

Dietary interventions affecting chylomicron and chylomicron remnant clearance

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Abstract

Interest in effects of diet on postprandial lipoproteins has increased in recent years as a result of accumulating evidence for adverse cardiovascular consequences of elevated concentrations of triglyceride rich lipoproteins. Particular attention has been given to ability of different fatty acids to modulate postprandial lipoprotein responses because of evidence for both harmful and protective cardiovascular properties of the saturated, monounsaturated and ω -6 and ω -3 polyunsaturated fatty acid (PUFA) classes. Evidence for direct atherogenic properties of chylomicron remnants has led to attempts to monitor effects of diet specifically on this lipoprotein class. Limitations in the methods employed to measure chylomicron remnants and the small number of human studies which have evaluated effects of meal, and background diet, fatty acid composition, makes it difficult to draw definitive conclusions at the present time. However consideration of data from both animal and human studies tends to support the conclusion that diets, and meals, rich in PUFA (particularly long chain ω -3 PUFA), result in attenuated postprandial responses of the intestinally-derived lipoproteins. Attenuated responses to high PUFA meals appear to be due to greater rates of clearance and greater activation of lipoprotein lipase (LPL). Attenuated responses to high PUFA background diets may be due to adaptive changes involving both accelerated rates of clearance in peripheral tissues and liver, as well as decreased output of the competitor for chylomicron clearance, very low density lipoprotein (VLDL). © 1998 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Considerable data is available from both animal and human studies concerning effects of diet and different dietary fatty acids on fasting lipoprotein concentrations. In contrast, information regarding effects of meal or background dietary fatty acid intake on circulating concentrations of postprandial lipoproteins is limited. Since the late 1980's there has been renewed interest in the measurement of postprandial lipoprotein responses to meal consumption, prompted by increasing evidence for adverse atherogenic consequences of elevations in these triglyceride-rich lipoprotein particles [1–5]. Published studies in the area of diet and postprandial lipoproteins remain few in number and although animal

studies are more numerous, discrepancies exist between the findings from animal studies (largely rat) and human investigations which make interpretation difficult. Some of these discrepancies may relate to the experimental approaches which can be employed in animal models compared with humans, but others may reflect fundamental differences between human and rodent lipoprotein metabolism with respect to their responses to meal ingestion.

2. Mechanisms underlying atherogenic consequences of postprandial lipoproteins

Adverse cardiovascular consequences of elevated postprandial lipoproteins may arise through proposed atherogenic properties of chylomicron and very low density lipoprotein (VLDL) remnants (CMr and

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VLDLr) themselves [6], or through indirect effects of the larger triglyceride rich particles (TGRL; chylomicrons and VLDL) on LDL and HDL particles size and density. These have been termed the *remnant* and *triglyceride intolerance* hypotheses, respectively, as a means of distinguishing two distinct but related pathways through which particles formed following fat ingestion may adversely affect the atherogenicity of circulating lipoproteins. Although the original remnant hypothesis was based on studies in rabbits [6], the fact that TGRL can cause both foam cell formation and cell death in human endothelial cells [7], and that CMr can gain access to human smooth muscle cells following endothelial injury [8] together with recent evidence for direct uptake of TGRL into human atherosclerotic plaques [9] support the possibility that CM and VLDL remnants possess the potential to cause cholesterol deposition in the arterial wall. However this issue continues to be debated and Karpe and Hamsten [5], and Nordestgaard and Nilson [10] have suggested that whilst VLDL remnants may have atherogenic potential, CM and CMr are removed from circulation before they attain a size that allows them to penetrate the vascular endothelium.

Because the mechanism(s) through which postprandial lipoproteins influence atherogenesis are as yet unclear, there is a need to evaluate effects of diet not only on the extent and duration of the triglyceride response to meal consumption, but also the effects on postprandial CM and VLDL particles and, in particular, on their remnant particles.

2.1. Distinguishing dietary derived and hepatic triglyceride rich lipoproteins

Although the measurement of plasma triglyceride response to meal consumption is straight forward, distinguishing the contributions made by dietary derived lipoproteins (CM and CMr) and endogenous lipoproteins (VLDL and VLDLr) is more problematical because the similarity in size and density of these two types of particles prevents their complete separation by ultracentrifugation. Even the classically-recognised CM preparation ($Sf > 1000$) contains significant amounts of apolipoprotein (apo) B-100, indicating the presence of endogenous VLDL particles. The fact that different diets may result in the formation of CM particles of different size and density [11] further obviates the use of separative techniques alone as a means of distinguishing the two types of particles in nutritional investigations. Many authors have used the retinyl palmitate labelling technique which involves the addition of exogenous retinyl palmitate to test meals, with measurement of retinyl palmitate or retinyl esters in lipoprotein fractions (commonly in $Sf > 1000$ (CM) and $Sf < 1000$ (small CM and CMr)) which enables particles of di-

etary origin (CM and CMr) to be distinguished from VLDL and VLDL remnants. Most dietary studies which have employed this method have measured RP in $Sf > 1000$ and $Sf < 1000$ [12]. Although this allows the separation of large CM's ($Sf > 1000$) from small CM's, partially delipidated CM's and CMr ($Sf < 1000$) this method does not allow interpretation of effects exclusively on the remnant fraction. In addition the RP technique has attracted criticism because of evidence that during the later postprandial phase significant amounts of RP are transferred onto other lipoproteins (notably VLDL and LDL) [13]. In recent years investigators have employed methods for direct measurement of apo B-48 and apo B-100 in lipoprotein fractions as a means of distinguishing dietary derived and hepatically-derived lipoproteins. In clinical studies of postprandial lipoprotein response to meal consumption investigators have employed measurements of apo B-100 and apo B-48 in lipoprotein fractions $Sf > 400$, $Sf 60-400$ and $Sf 20-60$ to enable effects on CM, VLDL and their remnant particles ($Sf 20-60$) [4]. Although some dietary studies have investigated effects on apo B-100 and apo B-48 concentrations, measurements have usually been confined to single fractions and none have evaluated effects on apo B-100 and apo B-48 in postprandial $Sf 20-60$ lipoproteins, the supposed remnant fraction.

From studies published to date it is possible to evaluate effects of different dietary fatty acids in test meals, and in background diets, on human postprandial plasma triglyceride response, with more limited information available on the contributions made by CM and VLDL particles. Lack of studies which have used extensive lipoprotein separations with simultaneous measurement of either RP or apo B-48 and apo B-100, make it difficult to draw conclusions regarding effects of diet on remnant lipoproteins. Available information is largely restricted to that derived from animal studies which have employed reinjection of radiolabelled CM and CMr's obtained from animals fed different background diets.

3. Meal fatty acid composition, postprandial lipaemia and remnant metabolism

There is clear evidence from animal studies to show that meals rich in polyunsaturated fatty acids (PUFA's) result in an attenuated postprandial triglyceride response compared with meals rich in saturated fatty acids (SFA's) [14,15]. In these studies, CM's obtained from animals fed PUFA's and reinjected into recipient animals, showed faster rates of clearance and greater uptake into liver than animals administered CM's from SFA fed animals [14,16,17]. Two studies showed significantly higher levels of post heparin lipoprotein lipase (LPL) with PUFA feeding, supporting the conclusion

that the attenuated triglyceride response was due to greater activation of this enzyme with faster rates of clearance of PUFA-rich CM particles [14,15]. Different findings were obtained when CMr prepared from fish oil, corn oil, olive oil, palm oil or butter fat fed animals were perfused in isolated rat livers, since rates of removal were greatest for butter fat and fish oil CM's and least for corn and olive CM's [18]. Discrepancy between this in vitro study and the other in vivo studies [14,16,17] may be due to the fact that in the latter, intact CM's were reinjected into the animals with opportunity for further action by LPL whereas the in vitro study perfused a preparation likely to contain predominantly CMr.

Information from human studies which have measured postprandial lipaemic responses to meals of different fatty acid composition [19,12,20–23] have produced less clear cut findings. Comparison of the studies is difficult, because even when comparisons of similar fatty acid classes are being made e.g. SFA vs. ω -6 PUFA, the nature of the fats and oils used as the basis for the SFA or PUFA meals has not always been the same.

In 1988, Weintraub et al. [12] compared postprandial lipoprotein responses to meals comprising predominantly of saturated (SFA) or ω -6 polyunsaturated fatty acids (PUFA). No differences in postprandial retinyl palmitate or triglyceride responses to the two meals were observed. In an earlier study, Harris et al. [19] found no difference in postprandial triglyceride response to liquid test meals containing either a mixture of peanut oil and cocoa butter (saturated fat meal) or Max EPA (fish oil meal). These findings are in contrast to those from another study [21] in which subjects were given three test meals which were identical apart from the oils used which were mixed (SFA), corn (ω -6 PUFA) and fish oil (long chain ω -3 PUFA). Postprandial triglyceride response to the ω -6 PUFA (corn oil) meal was lower than to the mixed oil meal but the major difference found was in response to the meal containing long chain ω -3 PUFA (fish oil), where marked attenuation in postprandial triglyceride levels were seen. Post heparin LPL measurements made at the end of the postprandial period showed LPL activities to be in line with the postprandial triglyceride response with higher activities in response to the fish oil and corn oil meals (fish oil > corn oil > mixed oil) [24]. Measurement of apo B-48 in the triglyceride rich fraction confirmed that the attenuation in part reflected reduced circulation of chylomicron particles [25]. A recent study [26] has shown that addition of only small amounts of long chain ω -3 PUFA (LC ω -3 PUFA) to a standard fat containing test meal significantly reduces the postprandial lipaemic response compared with the same meal without added

LC ω -3 PUFA and suggest that the fatty acids in fish oil alter the rate of synthesis and/or removal of chylomicron triglyceride, independently of the remaining fatty acid substrate supplied. Despite the negative findings of Weintraub et al. [12], with respect to the lipaemic response to SFA and PUFA rich meals, when CM's isolated from subjects fed SFA, ω -6 PUFA or ω -3 PUFA meals were incubated with milk lipase, the lipolytic rates were in the order ω -3 PUFA > ω -6 PUFA > SFA, in vitro data which is in concordance with the observations of Zampelas et al. [20] and Yahiah et al. [26] and with the animal studies reported above.

Test meal studies which have compared three meals of varying decreasing SFA and increasing monounsaturated fatty acid content (MUFA) have observed no difference in either postprandial triglyceride and non-esterified fatty acids [22,23] or retinyl ester and apo B-48 responses in the triglyceride rich fraction [27] and suggest that there is no difference in the rates of appearance or clearance of CM's enriched in SFA or MUFA. de Bruin et al. [20] compared postprandial triglyceride and RP response to oral lipid emulsions containing olive oil or sunflower oil and found no difference in triglyceride response, but a slightly raised RP response and a higher peak RP, to the olive oil emulsion. Measurement of apo B-48 in the density range 1.006–1.019 also showed a higher apo B-48 response to the olive oil than the soybean oil emulsion. Although the authors suggested the data indicated higher rates of clearance of soybean than olive oil remnants, most of the difference was in the rising part of the postprandial curve suggesting the differences may reflect faster rates of entry of MUFA-rich CM's. Their conclusions were, in part, based on the findings from a complementary study which measured rates of clearance of intravenously administered olive and soybean oil emulsions which demonstrated both a higher triglyceride response and a slower rate of clearance of olive compared with soybean oil emulsions [28]. However clearance of lipid emulsions appears to occur, in part, through non-receptor mechanisms of the reticulo endothelium system so that this model has been criticised as a basis for simulating removal rates of lipoprotein particles.

Based on this small number of studies it is concluded that there is some evidence of differences in postprandial lipaemic responses to meals containing predominantly SFA, MUFA, ω -6 PUFA and ω -3 PUFA, with levels of triglyceride response in the order ω -3 PUFA < ω -6 PUFA < MUFA = SFA. Animal studies and some data from humans suggest this effect may be mediated by preferential hydrolysis of PUFA-containing CM's and greater activation of LPL.

4. Background diet fatty acid composition, postprandial lipaemia and remnant metabolism

Animal studies which have evaluated effects of background diet on postprandial lipaemia provide data which is generally consistent with single meal studies, demonstrating lower fasting and postprandial triglyceride responses to diets and meals containing unsaturated fatty acids [29,30,14,16,15]. Levy et al. [16] showed higher levels of adipose tissue (but not heart or liver) LPL, greater rates of uptake of labelled fatty acids into adipose tissue, and greater rates of clearance of labelled CM's obtained from chow fed animals, in experimental animals fed unsaturated compared with saturated fat diets. Groot et al. [14], and Lai and Ney [15] also showed higher rates of postprandial activation of LPL in PUFA compared with SFA fed animals. In a comparison of a mixed (SFA), corn and fish oil diets, Murphy et al. [31] demonstrated lower fasting triglycerides and higher levels of adipose tissue LPL activity and LPL mRNA in ω -3 PUFA fed animals. These data consistently suggest that the lower levels of fasting and postprandial triglycerides observed with high PUFA diets are largely due to faster rates of plasma triglyceride clearance due to adaptive changes in tissue LPL activity.

Dietary studies conducted in human volunteers also generally support the view that high PUFA diets are associated with an attenuated response to both high-PUFA and standard SFA-containing meals, although there is less consensus regarding the mechanism underlying this response. There are a number of different types of studies which have evaluated the impact of altered background diet on postprandial lipaemia. Six studies used a whole diet approach in which total dietary fat was altered [19,32,12,33–35] whereas others have used capsule supplements [36–39] and one study has employed microencapsulated oils incorporated into conventional foods [40]. Another study has compared effects of different PUFA and MUFA-containing diets on fasting and postprandial triglyceride values but the limited data presented makes the findings difficult to compare with other studies [41]. Attenuated postprandial lipaemic response are observed in most studies in which ω -3 PUFA are fed at levels in excess of 2 g/day. Effects of ω -6 PUFA are less consistent although these have been studied less extensively.

In those studies which have altered total background diet, most investigators have carried out randomised cross over controlled studies with measurement of subjects responses to a standard meal at the end of a control and a test diet period. In some instances investigators have chosen to measure response to a test meal which has the same fatty acid composition as the background diet being fed. This is the case with the study of Demacker et al. [33], who altered the diets of

free living subjects so that either butter fat or safflower oil were the predominant fats used in cooking and in meals prepared at their work place. After 3 weeks on each diet, subjects responses to a breakfast, lunch and dinner were monitored over a 24 h period. On each occasion the test meal given was the same as that of the background diet. In this type of study it is difficult to distinguish the effect of altering the background diet from that of altering the test meal fatty acid composition, since as indicated above, PUFA-rich meals may result in an attenuated triglyceride response through acute effects on LPL activity. Nevertheless, this particular study showed that when a diet and a test meal consisting largely of ω -6 PUFA is fed, the 24 h postprandial apo B-48 concentrations in the $d = 1.019$ fraction, were 42% lower than when a diet and a meal rich in SFA was fed. The authors suggested that these data reflect increased clearance of chylomicron remnants in subjects consuming a high PUFA diet.

In the study of Weintraub et al. [12] subjects were randomised to receive three different background diets for three weeks over a 12 week period. Subjects postprandial RP responses to a standard SFA containing test meal were reduced by 36 and 47%, respectively, when ω -6 or ω -3 PUFA diets were fed. Effects were greatest with the ω -3 PUFA diet but the attenuating effects of the ω -6 PUFA diet were increased when an ω -6 PUFA test meal was given, supporting the findings of Demacker et al. [33] which indicates there may be synergism between the adaptational response and acute meal mechanism reported above. RP responses in both $Sf > 1000$ and $Sf < 1000$ fractions were reduced in subjects consuming the ω -3 PUFA diet suggesting the background diet influences not only the metabolism of the larger CM particles but also the smaller CM's, products of CM hydrolysis and CMr. Because subjects fed the PUFA rich diets showed no changes in post heparin levels of LPL activity and because postprandial changes were generally in line with the reduced levels of fasting triglycerides in these subjects the authors concluded that the primary effects of the PUFA rich diets were due to reduced synthesis and/or increased catabolism of hepatically-derived PUFA-containing lipoproteins.

Bergeron and Havel [34] studied effects, on postprandial lipoproteins, of high SFA and high ω -6 PUFA diets in a parallel design in which half the subjects were allocated to receive a high PUFA test meal and half a high SFA test meal at the end of the dietary period. Postprandial responses of triglycerides, apo B-48, apo B-100, cholesterol and apo E were measured in the triglyceride rich fraction (TRL). Although TRL apo B-48 and triglyceride responses to both the PUFA and SFA test meals, were lower in subjects on the high ω -6 PUFA diet, the authors emphasised that this was largely determined by the lower fasting concentrations

for these parameters (40 and 42% lower for TRL apo B-48 and triglycerides, respectively) and was not a reflection of greater rates of clearance of dietary derived lipoproteins. However although fasting triglyceride levels were consistently lower on the PUFA diet, the subjects who consumed the SFA test meal at the end of the PUFA diet did not have apo B-48 levels lower than those on the SFA diet who took the SFA test meal. The markedly lower levels of postprandial apo B-48 observed in these subjects cannot therefore be attributed to lower fasting apo B-48 levels and could reflect a greater rate of clearance of small CM particles on a high PUFA diet. The authors emphasised the importance of their data which suggested that the accumulation of hepatically-derived lipoproteins was greater in subjects on a high SFA diet than a high ω -6 PUFA diet.

Although different interpretations have been placed on the findings from these human diet studies it is evident the overall conclusion which can be drawn is that high PUFA diets, particularly high ω -3 PUFA diets, result in reduced concentrations, and decreased residence time within the circulation, of both CM and VLDL particles. The data are consistent with findings from animal studies although in the latter case the primary site of action has been suggested to be LPL, whereas human studies suggest that modification of hepatic output and/or catabolism of VLDL particles are important loci for effects of background diet on postprandial lipoproteins.

One animal study has provided evidence of an attenuated postprandial triglyceride response in animals fed high MUFA compared with high SFA diets [30]. In a recent human diet study, subjects given a standard test meal at the end of a high MUFA diet showed similar fasting and postprandial TRL triglyceride and apo B-48 responses as at the end of a high SFA diet [35]. However, although the areas under the postprandial response curves were similar for the two diets, the patterns of response differed with an earlier postprandial triglyceride and apo B-48 peak responses on the high MUFA than the SFA diet. These data are of interest in the light of similar differences in response to a standard test meal between subjects from Southern and Northern Europe habituated to high MUFA and high SFA diets, respectively [42]. The differences in the patterns of postprandial response were more marked than in the diet study, with Southern European showing a marked and early peak triglyceride response with faster return to fasting concentrations. In particular, apo B-48 concentrations declined rapidly suggesting faster rates of clearance of CM and CMr in these subjects. The authors suggested these findings may reflect faster rates of fat digestion and absorption and/or secretion of CM's in subjects habituated to high MUFA diets, raising the possibility of the gut as an

additional site of interest for understanding effects of diet on postprandial lipoprotein metabolism. Recent demonstration, using the Caco-2 cell line, of larger CM's when cells were incubated with oleic acid than palmitic acid [11], illustrates the potential for modulatory effects of dietary fatty acids at this locus, since larger CM's have been shown to be hydrolysed more rapidly and removed from circulation earlier than smaller CM's in the VLDL density range.

Based on a relatively small number of animal and human studies, it is concluded that high PUFA diets result in attenuated postprandial lipoprotein responses, although clear evidence for effects specifically on remnant particles is lacking. Effects of diet and meal fatty acid composition are similar with elevations in postprandial lipoproteins in the order ω -3 PUFA < ω -6 PUFA < SFA. High MUFA diets have been less well studied, although there is evidence to suggest effects on patterns of response which may be beneficial in long term diets.

5. Conclusions

Studies of effects of diet on postprandial lipoproteins in humans are sparse although some additional information is available from animal models. Investigations of mechanisms underlying effects of diet are in part limited by suitable in vivo techniques for studying CM and VLDL particles and their remnants. Available data support the view that meals and diets containing PUFA, particularly ω -3 PUFA, result in attenuated responses of triglycerides and of CM and VLDL particles. MUFA-containing meals do not appear to be cleared faster than SFA meals but MUFA in the background diet may lead to faster rates of triglyceride entry and clearance. Mechanisms underlying effects of PUFA and MUFA on postprandial lipoprotein metabolism may operate at a number of loci including the gut, adipose tissue (LPL) and the liver (VLDL synthesis and secretion).

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