Effect of long-chain n−3 polyunsaturated fatty acids on fasting and postprandial triacylglycerol metabolism[1,2]

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ABSTRACT Elevated plasma triacylglycerol concentrations have been associated with increased risk of coronary heart disease (CHD). In the past, the epidemiologic evidence about the causal role of triacylglycerols in CHD has not been well regarded, but recent prospective evidence shows that nonfasting plasma triacylglycerol concentration is a strong and independent predictor of future myocardial infarction. Elevated plasma triacylglycerol concentrations are associated with other CHD risk factors, namely reduced HDL-cholesterol concentrations and a preponderance of highly atherogenic, small, dense LDL particles. Plasma triacylglycerol concentrations increase after the ingestion of a fat-containing meal, and elevated postprandial triacylglycerolemia leads to a series of metabolic reactions that reduce HDL-cholesterol concentrations and promote the formation of small, dense LDL particles. The magnitude of the postprandial response is largely determined by fasting plasma triacylglycerol concentrations. Metabolism of plasma triacylglycerols also influences postprandial factor VII activation and the postprandial lipemic responsiveness to dietary cholesterol. Therefore, dietary factors that improve fasting plasma triacylglycerol concentrations must have a role in a healthy diet. Eicosapentaenoic and docosahexaenoic acids are n−3 polyunsaturated fatty acids (PUFAs) in fish oil that effectively reduce plasma triacylglycerol concentrations. Because n−3 PUFAs are effective at low doses (1 g n−3 PUFA/d), they provide a realistic option for the optimization of plasma triacylglycerol metabolism. *Am J Clin Nutr* 2000;71 (suppl):232S–7S.

KEY WORDS Triacylglycerol, postprandial lipemia, n−3 polyunsaturated fatty acids, PUFAs, fish oil, eicosapentaenoic acid, EPA, docosahexaenoic acid, DHA, coronary heart disease

INTRODUCTION

Fish oils are rich sources of the long-chain n−3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA; 20:5n−3) and docosahexaenoic acid (DHA; 22:6n−3). Epidemiologic evidence has shown that consumption of n−3 PUFAs is inversely associated with incidence of coronary heart disease (CHD; 1, 2). Prospective studies have shown that relatively low doses of n−3 PUFAs reduce the risk of secondary coronary events (3, 4). The biochemical bases of the ameliorative effect of n−3 PUFAs are thought to be inhibition of coagulation (5), promotion of vasodilation (6), attenuation of inflammation (7), and modification of plasma lipid and lipoprotein concentrations (8). The effect of n−3 PUFAs on plasma lipid and lipoprotein metabolism has been reviewed extensively. In a review of 44 intervention studies that supplemented with a range of 0.5 to 25 g n−3 PUFA/d for an average of 6 wk, it was shown that supplementation had little effect on plasma LDL- and HDL-cholesterol concentrations, but that it consistently and significantly reduced plasma triacylglycerol concentrations (9).

Although elevated plasma triacylglycerol concentrations have been associated with increased risk of CHD, the role of triacylglycerol as an independent risk factor has remained unclear. The epidemiologic evidence regarding the role of plasma triacylglycerol concentrations in CHD was reviewed (10), and multivariate statistical analysis showed no consistent relation between plasma triacylglycerol metabolism and CHD in 5 of the 8 prospective epidemiologic studies. Therefore, the NIH Consensus Development Panel on Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease concluded that "For triglyceride, the data are mixed, and although strong associations are found in some studies, the evidence of a causal relationship is still incomplete" (11). However, more recently, a body of evidence has grown that supports the hypotheses that postprandial triacylglycerol metabolism plays a causal role in the pathogenesis and progression of CHD, and that nonfasting plasma triacylglycerol concentrations are a strong and independent predictor of future myocardial infarction. This article reviews both the evidence in relation to triacylglycerol metabolism and CHD and the efficacy of n−3 PUFAs as hypotriacylglycerolemic agents.

IS PLASMA TRIACYLGLYCEROL CONCENTRATION A RISK FACTOR FOR CHD?

The controversial nature of the triacylglycerol-CHD hypothesis is probably a function of the dynamic nature of the lipid and its carrier lipoproteins. Plasma triacylglycerol concentrations are highly variable, both within and between individuals. Furthermore, plasma triacylglycerol metabolism affects the composition

and metabolic fate of the HDL and LDL fractions. There is a consistent, negative correlation between plasma triacylglycerol and HDL-cholesterol concentrations, which reflects the physiologic relation between both indexes. Several researchers have proposed *1*) that the correlation between plasma triacylglycerol and HDL_2-cholesterol concentrations may explain why triacylglycerol does not emerge as an independent risk factor in epidemiologic studies, and *2*) that lowered HDL-cholesterol concentrations may only be a marker of plasma triacylglycerol metabolism, not an independent risk factor for CHD (12, 13). This hypothesis is supported by results of the Lipid Research Clinics 12-y follow-up study (14), which showed that individuals with low HDL-cholesterol and high plasma triacylglycerol concentrations showed elevated coronary mortality. Retrospective analysis of the Framingham Heart Study data also showed that high plasma triacylglycerol concentration was a significant risk factor when HDL-cholesterol concentrations were also low (15). The Caerphilly and Speedwell Collaborative Heart Disease Studies concluded that high plasma triacylglycerol concentrations associated with low HDL-cholesterol concentrations predicted subsequent ischemic heart disease events (16). A meta-analysis of 12 population-based, prospective studies showed that the relative risk of CHD increased significantly with increasing plasma triacylglycerol concentrations, and when the relation between triacylglycerol and CHD was adjusted for HDL cholesterol, plasma triacylglycerol concentration remained a significant risk factor (17).

In light of the close metabolic relation between plasma triacylglycerol and HDL-cholesterol concentrations, Sprecher et al (18) proposed the "conjoint trait" hypothesis, which purports that the combination of low HDL-cholesterol and high plasma triacylglycerol concentrations represents a single, inherited phenotype. Subsequent studies have extended this hypothesis and have shown that this phenotype is transmitted across generations as a combined phenotype, or conjoint trait. Multivariate statistical genetic analysis of the qualitative variation in plasma lipid concentrations in first degree relatives has shown that 25% of the genetic variance in plasma triacylglycerol and HDL-cholesterol concentrations may be explained by shared genes, whereas the remaining variability may be accounted for by other unshared genes, environmental factors, or both (19).

High plasma triacylglycerol concentrations are also associated with a preponderance of small, dense LDL particles. This highly atherogenic lipoprotein fraction has been associated with an increased risk (4–6-fold) of coronary artery disease (CAD; 20). Plasma triacylglycerols have a major metabolic influence on the physicochemical properties of LDLs (21). A recent prospective study that investigated the association between LDL particle size and CAD showed that LDL particle size was significantly smaller in CAD patients than in control subjects. Furthermore, multiple stepwise regression analysis identified triacylglycerol as the single most important explanatory variable for LDL size ($R^2 = 0.52$) (22).

This extensive evidence shows the central role of plasma triacylglycerol metabolism in determining the composition and metabolic fate of the other lipoproteins (LDL and HDL); therefore, the causal role of plasma triacylglycerol in the pathogenesis of CHD may have been underestimated. This view is supported by prospective evidence that nonfasting triacylglycerol concentration is a strong and independent predictor of future myocardial infarction (23). In this study, increased nonfasting plasma triacylglycerol concentrations were also associated with the presence of small, dense LDL particles and low HDL-cholesterol concentrations.

POSTPRANDIAL TRIACYLGLYCEROL METABOLISM AND CHD

In light of the importance of plasma triacylglycerol concentrations and the variability in plasma triacylglycerols associated with dietary fat intake, the body of research investigating the relation between postprandial triacylglycerol metabolism and CHD is growing. The postprandial triacylglycerolemic response refers to a series of metabolic events that occur after ingestion of a fat-containing meal. This process has been reviewed extensively elsewhere (24, 25), and a brief synopsis is presented here.

Dietary fat is composed principally of triacylglycerol, which, after digestion and absorption (26, 27), stimulates the production of chylomicrons. These triacylglycerol-rich lipoproteins (TRLs) transport dietary triacylglycerol within the circulation, causing an increase in plasma triacylglycerol concentrations. The magnitude of the postprandial response is determined by several factors; it increases with fasting plasma triacylglycerol concentration, age, and sedentary lifestyle and is greater in males than in females. Nutritional factors, including fat dose and habitual dietary fat composition, affect the magnitude of the postprandial lipemic response, which is attenuated markedly by chronic n−3 PUFA intake.

Several clinical studies have shown that postprandial lipemia is an important factor in the pathogenesis and progression of CHD. It has been shown that men with CAD had pronounced and delayed postprandial lipemia compared with control subjects (28). It has also been shown that postprandial, but not fasting, triacylglycerol concentration was the most accurate (68%) predictor of the presence and progression of atherosclerosis (29), even when all the traditionally accepted risk factors of CHD were included in the multivariate regression analysis. Karpe et al (30) investigated the postprandial lipemic response in male postinfarction patients and age-matched control subjects and showed that the concentration of postprandial chylomicron remnant apolipoprotein B48 was directly related to the rate of progression of coronary lesions.

ELEVATED POSTPRANDIAL TRIACYLGLYCEROL CONCENTRATIONS AND LIPOPROTEIN METABOLISM

An increase in plasma triacylglycerol concentrations is a normal metabolic consequence after ingestion of dietary fat. However, elevated postprandial plasma triacylglycerol concentrations are associated with several adverse metabolic events, including the formation of atherogenic chylomicron remnants, the formation of small, dense LDL particles, and the reduction of plasma HDL-cholesterol concentrations (24). Zilversmit (31) was the first to propose that cholesteryl ester–rich chylomicron remnants were as atherogenic as LDLs. Since then it has been shown that an elevated postprandial response is associated with the formation and increased concentrations of small, cholesteryl ester–enriched chylomicron remnants. These remnants share with LDL the ability to mediate cholesterol influx into the arterial wall intima in humans (32), thereby promoting atherogenesis. The close inverse association between HDL cholesterol and plasma triacylglycerol concentrations may be explained by the metabolic effects of elevated postprandial plasma triacylglycerol concentrations. Efficient postprandial lipid metabolism, with rapid clearance of chylomicrons, promotes HDL formation (33, 34). In contrast, excessive
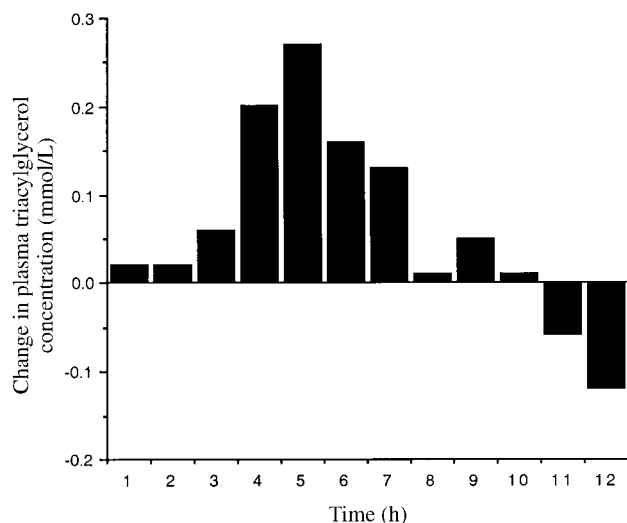
FIGURE 1. Change in plasma triacylglycerol concentration after ingestion of a meal containing 40 g fat. From reference 40.

postprandial triacylglycerol concentrations lead to excessive enrichment of HDL2 with triacylglycerol (35, 36). Hepatic lipase delipidates the triacylglycerol-rich HDL2 particles, converting them to small, dense HDL3 particles, thus lowering the concentration of the cardioprotective and metabolically active HDL2 fraction.

Excessive postprandial triacylglycerol concentrations promote the formation of the highly atherogenic small, dense LDL particles (20). Cholesterol esterification accelerates during postprandial lipemia and cholesteryl-ester transfer protein (CETP) catalyzes the heteroexchange of cholesterol ester from LDL for triacylglycerol from TRLs. These triacylglycerol-enriched particles then become dense LDLs. Karpe et al (37) showed that the magnitude of the postprandial TRL response and lipoprotein lipase (LPL) activity accounted for ≈50% of the variability of the distribution of LDL particles between the light and dense subfractions. A moderately high plasma triacylglycerol concentration, a low HDL-cholesterol concentration, and an increased proportion of LDL as small, dense LDLs comprise the atherogenic lipoprotein phenotype (ALP), which is accepted as the most common dyslipidemia associated with increased risk of CHD (38). Although the metabolic interplay between these lipoproteins provides a plausible explanation for this lipoprotein profile, it is proposed that there may also be a genetic basis for this common phenotype, such as the conjoint trait hypothesis discussed previously.

CRITICISMS OF CURRENT APPROACHES TO THE INVESTIGATION OF POSTPRANDIAL TRIACYLGLYCEROL METABOLISM

Postprandial investigations usually collect a series of postprandial blood samples from subjects who fasted overnight and consumed a single fat-rich test meal. It is important to realize that the requirement to standardize clinical postprandial investigations leads to an artificial situation that may not necessarily reflect the free-living postprandial state. Issues relating to the preprandial fast, the dose of fat, and the timing of fat intake represent key issues that affect the postprandial response but do not necessarily reflect a free-living situation.

Fasting plasma triacylglycerol concentration is the single most influential factor in the magnitude of the postprandial triacylglycerol response. There is a strong positive association between fasting plasma triacylglycerol concentrations and the magnitude of the postprandial triacylglycerolemic response (39); therefore, factors that affect fasting plasma triacylglycerol concentrations are important. The definition of fasting is unclear, but it generally means an overnight or 12-h fast. A typical postprandial triacylglycerolemic response after the ingestion of a meal containing 40 g fat is presented in **Figure 1** (40). Plasma triacylglycerol concentrations peaked 4–5 h after the meal and returned to baseline by 8 h after. As the test progressed, plasma triacylglycerol concentrations fell below baseline values and appeared to decrease linearly with time. Therefore, 12 h after meal ingestion, subjects' triacylglycerol concentrations were lower than the initial, fasting concentrations. There is a need to determine the optimum pretest conditions for postprandial investigations because the pretest diet, physical activity, and the timing and composition of the last meal all influence the preprandial or fasted state and also affect the postprandial response.

A second difficulty in relation to postprandial triacylglycerol studies is the dose of fat used. In the literature this has ranged from 20 to 120 g (41, 42). The mean amount of dietary fat consumed by 38 free-living volunteers consuming self-selected diets at different eating occasions throughout the day is shown in **Figure 2** (43). Note that the mean fat intake at each eating occasion ranged between 12 and 30 g, the fat dose being low in the early morning and higher in the early evening. These data challenge the relevance of postprandial investigations because *1*) the quantities of fat consumed as part of a habitual diet are much lower than those used in postprandial investigations, *2*) individuals consume dietary fat as part of 3–6 eating occasions (44) rather than as 1 bolus, and *3*) most postprandial investigations begin in early morning, a stage in the circadian rhythm when fat intake tends to be low. Whereas it is understandable that high fat doses are used to exaggerate the metabolic sequelae of the postprandial response to understand the biochemical basis of the postprandial triacylglycerolemic response, it cannot be assumed that the observed effects also occur in free-living situations. This hypothesis is to some extent borne out by the Physicians Health Study, in which nonfasting plasma triacylglycerol concentrations strongly and independently predicted subsequent myocardial infarction, and this relation was not influenced by the duration of fast before plasma triacylglycerol was measured (23). Clearly, investigations of postprandial lipid metabolism in the free-living situation are needed.

FASTING PLASMA TRIACYLGLYCEROL AND RISK FACTORS FOR CORONARY HEART DISEASE

Although the continued investigation of postprandial lipemia to elucidate the biochemical basis of plasma TRL metabolism in relation to CHD is important, there is ample evidence that elevated fasting plasma triacylglycerol concentrations as such are indicative of abnormal postprandial lipoprotein metabolism. Therefore, the relation between fasting plasma triacylglycerol concentrations and other CHD risk factors should not be ignored. For example, increased fasting triacylglycerol concentrations are associated with reduced concentrations of HDL cholesterol and, as previously discussed, this results from the remodeling of HDLs during postprandial lipemia that affects the composition and metabolic fate of HDLs. Likewise, 2 recent studies showed that fasting plasma triacylglycerol concentration, a marker for
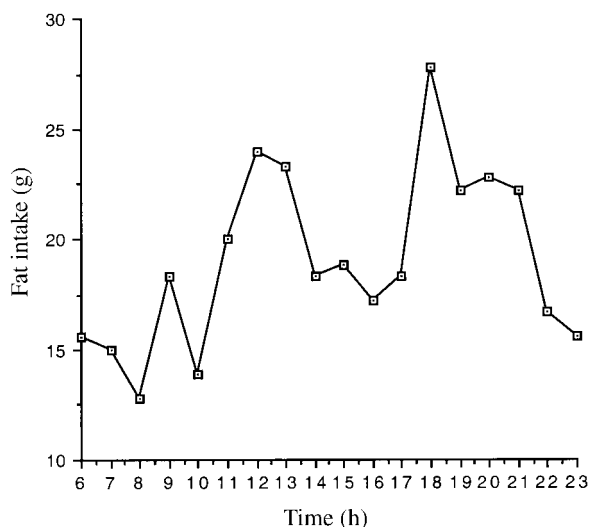
**FIGURE 2**. Fat intake of free-living volunteers consuming self-selected diets over 18 h. From reference 43.

the postprandial triacylglycerol response, has important effects on other CHD risk. The first relates to the activation of factor VII during postprandial lipemia (45). Several investigators have shown that coagulation factor VII is activated during postprandial triacylglycerolemia and that this response is affected by other lifestyle factors, including age (46), habitual dietary fat composition (47, 48), test-meal fat dose (49) and test-meal composition (49, 50). Although these factors play a role in the postprandial response, this effect is minimal compared with the effect of fasting plasma triacylglycerol concentrations (45). The importance of fasting plasma triacylglycerol was shown with multiple regression analysis that identified fasting plasma triacylglycerol concentration as the most important determinant of fasting factor VII activity, which in turn determined the magnitude of the postprandial response. Therefore, fasting plasma triacylglycerol concentrations determine not only the magnitude of the postprandial triacylglycerol response but also that of the postprandial thrombotic response.

Fasting plasma triacylglycerol concentrations also determine the effect of dietary cholesterol. The postprandial response to a low-fat, high-cholesterol test meal was investigated in 3 groups with different lipoprotein phenotypes (normal lipid concentrations, high LDL-cholesterol concentrations, and high plasma triacylglycerol concentrations; 51). This study showed that the group with high fasting plasma triacylglycerol concentration had a greater increase in the concentration of triacylglycerol and cholesterol in the TRL fraction. Considering the strong association between plasma triacylglycerol and cholesterol concentration with CHD, this study provides considerable evidence that fasting plasma triacylglycerol concentration is an important determinant of the effect of dietary cholesterol on postprandial lipemia. These effects of fasting plasma triacylglycerol concentrations on HDL-cholesterol concentration, factor VII activity, and cholesterol absorption are mediated through an abnormal postprandial triacylglycerol metabolism. Even so, fasting plasma triacylglycerol concentration is a marker for this abnormal state; therefore, lifestyle factors—including diet—that alter fasting plasma triacylglycerol deserve intensive research.

LIFESTYLE FACTORS THAT INFLUENCE PLASMA TRIACYLGLYCEROL CONCENTRATIONS

Several physiologic factors affect plasma triacylglycerol concentrations and the magnitude of the postprandial lipemic response. Fasting and postprandial plasma triacylglycerol concentrations are greater in men than in women (52, 53) and tend to increase with age (52, 54). Therefore, fasting plasma triacylglycerol concentrations account, in part, for differences in magnitude of postprandial lipemia associated with age and sex. The lower fasting triacylglycerol concentrations and postprandial lipemic response found in female subjects could be mediated through greater activity of lipoprotein lipase (LPL), the hydrolytic enzyme responsible for the removal of the TRL triacylglycerol from the circulation (55). Women have more adipose tissue LPL than do men (53). LPL activity is also increased after physical exercise conditioning (56), which accounts for reduced postprandial triacylglycerolemia in subjects who participate in physical exercise (56, 57). Obesity is associated with a greater postprandial triacylglycerol response, which may also be related to greater fasting triacylglycerol concentrations (58).

Dietary factors also affects the magnitude of the postprandial lipemic response. n−3 PUFAs are well known hypotriacylglycerolemic agents. Several studies have shown that n−3 PUFAs reduce plasma triacylglycerol concentrations dose dependently (59–61). When the data from these studies were pooled (**Figure 3**), it emerged that the change in fasting plasma triacylglycerol (ΔT) is related to the dose of n−3 PUFA intake (P) according to the equation $\Delta T = -7.67 - 3.05P$ ($R^2 = 0.874$). However, this equation relates to doses of n−3 PUFAs ranging between 1 and 9 g/d. Furthermore, this analysis does not take into account other important factors, ie, initial (preintervention) n−3 PUFA intake and duration of supplementation, which affect the triacylglycerol-lowering capacity of n−3 PUFAs. Lower doses of n−3 PUFAs supplemented over a longer intervention period (16 wk) have been shown to be effective hypotriacylglycerolemic agents. In that study, 1 g n−3 PUFAs/d reduced fasting plasma triacylglycerol concentrations by 21.2%, a level much greater than predicted from the above equation (10.7%) (8). This low dose of
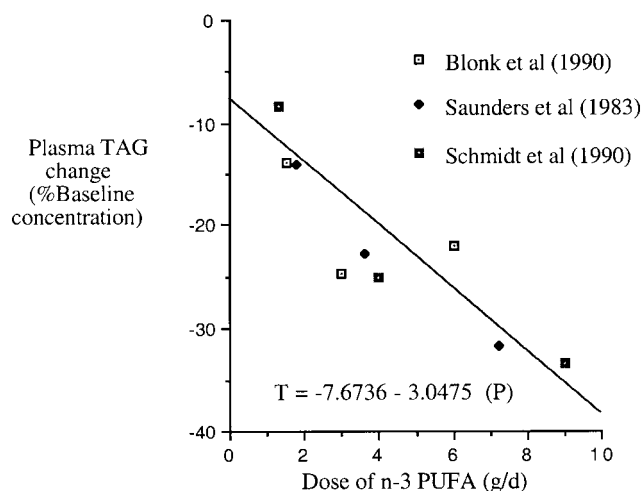
FIGURE 3. The dose-dependent hypotriacylglycerolemic effect of n−3 PUFA supplementation. Data from references 59–61. Reproduced with permission from reference 8.

n−3 PUFAs also reduced postprandial triacylglycerol concentrations significantly, to a degree similar to that seen in studies that used a much higher dose of n−3 PUFAs (24 g/d) (62, 63).

This hypotriacylglycerolemic effect of n−3 PUFAs may be mediated through reduced endogenous TRL synthesis, increased TRL removal, or a combination of both. Diminished endogenous TRL production has been shown in kinetic studies, in which the protein moiety of VLDLs was radiolabeled and n−3 PUFAs reduced VLDL synthesis (64). Chylomicrons and VLDLs compete for LPL-mediated removal from the circulation (65). Therefore, reduced VLDL synthesis would promote chylomicron removal, thus reducing the postprandial triacylglycerolemic response. The presence of n−3 PUFAs in a meal also promotes removal of TRL from the circulation (63), and postheparin LPL activity is significantly greater after a n−3 PUFA meal compared with a saturated fatty acid–rich test meal (66). Rat studies have shown that fish-oil consumption leads to significantly higher expression of adipose tissue LPL messenger RNA (67), which suggests that n−3 PUFA supplementation increases LPL-mediated TRL clearance. It is probable that n−3 PUFAs mediate their effect on plasma triacylglycerol concentrations by both reducing endogenous VLDL production and increasing TRL removal.

CONCLUSION

It is clear that in the future, plasma triacylglycerol concentrations should be considered an important factor in relation to the development of CHD. Although studying the postprandial triacylglycerol response allows investigation of the metabolic sequelae that occur postprandially, the standard protocol whereby subjects consume a high-fat dose in the early morning may not reflect the free-living situation. Fasting plasma triacylglycerol concentrations are reliable markers for the magnitude of the postprandial response. Therefore, this measure should be used to indicate abnormalities of postprandial triacylglycerol metabolism, namely reduced HDL-cholesterol concentration, a preponderance of small, dense LDL particles; excessive factor VII activation; and excessive cholesterol absorption. n−3 PUFAs are effective hypotriacylglycerolemic agents, even when consumed at low doses; therefore, increasing consumption of n−3 PUFAs will improve triacylglycerol metabolism both in the fasted and postprandial state and should be promoted as part of a healthy diet.

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