

## Dietary carbohydrates and triacylglycerol metabolism

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There is a growing body of scientific evidence which demonstrates that plasma triacylglycerol (TAG) concentration, especially in the postprandial state, is an important risk factor in relation to the development of CHD. Postprandial hypertriacylglycerolaemia is associated with a number of adverse metabolic risk factors, including the preponderance of small dense LDL, low HDL-cholesterol concentrations and elevated factor VII activity. Traditionally, a low-fat high-carbohydrate diet was used to prevent CHD because it effectively reduces plasma cholesterol concentrations, but this dietary regimen increases plasma TAG concentrations and reduces HDL-cholesterol concentrations. There is substantial epidemiological evidence which demonstrates that high plasma TAG and low plasma HDL concentrations are associated with an increased risk of CHD. Thus, there is reason for concern that the adverse effects of low-fat high-carbohydrate diets on TAG and HDL may counteract or negate the beneficial effect of reducing LDL-cholesterol concentrations. Although there have been no prospective studies to investigate whether reduced fat intake has an adverse effect on CHD, there is strong epidemiological evidence that reducing total fat intake is not protective against CHD. On the other hand, high-fat diets predispose to obesity, and central obesity adversely affects TAG metabolism. There is substantial evidence that in free-living situations low-fat high-carbohydrate diets lead to weight loss, which in turn will correct insulin resistance and plasma TAG metabolism. Clearly there is a need for prospective studies to resolve the issue as to whether low-fat high-carbohydrate diets play an adverse or beneficial role in relation to the development of CHD.

### Triacylglycerol metabolism: Postprandial lipaemia: Coronary heart disease: Dietary carbohydrates

#### Plasma triacylglycerol as a risk factor for CHD

Traditionally, fasting plasma triacylglycerol (TAG) concentrations have not been recognized as an independent risk factor affecting the pathogenesis and progression of CHD (NIH Consensus Development Panel on Triglyceride, High-density Lipoprotein, and Coronary Heart Disease, 1993). However, more recent epidemiological, prospective and clinical information suggests that the relative importance of TAG as a risk factor for CHD may have been underestimated. A large meta-analysis of seventeen population-based prospective studies showed that plasma TAG concentration was an independent risk factor for CHD (Hokanson & Austin, 1996). This analysis also showed that plasma TAG concentrations were particularly important in relation to CHD risk in women, whereby a 1 mmol/l increase in plasma TAG concentration increased cardiovascular risk by 32 % in men and 76 % in women

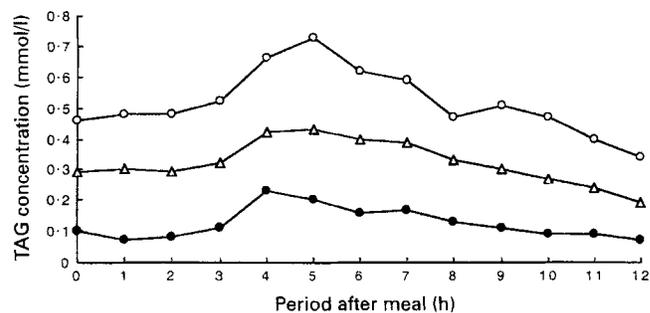
(Hokanson & Austin, 1996). Plasma TAG concentrations show considerable diurnal variation (Roche *et al.* 1998), increasing following the ingestion of a meal containing fat. It now appears that non-fasting or postprandial plasma TAG concentrations may be the critical aspect of TAG metabolism in relation to CHD. The prospective Physician's Heart Health Study demonstrated that non-fasting serum TAG concentration was a significant predictor of future myocardial infarction (Stampfer *et al.* 1996). Furthermore, a number of clinical studies have related the magnitude and duration of postprandial TAG metabolism to the presence and progression of atherosclerosis in both men and women (Patsch *et al.* 1993; Meyer *et al.* 1996). Karpe *et al.* (1994) demonstrated that the concentration of postprandial chylomicron remnant apolipoprotein (apo) B-48 was directly related to the rate of progression of coronary lesions in male post-myocardial infarction patients.

**Abbreviations:** apo, apolipoprotein; LPL, lipoprotein lipase; NEFA, non-esterified fatty acids; TAG, triacylglycerols; TRL, triacylglycerol-rich lipoproteins.  
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The precise way in which postprandial TAG metabolism affects the pathogenesis and progression of CHD has not been elucidated, but at least four possible mechanisms have been identified (Roche & Gibney, 1995). Whilst TAG itself is not a component part of the atherosclerotic lesion, Zilversmit (1979) was first to propose that elevated postprandial TAG concentrations exert their adverse effect by promoting the production of atherogenic chylomicron remnants. These remnants have the ability to mediate cholesterol influx into the arterial wall intima in human subjects, thereby promoting atherogenesis (Shaikh *et al.* 1991). It is important to realize that the postprandial lipaemic response not only represents the influx of dietary TAG within the circulation, but it also represents a very significant period during which the composition and metabolic fate of the cholesterol-rich lipoproteins, LDL and HDL, are determined. The extent of lipoprotein re-modelling which occurs during postprandial lipaemia is directly related to the magnitude and duration of postprandial triacylglycerol-aemia (Cohn, 1994). Elevated postprandial lipaemia promotes the catabolism of HDL (Patsch *et al.* 1987), and low concentrations of HDL-cholesterol are associated with an increased risk of CHD (Gordon & Rifkind, 1989). Postprandial hypertriacylglycerolaemia also stimulates the formation of small dense LDL (Karpe *et al.* 1993), which are highly atherogenic and significantly increase the risk (4 to 6-fold) of CHD (Griffin *et al.* 1994). TAG-rich lipoproteins (TRL) have the ability to activate coagulation factor VII (Roche & Gibney, 1997), and factor VII activity is positively associated with CHD mortality (Ruddock & Meade, 1994). Thus, it is probable that the combination of these metabolic factors underlies the positive association between postprandial TAG metabolism and the risk of CHD.

### Postprandial triacylglycerol metabolism

Postprandial TAG metabolism refers to the metabolic events which occur following the ingestion, digestion and absorption of a meal containing fat (Sethi *et al.* 1993; Roche & Gibney, 1995). Dietary fat is principally composed of TAG, which after digestion and absorption stimulates the production of chylomicrons within the enterocyte (Carey *et al.* 1983; Tso & Balint, 1986; Small, 1991). Chylomicrons are TRL which are secreted from the intestinal enterocyte and transport exogenous dietary TAG within the circulation. Chylomicrons are identified by virtue of their density as well as their unique apolipoprotein, apoB-48 which is formed exclusively in the intestine after tissue-specific editing of apoB-100 mRNA (Chan, 1992). Within the circulation, the nascent chylomicron acquires numerous apolipoproteins from the HDL fraction, these include variants of apoC which modulate lipoprotein lipase (EC 3.1.1.34; LPL) activity, and variants of apoE which determine chylomicron remnant removal (Brewer *et al.* 1988). The half-life of chylomicrons is relatively short, approximately 5 min (Patsch, 1987). The removal of chylomicron TAG is catalysed by adipose tissue LPL (Goldberg, 1996). LPL is also present in other tissues with a high fatty acid requirement, including skeletal muscle, cardiac muscle and the



**Fig. 1.** Postprandial triacylglycerol (TAG) concentrations in plasma (O), chylomicrons (●) and VLDL (△). (Adapted from Gibney & Daly, 1994.)

mammary gland (Coppack *et al.* 1994). However, in the postprandial state insulin secretion exclusively activates adipose tissue LPL and inhibits LPL activity in the other tissues (Goldberg, 1996). The hydrolysis of chylomicron TAG by LPL generates monoacylglycerol and non-esterified fatty acids (NEFA). Most of these hydrolytic products are rapidly transported across the endothelium into parenchymal cells, where they are re-esterified into TAG for storage in adipose tissue. Since LPL is the rate-limiting hydrolytic enzyme which controls TRL removal from the circulation, LPL activity in turn determines the extent and duration of postprandial lipaemia. The resultant de-lipidated chylomicron, now termed a chylomicron remnant, is catabolized by the liver.

Fig. 1 illustrates the relative contribution of chylomicrons and VLDL to plasma TAG concentrations (Gibney & Daly, 1994); clearly, VLDL are significant carriers of TAG during the postprandial response. VLDL are characterized by their apoB-100 content and transport endogenous TAG (Karpe, 1997). VLDL are synthesized continually in the liver, and the secretion rate of VLDL is primarily determined by the availability of TAG, because apoB-100 is continually produced (Chan, 1992). If sufficient TAG is not available the nascent TAG-poor VLDL are degraded intracellularly. TAG for VLDL synthesis is derived from three sources. Plasma NEFA are the principal substrate for hepatic TAG synthesis, while hepatic uptake of partly-lipolysed chylomicron and VLDL remnants that contain small amounts of TAG and *de novo* synthesis of TAG from carbohydrate represent alternative sources of hepatic TAG (Karpe, 1997). In the fasted state, NEFA are liberated from adipose tissue TAG through the action of hormone-sensitive lipase (EC 3.1.1.3), which catalyses the hydrolysis of adipose tissue TAG (Frayn *et al.* 1994). In the postprandial state, an appreciable quantity (up to 50%) of TRL-TAG escapes into the circulation as NEFA during TRL lipolysis (Binnert *et al.* 1996; Frayn *et al.* 1996), this provides ample substrate for TAG synthesis and promotes VLDL secretion during the postprandial response (Schneeman *et al.* 1993). The increase in VLDL concentration during the postprandial response may also be due to the accumulation of VLDL. During postprandial lipaemia chylomicrons and VLDL compete for LPL-mediated hydrolysis, and chylomicrons are preferentially hydrolysed by LPL (Karpe & Hultin, 1995). Thus, VLDL removal is

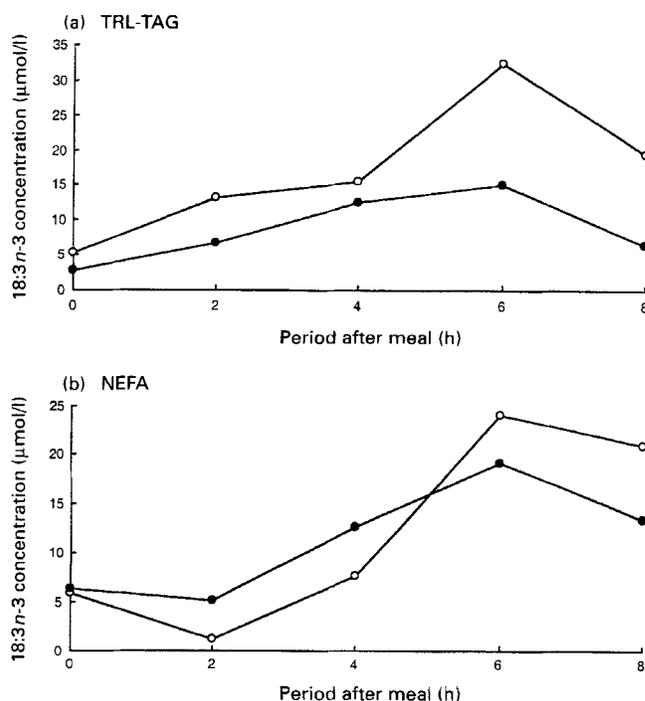
delayed, and there is an increase in VLDL concentration 4–6 h following meal ingestion (Potts *et al.* 1991; Berr, 1992).

### The acute effect of carbohydrate feeding on postprandial triacylglycerol metabolism

The magnitude of the postprandial lipaemic response is determined by a number of physiological factors, such as age, gender, body weight and nutritional factors (Roche & Gibney, 1995). Usually there is a direct dose–response relationship between the magnitude of the postprandial triacylglycerolaemic response and the quantity of fat ingested, when the protein and carbohydrate content of the test meal is kept constant (Cohen *et al.* 1988; Murphy *et al.* 1995; Dubois *et al.* 1998). The addition of sucrose to a fat-rich test meal amplifies the postprandial TAG compared with a test meal containing fat only (Grant *et al.* 1994). An equal quantity of sucrose increases the postprandial TAG response to a greater extent than glucose (Mann *et al.* 1971). Cohen & Schall (1988) investigated the relative effects of glucose, fructose and sucrose on postprandial TAG metabolism. It was demonstrated that when compared with a fat-only test meal the addition of 50 g glucose increased postprandial TAG concentrations, while 50 g fructose caused a much greater increase which was almost equivalent to that associated with the addition of 100 g sucrose. Thus, it was concluded that fructose was the hypertriacylglycerolaemic component of sucrose.

It is difficult to explain the acute effect of carbohydrate intake on postprandial lipid metabolism, but there are three possible mechanisms: (1) increased intestinal lipid absorption; (2) increased endogenous TRL synthesis; (3) decreased TRL lipolysis. First, it is unlikely that differences in the rate of gastric emptying and intestinal lipid absorption can explain these effects, because it has been demonstrated that the initial postprandial rise in plasma TAG concentration was of the same magnitude, whether in the presence or absence of carbohydrate (Grant *et al.* 1994). Furthermore, the greater osmolarity of the carbohydrate-rich test meals should reduce the postprandial TAG amplification rather than add to it. Second, carbohydrate in the test meal could stimulate the synthesis of glycerol via  $\alpha$ -glycerolphosphate in the intestinal mucosa; this again is unlikely because it has been demonstrated that a test meal of glucose alone does not increase the plasma TAG concentration (Grant *et al.* 1994). Fructose is known to stimulate hepatic TAG synthesis and VLDL secretion; however, this is probably more a feature of chronic carbohydrate feeding rather than an effect of an acute carbohydrate load. Finally, the acute effect of fructose on postprandial TAG metabolism is probably related to delayed clearance of TRL. Jeppesen *et al.* (1994) demonstrated that the addition of fructose to a test meal delayed the removal of retinyl palmitate-labelled TRL derived by intestinal clearance. Furthermore, Grant *et al.* (1994) have demonstrated that the clearance of an intravenously-administered lipid emulsion was significantly reduced following the ingestion of sucrose. However, the precise biochemical basis for this mechanism has not been elucidated.

There is evidence to suggest that inclusion of carbohydrate may affect the nature of the postprandial response.



**Fig. 2.** Postprandial concentrations of fatty acid 18:3n-3 ( $\mu\text{mol/l}$ ) in (a) triacylglycerol-rich lipoprotein-triacylglycerol (TRL-TAG) and (b) non-esterified fatty acid (NEFA) following high (○)- and low (●)-carbohydrate test meals. (Adapted from Shishehbor *et al.* 1998.)

Shishehbor *et al.* (1998) investigated the acute effect of the carbohydrate load on the mono- and biphasic nature of the postprandial lipaemic response. While the magnitude of the TAG response was not different between the two meals, the high-carbohydrate meal caused a biphasic increase in postprandial TAG concentrations. Soyabean oil containing fatty acid 18:3n-3 (12 g/100 g) was the test fat to allow identification of exogenous TAG derived from the test meal. Fig. 2 demonstrates that there was a greater concentration of 18:3n-3 in the TRL-TAG and NEFA fractions following the high-carbohydrate meal. The greater release of NEFA derived from the test fat into the circulation could have provided more substrate for VLDL-TAG synthesis, which may account for the biphasic response after the high-carbohydrate meal, even though an equal quantity of fat was provided in both test meals. Whilst the biochemical basis for this effect is difficult to explain, it may have been mediated by the greater postprandial plasma glucose, insulin or gastro-inhibitory polypeptide response after the high-carbohydrate meal, which in turn affected chylomicron hydrolysis, NEFA release and hepatic VLDL-TAG synthesis and secretion.

### The effect of chronic carbohydrate feeding on VLDL-triacylglycerol metabolism

The extent to which carbohydrate overfeeding induces hepatic TAG synthesis and VLDL secretion depends on the supply of carbohydrate which exceeds NEFA oxidation requirements for energy production. Carbohydrate feeding stimulates *de novo* lipogenesis by increasing the flux of either glucose or fructose along the glycolytic pathway,

thereby increasing the availability of acetyl Co-A and stimulating fatty acid synthesis (Frayn & Kingman, 1995). Carbohydrate feeding also up-regulates the activity of the enzymes which synthesize fatty acids. The activity of hepatic synthases and the NADPH-generating enzymes were significantly increased in rats fed on glucose and fructose, which in turn led to a significant increase in the rate of TAG secretion (Kazumi *et al.* 1997).

The supply of NEFA is also an important determinant of VLDL-TAG synthesis and secretion. Studies in rats have demonstrated that the infusion of physiological concentrations of fructose results in a greater use of  $^{14}\text{C}$ -labelled NEFA for  $^{14}\text{C}$ -labelled VLDL-TAG synthesis rather than for fatty acid oxidation (Mayes & Laker, 1993). Furthermore, it has been shown in rats receiving high-fructose diets that hepatic TAG synthesis is increased by enhancing the release of NEFA from adipose tissue (Vrana *et al.* 1974). In addition to increasing VLDL-TAG synthesis there is considerable evidence, albeit conflicting, that carbohydrate feeding impairs VLDL catabolism and removal by inducing physical and/or chemical changes in VLDL particles (Hirano *et al.* 1989; Mamo *et al.* 1991) or by affecting LPL activity (Frayn & Kingman, 1995).

#### Low-fat high-carbohydrate diets and lipoprotein metabolism

Traditionally low-fat diets, especially low-saturated-fat diets, have been advocated to prevent and/or reduce the incidence of CHD, because they effectively reduce plasma cholesterol concentration. However, high-carbohydrate low-fat diets are also associated with a number of adverse effects, i.e. increased plasma TAG concentration and lower plasma HDL concentrations (Mensink & Katan, 1992). There is substantial epidemiological evidence which would suggest that high plasma TAG and low plasma HDL concentrations are associated with an increased risk of CHD (Gordon & Rifkind, 1989; Hokanson & Austin, 1996). It may be that the adverse effects of low-fat diets may counteract or negate the beneficial effects of reducing LDL-cholesterol concentrations. Although there have been no prospective studies to investigate whether reduced fat intake has an adverse effect on the prevalence of CHD, there is strong epidemiological evidence that reduced total fat intake is not protective against CHD (Hu *et al.* 1997).

Furthermore, there is recent evidence that low-fat dietary treatment adversely affects the distribution of the LDL fraction. The distribution of LDL affects the atherogenicity of the lipoprotein, whereby LDL pattern B characterized by the predominance of small dense lipoproteins is significantly more atherogenic than the LDL pattern A (Griffin *et al.* 1994). It has been demonstrated that while a low-fat diet significantly reduced LDL-cholesterol concentration, this dietary change caused 44 % of LDL pattern A subjects to convert to LDL pattern B (Krauss & Dreon, 1995). The low-fat diet also significantly increased plasma TAG concentrations and significantly reduced HDL-cholesterol concentrations. Thus, this may represent another potentially

adverse effect of low-fat dietary treatment which has not yet been fully realized.

Conditions of insulin resistance such as non-insulin-dependent diabetes mellitus, syndrome X (Reaven, 1996), and the atherogenic lipoprotein phenotype (Austin *et al.* 1990) represent important conditions with greater risk of CHD, which may be partly explained by altered plasma TAG metabolism (Jeppesen *et al.* 1995; Daly *et al.* 1997). For this reason, there have been a number of studies which have investigated the effect of chronic low-fat high-carbohydrate diets on postprandial TAG metabolism in this high-risk group. Chen *et al.* (1993) showed that a very-low-fat high-carbohydrate diet (25 and 60 % dietary energy from fat and carbohydrate respectively) for 2 weeks significantly increased the magnitude of the postprandial lipaemic response. Even at more realistic dietary fat levels (30 and 55 % dietary energy from fat and carbohydrate respectively) fasting and postprandial TAG concentrations were increased compared with those with a high-fat diet (45 % dietary energy from fat) (Blades & Garg, 1995; Chen *et al.* 1995).

In these studies the biochemical basis for the postprandial hypertriacylglycerolaemic effect was also investigated. Blades & Garg (1995) showed that the postprandial lipaemic response following test meals labelled with retinyl palmitate, which reflected the macronutrient composition of the background diet (30 and 45 % dietary energy from fat), was significantly greater following the low-fat high-carbohydrate meal, even though it contained less fat. The incremental area under the TAG v. retinyl palmitate curves and LPL activity were not significantly different between diets, therefore it was proposed that the increase in postprandial TAG concentrations was due to increased hepatic secretion of VLDL-TAG. In contrast, Chen *et al.* (1995) measured the postprandial response to the same fat load following both diets (i.e. 30 and 45 % dietary energy from fat) and demonstrated significantly greater accumulation of chylomicrons and chylomicron remnant particles following the low-fat high-carbohydrate diet. In that study, endogenous VLDL-TAG turnover was measured by giving an intravenous bolus of [ $^3\text{H}$ ]glycerol-labelled VLDL-TAG. This showed that the VLDL-TAG pool size was significantly increased, and this was attributable to a significant reduction in the VLDL-TAG fractional catabolic rate and a significant increase in VLDL-TAG production rate after the high-carbohydrate diet.

There are a number of other ways in which a high-carbohydrate diet can be introduced without adversely affecting plasma TAG metabolism. Ullman *et al.* (1991) showed that the gradual introduction of a high-carbohydrate diet prevented the hypertriacylglycerolaemic effect which occurred upon immediate introduction of a high-carbohydrate diet. The combination of a low-fat high-carbohydrate diet with fish oils can prevent an increase in plasma TAG concentrations in the fasted state but not in the postprandial state (Roche & Gibney, 1996). Exercise also improves postprandial plasma TAG status (Tsetsonis *et al.* 1997); therefore it is possible that exercise could prevent the hypertriacylglycerolaemic effect of a high-carbohydrate diet.

### Dietary carbohydrates: friend or foe?

There is substantial scientific evidence to suggest that high-carbohydrate diets adversely affect plasma TAG metabolism. Elevated plasma TAG concentrations are associated with an increased risk of CHD, also elevated plasma TAG concentrations are associated with low HDL-cholesterol concentrations, the preponderance of small dense LDL and elevated factor VII activity, all of which are associated with increased risk of CHD. Thus, there is reason for concern that low-fat high-carbohydrate diets may not be as beneficial as previously understood. However, it is important to note that all the studies cited in the present review were conducted in a clinical setting and used isoenergetic amounts of fat or carbohydrate to maintain weight stability.

On the other hand, high-fat diets predispose to obesity, and central obesity adversely affects TAG metabolism. It is proposed that high-fat diets play a central role in the development of obesity (Prentice & Poppitt, 1996). There is substantial evidence that in free-living situations low-fat high-carbohydrate diets lead to weight loss (Kasim *et al.* 1993; Leenen *et al.* 1993), which in turn will correct insulin resistance and plasma TAG metabolism (Purnell & Brunzell, 1997). Clearly, there is a need for prospective studies to resolve the issue as to whether low-fat high-carbohydrate diets play an adverse or a beneficial role in relation to the development of CHD.

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