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Impact of fasting and postprandial state on plasma carnitine concentrations during aerobic exercise in type 2 diabetes

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Abstract The effects of metabolic states of fasting and post-absorption on plasma concentrations of free carnitine (FC), acylcarnitine (AC) and total carnitine (TC) were compared during submaximal exercise in subjects with type 2 diabetes mellitus. Ten sedentary men (54±5 years) treated with oral hypoglycaemic agents were tested on two separate occasions: following an overnight fast and 2 h after a 395-kcal standardised breakfast. Exercise was performed at 60% of $\dot{v}O_{2peak}$ on a cycle ergometer for 60 min. Blood samples were drawn at rest for baseline values and following 60 min of exercise and 30 min of recovery. Our results show that: (1) baseline levels of TC, FC and AC were similar in fasted and postprandial groups, (2) TC and AC levels were increased during exercise in the fasted group only, (3) FC levels were decreased during exercise in both fasted and postprandial state and (4) the AC/FC ratio increased during exercise in the fasted group. Our results indicate that the metabolic state of the diabetic patient is associated with a different plasma carnitine status. These patterns may reflect differences in energy metabolism associated with fasting and postprandial hyperglycaemia.

Key words Plasma carnitine • Type 2 diabetes • Aerobic exercise • Fasted state • Postprandial state

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Introduction

We have shown that aerobic exercise performed in the fasted and the postprandial states induces a different response on glucose and insulin levels in patients with type 2 diabetes [1]. Hyperglycaemia and hyperinsulinaemia, characteristic of the postprandial state, not only favour a greater peripheral use of glucose during exercise, but also induce a dramatic reduction in plasma glucose levels from pre-exercise levels. This reliance on glucose is further enhanced as hyperinsulinaemia also inhibits lipolysis during exercise [2]. In fasting type 2 diabetic patients, the hyperinsulinaemic state is not as dramatic, and in sharp contrast to postprandial state, pre-exercise blood levels of glucose and insulin are lower and remain constant throughout exercise. The fasted state in these diabetic patients is not always associated with greater reliance on free fatty acids (FFAs) because FFA oxidation is impaired in these patients [3]. Based on these different patterns in energy preference induced by the fasted and postprandial states, the question that arises is whether the plasma carnitine profile is altered under these conditions in type 2 diabetic patients during exercise. Carnitine (β-hydroxy-δ-trimethylaminobutyric acid) is essential in lipid metabolism, where it shuttles long-chain fatty acids across the inner mitochondrial for energy production by β-oxidation [4]. The typical changes in carnitine metabolism during exercise in the non-diseased state include an elevation in

the plasma total carnitine (TC), presumably from loss of muscle carnitine [5], and a rise in plasma acylcarnitine (AC) due to a reduction in free carnitine (FC) reflecting AC ester production [6]. This change in plasma carnitine reflects the increase in energy demand and lipolysis, the latter facilitated by reduced insulin secretion. Evidence for the role of insulin in carnitine metabolism is supported by the observation that the decrease in plasma FC is blunted in type 1 diabetes patients treated with subcutaneous insulin therapy as well as in non-diabetics patients receiving an intravenous infusion of insulin [7, 8]. In the light of the above findings, we have therefore undertaken to investigate the influence of the metabolic state of fasting and post-absorption on plasma carnitine concentrations during exercise in subjects with type 2 diabetes.

Materials and methods

Subjects

The study group consisted of 10 sedentary men with type 2 diabetes. Subjects did not suffer from clinical or laboratory evidence of diabetic complications, cardiac, hepatic, renal, pulmonary or other endocrine disease, besides their diabetes. All patients were treated with hypoglycaemic agents (glyburide alone or in combination with metformin). None of the patients were currently being treated with insulin or thiazolidenediones. A blood sample was taken at the time of the first test for the determination of glycated haemoglobin (HbA_1) by using the method of Trivelli et al. [10]. All participants were asked to eat their usual diets and requested not to restrict their caloric intake for purposes of weight reduction until the entire protocol was completed. None were engaged in a regular exercise programme for 3 months before they were enrolled in the study. The study was approved by the local hospital ethics committee in accordance with the Helsinki declaration; all subjects gave signed informed consent.

Measurement of maximal oxygen uptake

Before the start of the study, the subjects performed a maximal exercise test on a stationary bicycle ergometer, using a protocol beginning with a 5-min warm-up at 50 W. Resistance was increased by 25 W every 3 min until subjects reached exhaustion, as previously published [1]. Gas analysis was determined using indirect calorimetric measurement consisting of an O_2 and CO_2 analysers. Blood pressure was measured every 2 min and a 12-lead electrocardiogram continuously recorded.

Exercise protocol

Each subject was asked to abstain from alcohol and caffeine consumption for 24 h before the exercise session. Each session consisted of exercising on a cycle ergometer (Monark 818, Stockholm, Sweden) for 60 min at a workload corresponding to 60% of their individual $\dot{v}O_2$, obtained previously from the $\dot{v}O_{2peak}$ test. None performed unusual exercise 48 h before the test and both experiments were separated by a minimum of 7 days. Each subject was randomly assigned to perform exercise in the fasted state and the postprandial state, serving as their own control. Heart rate, power output and oxygen consumption were measured and recorded using an open-circuit indirect calorimetry system (Energy Expenditure Unit, Model 2900, SensorMedics, Anaheim, CA, USA). Each exercise session was performed under the direct supervision of an exercise physiologist.

Preparation and sample collection

The subjects reported to the Diabetes Research Unit of Laval University Medical Center after a 10–12-h overnight fast at 8:00 a.m. on the day of the study. Subjects were randomly designated to exercise in the fasted state or two hours after a standardised breakfast taken at the medical centre (395 kcal, consisting of 49% carbohydrate, 34% fat, 17% protein). To eliminate any potential effects of either glyburide or metformin on plasma carnitine levels, subjects were instructed to take their last dose of medication on the evening before the test. Indeed, there were no significant differences in plasma carnitine levels between patients receiving different doses of either glyburide or metformin before the onset of exercise. Following breakfast, consumed within a 20-min period, a 20-gauge polyethylene catheter was inserted into the left forearm vein and kept patent with a slow infusion of 0.9% saline. Blood samples were drawn at rest, at the end of the exercise bout and 30 min into the recovery period, corresponding to time 90 min. Baseline samples were drawn after 2 h of rest, when subjects were sitting on the bicycle before the beginning of the exercise session.

Measurement of plasma metabolites

Plasma concentrations of TC (expressed as the sum of AC and FC), glucose [11], insulin [12] and FFAs [13] were measured as previously described [1]. Plasma carnitine was measured by radioenzymatic assay using carnitine acetyltransferase and [^{14}C] acetyl CoA [14]. Some glucose, insulin and FFA data have been previously reported [1]. However, these parameters are added here for better comprehension of the whole set of data.

Indirect calorimetry

Rates of whole body substrate oxidation and oxygen uptake were measured throughout each exercise experiment using indirect calorimetric measurement (Energy expenditure unit, Model 2900, Sensor Medic, Anaheim, CA, USA). The first 2 min of each 5-min measurement were used for the adaptation to the mouth piece and the nose clip, and the 3 subsequent minutes for the measurement of oxygen consumption ($\dot{v}O_2$) and carbon dioxide production (CO_2). These measurements were used for the

determination of the respiratory exchange ratio (RER), corresponding to the mean of each 20-s period calculated during the 3-min period. The oxidation rates of carbohydrates (CHO) and fat were calculated from indirect calorimetry using the non-protein respiratory quotient with the following equations [15]:

$$\text{Fat oxidation rate}=1.695\ \dot{v}O_2-1.701CO_2, \quad (a)$$
$$\text{CHO oxidation rate}=4.585\ CO_2-3.226O_2, \quad (b)$$

with $\dot{v}O_2$ and CO_2 expressed in litres per minute (l/min), and total fat and CHO oxidation in grams per minute (g/min).

Statistical analysis

Values are reported as mean±SD unless otherwise specified. For each variable, the split-plot design was used to analyse the two experimental factors, one associated to the comparison between nutritional status and one linked to the three time concentrations (0, 60 and 90 min). This level was analysed as a repeated-measures factor. A mixed model analysis was performed with an interaction term between the fixed factors. A common correlation among the observations was introduced using an autoregressive covariance structure for all variables. For some variables, the graphical analyses of residuals with predicted values have revealed a relationship between the variances of the observations and the means for these variables. To estimate the form of the required transformation associated to these variables, a regression approach was performed between the logarithm of the standard deviations and the logarithm of the means from different conditions. This approach was useful to stabilise the variance [16]. For these variables, statistical results were calculated with the log-transformed values. The Tukey's multiple comparison technique was applied post hoc to the ANOVA. The univariate normality assumption was verified with the Shapiro-Wilk test. The Brown and Forsythe's variation of Levene's test statistics was used to verify the homogeneity of variances. Multivariate normality was verified with Mardia tests [17]. Paired *t*-tests were used for comparisons of mean changes between groups. The results were considered significant with *p*-values ≤0.05. Certain blood parameters (glucose, FFAs, insulin) were expressed as a delta between time points. The data were analysed using the statistical package program SAS v8.2 (SAS Institute Inc., Cary, NC, USA).

Results

The characteristics of subjects are reported in Table 1. The mean age of the subjects was 54±5 years (range: 43–60), the diabetes duration was 8±6 years (range: 2–19) and the mean body mass index (BMI) was 26.9 kg/m^2 (range: 23.7–31.1). The mean percent HbA_1 was 9.7% (range: 7.5%–13.0%). The exercise bouts were performed at an average power output of 96±13 W (range 80–120 W) during the postprandial and the fasted state, corresponding to a mean peak oxygen uptake ($\dot{v}O_{2peak}$) of the subjects of 34.2±4.6 ml/kg/min. No significant differences were observed in oxygen consumption by the patients during the exercise sessions (55.5±3.6 *vs*. 56.0%±3.1% of $\dot{v}O_{2peak}$, in the fasted and the postprandial state, respectively).

Plasma carnitine levels at rest, following exercise and during recovery are shown in Table 2. At rest, there were no differences in TC between groups. At the end of exercise, TC levels were significantly higher in the fasted group compared to the postprandial group. During the recovery period, however, TC levels were higher in the postprandial state. No differences in FC levels were observed at rest between groups (p=0.1). FC levels were decreased in both fasted and postprandial states (p=0.01) at the end of exercise and remained decreased during recovery in both groups (p<0.0001 compared to baseline). Plasma AC levels were similar between the fasting and the postprandial state prior to exercise but increased

Table 1 Clinical characteristics of subjects with type 2 diabetes (n=10)

Age (years)	BMI (kg/m^2)	HbA_1 (%)[a]	$\dot{v}O_{2peak}$ (ml/kg/min)	Total daily dose (oral hypoglycaemic agent)[b]
43	27.0	8.9	43.7	10 mg G+2 g M
49	26.3	7.5	31.8	10 mg G
52	31.1	9.9	32.7	20 mg G+1 g M
52	26.4	11.5	31.3	15 mg G
55	29.8	8.0	28.5	10 mg G
56	23.7	7.6	38.1	10 mg G+500 mg M
56	26.1	12.1	32.9	20 mg G+1 g M
59	27.4	13.0	33.3	10 mg G
60	25.6	9.8	39.2	5 mg G
60	25.5	8.5	30.9	15 mg G
Mean±SD				
54±5	26.7±2.1	9.7±1.9	34.2±4.6	

[a]Normal range: 6.0%–9.0%

[b]*G*, glyburide; *M*, metformin

Table 2 Plasma carnitine fraction at rest, following 60 min of aerobic exercise and after a recovery period in fasted and postprandial state in type 2 diabetic subjects

Group	Total carnitine (mmol/l)			Free carnitine (mmol/l)			Acylcarnitine (mmol/l)		
	Time (min)			Time (min)			Time (min)		
	0	60	90	0	60	90	0	60	90
Postprandial state	45.1±8.7	44.0±9.3	51.1±11.8*	37.4±8.7	34.4±8.7†	32.5±8.4†	7.7±4.6	9.5±0.9	18.6±6.9*†
Fasted state	43.2±8.2	49.0±8.2*	46.1±9.6	34.3±8.1	32.6±7.0†	32.3±7.0†	8.8±4.0	16.4±4.8*	13.8±4.5†

Values are expressed as means±SD
*p=0.05 fasted *vs*. postprandial state
†p=0.01 baseline *vs*. 60 or 90 min

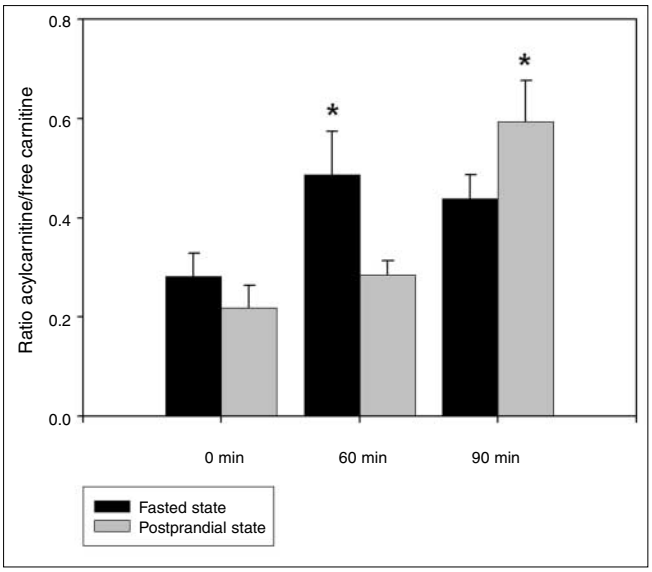

Fig. 1 Ratio of AC/FC at baseline (0 min), at 60 min of exercise and after the recovery period. Values are expressed as means±SE. *p=0.05 fasted *vs*. postprandial state

(p=0.002) in the fasted state only. During recovery, AC levels were increased significantly (p=0.04) in the postprandial state compared to the fasted state.

The ratio of AC/FC is shown in Figure 1. As expected, the AC/FC ratio was significantly higher (p=0.002) and also increased from rest (p=0.02) in the fasted state. In contrast, the AC/FC ratio was increased (p=0.05) during recovery in the postprandial state compared to the fasted state. Compared to baseline, the AC/FC ratio was increased (p=0.0008) in this group.

Plasma glucose, insulin and FFAs levels are shown in Table 3. Baseline plasma levels were not different between fasted and postprandial groups. During exercise and recovery, glucose levels were decreased in the postprandial group only and were lower compared to the fasted group. Expressed as delta change, Figure 2 shows that the change in plasma glucose was significant in the postprandial state only.

Plasma insulin levels were higher in the postprandial group compared to the fasted group at rest, and were decreased with exercise in the postprandial group only.

Table 3 Plasma glucose, insulin and FFA concentrations at rest, following 60 min of aerobic exercise and after a recovery period in fasted and postprandial state in type 2 diabetic subjects

Group	Plasma glucose (mmol/l)			Plasma insulin (pmol/l)			Plasma FFAs (mmol/l)		
	Time (min)			Time (min)			Time (min)		
	0	60	90	0	60	90	0	60	90
Postprandial state	12.4±4.1	7.6±3.5†	7.9±3.5†	177±83*	106±75†	139±73	162±62	289±149†	436±189†
Fasted state	11.1±3.3	10.1±3.1*	10.6±3.2*	108±60	92±61	123±46	279±103**	350±151†	481±128†

Values are expressed as means±SD
*p=0.001 postprandial *vs*. fasted state
**p<0.05 postprandial *vs*. fasted state
†p=0.001 baseline *vs*. 60 or 90 min

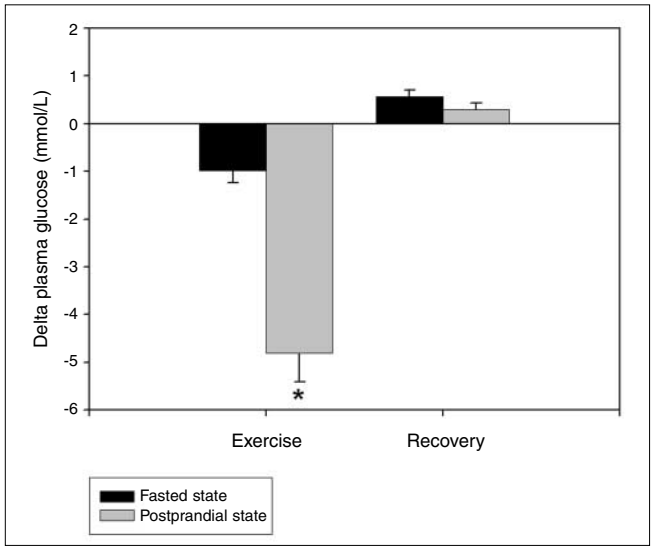

Fig. 2 Plasma glucose changes calculated as the difference (Δ) between time 60 and time 0 (exercise) and time 90 and time 60 (recovery), in mmol/l. Values are expressed as means±SE. *p<0.001 fasted *vs*. postprandial state

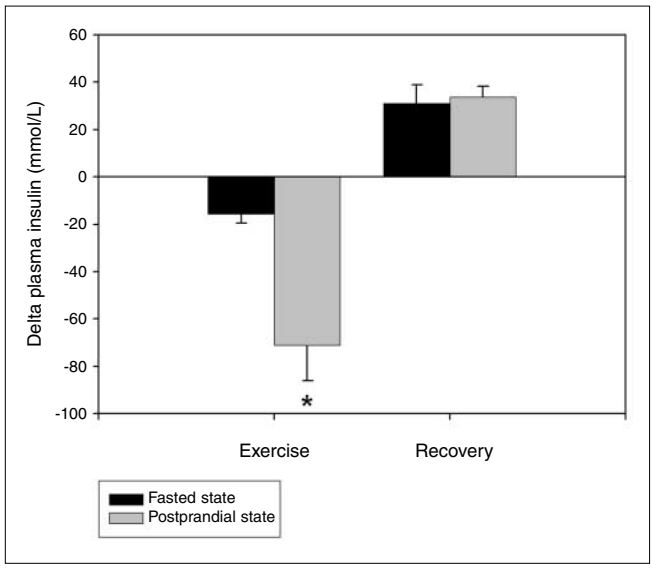

Fig. 3 Plasma insulin changes calculated as the difference (Δ) between time 60 and time 0 (exercise) and time 90 and time 60 (recovery), in mmol/l. Values are expressed as means±SE. *p<0.01 fasted *vs*. postprandial state

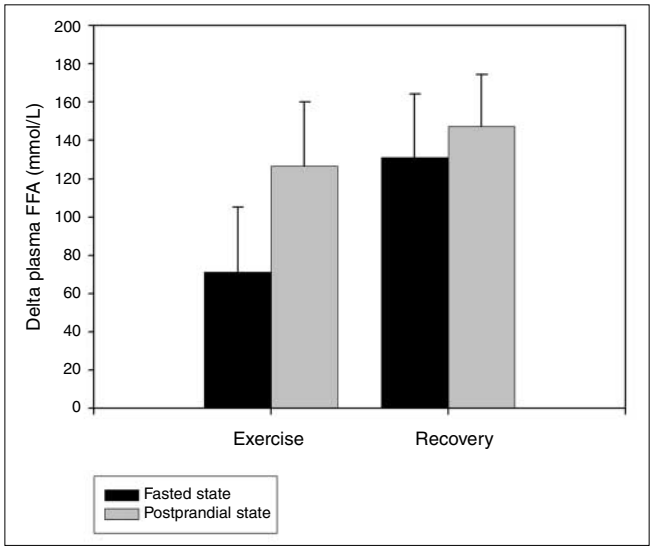

Fig. 4 Plasma FFAs changes calculated as the difference (Δ) between time 60 and time 0 (exercise) and time 90 and time 60 (recovery), in mmol/l. Values are expressed as means±SE

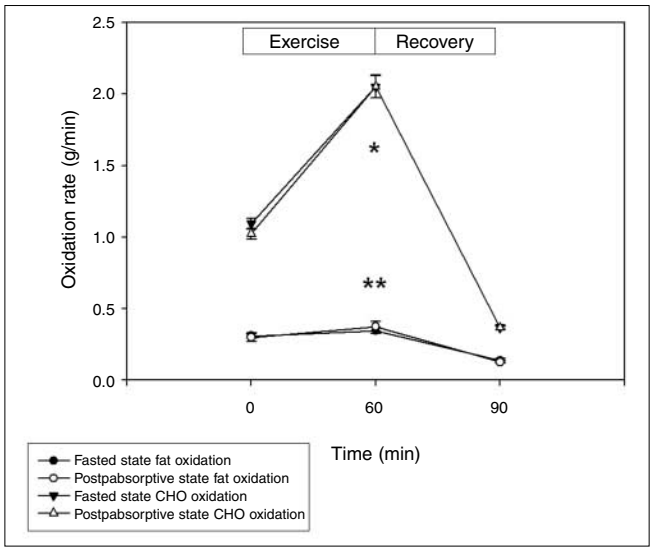

Fig. 5 Oxidation estimation rates of fat (circle symbols) and carbohydrates (CHO) (triangle symbols) in 10 subjects with type 2 diabetes in the postprandial state (closed symbols) and the fasted state (open symbols) measured at 0, 60 and 90 min. *p<0.0001 baseline *vs*. 60 min; **p=0.05 baseline *vs*. 60 min. Values are mean±SE

The delta change during exercise, as shown in Figure 3, was also significant in the postprandial group. However, throughout exercise and recovery, there were no differences in insulin levels between groups.

In the fasted state, as expected, plasma FFA levels were higher at rest in the fasted group compared to the postprandial group. An increase in FFA levels during exercise and after exercise occurred in both groups. However, the delta change in FFAs was not different during exercise, recovery and between groups (Fig. 4).

Rates of total CHO and fat oxidation from indirect calorimetry are depicted in Figure 5. CHO oxidation was increased (p<0.0001) after exercise in both groups followed by a decrease in CHO oxidation during the recovery period. However, rates of CHO oxidation were similar between the postprandial and the fasted groups throughout the entire protocol. Rates of oxidation increased during exercise, and afterwards, decreased during recovery in the fasted and postprandial groups. No differences in fat oxidation were observed between groups.

Discussion

We chose to compare plasma carnitine levels in fasted and postprandial states in patients with type 2 diabetes because exercise performed under these conditions induces a different response in plasma glucose and insulin levels [1]. In the postprandial state, although hyperinsulinaemic and hyperglycaemic states prevail, a parallel decrease in both glucose and insulin level occurs throughout exercise. In the fasted state, on the other hand, the extent of the hyperinsulinaemic and hyperglycaemic states is not as severe, yet plasma glucose and insulin levels remain constant throughout exercise [2–18]. The reason for this discrepancy has not been determined in these patients, but may relate to differences in whole body substrate utilisation during exercise. Exercise performed in the postprandial state is associated with an increase in peripheral utilisation of glucose [19, 20] and under these conditions, both endogenous glucose production [21] and lipolysis are inhibited during exercise [2]. In the fasted state, the observation that plasma glucose levels remain constant indicates that there is a balance between endogenous glucose production and peripheral glucose utilisation, largely mediated by a reduction in insulin secretion.

Based on these observations, we determined whether the metabolic states of fasting and post-absorption would, in turn, induce changes in plasma carnitine levels during exercise. The plasma carnitine response to exercise in the non-insulin-resistant state has been fully characterised and is associated with an elevation in TC, and a rise in plasma AC due to a reduction in the FC form [5, 6]. As this profile has not been determined in type 2 diabetes, the same subjects served as their own control by exercising, in random order, in the fasted and in the postprandial state. Our data indicate that plasma carnitine profile is indeed altered by the nutritional status. When diabetic patients exercised in the fasted state, the plasma concentrations of FC decreased while the AC fraction increased, resulting in an increase in the total plasma carnitine pool. In the postprandial state, although the level of plasma FC decreased throughout exercise, the AC fraction remained unchanged, resulting in no change in the TC content. This suggests that plasma carnitine content and its distribution to the esterified form is modulated by the metabolic state in patients with type 2 diabetes during exercise.

Although conjectural, it appears that insulin is involved in regulating plasma carnitine concentrations during exercise in diabetes. This would be appropriate as the hyperinsulinaemia frequently seen in diabetes during exercise induces changes in whole body substrate utilisation. The hyperinsulinaemic state increases glucose uptake into tissues and also limits the availability of FFAs by inhibiting lipolysis [8]. The role of insulin on carnitine metabolism is evident in type 1 diabetes treated with subcutaneous insulin by the observation that the decrease in FC does not occur during exercise [7]. A similar response was confirmed in non-diabetics patients receiving an intravenous infusion of insulin during exercise [7, 8]. In type 2 diabetes, it appears that insulin preferentially regulates the AC rather than the FC fraction. Pre-exercise plasma FC concentrations were similar in the fasted and postprandial states, despite differences in the plasma insulin level, and exercise resulted in a comparable reduction in FC regardless of the metabolic state. The level of AC as well as the AC/FC ratio, however, both failed to increase significantly in the postprandial state. This was clearly not the case in the fasted state in which the AC fraction increased by ~86% and the AC/FC by ~71%. The reason for these differences between nutritional states cannot be explained at the present time, largely because no studies have addressed carnitine metabolism in skeletal muscle of diabetic patients during exercise and the lack of an appropriate available experimental model of acute exercise in diabetes. Therefore, the relationship between plasma carnitine and energy metabolism in skeletal muscle cannot be established. Further, while the intent of this study was to describe changes in plasma carnitine in these patients, we can only speculate that either an increased use of glucose by muscle or a disturbance in fatty acid metabolism accounted for this blunted increase in AC levels.

In conclusion, the present study describes that a 60-min aerobic exercise session performed in the fasted type 2 diabetic patients is associated with an increase in plasma TC and AC, and decrease in FC concentrations. An increase in the AC/FC ratio was also seen under these conditions. However, when exercise was performed in the postprandial state in the same subjects, the plasma carnitine profile was clearly different. No increases in TC and AC concentrations or the AC/FC ratio were observed. Further research is needed to determine whether the impact of the metabolic state on plasma carnitine levels during exercise in patients with type 2 diabetes is linked to differences in skeletal muscle metabolism.

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