.1 (2.02−8.24), 1.6 (0.73−3.58), 3.0 (1.68−5.86), 45.2 (4.92−415.5) and 6.4 (2.28−18.01) in the apoA5−1131C, apoE2, apoE4, apoE2/apoA5−1131C and apoE4/apoA5−1131I carrier subgroups respectively, relative to the wild-type genotype [56].

Emerging evidence is also indicative that the apoA5 genotype influences the hypotriglycerideremic response to fibrates, with 2 studies examining the postprandial TG response. In a RCT in patients with the metabolic syndrome (Mets), intervention with 160 mg fenofibrate per day for three months resulted in a 38% and 43% reduction in TG at 3 and 4 h postprandially in apoA5−1131C allele carriers compared to a 27% and 23% reduction in wild-type subjects [57]. In the large (n=791 US) GOLDN cohort, no significant impact of the −1131T>C variant on the response was evident to the same dose of fenofibrate taken for 3 weeks. However, responsiveness was modestly, but significantly, influenced by the nonsynonymous apoA5 56C>G genotype (rs3135506) with a 36% reduction of TG AUC in G allele carriers compared to a 28% reduction in CC homozygotes [58]. Further research is needed to qualify and quantify the impact of apoA5 genotypes on the postprandial TG response to fibrates. Furthermore, although the hypotriglycerideremic action of the fish oil derived LC n−3 PUFA is also via PPAR-activation, the impact of ApoA5 genotype on the TG lowering capacity of fish oil is unknown and represents a research gap.

Although the impact of apoE genotype (rs7412 and rs429358) on the postprandial TG response has been widely investigated, the impact of the E4 allele on the extent of lipemia remains controversial [59]. In the GOLDN cohort, postprandial TG were higher in e2 but not in e4 carriers whereas in the DISRUPT cohort, e4 carriers had a 22% higher TG AUC relative to the wild type e3/e3 genotype which was due to higher fasting TG in this subgroup [60]. Subdivision of the group according to age (≤50 years and >50 years) revealed the effect was only evident in the >50 years age group, again highlighting the relative importance of genotype in certain population subgroups and not in others. Such differences of impact of genotype according to other key physiological variables, may to some extent explain the apparent genotype-phenotype inconsistencies in the literature.

FABP2 is involved in the binding and absorption of long chain SFA and unsaturated fatty acids (USFA) in the enterocyte. In 2007, Helwig et al. reported a significant impact of the Ala54Thr variant (rs1799883) on the postprandial response in 700 males with the MetS [61]. A greater response in Thr54Thr individuals is consistent with the reported 2-fold higher affinity of recombinant FABP-Thr relative to FABP-Ala for long chain USFA [62]. In contrast, no association was evident in the DISRUPT (unpublished) or European Atherosclerosis Research Study (EARS) II cohorts [63]. It is likely
that the impact of this variant on postprandial TG concentration may depend on the meal fatty acid composition.

In addition to confirming earlier identified associations between postprandial lipemia and SNPs in apoproteins and lipid metabolising enzymes, a number of other potentially important gene loci have recently been reported in the literature, namely PPAR-α [64], PPARγ [65], and angiopoietin like protein 4 (ANGPTL4) [66] and as highlighted in Perez-Martinez et al. [49] perilipin (PLIN) [67] and IL-6 [68]. Given the central role played by PPAR-α in hepatic lipogenesis and fatty acid oxidation, PPAR-γ in adipose tissue fat storage, ANGPTL4 as a relatively recently characterised regulator of LPL, and perilipin in adipose tissue fatty acid storage, and the increased recognition of the link between a proinflammatory status and dyslipidemia, it may be predicted that SNPs in these genes may be important regulators of the TG response following fat consumption. Furthermore, although currently unknown, it may be hypothesised that variants in genes which regulate vascular tone, such as endothelial nitric oxide synthase (eNOS), may modulate the postprandial lipemic response, given the known role of adipose tissue and muscle perfusion in modulating macronutrient flux.

7. Relative impact of common gene variants on postprandial lipemia compared to established regulators

Although Lopez-Miranda and co-authors attempted to compare the relative impact of the various factors thought to influence postprandial lipemia (Table 4 in the original paper), this was done in a semi-quantitative manner, with no consideration of potentially important gene variants [1]. In a preliminary univariate analysis of the DISRUPT cohort, higher TG AUC was evident in subjects in the 51–60 years vs. 20–40 years age range (27%), those with a BMI ≥ 25 kg/m² vs. <25 kg/m² (50%), men vs. women (68%) (note that 53 of 152 males were recruited prospectively to have mild hypertriglyceridemia of 1.5–4.0 mmol/l), apoA5-1131 C allele carriers vs. non-carriers (20%), and apoE4 carriers vs. wild-type E3/E3 genotype (21%). In linear regression analysis, these variables collectively explained 32% of the variability in TG AUC with gender, BMI and apoA5-1131 T>C independently accounting for 18%, 5% and 2% of the variability respectively (unpublished data). A comparable analysis in independent cohorts is needed to gain further understanding of the relative impact of the important determinants of postprandial TG concentrations.

However it is evident from the data presented here and from the available literature which examines the impact of age, BMI and gender on postprandial lipemia [1], that relative to these physiological mediators, the contribution of identified gene variants to the observed heterogeneity in the postprandial TG response is likely to be relatively small. Available data which examines genotype-lipemia associations is predominantly derived from small studies with less than 100 participants, where retrospective genotyping results in low numbers in the rare allele group and often a lack of power to detect inter-group differences. As a result, incorrect null findings may be observed and reported even though a clinically relevant impact of the gene variant may exist. Furthermore the trials to date have exclusively taken a candidate gene approach, which typically genotypes only for SNPs with a rare allele frequency >5%. Such an approach will not identify potentially important variants in genes encoding for as yet unknown regulators of TG metabolism, or those present in <5% population with large metabolic effects. The future use of more comprehensive genotyping approaches such as whole genome sequencing or more targeted gene or exome sequencing is likely to lead to the identification of numerous additional genetic determinants of the postprandial TG response.

8. Regulation of postprandial inflammation, hemostasis, and vascular function by physiological factors

8.1. Inflammation

In early clinical studies, the lipemic response to a high-fat meal was associated with a highly variable inflammatory response. In summarising this previously [26] we showed lipemia to both be associated with, or have little effect on, proinflammatory excursions and the conclusions were limited. Available studies now include overweight/obese, hypertriglyceridemic, MetS, and diabetic populations alongside healthy individuals. Whilst within-study divergent responses remain [29,35,69,70], many of these studies [27–30,33,36,69,71–73], although not all [32,74–76] report an adverse inflammatory response in at least one marker. Much of the debate now focuses on whether underlying proinflammatory pathologies may enhance the response and in turn explain some of the variability observed between individuals. A recent ex vivo study of TRLs from hyperlipidemic patients showed endothelial inflammation to increase only in the presence of TNF-α, suggesting enhanced effects when pre-existing proinflammatory conditions such as obesity or T2DM occur [77].

Overweight individuals, in whom chronic low-grade inflammation is well documented, may also have an enhanced postprandial response relative to lean individuals, with evidence of up to 2-fold increase in concentrations of IL-6 [69,70,73] and less marked increase in TNF-α [69,70,73] and C-RCP [69,70,75,76]. Jellema et al. [70] showed weight loss of ~10 kg to ameliorate postprandial excursions in a study of 8 obese men. An enhanced proinflammatory response may occur with raised (>1.69 mmol/l) fasting TGs [30, MetS [72], hypertension [36], and T2DM [71]. More studies are required for consensus since hypertriglyceridemia [75] and MetS [74] do not always lead to an exaggerated response.

Little is known of gender differences. A study in 80 overweight, middle-aged Canadians [69] showed postprandial increases in IL-6 to be up to 3-fold higher in women than men, but with no difference between pre- and post-menopausal women. Conversely, there were no gender differences in serum TNF-α or C-RCP, neither of which increased postprandially. Little is also known of age effects independent of disease status, since studies have been conducted in older, commonly overweight individuals with metabolic dysregulation or disease.

The contribution of genetic factors to postprandial inflammation is little studied. Circulating IL-6 levels are a heritable trait and polymorphisms which alter gene transcription and protein production have long been known. Homozygotes (GG) and heterozygotes (CG) of the −174C/G (rs1800795) variant display higher fasting plasma IL-6 concentrations and a greater postprandial TG response, and it has been hypothesised that it may affect postprandial IL-6 [68]. In a review of genetic determinants of postprandial lipemia, Perez-Martinez et al. [49] commented on the importance of IL-6 as a regulator of postprandial lipid metabolism which Shen et al. [68] underpins. Estimates of the heritability of fasting levels are 20–40% for C-RCP and WBC [33]. The US HAPI Heart Study [33] evaluated genetic influences on C-RCP, IL-1beta, MMP-1, MMP-9 and WBC count following a high-fat meal and showed that only WBC changes were modestly heritable. As recently reviewed, the C-RCP gene is highly polymorphic with ~40 SNPs reported to date [78]. An association between at least 2 biologically functional SNPs that directly alter fasting C-RCP levels has been observed in healthy individuals (~409G/A; rs3093062, C-RCP is highest in GG; −390C/T/A, rs3091244, C-RCP is highest in TT). Whether they are linked to prevalence of disease remains undefined. The effects of these SNPs on postprandial C-RCP levels are also still to be determined.

Less is known of the effects of meal lipid composition on the postprandial inflammatory response. Whilst it has been
hypothesised that SFAs may be proinflammatory this remains to be demonstrated. Postprandial serum levels of TNF-α, IL-6 and CRP appear relatively unresponsive to changes in degree of fatty acid saturation in healthy individuals [29–31], and also hypertriglycerideremias [30], although mRNA expression may be altered [31]. NF-κB activation following high-SFA meals has been shown to be ameliorated by MUFA [79]. TNF-α (rs1800629) and IL-6 (rs1800797) gene polymorphisms, associated with increased MetS risk, are exacerbated by a low serum PUFA:SFA ratio but postprandial effects are yet to be elucidated [80]. It has also been hypothesised that habitual n-3 and n-6 PUFA intake may have divergent effects on the postprandial inflammatory response [23], although there are few studies other than in MetS [72] where there was no amelioration by n-3 PUFA. This is an area worthy of further research.

8.2. Hemostasis

Our earlier review showed that despite variability in response, circulating levels of FVIIa and FVIIIc tended to increase following a fatty meal [26], although the mechanism was uncertain, as was the fat load required to initiate the response. All studies reviewed were of healthy, predominantly young individuals [26]. Recent studies have confirmed the procoagulant effects of lipemia [81], and extended to middle-aged healthy and older CHD patients [82], but more studies are warranted to resolve questions of the impact of age, gender and pathology on postprandial hemostatic status. PAI-1 has been shown to be induced postprandially in hypertensives [36] but not healthy individuals [36], or hypertriglycerideremic older adults [30,83].

Multiple mutations have been identified in the FVIII gene (F7), with the influence of R353Q (rs6046) on FVIIa shown in an early study of elderly women [84] although not in middle-aged men [85], but with few postprandial investigations on hemostasis since. Postprandial modulation of clotting by the PAI-1 −675 4G/5G genotype was shown following low fat, high-SFA and high-MUFA meals [83], where PAI-1 and dilute clot lysis time decreased following all meals. The −675 4G/5G polymorphism (rs1799889) at the PAI-1 gene appears to modulate fasting plasma PAI-1 concentrations (lowest in 5G/5G), whilst chronic fat consumption leads to decreased PAI-1 in 4G allele carriers on a high-MUFA diet [86].

Again, less is known of the effects of fat type and whether changes in meal fatty acid profile have variable effects. In line with several earlier trials we showed that high-SFA vs. high-UFSA meals had no differential effect on FVIIc or fibrinogen in young, healthy men [87], although conversely, and perhaps surprisingly, some studies (for review see [26]) have shown high-MUFA meals to adversely promote FVIIc. Habitual diet may be of considerable importance, since in a 4 week study of high-SFA vs. high-MUFA vs. high-CHO with n−3 PUFA [81], showed FVIIc to decrease postprandially following a high-MUFA test meal. Delgado-Lista et al. [81] hypothesised that the capacity of large TRLs to transport lipid particles is increased by a high-MUFA diet which in turn decreases the number of TRL particles in the circulation, and, since FVII binds to TRLs, this may decrease activation of FVII. Clearance of TRLs from the circulation may also be more rapid than for a chronic high-SFA diet. With respect to PUFA, long-term supplementation studies such as OPTILIP showed no differential postprandial changes in FVII when the n−3:n−6 ratio was manipulated in favour of enriched n−3 PUFA [88]. PAI-1 may also be sensitive to changes in fatty acid ratio with SFA-enriched fatty meals differently increasing PAI-1n the 4-week study above [81], but not in a recent study of older normo- and hypertriglycerideremic men [30].

9. Vascular function and reactivity

Over the past decade, a number of studies have examined the effects of meal fatty acid composition on postprandial vascular reactivity (as summarised in [41]). Although the majority have shown the ingestion of moderate to high fat meals lead to a transient impairment in vascular function, the effects of different fatty acid classes are inconsistent. Whereas test meals rich in MUFA (refined olive oil and high-oleic sunflower oil) and SFA lead to a decrease in FMD, evidence is emerging to show the addition of LC n−3 PUFA (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) to high-fat meals to have beneficial effects on postprandial arterial stiffness [89,90] and vascular reactivity [91–93] compared with baseline or a control meal. Although the magnitude of the postprandial TG response has been proposed to be responsible for the impairment in vascular function [94], several studies have suggested that fat-containing meals may impair vascular reactivity via the induction of a temporary state of fat induced oxidative stress [95,96]. Improvements in vascular reactivity with LC n−3 PUFA has been attributed to an increase in the bioavailability of NO in the vascular wall due to a reduction in tissue ROS and induction of antioxidant enzyme activity. Findings from our ex vivo cell culture studies have shown that TRLs isolated 4 h after a high-fat meal containing LC n−3 PUFA, down-regulated the expression of NADPH oxidase [91], suggesting n−3 PUFA may exert beneficial effects on postprandial endothelial function by modulating the redox status of the vascular wall. It has been proposed that DHA, but not EPA supplementation improves vascular tone [97] a finding that warrants further investigation within an acute setting.

Numerous SNPs have been identified in the eNOS (NOS3) gene, with a polymorphism in exon 7 leading to an amino acid substitution at position 298 of the mature protein (Glu298Asp; rs1799983). This SNP has been suggested to have a functional effect on enzyme activity [98] and potentially on endothelium dependent vasodilatation. A large meta-analysis of eNOS polymorphisms in CHD revealed per-allele OR of 1.17 (95% CI: 1.07, 1.28), with some evidence for associations with insulin resistance and T2DM [99]. Although findings have been inconsistent in the literature, a reduced vascular reactivity in the fasting state in Asp298 subjects has been reported in a small number of studies, with variability in the findings between studies attributed to retrospective genotyping and unequal genotype groups (Asp298 homozygotes 6–10% of Caucasian populations). Whilst a number of acute and chronic studies have shown vascular function to be modulated by dietary fatty acid composition, a genotype-specific relationship between FMD and habitual LC n−3 PUFA intake has been observed in Asp298 carriers only [100]. Furthermore, the LIPGENE study conducted in individuals diagnosed with MetS, have shown an inverse association between plasma LC n−3 PUFA status and fasting plasma TG in Asp298 carriers, with a greater change in fasting TG with LC n−3 PUFA supplementation observed in these individuals [101]. These data suggest that Asp298 carriers might show greater beneficial effects of LC n−3 PUFA consumption on both fasting lipids and vascular function. However, the impact of the eNOS Glu298Asp polymorphism on vascular reactivity during the postprandial phase has yet to be determined.

Both gender and age have been shown to influence vascular function. In younger adults, a more pronounced endothelial dependent vasodilation has been observed in women, with similar responses observed in postmenopausal women and age-matched men [102]. The differences in vascular function between genders have been suggested to be due to the smaller vessel size in females as opposed to hormonal differences [38]. However, it should be noted that during the menstrual cycle, maximal endothelial dependent vasodilation has been observed during the follicular and luteal phases (elevated serum estradiol); whilst in the menstrual phase a
similar response to men has been reported. The progressive decline in endothelial function with ageing is thought to be attributable to increased oxidative stress, lower antioxidant capacity [103] and reduced bioavailability of NO in the vascular endothelium [104]. Few studies have examined the effects of ageing on postprandial vascular function, with a trend for the increase in forearm blood flow to be blunted in older men (50–68 years) after a SFA-rich meal [105], and significantly lower vasodilatory responses to both acetylcholine and sodium nitroprusside in older men (>50 years) 4 h after a LC n–3 PUFA-rich meal [106], compared with the younger age groups. The lack of responsiveness of the older men to the fish oil enriched meal was speculated to be due to the structural changes in the vascular wall with ageing leading to a reduced diffusion of NO to the smooth muscle layer [106]. Further work is required to determine the mechanisms responsible for the lack of effect of meal ingestion on postprandial vascular reactivity in older men.

10. Closing remarks

The current review highlights the importance of non-fasting TG as a clinically significant CVD risk factor. It shows that, in addition to being lipid and lipoprotein mediated, the impact on disease risk is also likely to be mediated through adverse effects on inflammation, hemostasis and vascular function. In addition to LPL and apoE variants, apoA5 and FABP2 genotype are emerging as important genetic determinants of postprandial TG, with a potentially different impact in men and women. An initial analysis of the DISRUPT Cohort identified BMI and gender as being the most important physiological determinants of these variables discussed (age, gender, BMI, and apoA5 and apoE genotype), however the relative importance of these and other mediators needs to be assessed in an independent cohort before any definite conclusions can be made. Although available evidence supports meal fatty acid composition and other lifestyle factors, along with physiological determinants such as gender, age, BMI, genotype and ‘health status’ as potentially important modulators of the postprandial inflammatory, oxidative, hemostatic and vascular responses to a fat containing meal, the available data is sparse and inconclusive. Given that a significant proportion of the pathological impact of raised postprandial lipemia may be due to dysregulation of these processes, greater insight into their modulation is of scientific and public health interest.

Research to date has taken a very simplistic approach, with individual studies examining the effect of a single SNP or dietary component of lifestyle or other physiological determinant in isolation. We need to evolve into the more realistic scenario and consider the combined impact of multiple SNPs, physiological and lifestyle factors. This will require large data sets from epidemiological studies and RCTs analysed using developing computational biology approaches.

Confirmation of the clinical importance of postprandial lipemia as a CVD risk factor, and insight into its regulation, has undoubtedly been hampered by the lack of a standardised methodology for postprandial lipid studies (as highlighted at the EAS Satellite Symposium on Postprandial Lipid Metabolism held in Hamburg in 2010, www.symposium-on-postprandial-lipid-metabolism.de), with a variety of protocols used in different laboratories, depending on the primary aim of the study and available resources and facilities. As a result, combinations and comparisons of available data sets are difficult. Arguably the most important issue to consider when deriving a standardised postprandial protocol are recent habitual diet (in particular standardisation of individuals in the 24 h prior to investigation), single vs. multiple test meals, fatty acid composition of the lipid dose, and macronutrient composition and format (liquid vs. solid) of the full test meal. Timing of the meal(s), and the frequency and duration of blood sampling also significantly impact on outcome, as do both the metabolic parameters measured (e.g. total plasma TG vs. TG in various TRL fractions) and the statistical methods used for analysis of data derived from multiple blood samples. A proportion of published postprandial investigations have administered the lipid dose per kg body or according to body surface area. However it may be argued that such an approach introduces more bias than it corrects for, as body weight and surface area do not distinguish between lean and adipose tissue, with adipose tissue LPL mediated TRL hydrolysis being a critical determinant of the postprandial lipaemic response. These issues have long been debated [9,107]. In agreement with other authors [107,108] we suggest a standard lipid load of 50–60 g total fat administered to a fasted individual as part of a breakfast meal with a fatty acid and overall macronutrient composition representative of a typical westernised meal (carbohydrate 40–100 g and protein 10–20 g). Although a 70–80 g dose total fat has been recently suggested as being most appropriate [9,109], this lipid load in a single meal is unphysiological, with delayed gastric emptying likely to result in unrepresentative postprandial responses, particularly in women. A fasting blood sample with hourly collection of blood samples throughout the postprandial period up to 6–8 h post-test meal is preferable for research purposes. For diagnostic purposes in a clinical setting such frequent blood sampling is unrealistic, and there is a need to develop a formal standardised oral triglyceride tolerance test (OTTT) which uses a simplified two or three time point measurement of TG concentrations (fasting plus one of two postprandial samples). Current available evidence is suggestive that peak TG concentrations are reached approximately 4 h post-test meal and that TG concentrations at this time point are most discriminatory with respect to CVD risk. However further investigation is needed to establish, the timing of the postprandial sample in different postprandial groups and to set clinical reference standards which can be used to define risk and therapeutic strategies.

Author’s contribution

The authors were involved in all aspects of the writing of the review article including decisions regarding the content and structure of the article.

Conflict of interest

None of the authors have any conflict of interest to report.

References


