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Review Articles

Physical Exercise and Fuel Homeostasis in Diabetes Mellitus*

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Summary. During the initial phase of physical exercise muscle glycogen is the primary source of fuel for contracting muscle in normal man. When exercise continues beyond the first 5–10 min blood glucose and free fatty acids (FFA) become increasingly important substrates. Glucose utilization may account for 25–35% of the total substrate supply during mild to moderately heavy exercise. The augmented glucose utilization by working muscle is balanced by a rise in hepatic glucose production. The latter is achieved primarily by hepatic glycogenolysis during brief work, but during prolonged exercise gluconeogenesis may account for as much as 40–50% of the hepatic glucose output. Muscle uptake of FFA is determined primarily by its availability to the working muscle, and it may account for 30–60% of the total fuel supply. Ketone bodies are not utilized by working muscle in normal man. In patients with diabetes mellitus the metabolic effects of physical exercise are to a large extent determined by the time interval between insulin administration and the onset of exercise. Thus, in insulin treated patients with mild hyperglycaemia and no or minimal ketonaemia the utilization of glycogen, blood glucose and FFA by working muscle is similar to that of healthy subjects, and exercise is accompanied by a fall in blood glucose levels. In contrast, patients with more marked hyperglycaemia and hyperketonaemia may respond to exercise with a further rise in both blood glucose and ketone body levels, reflecting augmented rates of hepatic gluconeogenesis as well as ketogenesis. The repletion of muscle and liver glycogen, which takes place for 24–48 h after exercise, requires – besides carbohydrate feeding – a minimum concentration of insulin. Glycogen resynthesis probably accounts for a major part of the empirically well established beneficial effect of physical exercise in diabetic patients. The above considerations underscore the importance of adequate insulin administration in connection with exercise in diabetic patients.

Key words: Body substrate depots, fuel homeostasis, physical exercise, diabetes mellitus, glucoregulatory hormones, muscle glycogen, liver glycogen, gluconeogenesis, glycogenolysis, ketogenesis, blood glucose, FFA, ketone bodies, amino acids.

Exercise featured prominently in the treatment of diabetes mellitus already in the days of Oskar Minkowski. A beneficial effect on the clinical course of this disease has in fact been recognized since ancient times [1]. Before the advent of insulin, however, evidence had accumulated to the effect that in severely diabetic patients, exercise resulted in more pronounced hyperglycaemia, hyperketonaemia and glycosuria; in fact strenuous exertion occasionally led to coma [2, 3, 4]. After the introduction of insulin, it soon became apparent that in diabetics treated with insulin, blood glucose levels fell during exercise and that regular exercise reduced the exogenous insulin requirement [5, 6, 7, 8].

Although in the last few decades the empirical view has prevailed that exercise is beneficial on the whole in insulin-treated diabetic patients, it is only recently that the interaction of exercise and diabetes has been studied in more detail. The purpose of this review is to examine some recent findings concerning the patterns of fuel utilization and production in diabetic patients and healthy subjects. Emphasis will be

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Table 1. Substrate reserves in normal postabsorptive man

	Weight kg	Energy kJ
Circulating substrates		
Glucose	0.020	330
Free fatty acids	0.004	16
		346
Tissue depots		
Adipose tissue triglycerides	15	600,000
Glycogen (liver)	0.085	1,500
Glycogen (muscle)	0.350	6,000
Protein (muscle)	6	100,000
		707,500

placed on the relative contributions of carbohydrate and fat to the oxidative metabolism of working muscle as well as the rates of hepatic gluconeogenesis and ketogenesis during exercise.

Body Substrate Depots

The potential energy that is available in the form of circulating substrates, primarily as glucose and free fatty acids (FFA), amounts to no more than 300–400 kJ (Table 1). In the resting state, normal man expends approximately 5 kJ/min and during exercise this value may rise to 50–75 kJ/min. Consequently, during exercise man must rely to a considerable extent upon the mobilization of substrates from tissue stores. These stores are listed in Table 1.

Although fat and carbohydrate each make up approximately 40% of the average diet, the body fuel stores consist almost entirely of fat in the form of triglyceride, stored in adipose tissue. In normal man, fat accounts for approximately 600,000 kJ or 80–85% of the substrate reserves – a proportion that is even greater in obesity. In contrast, stored carbohydrate accounts for less than 8,000 kJ – 300–400 g in the form of muscle glycogen and 80–90 g as glycogen in the liver. It should be noted that since muscle does not have the enzyme glucose-6-phosphatase, muscle glycogen cannot contribute directly to the addition of glucose to the blood. Muscle glycogen is thus of use in meeting the energy requirements of the muscle fibres in which it is contained, but does not contribute to the maintenance of blood glucose homeostasis, except via the Cori cycle. Liver glycogen, on the other hand, is an important source of blood glucose which may be mobilised rapidly in response to exercise or hypoglycaemia. Although the liver glycogen reserve is small, hepatic glycogenolysis serves an important function in the body's adjustment to varying energy requirements by contributing to the maintenance of blood glucose homeostasis. Replenishment of the blood glucose pool occurs continuously from the liver. The major portion of the glucose output from the liver in normal, post-absorptive man derives from hepatic glycogenolysis (70–75%), while a smaller fraction (25–30%) is synthesized de novo in the liver from glucose precursors such as lactate, amino acids, glycerol and pyruvate (gluconeogenesis).

In normal man, the body protein contains a substantial amount of potential energy (100,000 kJ) and accounts for approximately 15% of the body fuel reserves. However, the usefulness of protein as a fuel is severely limited since its consumption calls for the dissolution of structurally and functionally important tissue in the form of skeletal muscle, the primary repository of body protein.

Diabetes mellitus influences the size of the body fuel reserves, primarily the carbohydrate store. Already in 1890 von Mehring and Minkowski reported that the glycogen content of both liver and muscle was decreased in animals with experimental diabetes [9]. These observations have been confirmed in subsequent studies on patients with diabetes, not receiving insulin treatment [10, 11]. The degree of glycogen depletion appears to be intimately related to the extent of insulin deprivation. Thus, after a 24-h period of insulin withdrawal, liver as well as muscle glycogen content are still within the normal range, while values in untreated patients are severely reduced [11, 12; Nilsson and Hultman 1977, personal communication].

Muscle Glycogen

During the initial phase of exercise the major fuel consumed is muscle glycogen. Its utilization is influenced chiefly by the duration and intensity[1] of the work performed. During prolonged, submaximal exercise the glycogen concentration decreases in a curvilinear manner [13, 14]. After the first 5–10 minutes of exercise, glycogen utilization slows down, possibly because the circulatory adaptation to exercise makes other substrates available to the contracting muscle. As exercise proceeds beyond 40–60 minutes, the rate of glycogen utilization drops still further; there is now a relative lack of muscle glycogen and the utilization of free fatty acids gradually increases. Seen in rela-

[1] The intensity of exercise may be graded in absolute terms (watts) or in terms of relative work capacity (per cent of maximal oxygen uptake). In this review, "mild" exercise refers to an intensity of approximately 65 W or 25–35% of maximal capacity, "moderate" exercise to approximately 135 W or 50–60% of maximal capacity and "heavy" exercise to 200 W or 70–80% of maximal capacity

tion to work intensity, during the initial period of exercise the rate of muscle glycogen utilization increases as a curvilinear function of the work load for dynamic exercise [15] as well as for static contractions [16]. The most rapid muscle glycogenolysis is seen in connection with short-term, heavy isometric contractions, when the rate may be tenfold that during heavy dynamic work.

Direct measurements of muscle glycogen content in acutely insulin-deprived diabetic patients indicate that the rate of glycogen utilization during exercise is no different from that in healthy subjects [12, 17]. However, resynthesis of muscle glycogen during post-exercise recovery is an insulin-dependent process. Thus, in the absence of insulin therapy, muscle glycogen repletion is minimal in diabetic patients, while with insulin, the rate of repletion is the same as in healthy subjects [18].

Blood Glucose Utilization

Uptake of blood glucose by contracting skeletal muscle was recognized more than 90 years ago by Chauveau and Kauffman [19], but it is only recently that the quantitative contribution of blood glucose to the energy needs engendered by exercise has been examined in man.

In the resting state, normal subjects show a small positive arteriovenous (a-v) difference for glucose across the forearm or leg tissues, indicating a net glucose uptake [20, 21, 22]. During exercise, the a-v difference for glucose increases together with a marked rise in muscle blood flow representing a substantially augmented net glucose uptake. During bicycle exercise for 10 to 40 minutes, glucose uptake by the working leg muscles rises to seven to 20 times the basal level, depending on the intensity of the work performed (Fig. 1). Glucose uptake may be sufficient to account for 25–35% of the total oxygen consumed by muscle [21]. In addition, blood glucose is responsible for 75–90% of the total carbohydrate consumed during 40 minutes of exercise – reflecting a gradual decline in the availability of muscle glycogen as exercise continues. Beyond 40 minutes of exercise the rate of glucose utilization by working muscle increases progressively to a peak at 90–180 minutes, after which it declines slightly in parallel with a gradual fall in the blood glucose level [23]. Thus, in healthy subjects, blood glucose is a quantitatively important substrate for contracting muscle during brief as well as prolonged work [20, 21, 23, 24].

Few direct observations are available in diabetic patients concerning the influence of exercise on glucose uptake by muscle. Augmented a-v differences for glucose across the working leg were, however, reported in two insulin-dependent diabetic patients by Sanders, Levinson, Abelman and Freinkel [25]. More recently, direct studies of net glucose uptake by the leg tissues during exercise in hyperglycaemic insulin-deprived diabetic patients have demonstrated that glucose uptake in these individuals is at least as great as in healthy controls [21, 23]. After 40 minutes of bicycle exercise at a work load corresponding to 55–60% of maximal oxygen uptake, glucose uptake in diabetic patients and controls had risen 13-18-fold above the basal value. Blood glucose could account for 25–28% of the total oxygen consumed by the working muscle, no differences being observed between the diabetics and the controls [26]. Moreover, mildly ketotic diabetics did not differ measurably from non-ketotic patients with regard to glucose uptake by the working leg. These findings, which have also been reported for depancreatectomized dogs [28], support the conclusion that increased glucose uptake by contracting muscle is not dependent upon an augmented availability of insulin.

The hormonal response to exercise in healthy subjects is characterized by a fall in plasma insulin and a rise in plasma glucagon (Fig. 2). These alterations are more pronounced when exercise is prolonged or severe [23, 29]. The decrease in insulin concentration during heavy exercise is noteworthy since hypoinsulinaemia then occurs in spite of a modest rise in the blood glucose level [21] – suggesting an inhibition of insulin secretion [30], possibly mediated by the adrenergic nervous system. The finding that glucose uptake is stimulated in spite of hypoinsulinaemia during exercise implies that the rise in glucose uptake is not modulated by insulin. On the other hand, animal experiments have demonstrated that in the complete absence of insulin, glucose uptake fails to increase during muscle contraction [31], suggesting that insulin may exert a permissive effect on exercise-induced glucose uptake. Such an action of insulin is demonstrable in animal experiments at concentrations of 0.2–1.2 μU/ml, which is well below the circulating concentration in exercising healthy subjects [21, 23], and probably also lower than the remaining insulin concentration in 24-hour insulin-deprived diabetic patients [26, 27].

Glucose Production and Blood Glucose Regulation

In healthy subjects, the blood glucose concentration changes little from the resting state during brief, mild to moderately heavy exercise, but it rises 15–25% with strenuous exertion (Fig. 1). When mild exercise continues beyond 90 minutes, however, the blood

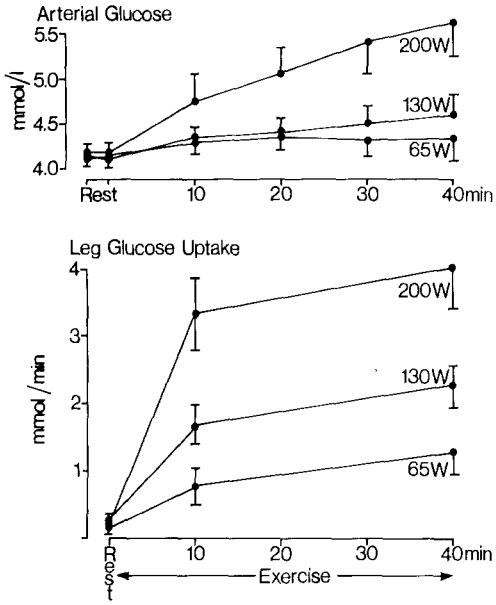

Fig. 1. Arterial glucose concentration and leg uptake of glucose at rest and during exercise at mild (65 W), moderate (130 W) and heavy (200 W) exercise in healthy subjects. Mean values ± SEM are given

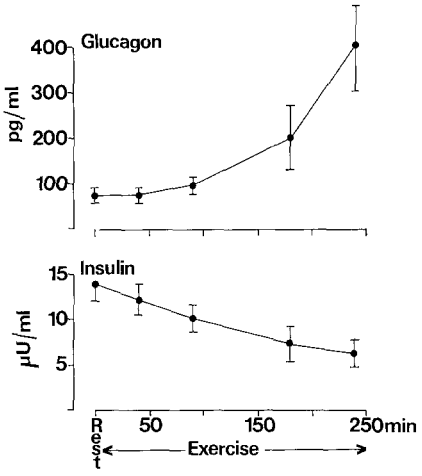

Fig. 2. Arterial concentrations of glucagon and insulin at rest and during mild exercise for four hours. Mean values ± SEM are presented

glucose concentration declines progressively (15–30%) [23]. Marked hypoglycaemia (< 2 mmol/l) during exercise is rare, although it has been observed in marathon runners [32], in patients on low carbohydrate diets [33], and in insulin-treated diabetics.

The increase in glucose uptake by muscle which characterizes exercise, indicates that during work involving large muscle groups there must be a continuous replenishment of the blood glucose pool. Except in very prolonged starvation, when glucose is produced by the kidney [34], the sole site of glucose production and release into the blood stream is the liver. In the resting basal state, the rate of hepatic glucose production is approximately 0.8–1.0 mmol/min, as documented in numerous studies with the hepatic venous catheterization technique (Fig. 3). Approximately 75% of the glucose output comes from hepatic glycogenolysis, the remainder from gluconeogenesis from amino acids, primarily alanine, and lactate, glycerol and pyruvate [21, 35]. During brief exercise, hepatic glucose output increases two to five times, depending on the intensity of the work, and keeps pace with the increment in glucose utilization by muscle tissue [13, 21]. The augmented output during exercise is supplied almost entirely from an acceleration of hepatic glycogenolysis; except for a transient rise in lactate uptake, the splanchnic uptake of glucogenic precursors hardly changes from the resting state. Because of the increase in total glucose output, the relative contribution from gluconeogenesis falls from 25–30% in the resting state to 15% after 40 minutes of mild bicycle exercise and to less than 5% after the same period of heavy exercise [21]. The total amount of glucose released from the liver during 40 minutes of severe exercise is estimated at 20 g, corresponding to 20–25% of the total hepatic glycogen store in the basal state.

When mild exercise continues beyond 40 minutes, splanchnic glucose output remains unchanged – at approximately twice the resting value – for three to four hours [23]. In this situation the relative contribution of gluconeogenesis to overall hepatic glucose output, estimated from splanchnic uptake of glucogenic precursors, increases from 25% in the resting state to 45% during prolonged exercise. This indicates a threefold rise in the absolute rate of gluconeogenesis [23]. The increased uptake of glucose precursors is largely a result of augmented fractional extraction. The overall importance of gluconeogenesis in prolonged exercise is underscored by the estimation that 50–60 g of liver glycogen is mobilized during four hours of mild exercise, corresponding to ca. 75% of the hepatic glycogen reserve.

Early observations in insulin-treated diabetics indicated that exercise caused the blood glucose level to fall. In contrast, severely insulin-deficient patients often responded to exercise with an increase in blood glucose and ketone levels [5, 6, 36, 37]. Recent findings employing graded bicycle exercise have confirmed these results; in non-ketotic diabetic patients with mild to moderate hyperglycaemia (< 15 mmol/l), moderately heavy exercise 24 hours after insulin withdrawal causes blood glucose levels to fall (Fig. 4). In contrast, in patients with more severe hyperglycaemia and mild ketonaemia (blood ketones 2–3 mmol/l), exercise is accompanied by a significant rise in blood glucose concentration [26, 38]. This ten-

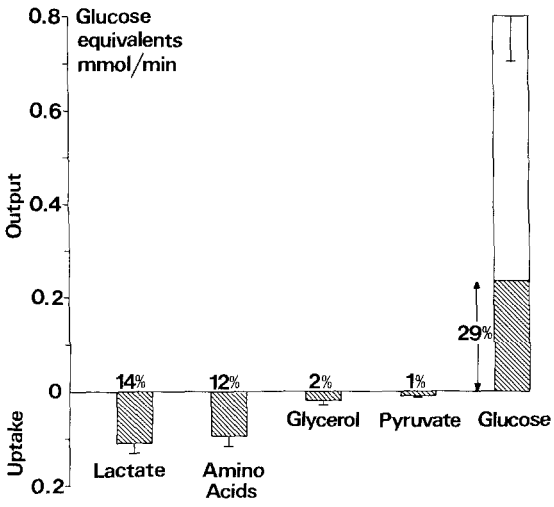

Fig. 3. Splanchnic production of glucose and uptake of glucogenic precursors in the post-absorptive basal state in healthy subjects. The hatched part of the glucose column indicates that portion of the glucose output which can be accounted for by precursor uptake. Mean values ± SEM are given

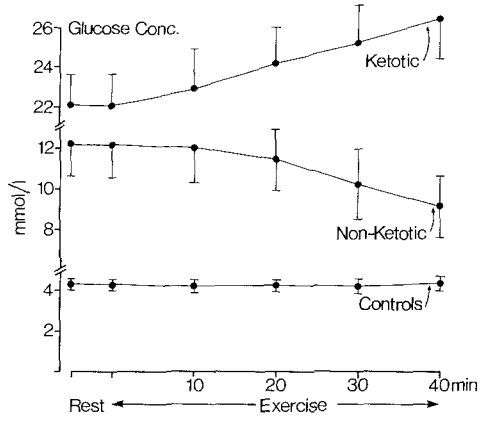

Fig. 4. Arterial glucose concentration in mildly ketotic and non-ketotic diabetic patients and healthy controls at rest and during exercise at a work load corresponding to 60% of their maximal oxygen uptake. Insulin was withheld for 24 hours prior to the study. Mean values ± SEM are presented

dency of exercise to intensify the diabetic state in certain circumstances may reflect either an overproduction of glucose from the liver, or an underutilization by the working muscle, or both. Which alternative applies cannot be determined from the available information [26, 27, 39].

Studies in diabetic patients, using the hepatic venous catheter technique, have demonstrated that 24 hours after insulin withdrawal, total glucose output in the basal resting state is similar to that of controls [26, 39, 40]. However, for patients in a more advanced diabetic state involving ketoacidosis and marked hyperglycaemia, an elevation of the splanchnic glucose output has been reported [41]. In both the mild and the severe diabetic state an augmented uptake of glucose precursors has been observed as a consequence of increased fractional extraction. Thus, after only 24 hours of insulin withdrawal in diabetic patients, the splanchnic uptake of glucose precursors had risen 80%, indicating an accelerated rate of hepatic gluconeogenesis in the basal state [40].

The rise of hepatic glucose output in response to exercise is similar in diabetic patients and controls [26, 39], but whereas the utilization of gluconeogenic precursors during short-term exercise rises to two to three times the basal level in diabetics, in controls it remains at the basal level. Thus, gluconeogenesis was estimated to account for 30% of the splanchnic glucose output at 40 minutes of exercise in diabetics, compared to no more than 11% for controls (Fig. 5). The observation of increased oxygen and FFA consumption by the splanchnic tissues in diabetics during work further supports the conclusion that hepatic

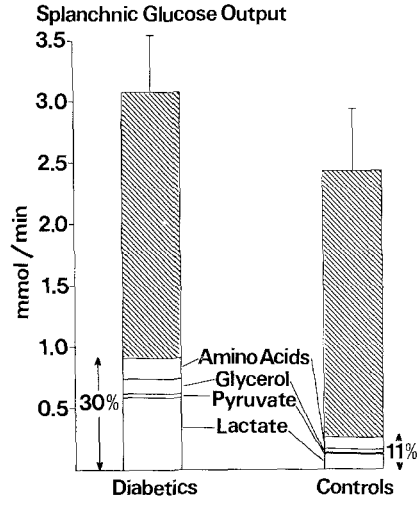

Fig. 5. Splanchnic glucose output during moderately heavy exercise in insulin-withdrawn diabetic patients and controls. The open part of the columns indicate that portion of the glucose output which may be accounted for by precursor uptake

gluconeogenesis is accelerated. The overall influence of brief (40 minutes) exercise on hepatic glucose metabolism in the diabetic patient is thus comparable to that of prolonged (four hour) exercise in normal subjects; in both instances there is a marked increment in hepatic gluconeogenesis [23, 26, 39].

The physiological mechanism behind the stimulation of hepatic glucose production during exercise has not been identified. Studies in healthy subjects have demonstrated an exquisite sensitivity of hepatic glycogenolysis to the inhibitory action of small increments in insulin [35]. Hypoinsulinaemia during exer-

cise may thus serve to facilitate the rise in glucose output. In prolonged or severe exercise, the rise in glucagon concentration [29] and the increments in growth hormone [42] and catecholamines [43] may also contribute to the glycogenolytic and gluconeogenic response. In addition, the liver possesses a rich adrenergic innervation and it is conceivable that changes in sympathetic activity during exercise are of importance for hepatic glucose output [44]. Recently, suppression of the exercise-induced rise in glucagon by the infusion of somatostatin has been demonstrated to cause hypoglycaemia and diminish or even abolish the rise in hepatic glucose output [45]. However, glucose output from the liver may rise even in the absence of measurable changes in glucagon concentration. Thus, it remains to be determined which of the possible mechanisms is of regulatory importance.

Free Fatty Acid Metabolism

The fact that fat-derived substrates serve as fuel for exercising human muscle was demonstrated by Christensen and co-workers in 1939 [46], although no evidence could be obtained about the form in which the fat was utilized. Methods for the direct measurement of fat metabolism did not become available until 1956. At that time the important role of the free fatty acids (FFA) in the transport of fuel from adipose tissue to muscle was identified [47]. Although the plasma concentration of FFA is low, the FFA pool is essential for the supply of fuel to body tissues. The turnover rate of FFA in the basal state is directly correlated to the arterial plasma concentration of FFA, indicating that FFA turnover is determined primarily by the rate of adipose tissue lipolysis.

The study of FFA metabolism in skeletal muscle in man is complicated by the simultaneous uptake and release of FFA which occurs at rest [48] as well as during exercise [49, 50]. The FFA released from muscle may derive from lipolysis in adipose tissue interspersed between the muscle fibres, or possibly from hydrolysis of intracellular triglycerides in the muscle tissue itself. This phenomenon necessitates the use of isotopic tracers for the determination of regional FFA uptake. Oleic or palmitic acid is generally used as a tracer for the entire FFA fraction since these are the individual FFA with the highest plasma concentrations and in each case their fractional uptake in both muscle and liver is very similar to that of total FFA [51].

In the resting basal state, the local RQ for muscle is close to 0.7, indicating that FFA are the primary fuel consumed by muscle [48]. In response to exercise, FFA uptake by muscle increases with time and after 40 minutes of mild bicycle exercise it may account for 25–35% of the oxygen consumed [23]. FFA utilization continues to increase during prolonged exercise; between one and four hours, the uptake of FFA by working leg muscle rises approximately 70%. Thus, after four hours of continuous mild exercise the relative contribution of FFA to total oxygen use is twice that of blood glucose (Fig. 6).

The uptake of FFA by exercising limb muscles during bicycle exercise or forearm work rises in direct proportion to the arterial FFA inflow, expressed as the product of arterial concentration and plasma flow, a relation that has been observed during both brief and prolonged work and during prolonged starvation [52]. It would thus seem that the magnitude of FFA uptake by muscle is determined primarily, not by the muscle itself but by external factors such as the rate at which FFA are mobilized from adipose tissue.

In non-ketotic diabetic patients with mild hyperglycaemia, as well as in normal subjects, an initial decline in FFA concentration is followed by a modest, gradual rise as exercise continues [25, 38]. In contrast, diabetics with marked hyperglycaemia and ketosis already show an elevated FFA level at rest and the rise during exercise is more marked [26, 38]. As a consequence of this greater FFA availability, uptake of FFA by working muscle is increased. Thus, bicycle exercise in mildly ketotic diabetic patients was accompanied by a 7-fold rise in FFA uptake by leg tissues, compared to only a 3-4-fold increment in the controls (Fig. 7).

Ketone Body Metabolism

The short-chain fatty acids, 3-hydroxybutyric acid and acetoacetic acid are present in plasma in low concentrations in normal, post-absorptive man. A quantitatively insignificant uptake by muscle has been demonstrated in the resting state, but during exercise the ketone bodies make no net contribution to the fuel supply of muscle [53, 54].

Significant utilization of both 3-hydroxybutyrate and acetoacetate by muscle is seen at rest also in diabetic patients. Unlike normal controls, the diabetics continue to utilize ketone bodies during exercise [26, 39]. Thus, mildly ketotic diabetic patients showed a 7-fold increase in total ketone body utilization by the leg muscle during exercise (Fig. 7). The background to this difference in ketone body utilization between diabetics and normal subjects remains to be examined.

Numerous reports have indicated that ketone body concentrations are unchanged during exercise

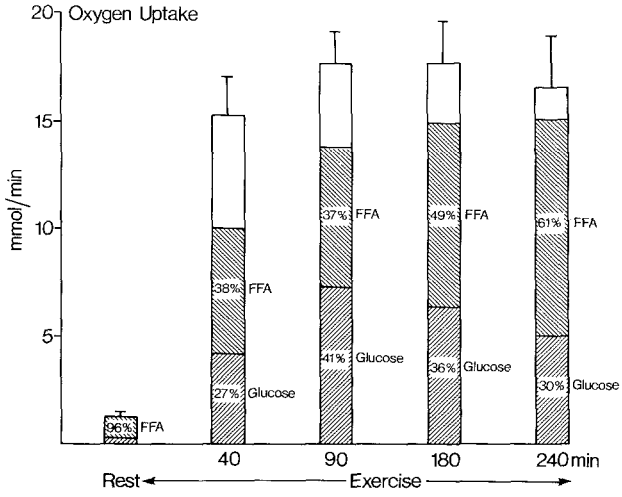

Fig. 6. Leg uptake of oxygen and substrates at rest and during prolonged exercise in healthy subjects

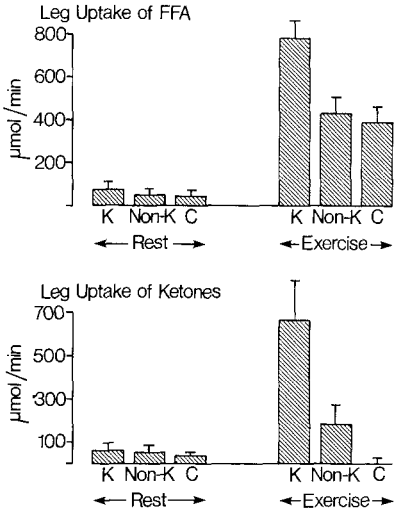

Fig. 7. Leg uptake of FFA and ketone bodies in mildly ketotic (K) and non-ketotic (NON-K) diabetics and healthy controls (C) at rest and during moderately heavy exercise. Insulin was withdrawn 24 h prior to the study. Mean values ± SEM are given

in patients with mild to moderately severe ketonaemia and hyperglycaemia. However, in severely insulin-deficient patients with marked hyperketonaemia, strenuous exercise is reported to cause a further rise in blood ketone body concentration [6, 26, 27, 38, 55]. In view of the fact that muscle uptake of ketone bodies rises during work in diabetics, unchanged or increased arterial levels of ketone bodies should indicate an augmented rate of ketogenesis. Direct examination of the splanchnic exchange of FFA and ketone bodies during exercise confirms this hypothesis and reveals different responses for non-ketotic and ketotic patients [26]. Marked increases in the splanchnic uptake of FFA (+ 50%) and the out-

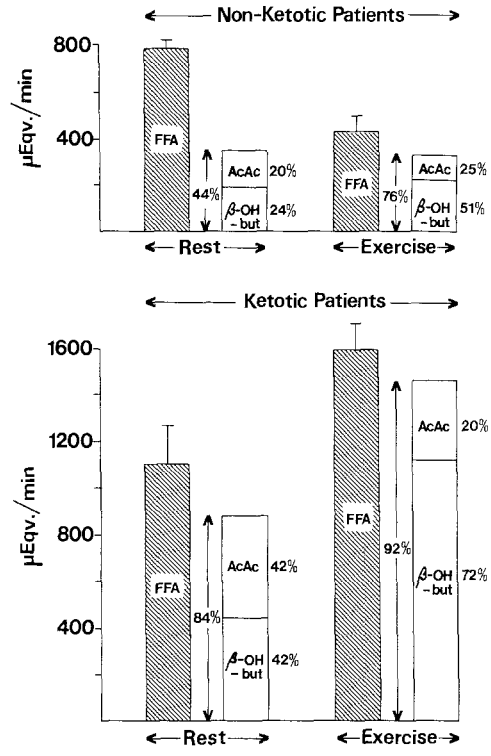

Fig. 8. Splanchnic uptake of FFA and production of acetoacetate (AcAc) and 3-hydroxybutyrate (β-OH-but.) in non-ketotic diabetics (upper panel) and mildly ketotic patients (lower panel) at rest and during exercise. Data are given as four-carbon equivalents. The proportion of FFA uptake which may be accounted for by ketone body output is noted. Insulin was withheld for 24 h before the study

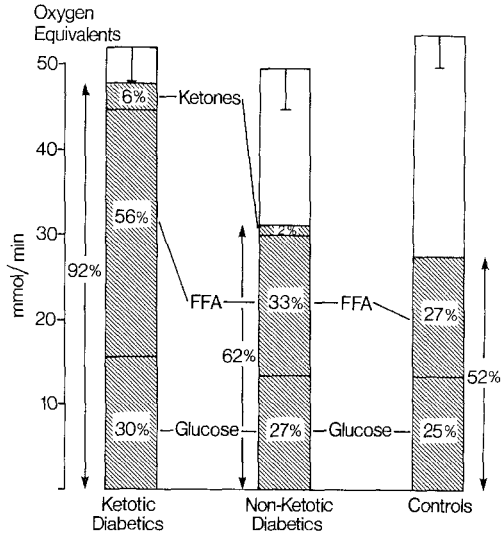

Fig. 9. Leg uptake of oxygen (total height of the bars) and substrates (hatched areas) after 40 min of moderately heavy exercise in mildly ketotic and non-ketotic diabetic patients and controls. Insulin was withheld for 24 h prior to the study

put of 3-hydroxybutyrate (+ 150%) were observed in the ketotic group, and much less pronounced changes in the non-ketotic group (Fig. 8). The ratio of the splanchnic release of 3-hydroxybutyrate to acetoacetate rose from 1:1 in the resting state to 3:1 during exercise, suggesting a more reduced state of mitochondrial adenine nucleotides. This is in agreement with the rise in [NADH]/[NAD] ratio observed in association with stimulation of ketogenesis [56]. These data thus demonstrate that production as well as utilization of ketone bodies accelerates during exercise in diabetes; in the severely hyperketonaemic and hyperglycaemic patient, ketone body production during exertion may rise in excess of the simultaneous utilization, leading to elevated levels of blood ketone bodies.

Utilization of Blood-Borne Substrates by Working Muscle in Diabetes

The estimated contribution of each fuel to the oxidative metabolism of working muscle in diabetic patients is illustrated in Figure 9. It appears that in spite of the hyperglycaemia and absolute or relative hypoinsulinaemia blood glucose may account for similar proportions of total metabolism in diabetics and controls. However, in the ketotic patients the FFA contribution (56%) is twice that of controls. In addition, there is a significant utilization of ketone bodies, corresponding to 6% of the oxygen consumption. Taken together, the blood-borne fuels may thus account for as much as 90% of the total metabolism in the ketotic diabetics. In contrast, the non-ketotic patients showed only a slightly augmented uptake of FFA (33%) compared to controls (27%), plus a minor contribution from ketone bodies. The total contribution from blood-borne substrates was 62% for the non-ketotics, compared to 52% in controls, indicating that this group of diabetic patients differs only slightly from healthy subjects in their fuel utilization by working muscle. With regard to the effects of diabetes on fuel metabolism during exercise, the response to short-term exercise in the ketotic group is similar to that in normal subjects during prolonged exercise. In both circumstances, as compared to short-term exercise in healthy controls, the contribution of FFA to total oxidative metabolism is strikingly increased. This similarity and the changes in the rates of gluconeogenesis described above, thus suggest that, compared to the normal state, diabetes may tend to accelerate the metabolic adaptation to exercise.

Beneficial Effects of Exercise in Diabetes

With regard to the beneficial effects of exercise on the diabetic state, it is apparent that the utilization of blood glucose, FFA and ketone bodies, as well as glycogen in liver and working muscle, is much increased by exercise. In insulin-treated diabetics, exercise is accompanied by a lowering of the blood glucose concentration. Perhaps more important than this acute effect of exercise is the more prolonged influence on glucose metabolism, that results from the replenishment of muscle and liver glycogen during the 24–48 hours after exercise. The exercise-induced fall in the glycogen content of liver and muscle gives rise to a prolonged stimulation of glycogen synthetase and glucose utilization in these tissues [12, 17]. As a consequence, glucose tolerance of the diabetic improves [8, 36, 57, 58] and insulin requirements are diminished [5, 59].

Since glucose uptake by muscle [31], as well as glycogen resynthesis in muscle [12, 17] and probably also in liver, require a minimum concentration of insulin, it is clear that the time interval between insulin administration and exercise is of importance for the metabolic adaptation during and after work. Thus, in diabetic patients in poor metabolic control – as evidenced by marked hyperglycaemia and hyperketonaemia – exercise is accompanied by augmented arterial levels of glucose and FFA as well as a rise in splanchnic ketone body production [26]. Moreover, in both ketotic and non-ketotic diabetics, exercise increases the splanchnic uptake of glucogenic precursors substantially above the rate observed at rest [26, 39]. Thus, with respect to ketogenesis as well as gluconeogenesis, short-term exercise, particularly in ketotic patients, may be viewed as intensifying rather than ameliorating the diabetic state. These observations, far from implying that exercise has a clinically deleterious effect in the diabetic state, simply highlight the importance of adequate insulin administration in connection with exercise in diabetic patients.

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