Original Article

Spillover of Dietary Fatty Acids and Use of Serum Nonesterified Fatty Acids for the Synthesis of VLDL-Triacylglycerol Under Two Different Feeding Regimens

Brian R. Barrows, Maureen T. Timlin, and Elizabeth J. Parks

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The present study quantified dietary fatty acid flux in healthy men (n = 6) who were fed a liquid formula through a duodenal feeding tube (continuous feeding group) or who consumed the same formula in meals (meal feeding group). A triacylglycerol (TAG) stable isotope was added to the formula to determine the entry of dietary fatty acids into the serum and its clearance to the liver and resecretion into serum via VLDL. The contribution of dietary fatty acids to serum nonesterified fatty acids (NEFAs) was higher with meal feeding (24.4 ± 2.6%) compared with continuous feeding (10.8 ± 2.9%, P < 0.01) and, when multiplied by the NEFA concentration, resulted in similar absolute fatty acid spillover. Diet-derived NEFAs subsequently represented 10.6 ± 1.2% and 4.7 ± 1.3% of hepatic VLDL-TAG (meal feeding vs. continuous feeding, respectively, P = 0.004). Chylomicron remnant uptake by the liver contributed 9.3 ± 1.9% of fatty acids to hepatic VLDL-TAG synthesis with meal feeding compared with continuous feeding (4.4 ± 0.8%, P < 0.03). These data suggest that the extent of dietary fatty acid recycling via serum NEFAs and VLDL-TAG is determined by the rate of delivery of dietary fat to the intestine. The inefficient removal of dietary fat from the circulation may maintain VLDL-TAG production but may also result in prolonged postprandial lipemia. *Diabetes* 54:2668–2673, 2005

Elevated postprandial lipemia has been shown to correlate with increased cardiovascular disease risk (1). Triacylglycerols (TAGs) taken in from the diet are primarily stored in adipose and utilized for energy by peripheral tissues, but a portion of these fatty acids can clear to the liver. That the liver may coordinate its use of fatty acids that flow to it from many different sources (e.g., adipose, diet, etc.) provides an elegant example of physiology. However, in settings of expansion of adipose stores, or higher dietary fat intake, the liver's ability to handle alterations in fatty acid flux may be compromised. Studies in fasting individuals have shown that dysregulation of hepatic fatty acid usage of adipose-derived nonesterified fatty acids (NEFAs) contributes to impaired glucose tolerance (2), and an understanding of liver fatty acid partitioning during fasting and feeding will be necessary to formulate future dietary and therapeutic strategies for the treatment of elevated blood lipids in insulin resistance and diabetes. In a companion article (3) in this issue of *Diabetes*, we have described the use of multiple stable isotopes to quantitate the flux of fatty acids into the liver, where they are subsequently reassembled to TAGs, incorporated into VLDL particles, and secreted from the liver. In that article, fatty acids derived from adipose, lipogenesis, and diet were quantified in healthy men. Little is known about the role dietary fatty acid flux plays in liver lipid metabolism, and in the present analysis, we focused specifically on routes of dietary fatty acid entry into the serum and liver. To assess the influence of the rate of fatty acid influx, we compared the metabolism of dietary fatty acids when they were infused slowly into the duodenum and when they were consumed by mouth in meals.

Dietary fatty acids can enter the liver via two routes. First, intestinally derived chylomicrons that carry dietary TAG release fatty acids at adipose and muscle through the action of lipoprotein lipase. Once this occurs, these chylomicrons become lipoprotein remnants that can clear to the liver via receptor binding. In rats, previous research (4) has shown that up to 50% of the original dietary lipids packaged in the chylomicron can be still present in the remnant when it clears to the liver. Once these particles are taken up, the lipids must be stored in the hepatocyte, oxidized, or repackaged and resecreted via VLDL. That chylomicron remnant TAG is delivered to the liver and used for subsequent VLDL-TAG synthesis is supported by the work of Heath et al. (5) who demonstrated the appearance of a dietary label in VLDL-TAG after meal ingestion. Time points earlier than 90 min were not obtained, and thus the potential immediate use of dietary

From the Department of Food Science and Nutrition, University of Minnesota, St. Paul, Minnesota.

Address correspondence and reprint requests to Elizabeth J. Parks, PhD, Department of Food Science and Nutrition, University of Minnesota, 1334 Eckles Ave., St. Paul, MN 55108. E-mail: eparks@umn.edu.

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AUC, area under the curve; NEFA, nonesterified fatty acid; TAG, triacylglycerol.

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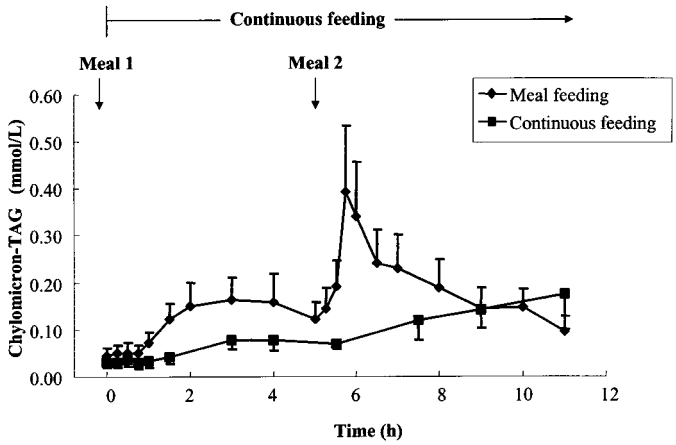

FIG. 1. Concentrations of TAG in the lipoprotein fraction S_F > 400 under two feeding regimens. Healthy male subjects were fed either continuously through a duodenal feeding tube for 11 h or consumed the liquid formula as two meals (arrows). Data are means ± SE, n = 6.

fatty acid by the liver could not be documented. The second route of dietary fatty acid entry into the liver is via chylomicron-TAG "spillover" into the serum NEFA pool (6–8). Human studies have shown that some chylomicron fatty acids can enter the serum NEFA pool after lipolysis of chylomicron-TAG by lipoprotein lipase (6–8). As with remnant fatty acids, these diet-derived NEFAs then have the potential to flow to the liver and be reused for TAG synthesis. Studies investigating dietary fatty acid spillover have not measured adipose fatty acid release concurrently; therefore, a comparison has not been made between the use of dietary- and adipose-derived fatty acids for VLDL-TAG synthesis. The goal of the present study in healthy subjects was to establish how the delivery of dietary TAG impacted serum NEFA concentrations, the flux of these lipids to the liver, and their subsequent recycling through synthesis and secretion of VLDL-TAG.

RESEARCH DESIGN AND METHODS

Research methods are described in detail in the companion article (3). Briefly, six healthy subjects were recruited by advertisement and gave written informed consent for all procedures. Recruitment criteria were nonsmoking, aged 20–55 years, stable body weight, and maintenance of normal exercise and activity patterns. Screening blood draws were performed on two separate occasions after subjects fasted for at least 12 h and abstained from alcohol for at least 48 h. Subjects participated in two metabolic studies on separate occasions at least 6 weeks apart. Three days before each metabolic study, subjects were placed on weight-maintaining diets formulated with comparison to 3-day dietary recalls of usual intake (9). Alcohol consumption was prohibited during this time. Subjects reported to the General Clinical Research Center between 1100 and 1200 on day 1. From 1200 to 1330, subjects consumed a standard meal prepared at the metabolic kitchen in the General Clinical Research Center. For the continuous feeding regimen, a size 8 French feeding tube inserted in the duodenum via the nasal cavity was placed in the subjects. Fluoroscopy was used to confirm the accurate placement of the tube, which was 15 cm distal from the pyloric sphincter. Between 1730 and 1800, an evening meal was consumed, representing 40% of daily energy needs. This meal consisted of whole foods and was consumed by mouth. Following this meal, no food or energy-containing beverages were allowed. For the continuous feeding regimen, at 0900 on day 2, a liquid formula was administered continually through the feeding tube for 11 h. For the meal feeding regimen, one-half of the liquid formula was consumed at 0700 and the remaining half at 1200.

Isotope infusion protocol and sample analysis. Potassium hexadecanoate-1,2,3,4-$^{13}C_4$ and glyceryl tri(hexadecanoate-d_{31}) were purchased from Isotec (Miamisburg, OH) and from Cambridge Isotope Laboratories (Andover, MA). At 1700 on day 1, an intravenous line was placed into the antecubital vein of each arm; one intravenous line was used for the administration of hexadecanoate-1,2,3,4-$^{13}C_4$ and the other intravenous line used to obtain blood samples. The glyceryl tri(hexadecanoate-d_{31}) was incorporated into the liquid formula. At 2400 on day 1, an infusion of hexadecanoate-1,2,3,4-$^{13}C_4$, complexed with human albumin, was started and continued until 11 h after the initiation of feeding on day 2. All intravenous line solutions were prepared under sterile conditions by the investigational pharmacy at Fairview University Medical Center, Minneapolis, Minnesota. The liquid formula, which supplied approximately two-thirds of the daily energy intake for each subject, was prepared in the metabolic kitchen of the General Clinical Research Center the day before infusion. The formula consisted of an enteral feeding solution (Boost; Mead Johnson Nutritionals, Evansville, IN), pasteurized egg yolk, heavy whipping cream, vegetable oil, and glyceryl tri(hexadecanoate-d_{31}). The glyceryl tri(hexadecanoate-d_{31}) was heated to its melting point (69°C), while the remaining ingredients were blended together and heated to the same temperature. All components were combined immediately and blended in a kitchen blender on high speed for at least 1 min. To ensure homogeneity, the solution was passed once through a microfludizer (Model 110 Y; Microfluidics, Newton, MA). The macronutrient composition of the formula was similar to the 3-day run-in diets. During fasting and feeding, blood samples were taken periodically and serum separated immediately by centrifugation at 1,500*g* for 10 min at 4°C and kept on ice while a preservative cocktail was added (10). Serum NEFA concentrations, fatty acid composition, and stable isotope enrichments were measured as previously described (11).

Calculations and statistical analyses.

- Percent NEFAs from dietary TAG lipolysis = (% hexadecanoate-d_{31} in NEFAs/% hexadecanoate-d_{31} in liquid formula TAG).
- Percent VLDL-TAG from diet-derived NEFAs = [(% hexadecanoate-d_{31} in NEFAs/% hexadecanoate-d_{31} in liquid formula TAG)/% hexadecanoate-$^{13}C_4$

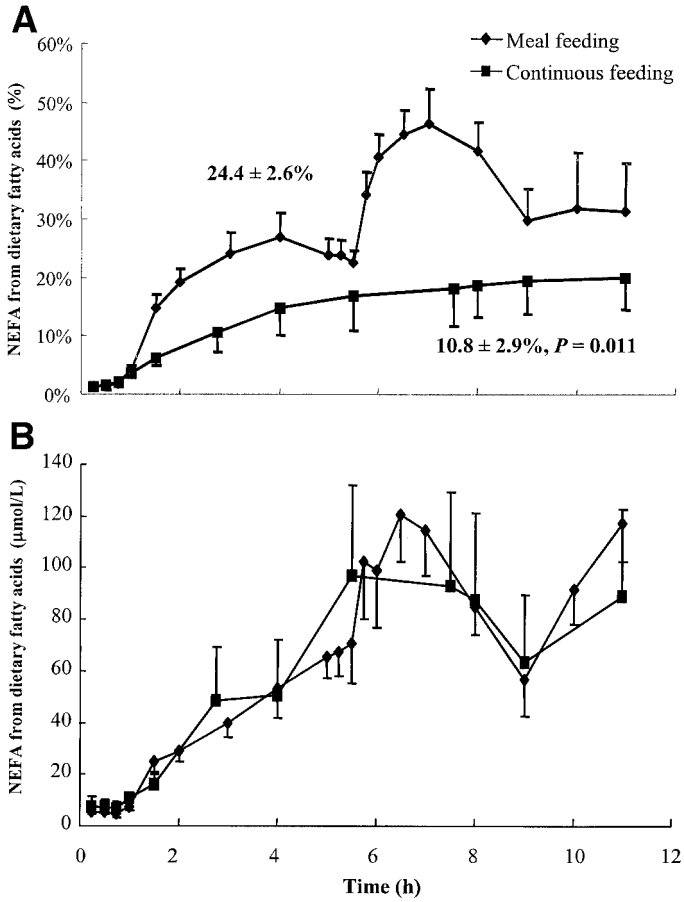

FIG. 2. Contribution of dietary fatty acids to the serum NEFA pool. Data are presented as percentage of NEFAs derived from TAG-rich lipoprotein–TAG fatty acid spillover (*A*) or as the absolute amount of NEFAs derived from TAG-rich lipoprotein–TAG spillover (*B*). Data are means ± SE, n = 6. Values listed on graph are the average of all points, with the *P* value for differences between feeding regimens.

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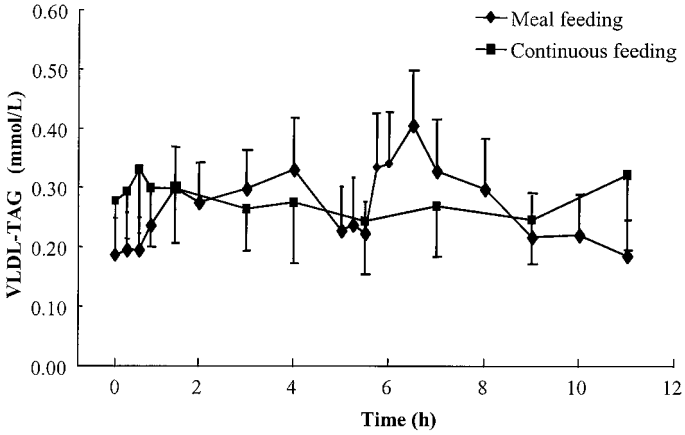

FIG. 3. Concentrations of TAG in the lipoprotein fraction S_f 60–400 under two feeding regimens. Data are means ± SE, n = 6.

in NEFAs] × (% hexadecanoate-$^{13}C_4$ in VLDL-TAG/% hexadecanoate-$^{13}C_4$ in NEFAs).

- Percent VLDL-TAG from chylomicron remnant TAG = % hexadecanoate-d_{31} in VLDL-TAG − % hexadecanoate-d_{31} derived from diet-derived NEFAs
- The rate of appearance (R_a) of fatty acids from adipose-TAG lipolysis discussed in this article (and presented graphically in the companion article [3]) has been calculated by taking into account the amount of unlabeled dietary fatty acid spillover into the plasma NEFA pool.
- R_a of adipose NEFAs (μmol · kg^{-1} · min^{-1}) = {[rate of infusion (R_i) hexadecanoate-$^{13}C_4$ (μmol/min)/% hexadecanoate-$^{13}C_4$ in adipose NEFAs]/% hexadecanoate in NEFAs}/body wt (kg).

Calculations were performed using Microsoft Excel 2000 (Seattle, WA) and statistical analyses on Statview for Windows (version 5.0.1; SAS Institute, Berkeley, CA). Differences between the two trials were analyzed using paired Student's t test. All values are means ± SE. A P value < 0.05 was considered statistically significant.

RESULTS

As described in the companion article (3), compared with meal consumption, continuous duodenal infusion of the liquid formula resulted in lower serum concentrations of glucose and insulin, as analyzed by incremental area under the curve (AUC). The average fed-state NEFA concentration with meal feeding was 0.27 ± 0.03 mmol/l, which was significantly lower compared with continuous feeding (0.38 ± 0.04 mmol/l, P = 0.039; for data, see companion article [3]; Fig. 2*C* and *D*). Although the meal feeding regimen produced greater insulin concentrations postprandially, the R_a NEFA from adipose was not significantly more suppressed with meal feeding (−1,045.8 ± 118.2 μmol/kg) compared with continuous feeding (−794.2 ± 318.9 μmol/kg, P = 0.242). Changes in chylomicron-TAG concentrations (Fig. 1) show that average fed-state chylomicron-TAG concentration was significantly higher with meal feeding (0.16 ± 0.04 mmol/l) compared with continuous feeding (0.08 ± 0.03 mmol/l, P = 0.028). Four of six subjects had greater chylomicron-TAG AUC values for the meal feeding regimen, and on average, the incremental AUC of chylomicron-TAG concentration tended to be greater for the meal feeding regimen (1.27 ± 0.37 mmol · h · l^{-1}) than for the continuous feeding regimen (0.63 ± 0.23 mmol · h · l^{-1}, P = 0.085). With meal feeding, chylomicron-TAG spillover resulted in a significantly greater percentage of these fatty acids in the serum NEFA pool (24.4 ± 2.6%, Fig. 2) compared with continuous feeding (10.8 ± 2.9%, P = 0.011). When the dietary percentages of NEFA were multiplied by the serum NEFA pool sizes, the absolute amounts of dietary fatty acids found in this pool were not different (Fig. 2*B*) (AUC for meal feeding = 0.66 ± 0.06 vs. continuous feeding = 0.57 ± 0.27 mmol · h · l^{-1}, P = 0.73). In other words, meal feeding tended to be associated with a lower NEFA concentration but a greater proportion of the NEFA pool derived from dietary spillover, the result of which was an absolute concentration of NEFAs from dietary TAG spillover equivalent to that with continuous feeding.

VLDL-TAG concentration following meal feeding increased from baseline (Fig. 3, AUC = 0.93 ± 0.51 mmol · h · l^{-1}), while the concentration remained constant with continuous feeding (−0.06 ± 0.26 mmol · h · l^{-1}, P = 0.050). As shown in Fig. 4*A*, the hepatic entry of dietary fatty acids through the NEFA pool resulted in VLDL-TAG with a greater day-long average percentage from dietary spillover after meal feeding (10.6 ± 1.2%) compared with continuous feeding (4.7 ± 1.3%, P = 0.004). The resulting product, VLDL-TAG concentration multiplied by the percentage of VLDL-TAG from diet-derived NEFAs, reflects the absolute VLDL-TAG derived from spillover (Fig. 4*B*). This tended to be higher with meal feeding compared with continuous feeding (P = 0.071 for AUC comparison). The total observed dietary label found in VLDL-TAG was greater than the amount

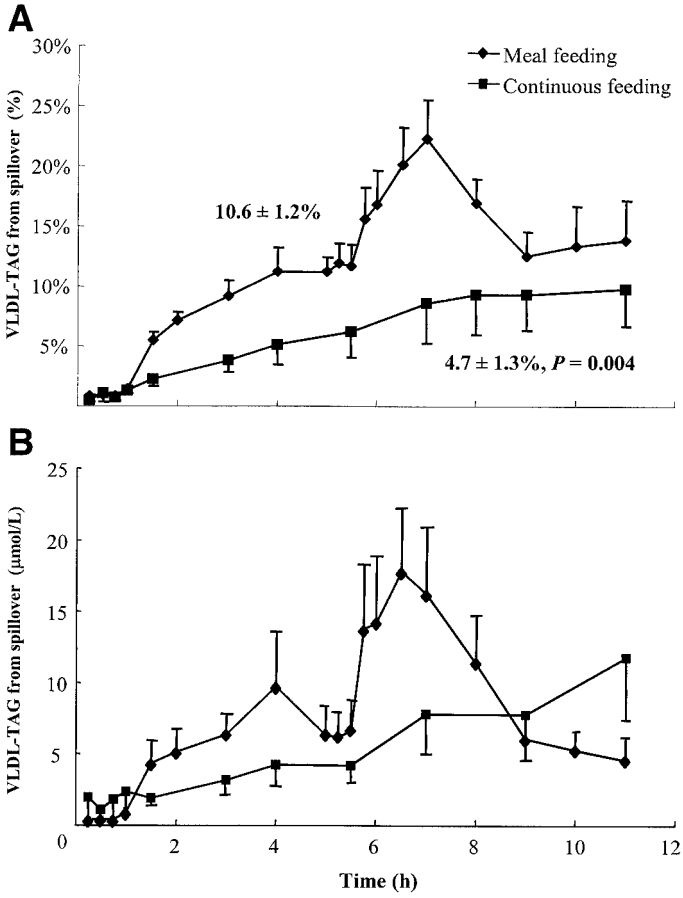

FIG. 4. VLDL-TAG derived from dietary fatty acid spillover. Data are presented as the percentage of VLDL-TAG palmitate derived from TAG-rich lipoprotein–TAG fatty acid spillover and clearance to the liver via the NEFA pool (*A*) or as the absolute amount of VLDL-TAG palmitate derived from this source (*B*). Data are means ± SE, n = 6.

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FIG. 5. VLDL-TAG derived from remnant TAG clearance. Data are presented as the percentage of VLDL-TAG palmitate derived from TAG-rich lipoprotein remnant uptake by the liver (*A*) or as the absolute amount of VLDL-TAG palmitate derived from this source (*B*). Data are means ± SE, $n = 6$.

that could be accounted for by dietary fatty acid spillover through the serum NEFA pool. This observation supports the concept of chylomicron remnant entry into the liver and dietary fatty acid recycling through incorporation into VLDL-TAG. Hereafter, this source will be referred to as chylomicron remnant TAG. The average percentage of VLDL-TAG from this fatty acid source (Fig. 5*A*) was significantly higher with meal feeding (9.3 ± 1.9%) compared with continuous feeding (4.4 ± 0.8%, $P = 0.030$). The absolute VLDL-TAG derived from remnant fatty acids is shown in Fig. 5*B*. Inspection of Fig. 5*B* suggests a greater use of remnant fatty acids with meal feeding and that the response of individual subjects to meal feeding demonstrated greater variability. When analyzed by AUC, the meal feeding area (5.3 ± 1.9 μmol · h · l^{-1}) tended to be higher than that for continuous feeding (2.1 ± 0.7 μmol · h · l^{-1}, $P < 0.093$). The total amount of dietary fatty acid found in VLDL-TAG, derived from the contribution of spillover and remnant clearance, was significantly higher with meal feeding when analyzed as the average over the postprandial period (meal feeding 12.9 ± 3.4 vs. continuous feeding 5.5 ± 1.9 μmol/l, $P = 0.026$) or by AUC (meal feeding 137 ± 42 vs. continuous feeding 65 ± 24 μmol · h · l^{-1}, $P = 0.051$). These data are depicted in companion article Fig. 3*F* (3).

The relationships between variables, for both meal

TABLE 1
Correlation coefficients for selected variables associated with meal feeding and continuous feeding

	Meal feeding						
Continuous feeding	R_a NEFA (mmol · kg^{-1} · min^{-1})	NEFAs (mmol/l)	Chylomicron-TAG (mmol/l)	Insulin (mU/ml)	dd NEFAs (% of NEFA pool)	dd NEFAs (mmol/l)	VLDL-TAG from diet (%)
R_a NEFA (mmol · kg^{-1} · min^{-1})		0.949 (0.004)	0.911 (0.012)	0.788 (0.063)	NS	NS	NS
NEFAs (mmol/l)	−0.473 (0.344)		0.894 (0.016)	0.799 (0.057)	NS	NS	NS
Chylomicron-TAG concentration (mmol/l)	−0.351 (0.495)	0.560 (0.248)		NS	NS	NS	NS
Insulin (mU/ml)	−0.261 (0.618)	0.062 (0.907)	NS		NS	NS	NS
dd NEFAs (% of NEFA pool)	NS	NS	NS	NS		0.909 (0.012)	0.424 (0.402)
dd NEFAs (mmol/l)	NS	NS	NS	NS	0.324 (0.531)		0.252 (0.630)
VLDL-TAG from diet (%)	NS	NS	NS	NS	0.823 (0.044)	0.654 (0.159)	

Data are *R* (P value). VLDL-TAG from diet (%) is the entry of dietary fatty acids via both spillover and remnant uptake. Each subject's values across the 11-h feeding period were averaged to derive a single value that was then used for correlations. For comparison, correlations found significant for one regimen are presented for the other regimen. dd NEFA, concentration of dietary-derived NEFA.

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feeding and continuous feeding, are presented in Table 1. It should be noted that the R_a NEFA values in the table reflect fatty acid release from adipose only (i.e., the values were calculated by excluding the rate of entry of dietary fatty acids into the NEFA pool). During meal feeding, the chylomicron-TAG concentrations were significantly and strongly correlated with both the R_a NEFA ($R = 0.911$, $P = 0.012$) and the total serum NEFA concentration ($R = 0.894$, $P = 0.016$). The hypothesis that higher chylomicron concentrations and greater dietary fatty acid spillover caused the higher NEFA concentrations postprandially was not supported by these data because NEFA concentration failed to correlate with dietary spillover, analyzed as either percentage of the NEFA pool from dietary TAG or the absolute amount of diet-derived NEFAs (Table 1). Chylomicron-TAG concentration also did not correlate with these measures of spillover. By contrast, insulin concentrations correlated positively with R_a NEFA and NEFA concentration. These data support the concept that individuals with the highest chylomicron-TAG concentrations were those who experienced both the highest postprandial insulin concentrations and the lowest suppression of adipose fatty acid release. These data suggest that among this group of healthy men, higher postprandial NEFA concentrations were due to elevated R_a NEFA, and this occurred within the setting of slower chylomicron-TAG clearance. By contrast, with continuous feeding, chylomicron-TAG was not related to NEFA pool size, and a significant correlation was not observed between R_a NEFA and NEFAs or R_a NEFA and chylomicron-TAG concentration. With continuous feeding, the percentage of VLDL-TAG derived from the diet was positively associated with the percentage of NEFAs derived from dietary fatty acids ($R = 0.823$, $P = 0.044$).

DISCUSSION

The present study was performed to quantify the flux of dietary fatty acids into the serum NEFA pool and the subsequent flux of diet-derived NEFAs into the liver for VLDL-TAG production. These data show that from 10 to 50% of plasma NEFAs were derived from dietary fatty acids during either meal feeding or continuous feeding regimens. Although the term "spillover" is used to define the appearance of dietary fatty acids in the NEFA pool during the fed state in these studies, it is not certain that these dietary fatty acids entered the plasma NEFA pool directly after lipolysis of chylomicron-TAG by lipoprotein lipase. These fatty acids could enter tissues first and then be resecreted before preformed tissue-TAG fatty acids are used (a mechanism referred to as "last in, first out"). In other words, recently cleared fatty acids could reside in an intracellular pool or be added to the periphery of the lipid droplet before being liberated and be preferentially released.

The spillover of dietary fatty acids found here confirms data from prior studies in which chylomicrons or chylomicron-like lipid emulsions were intravenously administered during fasted conditions (7,12) as well as after consumption of a high-fat meal (5). With continuous feeding, spillover of dietary fatty acids resulted in their slow accumulation in the serum NEFA pool. For meal feeding, the pattern of appearance of diet-derived fatty acids in the NEFA pool during the first meal (Fig. 2*A*) mirrored that of chylomicron-TAG concentrations (Fig. 1). This observation suggests that chylomicron-TAG flux can determine the rate of spillover into the serum NEFA pool and influence NEFA concentrations. Meal feeding displayed a greater percentage of serum NEFAs from dietary fatty acids compared with continuous feeding, and the percentage of these fatty acids in VLDL-TAG was also greater under the meal feeding regimen. However, within the meal feeding data, the amount of diet-derived NEFAs did not correlate with either the total amount of serum NEFAs or chylomicron-TAG postprandially. These data suggest that the rate of adipose fatty acid release remained the primary driver of postprandial NEFA concentration. With respect to clearance of chylomicron remnants, the VLDL-TAG concentration made from remnant clearance during meal feeding tended to be higher than that made during continuous feeding. To our knowledge, this is the first study to investigate chylomicron remnant uptake relative to other fatty acid sources used for liver-TAG synthesis. Since the fat content of the liquid formula (30% of energy) used in this study was similar to that typically consumed by individuals eating ad libitum, these data suggest that the amount of fat ingested on a typical Western diet does not overload the catabolic pathway of chylomicron-TAG in the serum.

In summary, meal consumption resulted in a greater percentage of NEFAs derived from the spillover pathway, but this contribution only partially made up for the loss of NEFAs resulting from suppression of adipose fatty acid release. The pattern of fatty acid spillover suggests that the greatest contributions of dietary fatty acids to the NEFA pool occur at peaks in postprandial lipemia. One question that remains unanswered is whether these processes can provide a potential benefit by maintaining fatty acid flux to the liver postprandially when adipose lipolysis is suppressed, or whether spillover and remnant clearance can contribute to the atherogenicity of the postprandial state by releasing fatty acids into the serum and delivering additional TAG to the liver. Additional research will be necessary to begin to answer these questions and to understand how these processes might be altered in insulin resistance and diabetes.

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REFERENCES

1. Roche HM, Gibney MJ: The impact of postprandial lipemia in accelerating atherothrombosis. *J Cardiovasc Risk* 7:317–324, 2000
2. Iozzo P, Turpeinen AK, Takala T, Oikonen V, Bergman J, Gronroos T, Ferrannini E, Nuutila P, Knuuti J: Defective liver disposal of free fatty acids in patients with impaired glucose tolerance. *J Clin Endocrinol Metab* 89:3496–3502, 2004
3. Timlin MT, Barrows BR, Parks EJ: Increased dietary substrate delivery alters hepatic fatty acid recycling in healthy men. *Diabetes* 54:2694–2701, 2005
4. Hultin M, Savonen R, Olivecrona T: Chylomicron metabolism in rats:

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lipolysis, recirculation of triglyceride-derived fatty acids in plasma FFA, and fate of core lipids as analyzed by compartmental modelling. *J Lipid Res* 37:1022–1036, 1996
5. Heath RB, Karpe F, Milne RW, Burdge GC, Wootton SA, Frayn KN: Selective partitioning of dietary fatty acids into the VLDL TG pool in the early postprandial period. *J Lipid Res* 44:2065–2072, 2003
6. Heimberg M, Dunn GD, Wilcox HG: The derivation of plasma free fatty acids from dietary neutral fat in man. *J Lab Clin Med* 83:393–402, 1974
7. Miles JM, Park YS, Walewicz D, Russell-Lopez C, Windsor S, Isley WL, Coppack SW, Harris WS: Systemic and forearm triglyceride metabolism: fate of lipoprotein lipase–generated glycerol and free fatty acids. *Diabetes* 53:521–527, 2004
8. Whitley HA, Humphreys SM, Samra JS, Campbell IT, Maclaren DPM, Reilly T, Frayn KN: Metabolic responses to isoenergetic meals containing different proportions of carbohydrate and fat. *Br J Nutr* 78:15–26, 1997
9. Harris JA, Benedict FG: *Biometric Study of Basal Metabolism in Man*. Washington DC, Carnegie Institute, 1919
10. Kotite L, Bergeron N, Havel RJ: Quantification of apolipoproteins B-100, B-48, and E in human triglyceride-rich lipoproteins. *J Lipid Res* 36:890–900, 1995
11. Parks EJ, Krauss RM, Christiansen MP, Neese RA, Hellerstein MK: Effects of a low-fat, high-carbohydrate diet on VLDL-triglyceride assembly, production and clearance. *J Clin Invest* 104:1087–1096, 1999
12. Teusink B, Voshol PJ, Kahlmans VEH, Rensen PCN, Pijl H, Romijn JA, Havekes LM: Contribution of fatty acids released from lipolysis of plasma triglycerides to total plasma fatty acid flux and tissue-specific fatty acid uptake. *Diabetes* 52:614–620, 2003

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