The Role of Insulin in the Metabolic Response to Exercise in Diabetic Man

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The metabolic responses to exercise in normal and diabetic man are influenced by many variables, including endocrine status, physical fitness, workload, and duration of exercise.[1–4] The principal hormonal changes implicated in the metabolic adjustments to exercise include a reduction in insulin secretion[3,5,6] and an increase in secretion of catecholamines,[7] glucagon,[7–9] growth hormone,[10–12] and cortisol.[3] Apart from these, a multitude of additional factors plays roles of variable importance. These factors include age, sex, anthropomorphic characteristics, nutritional status, nature of exercise, cardiorespiratory status, and emotions. Against this background, it would be predicted that diabetics would respond differently than normals, primarily because of altered insulin secretion. However, diabetics show alterations in the secretion of other regulatory hormones as well and are prone to many other abnormalities of the other factors listed.

In normal man undergoing moderate exercise, the provision of energy substrates for the augmented muscle oxidative requirements is regulated precisely. Except after prolonged exercise, plasma glucose remains constant because the increase in muscle glucose utilization is quantitatively matched by an increase in hepatic glucose production.[5,13,14] In contrast, diabetics receiving subcutaneous insulin have demonstrated a fall in plasma glucose during such exercise,[15–17] which may result in symptomatic hypoglycemia. This effect of exercise has long been recognized in clinical practice, though its mechanism has only recently been studied in detail.[13,18–20] However, the interpretation of all studies of exercise in diabetics must take into account all the possible variables mentioned and whether they were controlled for in the specific protocols employed. In addition, since insulin is exogenously administered in juvenile-onset diabetics, a new set of variables is introduced. This includes the type of insulin used, the site of injection in relation to the type of exercise, the time between insulin injection and onset of exercise, the temporal relationship of exercise to the last meal, the route by which insulin is injected, the possible effects of the presence of insulin antibodies, and the sensitivity of the individual to insulin. For example, recent studies have varied in respect to the time from injection to onset of exercise by 10 min to 24 h.

The present report summarizes the results of our previous studies,[13,21] which were designed in such a way as to control for as many of the recognized variables as possible. The role of insulin in the metabolic responses to moderate, 45-min bicycle exercise was examined by comparing two routes of insulin administration to overnight-fasted diabetics. Insulin was given either as a constant intravenous infusion throughout exercise or by subcutaneous injection 1 h prior to exercise. Appropriately matched nondiabetic subjects were studied as controls. Glucoregulation was assessed by continuous glycemic monitoring and measurement of isotopic glucose turnover. The circulating levels of pyruvate, lactate, β-hydroxybutyrate, glycerol, free fatty acids (FFA), and, when possible, immunoreactive insulin (IRI) were measured at rest, during exercise, and during recovery.

MATERIALS AND METHODS

Subjects. Sixteen insulin-dependent diabetics and seven control subjects were studied in the Clinical Investigation Unit and Respiratory Research Laboratory of the Toronto General Hospital. All subjects were nonobese, and the diabetic group consisted of 10 males and 6 females with duration of disease from 0.2 to 39 yr. The control group comprised five males and two females. The maximum work capacity was estimated during steady state exercise on a bicycle ergometer at two different workloads. The level of exercise giving maximum oxygen uptake was determined and corrected for age, standardized for weight, and graded on a five-level scale for cardiorespiratory fitness.[22,23] The controls and diabetics were similar with respect to age,

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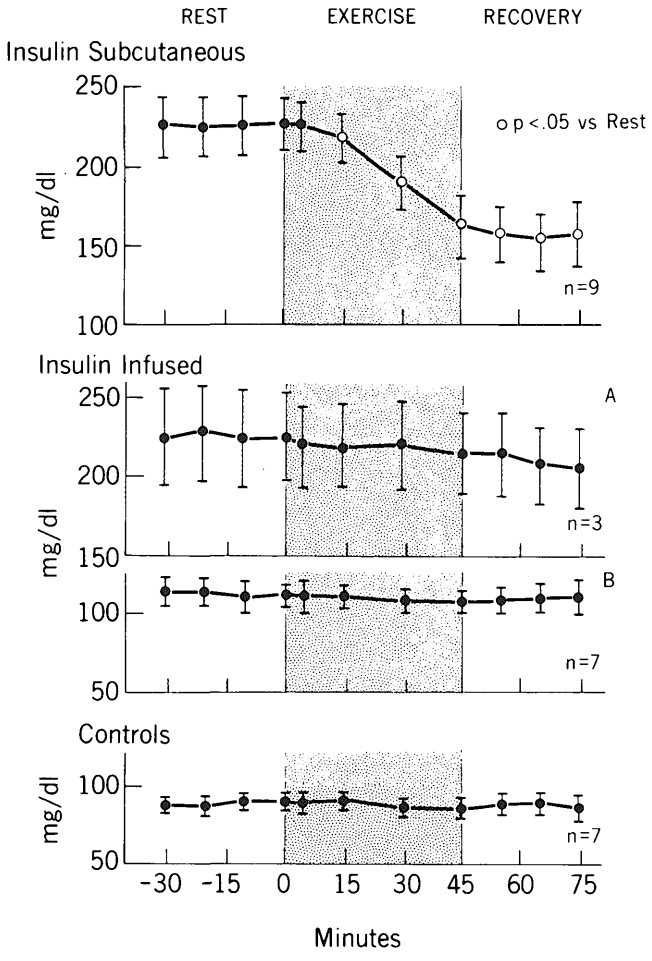


FIGURE 1. The effect of exercise (shaded area) on plasma glucose (mean ± SEM) in fasting postabsorptive diabetics given one-third their usual insulin dose subcutaneously 1 h prior to exercise (upper panel), maintained hyperglycemic (middle panel A) or normoglycemic (middle panel B) by constant insulin infusion, and normal controls (lower panel). (*From* Zinman, B., Murray, F. T., Vranic, M. et al. J. Clin. Endocrinol. Metab. 45:641–52, 1977. Reproduced with permission.)

physical fitness, and oxygen uptake in exercise as a proportion of maximal oxygen consumption. Anthropomorphic data and physical fitness are as previously specified.[13] The nature, purpose, and possible risks involved in the study were explained and voluntary consent was obtained.

Protocol. All studies were performed in the morning after a 12–14-h fast. The exercise was performed on a vertical bicycle ergometer (Siemens-Elema model 380, Stockholm, Sweden) at a workload calculated to result in pulmonary oxygen uptake of 50% of the previously estimated maximum value. The subjects were divided into three groups. (a) Nine diabetic subjects received one-third their total daily intermediate-acting insulin dose in the right thigh 1 h before exercise. (b) Ten diabetic subjects received a constant intravenous infusion of insulin at rates between 8 and 20 mU/min commencing the night prior to the experiment and adjusted to maintain normoglycemia in seven subjects and hyperglycemia in three subjects. To insure complete absence of intermediate-acting insulin, they were treated with four daily injections of crystalline zinc insulin for 2 days prior to the study. (c) In seven normal controls, no exogenous insulin was given. Three diabetics were studied both with subcutaneous insulin and intravenous insulin infusion.

A 30–100-min period of rest, during which steady state glycemia was obtained, was followed by 45 min of exercise and a 60-min recovery period.

The morning of the experiment, an 18-gauge catheter (Argyle Medicut, Aloe Medical Co., St. Louis, Missouri) was introduced into an antecubital vein for sampling of blood for glucose, β-hydroxybutyrate, FFA, glycerol, lactate, pyruvate, insulin, and [3-^{3}H]glucose. In an ipsilateral forearm, a double lumen catheter (Abjad Industries, Willowdale, Ontario) was inserted for continuous glucose sampling as previously described.[24,25] A third catheter (18 gauge) was introduced into the contralateral forearm for delivery of [3-^{3}H]-glucose for the measurement of glucose turnover and for the infusion of insulin.

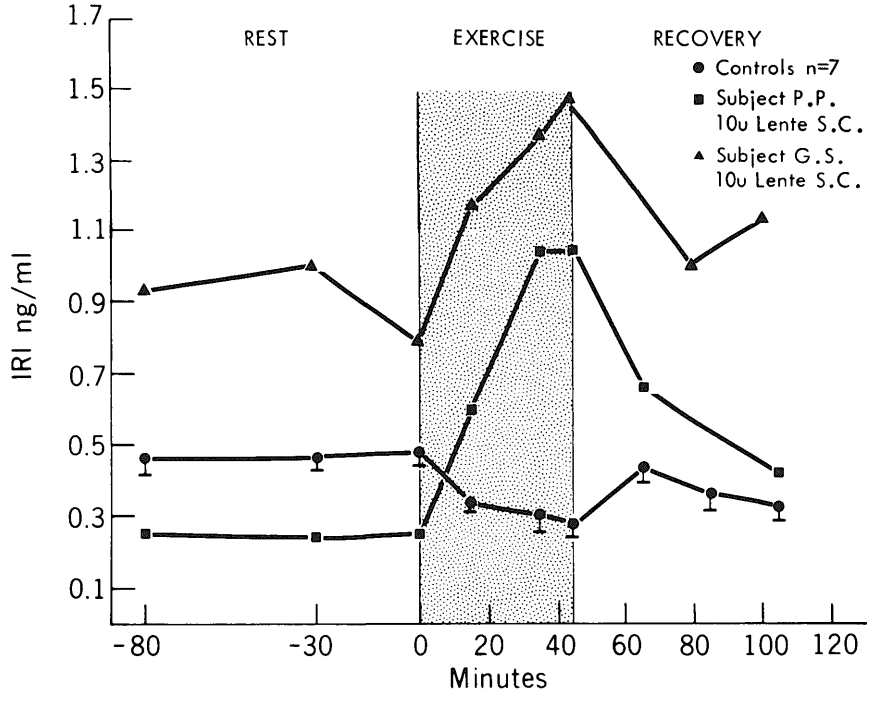


FIGURE 2. Plasma immunoreactive insulin at rest, exercise (shaded area), and recovery in seven controls and two diabetic subjects given subcutaneous insulin 1 h prior to exercise. (*From* Zinman, B., Murray, F. T., Vranic, M. et al. J. Clin. Endocrinol. Metab. 45:641–52, 1977. Reproduced with permission.)

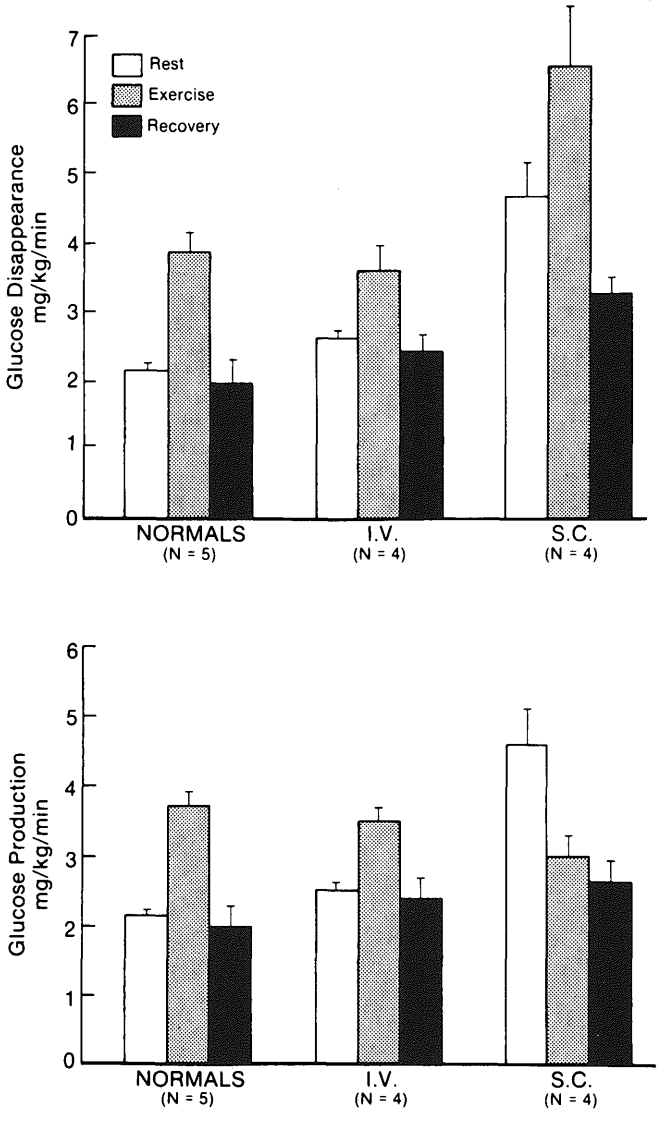


FIGURE 3. Glucose turnover: glucose disappearance (upper panel) and glucose production (lower panel) at rest, at 45 min of exercise, and 60-min recovery for the normal controls, insulin-infused (i.v.), and subcutaneous (s.c.) insulin-treated diabetics.

Tracer method and calculation of glucose turnover. For experiments in which glucose turnover was measured, a priming bolus (22 μCi) of [3-^{3}H]glucose (New England Nuclear, Boston, Mass.) was injected intravenously at the beginning of the rest period and a continuous infusion (2 μCi/ml 0.9% saline) of labeled glucose was infused through a Lambda pump (Harvard Apparatus Co., Millis, Mass.) at a rate of 0.109 ml/min throughout rest, exercise, and recovery. The rates of production and disappearance of endogenous glucose were determined by the method detailed previously[26–28] and validated for both steady state and rapidly changing nonsteady state conditions.[29] Samples for glucose turnover were collected in tubes containing heparin and sodium fluoride. The plasma was deproteinized with a mixture of equal volumes of zinc sulfate (5% wt/vol) and barium hydroxide (0.3 N). An aliquot of the supernate was evaporated to remove tritiated water, and the precipitate was redissolved in 1 ml distilled water. The activity of labeled glucose in the samples was measured by liquid scintillation counting, and the concentration of unlabeled glucose was determined using a glucose analyzer (Beckman Instruments, Inc., Fullerton, Calif.). Since it has been reported[30] that [3-^{3}H]glucose does not recycle into circulating metabolites, the present method does not require that glucose be isolated from plasma by ion exchange chromatography.

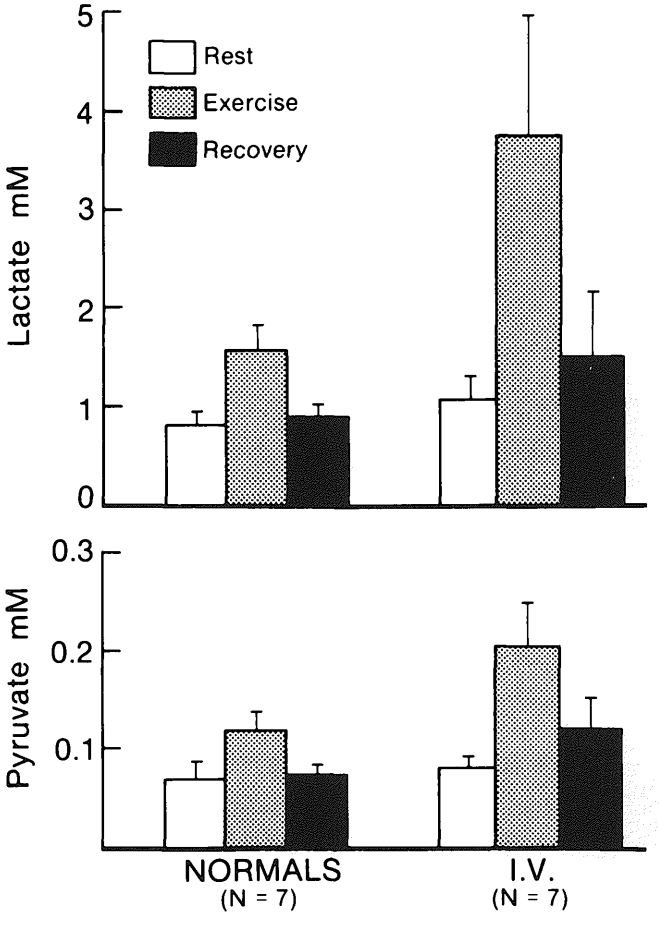
Analytic methods. Samples for insulin assay were centrifuged with minimal delay at 4°C and supernatants frozen at −20°C until assayed. IRI was determined using an antibeef insulin antiserum (supplied by Dr. Peter Wright, Minneapolis, Minn.), purified human insulin standard (25.7 μU/ng), ^{125}I-labeled pork insulin (Novo Research Institute, Copenhagen, Denmark), and a dextran-coated charcoal separation of free from bound insulin.[31] Microfluorimetric adaptations of standard enzymatic methods were used employing an Aminco Fluoromicrophotometer, (American Instrument Co., Division of Travenol Laboratories Inc., Silver Spring, Md.) for determinations of β-hydroxybutyrate, lactate, pyruvate, and glycerol.[32] FFA were estimated by the radiochemical microtechnique of Ho.[33]

Standard statistical methods were employed with a Student's paired t test being used to examine for the significance of changes during exercise and recovery compared with rest and the unpaired t to compare the diabetic group with the normal controls.

RESULTS

Glycemic response to exercise. In Figure 1 glycemia during rest, exercise, and recovery is shown for the controls, both hyperglycemic and normoglycemic insulin-infused, and subcutaneous insulin subjects. Glycemia was constant

FIGURE 4. Lactate and pyruvate for the normal controls and insulin-infused diabetics at rest, 45 min of exercise, and 60-min recovery period.

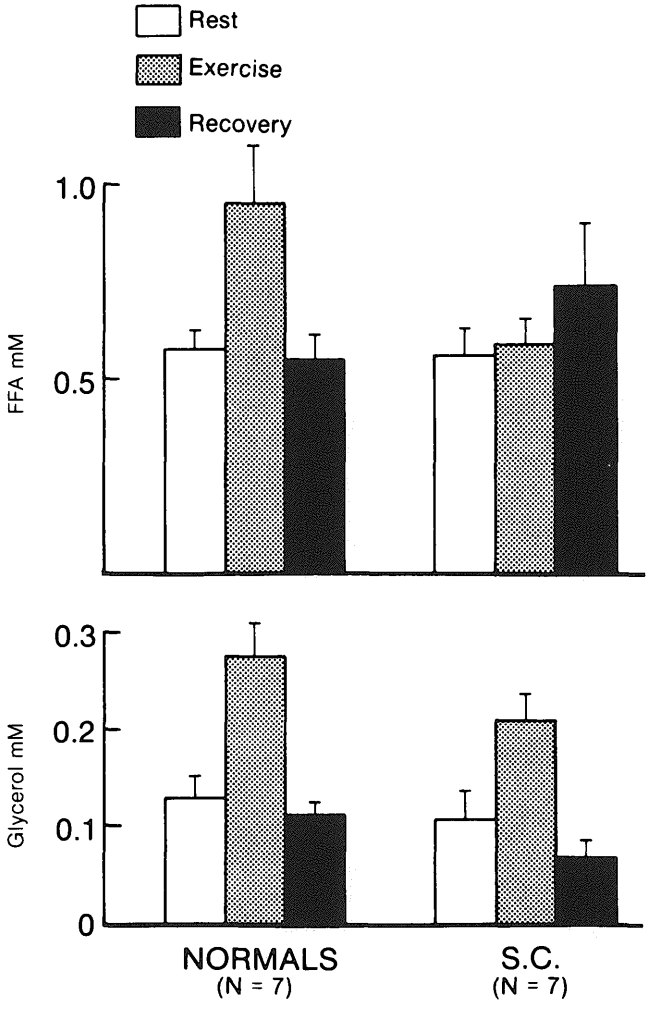


for the subcutaneous insulin group at rest (227 ± 16 mg/dl), and exercise produced a progressive mean fall of 71 mg/dl over 45 min. Glycemia in the insulin-infused hyperglycemic and normoglycemic subjects at rest was 224 ± 28 and 110 ± 9 mg/dl, respectively, and was unaffected by exercise. In the normal controls, glycemia was 90 ± 6 mg/dl at rest and did not change with exercise.

IRI during exercise. In most of the diabetic subjects studied, insulin measurement was precluded by the presence of insulin antibodies. However, in two subjects receiving subcutaneous insulin, therapy was recently initiated and IRI measurements were compared with normals (Figure 2). In the normal controls, insulin decreased significantly during exercise ($P < 0.01$) and rose to basal levels during recovery. In both subcutaneous insulin subjects, IRI rose linearly during exercise to concentrations twofold and threefold their resting levels. In the recovery period, IRI decreased toward preexercise concentrations.

Glucose turnover. In Figure 3 the glucose disappearance (upper panel) and glucose production (lower panel) are shown. At rest, glucose disappearance was elevated for the subcutaneous insulin group as compared with the normals and the near normoglycemic insulin-infused subjects ($P < 0.005$). A similar increment in glucose disappearance occurred with exercise for all three groups. Glucose production during exercise increased in the normals ($P < 0.005$) and insulin-infused subjects ($P < 0.02$) and was synchronous and parallel to glucose disappearance. In contrast, glucose production in the subcutaneous insulin group fell during exercise despite an increase in glucose disappearance.

FIGURE 5. Free fatty acids and blood glycerol for the normal controls and subcutaneous insulin (s.c.) at rest, 45 min of exercise, and 60-min recovery period.



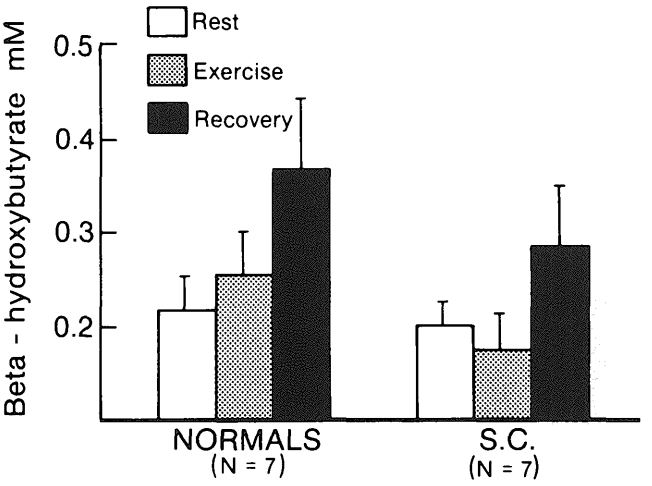


FIGURE 6. Blood β-hydroxybutyrate for the normal controls and subcutaneous insulin (s.c.) at rest, 45 min of exercise, and 60-min recovery period.

Lactate and pyruvate. The blood lactate and pyruvate concentrations for the normals and insulin-infused subjects are shown in Figure 4. At rest the lactate concentrations for the controls (840 ± 125 μM) and insulin-infused subjects (1080 ± 226 μM) were not significantly different. With exercise, there was a greater increase in lactate in the insulin-infused subjects as compared with controls. Blood pyruvate changes were parallel to those of lactate. The lactate response to exercise in the subcutaneous insulin subjects (results not shown) was the same as that of controls.

FFA, glycerol, and β-hydroxybutyrate. In Figure 5 the FFA and glycerol concentration for the normal controls and subcutaneous insulin group are shown. At rest the FFA concentrations were the same in controls (521 ± 48 μM) and the subcutaneous insulin (519 ± 79 μM) groups. With exercise, FFA rose twofold ($P < 0.05$) in the normal controls but remained unchanged in the subcutaneous insulin group. The glycerol concentrations were similar at rest (N = 128 ± 18 μM; subcutaneous insulin = 106 ± 20 μM), and the response to exercise was attenuated in the subcutaneous insulin group. The β-hydroxybutyrate concentration (Figure 6) was similar at rest for the controls and subcutaneous insulin groups, and no significant change occurred with exercise. After exercise the β-hydroxybutyrate rose in the normal controls ($P < 0.05$). The smaller rise during recovery for the subcutaneous insulin group was not significant by paired analyses.

Glycemic response in relation to insulin injection site. To determine if subcutaneous depot insulin absorption was affected by local exercise, one subject was studied on three separate occasions (Figure 7). Subcutaneous insulin injected into an exercising thigh resulted in a 100 mg/dl fall in glycemia (top panel). When insulin was administered at the same site but without exercise, a slight decrease in glycemia occurred (middle panel). Exercise was without effect in lowering glycemia when insulin was injected subcutaneously into an immobilized arm (lower panel).

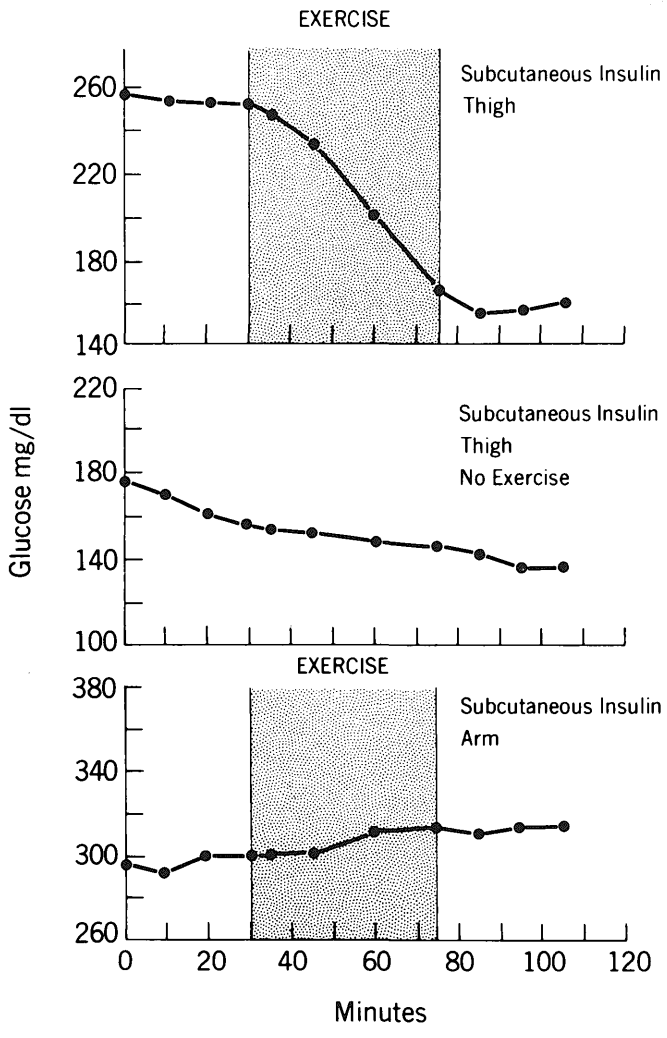


FIGURE 7. Glycemic response to exercise in one subject studied on three separate occasions. (a) Subcutaneous insulin in an exercising thigh (upper panel). (b) Subcutaneous insulin in the thigh without exercise (middle panel). (c) Subcutaneous insulin into an immobilized arm during bicycle exercise (lower panel). (*From* Zinman, B., Murray, F. T., Vranic, M. et al. J. Clin. Endocrinol. Metab. *45*:641–52, 1977. Reproduced with permission.)

DISCUSSION

The results of the present study underscore the central role of insulin in mediating the metabolic response to exercise. This role is expressed in at least three phases of the response: the uptake of glucose by the exercising muscle, hepatic production of glucose, and peripheral release of energy substrates. For enhanced muscle glucose uptake to occur during exercise, a minimal concentration of insulin is a prerequisite. When severe insulin deficiency is present, no increase in muscle uptake can occur. This has been shown with isolated muscle preparations[34] in animals[12] and in diabetic man.[35] The requirement for such enhanced uptake to occur would appear to be a small, "permissive" insulin concentration. Higher concentrations of insulin do not further augment the increment in muscle glucose translocation due to exercise. This is demonstrated in the subcutaneous insulin subjects, in whom depot insulin absorption resulted in elevated IRI during exercise. The increment in glucose disappearance of 2 mg/kg/min was the same as in normal controls and in insulin-infused subjects. Similar results have been obtained in diabetic dogs.[18] Other investigators[36] have shown a similar phenomenon in normal subjects, when exercise was preceded by ingestion of glucose. They showed that, although glycemia at rest was elevated, the increment in muscle glucose uptake with exercise was not different from that of controls despite elevated plasma IRI as a result of the ingested glucose.

Unlike exercise-enhanced glucose disappearance, the hepatic production of glucose is responsive to increases in plasma IRI.[13,18] This is particularly evident in the subcutaneous insulin subjects in whom the initially elevated glucose production as a result of underinsulinization at rest was followed by a rapid decline in production with exercise. This would be the expected result of hyperinsulinemia from depot insulin absorption. That hyperglycemia itself, or some metabolic concomitant thereof, is not responsible for the fall with exercise is further supported by the absence of a fall in the insulin-infused, hyperglycemic subjects (Figure 1). Thus, exercise-induced hypoglycemia in patients receiving subcutaneous insulin is the result of accelerated depot insulin absorption inhibiting the normal increase in glucose production in response to exercise.

The rise in IRI with exercise in the subcutaneous insulin subjects not surprisingly affects the concentration of other circulating metabolites. FFA are an important substrate for muscle,[4] and their mobilization during exercise in normals is facilitated by a fall in IRI with a concurrent increase in other lipolytic hormones. As is evident in the subcutaneous insulin group (Figure 5), elevated IRI during exercise results in a failure of FFA to rise with exercise, presumably due to decreased mobilization mediated by insulin's antilipolytic effect. The smaller increase in glycerol during exercise in these subjects supports this observation. The rate of hepatic ketone body production is determined by the provision of FFA substrate and the ketogenic capacity of the liver.[37,38] The lower β-hydroxybutyrate concentration during recovery in the subcutaneous insulin group as compared with normals (Figure 6) would be consistent with a decreased presentation of FFA to the liver and/or an altered rate of ketogenesis.

The data demonstrate that, in man, exercising the region in which insulin is given subcutaneously influences its rate of absorption (Figures 2 and 7). This finding is consistent with that of other studies in dogs[18] and rats.[19] Recently Koivisto and Felig[20] confirmed these observations indirectly by measuring the rate of [^{125}I]insulin disappearance from different injection sites during bicycle exercise.

The extrapolation of all such research observations to the clinical management of diabetes must be cautious. The effects observed are clearly related to the specific protocols employed. It must be emphasized that exercise continues to be an important modality for improved diabetic control.[15–17] The same mechanisms that cause exercise hypoglycemia in some diabetics will improve glycemic control of the larger number in whom control of hyperglycemia is a more prevalent problem. Integration of all available data would seem to justify the following recommendation as to insulin therapy in relation to exercise. For those uncommon physical activities that involve uniquely arm or leg exercise, injection into the less active site should be tried if hypoglycemic symptoms occur. For the vast majority of activities, however, many muscle groups are involved. Therefore, since increased absorption from a smaller depot is still likely, one should advise patients who develop hypoglycemia to take extra, rapidly assimilated carbohydrate prior to exercise rather than decrease their insulin dose.

Inferences as to insulin's physiologic role and potential clinical extrapolations are possible based upon the data of the intravenous insulin studies. It is recognized that a completely normal physiologic insulin response was not mimicked by the experiments. The insulin infusion was into a peripheral vein, the infusion rate was not decreased during exercise, and absolutely normal resting glucose turnover was not achieved (Figure 3). Despite this, the normal response to exercise was maintained (hypoglycemia did not occur), due to normal increments in glucose production and disappearance. This may reflect mild underinsulinization of the liver at rest but not during exercise. The fact that total metabolic normalization was not obtained by this approach is also suggested by the exaggerated lactate response to exercise. The mechanism of this is speculated upon elsewhere.[21] Further studies are in progress in which absolute normalization of resting glucose production is obtained by slightly higher insulin infusion rates. These will define the relative roles of site versus amount of insulin delivery in achieving total normalization of response.

The practical clinical application of these findings is to be found in the future deployment of the "artificial pancreas" or portable insulin infusion systems. It is essential to determine whether specific control parameters will be required to achieve complete normalization of exercise responses. In the present state of the art, it would appear that near normalization would not require such additional parameters, though further investigation, along the lines described above, in differing nutritional states and with different exercise loads and durations is required.

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