Metabolism of Free Fatty Acids and Ketone Bodies During Exercise in Normal and Diabetic Man

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The triglycerides stored in adipose tissue constitute the largest energy depot of the human body. In order to become available to the tissues the triglycerides must be hydrolyzed to fatty acids and glycerol, which are both released from adipose tissue in response to various hormonal and nervous stimuli. The free fatty acids (FFA) are then transported through the plasma compartment bound to albumin. This paper will review quantitative aspects of this transport with special reference to exercise in normal and diabetic man.

The plasma FFA fraction is composed of a mixture of saturated and unsaturated fatty acids of different chain lengths.[1] Two fatty acids, palmitic and oleic acid, dominate and make up approximately 60% of the total plasma FFA. The measurement of turnover rate and tissue uptake of fatty acids requires the use of a radioactive tracer. Labeled palmitic and oleic acid have been used most frequently for this purpose, and results obtained with any of these tracers are valid for the major part of the FFA fraction under most experimental conditions.[2] With regard to the splanchnic uptake of FFA, results obtained with a single tracer fatty acid must, however, be interpreted cautiously. Hepatic uptake differs considerably among the fatty acids, being higher for those with shorter chain length and for those with one or more double bond.[2] It should also be noted that some of the minor constituents of the FFA fraction, e.g. arachidonic acid,[3] also behave quite differently from the major fatty acids in other respects.

FFA METABOLISM AT REST

The turnover rate of plasma FFA in the postabsorptive state is linearly related to the arterial concentration.[2] Measured regionally in the leg, uptake of FFA is also linearly related to the inflow both at rest and during exercise (Figure 1). Similar results have been obtained for forearm muscle uptake.[5] The arterial concentration of FFA, and hence the rate of lipolysis in adipose tissue, thus seems to be the most important factor influencing the rate of disappearance of plasma FFA and its muscle uptake.

Uptake by muscle tissue accounts for approximately 45% and splanchnic uptake for 25% of the turnover of FFA at rest (Table 1), leaving 30% of the turnover for other tissues. Conversion of these rates into oxygen equivalents shows that the transport of FFA in the postabsorptive state is actually in excess of what is needed for the oxidative metabolism. The difference between FFA uptake and oxygen consumption is proportionately greatest for the splanchnic area where hepatic ketogenesis and incorporation into very low-density lipoproteins are important alternatives to fatty acid oxidation.

Experiments in vitro have shown that fatty acids inhibit glucose utilization in both rat heart and diaphragm muscle.[7,8] Increased availability of FFA interferes at the level of glucose phosphorylation[7] as well as in the oxidation of glucose-derived pyruvate.[8] The effect on glucose uptake has been confirmed in vivo by the demonstration of a decreased glucose tolerance after the elevation of plasma FFA by heparin administration.[9] An in vivo effect of FFA on pyruvate oxidation can be inferred from the data presented in Figure 2, showing that the lactate release from the leg at rest increases with increasing uptake of FFA. The preferential use of FFA (and ketone bodies) by muscle forms the basis of the glucose–fatty acid cycle, in which plasma FFA are ascribed an important function in regulating glucose homeostasis.[10]

FFA METABOLISM DURING EXERCISE

At the onset of work involving the large muscle groups, such as bicycle exercise, the arterial FFA level drops transiently during the first 10 min (Figure 3). This fall in FFA concentrations is accompanied by a decrease in specific activity (during continuous tracer infusion) indicating that it is caused by an increased removal of FFA from plasma rather than an inhibition of lipolysis.[11] During

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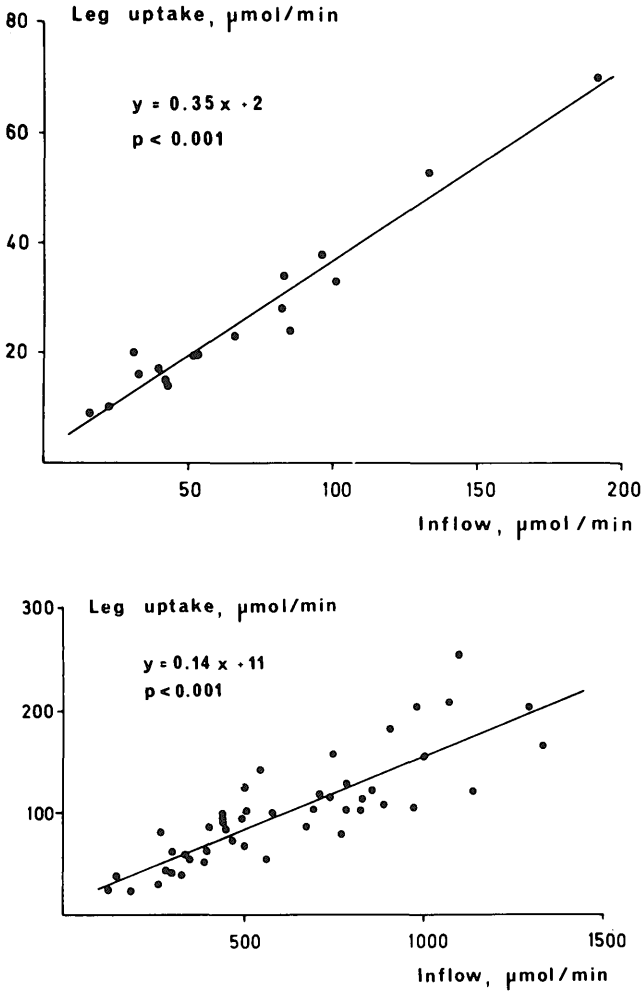


FIGURE 1. Relationship between leg uptake of free oleic acid and inflow of free oleic acid to the leg at rest (*upper panel*) and during exercise (*lower panel*). Leg uptake of free oleic acid was measured during a continuous infusion of radioactive oleic acid.[4] Inflow of free oleic acid was calculated as its arterial plasma concentration times the plasma flow through the leg. The exercise values represent observations on 23 subjects after 40 min of moderately heavy exercise (50–60% of maximal oxygen uptake) and 24 observations on six subjects after 40, 90, 180, and 240 min of light exercise (30% of maximal oxygen uptake).

exercise involving the small muscle groups (forearm exercise) or at a low-level intensity, balance between removal and mobilization of FFA can be maintained during the initial phase and no fall in arterial FFA occurs.[12] When exercise is carried on beyond 10–20 min, there is a gradual rise in the arterial level of FFA. At moderately heavy work loads (50–60% of maximal oxygen uptake) a steady level is reached after 30–40 min of exercise (Figure 3), while a continuous rise of arterial FFA above the basal level is observed during exercise at lower work intensities that can be maintained for longer periods.[13,14]

As in the resting state, there is during exercise a linear relation between FFA turnover and arterial concentration. The turnover rate during exercise is, however, greater than at rest for a given arterial level of FFA.[14] Exercise is thus accompanied by an increase in the fractional turnover of FFA, which seems to be related to the augmented cardiac output.[15,16]

The linear relationship between inflow and uptake of fatty acids in the leg persists during exercise (Figure 1). The

TABLE 1
Representative values for FFA turnover in postabsorptive man at rest

	FFA (μmol/min)	Oxygen equivalents (mmol/min)
Turnover rate	580	14.2
Muscle uptake	260	6.4
Splanchnic uptake	150	3.7
Pulmonary oxygen uptake		12.5
Muscle oxygen uptake		5.0
Splanchnic oxygen uptake		2.5

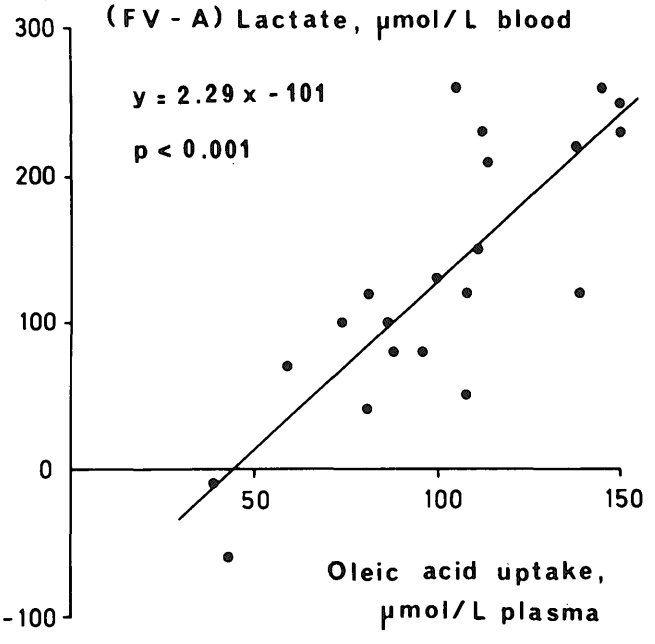
Data from refs. 2, 4, and 6.

mobilization of FFA from adipose tissue is thus the dominating factor determining the muscle utilization of FFA also during exercise. During brief heavy exercise or during the initial phase of moderate exercise, the availability of plasma FFA is low and muscle glycogen is the main substrate for energy production.[17] The contribution of plasma FFA to the substrate supply of exercising muscle becomes more important at lower work intensities and as work is continued for prolonged periods of time (Figures 4 and 5).

FFA AND KETONE BODY METABOLISM IN DIABETES MELLITUS

The turnover rate and the fractional turnover of FFA are similar in diabetics and control subjects.[4,18] In insulin-dependent diabetics (24 h after insulin withdrawal) leg uptake of FFA shows the same concentration dependence as in control subjects (Figure 1) unless hyperketonemia is present. There is therefore no indication that the diabetic state affects the transport of FFA. In ketotic diabetic patients (blood ketones 3–4 mmol/L), the leg fractional uptake of FFA at rest is decreased (0.28 ± 0.05 compared with 0.48

FIGURE 2. Relationship between the femoral venous–arterial (FV-A) concentration difference of lactate and leg uptake of free oleic acid in 21 subjects at rest. Leg uptake was measured during a continuous infusion of radioactive oleic acid.



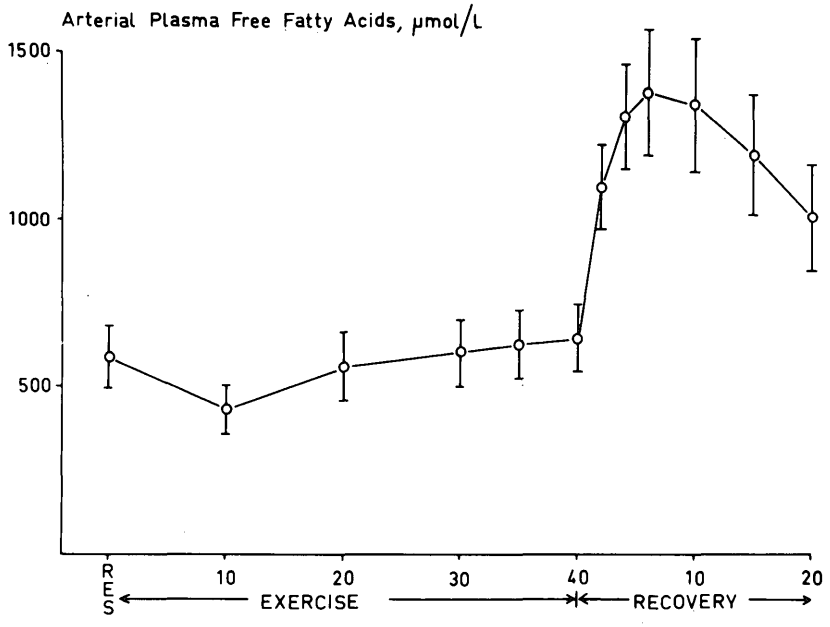


FIGURE 3. Arterial plasma concentration of FFA during and after 40 min of exercise at a moderately heavy work load. Means ± SEM are given.

± 0.01 in nonketotic diabetes and 0.49 ± 0.05 in controls). This diminished extraction of FFA is probably related to a preferential use by the leg muscle of ketone bodies.[19]

During exercise, nonketotic diabetics show the same changes as do control subjects in arterial concentration and leg uptake of FFA[4] (Figure 6). In contrast, diabetic patients with ketosis have elevated FFA levels at rest and the rise during exercise is greater.[4,20] Consequently, leg uptake of FFA is higher during exercise (Figure 6), and the contribution of FFA to the substrate supply of the exercising muscles is also greater.[4]

With regard to the splanchnic metabolism of FFA, diabetic subjects behave more aberrantly. In nonketotic diabetics, the splanchnic FFA uptake at rest is the same as in controls but they convert a substantially greater fraction of these fatty acids to ketone bodies[21] (Figure 7). The splanchnic uptake of FFA falls during exercise in these patients, as it does in control subjects (mainly due to a decrease in splanchnic blood flow), while ketone body production remains unchanged. There is some utilization of ketones by the exercising leg (Figure 6) and no significant change[4] or a slight decrease[21] in ketone body concentrations. In diabetic subjects with ketosis, the splanchnic uptake of FFA is higher already at rest and an even greater fraction of these fatty acids is converted to ketones (Figure 7). This situation becomes aggravated during exercise with an augmented splanchnic FFA uptake and a 65% increase in ketone body production. Simultaneously, leg uptake of ketones

FIGURE 4. Contribution of FFA to leg muscle substrate supply in relation to work intensity measured as the oxygen uptake of the exercising legs. Each point represents the mean value for five to six subjects.

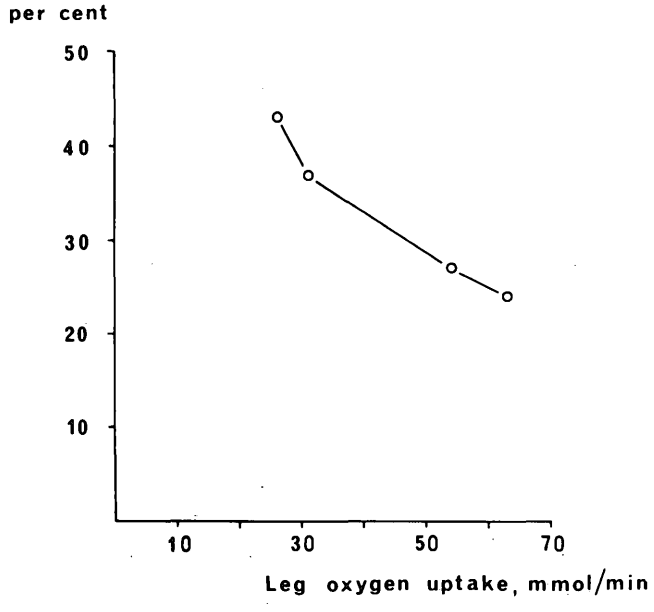
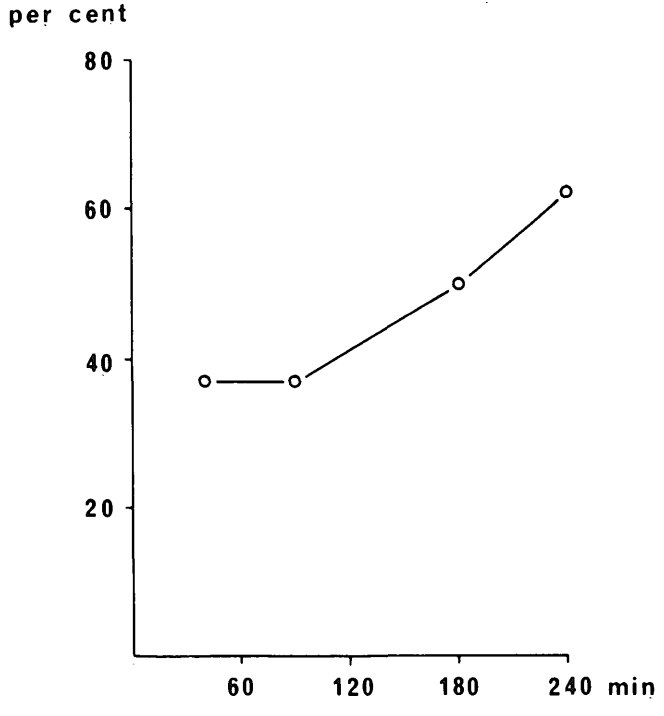


FIGURE 5. Contribution of FFA to leg muscle substrate supply in relation to time during prolonged light exercise. Mean values for six subjects are shown.



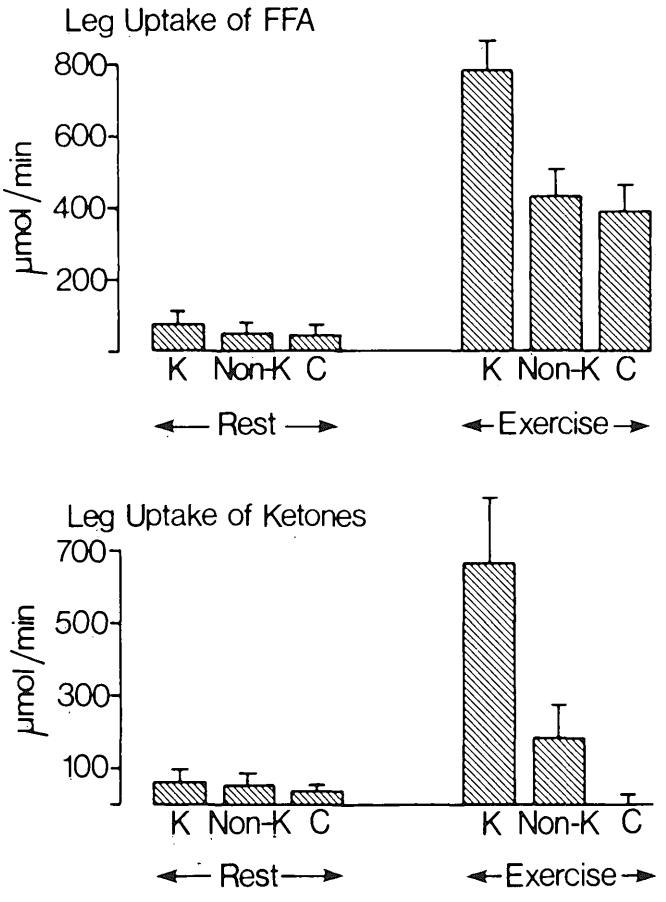


FIGURE 6. Leg uptake of FFA and ketone bodies at rest and during moderately heavy exercise in ketotic (K) and nonketotic (non-K) diabetic patients (insulin withdrawn for 24 h prior to the study) and in control subjects (C).

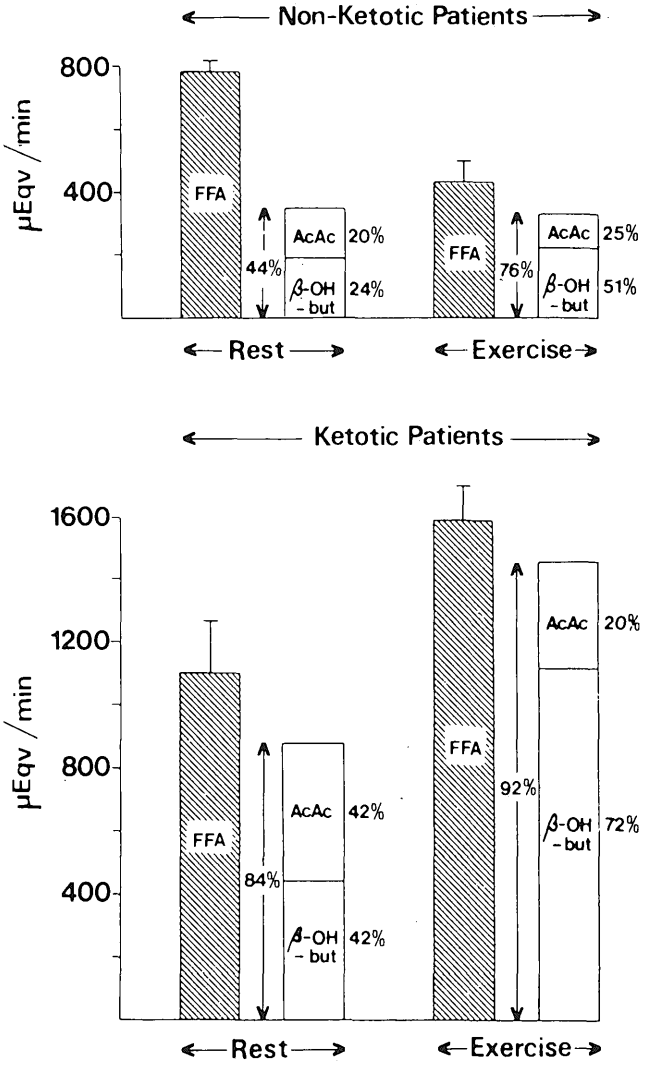


FIGURE 7. Splanchnic uptake of FFA and production of acetoacetate (AcAc) and 3-hydroxybutyrate (β-OH-but) in nonketotic (upper panel) and ketotic (lower panel) diabetic patients at rest and during exercise. FFA uptake has been recalculated to four-carbon equivalents. Insulin was withdrawn for 24 h prior to the study.

increases markedly (Figure 6). Ketone body levels remain unchanged[4] or increase[20] during exercise in ketotic patients.

With reference to FFA and ketone body metabolism, physical exercise in diabetic patients has essentially the same effects as in normal subjects, provided their metabolic control is fairly good. When insulin deficiency has led to a developing ketosis, exercise accelerates lipolysis and ketogenesis to an extent that may or may not just be balanced by the extra substrate consumption of the muscles during the exercise. The greatly enhanced turnover of FFA that occurs immediately after an exercise period[16] will provide an additional load on the failing metabolism.

ACKNOWLEDGMENTS

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