Seeing Is Believing: Dietary Fatty Acids Hurry Up From the Stomach to the Heart of Patients With Impaired Glucose Tolerance

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Cardiovascular disease and heart failure are leading complications in patients with type 2 diabetes, prediabetes, and obesity in whom circulating fatty acid (FA) levels are commonly elevated. Abnormalities in FA handling in skeletal muscle, liver, and adipose tissue may initiate or perpetuate a cycle of insulin resistance, impaired glucose utilization, and dyslipidemia, thereby leading to substrate overflow to the heart. From animal studies, we learn that once an excess of FA is forced to enter myocardial cells, lipotoxicity and functional loss occur (1–4). However, less is known about the organ-specific fate of endogenous or ingested lipids in humans. This is because systemic fluxes of nonesterified fatty acids (NEFAs) and triglycerides (TGs) cannot be extrapolated to individual organs because local mechanisms such as perfusion, lipolysis, oxygen availability, and inward transport may intervene in the response of individual tissues to the oversupply of FAs. In this issue of *Diabetes*, Labbé et al. (5) report on the use of positron emission tomography (PET) to image the organ-specific fate of ingested FAs, including chylomicron-derived FA in the myocardium, adipose tissue, skeletal muscle, and liver in subjects with impaired glucose tolerance (IGT) and normal glucose tolerance.

PET is a nuclear imaging technique that uses short-lived positron-emitting radioisotopes (e.g., ^{18}F, ^{11}C) to label molecules of interest (e.g., substrates) and visualize their fate in individual organs. Native substrates, such as ^{11}C-labeled glucose or long-chain FAs have a complex fate in tissue because they enter many metabolic pathways and part of the label is washed-out during oxidation or substrate output. Their labeled analogs ^{18}F-2-fluoro-2-deoxyglucose (^{18}F-FDG) and 14(*R*,*S*)-^{18}F-fluoro-6-thia-heptadecanoic acid (^{18}F-FTHA) cannot, or can only partially go through oxidative catabolism. Therefore, they become trapped in tissue in proportion to their uptake, discounted for the amount of tracer that is released back to the blood in its original form (especially from substrate-releasing organs such as fat or liver) or after its incorporation in TGs in the liver. This property allows simpler modeling, although limited information can be gained on the fate of substrates beyond their uptake. Furthermore, analogs are not necessarily handled by the body like native molecules. As a result, lumped constant terms have been introduced to translate ^{18}F-FDG into glucose uptake values, and the nonoxidative partition of ^{18}F-FTHA in body tissues—compared with native long-chain FAs—favors diglyceride at the expense of TG incorporation (6,7).

Most PET studies addressing FA metabolism have been conducted under fasting conditions because the direct release of NEFA or TGFA into the circulation occurring at fasting—as opposed to the more complex absorption of dietary FA—can be fairly reproduced by an intravenous delivery of tracer while preserving the steady-state conditions required in the conventional mathematical models used in PET studies. However, humans spend a great portion of their day in a fed state. For several hours after meal intake, human organs are engaged in handling nutrients deriving from gut absorption. This process is finely regulated via changes in gut perfusion and the release of hormones to maximize glucose utilization by insulin-sensitive organs, while simultaneously reducing FA oxidation in favor of TG storage. Studies in perfused hearts have shown that both chylomicrons and NEFAs contribute significantly to myocardial FA oxidation, and a two- to threefold elevation in oxidation from each of these two FA sources occurs in diabetic animal models (8). It follows that the quantification of FA coming directly from dietary intake is important to understand their contribution to lipotoxic tissue injury.

The team led by André C. Carpentier has introduced elegant and innovative approaches to address the postprandial fate of FA in body organs by the use of PET and ^{18}F-FTHA. In one recent study of humans, Labbé et al. (9) administered a continuous (i.e., 28.4 mL every 15 min) standard liquid meal to clamp postprandial NEFA and TG levels for 6 h. This protocol also included intravenous injection of ^{18}F-FTHA to acquire PET images during the later phase of the meal, approximating the steady-state requirements of conventional PET data modeling. However, the postprandial period is typically a non–steady-state condition, and the intravenous route of ^{18}F-FTHA administration neglects the transport of FAs in chylomicrons, which is preponderant in postprandial conditions. The investigators went on to evaluate whether orally administered ^{18}F-FTHA could be incorporated into chylomicrons similar to ^{3}H-triolein (10). This time, the intake of the standard liquid meal was shortened to a physiological duration of 20 min, and the meal contained ^{3}H-triolein and encapsulated ^{18}F-FTHA, showing that most plasma ^{18}F was recovered in chylomicrons. In this issue of *Diabetes*, Labbé et al. (5) report on the implementation of this very innovative approach to study organ-specific postprandial FA partitioning in subjects with impaired glucose tolerance (IGT) and healthy controls. Their experiments involved ingestion of a labeled meal, followed by dynamic PET imaging of the heart and liver at

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90–120 min postingestion, and then by a whole-body PET scan starting at 360 min after meal consumption. On a second day, myocardial perfusion, oxidative metabolism, and left ventricular function (in an electrocardiogram-gated subgroup) after 90 min of the same meal ingestion were measured by using PET imaging of intravenously injected ^{11}C-acetate. The organ-specific FA fractional extraction was estimated by a steady-state graphical approach in dynamic images of the myocardium and liver and by a semiquantitative index, i.e., the standardized uptake value (given by tissue-radioactivity/ingested-dose/kg) from delayed whole-body images of the myocardium, liver, skeletal muscle, and subcutaneous and perirenal adipose tissue. The authors emphasized that the length of meal absorption makes it difficult to design an imaging protocol to precisely quantify substrate fluxes. The lack of information during the first 90 min of meal absorption prevents detection of early group differences in circulating ^{18}F-chylomicrons. This impacts the results obtained with graphical analysis, and the use of graphical or standardized uptake value approaches underestimates FA uptake in the liver and adipose tissue, making it difficult to draw conclusions regarding the pathogenesis of steatosis or adiposity. New or existing algorithms need to be developed or adapted to non–steady-state conditions, and the validation of PET results against organ-balance measurements would consolidate this methodology. The radioactivity exposure of the gastro-intestinal epithelium also requires careful evaluation, and it is important to understand to what extent the oral route of tracer administration is indispensable or can be compromised, as described in ref. 9.

Fasting PET studies have shown that obesity, especially in women, is characterized by an enhanced myocardial oxygen consumption and FA fractional extraction or oxidation (11–13), increased skeletal muscle and liver FA oxidation, and impaired subcutaneous adipose tissue esterification (14). Similar findings were reported in the myocardium of patients with type 2 diabetes with high circulating glucose, FA, and TG levels (15,16). Conversely, in subjects with obesity and/or IGT, in whom FA levels were not elevated, NEFA uptake or oxidation rates were normal in the myocardium (14,17,18) and reduced in the liver and skeletal muscle of IGT subjects (18,19). We speculated that hyperglycemia in IGT individuals may partially counteract FA utilization, especially when the blood supply of FA is not high. The study of Labbé et al. (5) extends the above evidence from endogenous to exogenous gut-absorbed lipids, as the authors observed a marked postprandial upregulation in myocardial FA-inward and oxidative rate-constants and a >50% impairment in abdominal adipose tissue FA uptake in subjects with IGT relative to those with normal glucose tolerance. Although these findings await to be confirmed in age- and sex-matched subjects, they illustrate that fasting and postprandial data complement each other. First, they support the hypothesis that hearts of subjects with IGT lack metabolic flexibility and are constantly fat avid. Second, they provide the first evidence that myocardial FA extraction parallels cardiac dysfunction, when both are measured in the postprandial state.

In summary, the current and previous data coherently emphasize that organ-specific differences exist in the handling of an oversupply of FA in humans and that lipid oversupply may contribute to heart dysfunction. However, our recent data prompt caution in completely suppressing circulating FA to treat cardiac dysfunction (20). Clinically, these observation support the development of organ-tailored metabolic therapies and the use of molecular imaging in drug target discovery and development. The scrupulous, systematic, and challenging work of Carpentier and colleagues has importantly contributed to proof these principles.

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