Skeletal muscle has a fundamentally important role in the maintenance of normal glucose homeostasis and in regulating whole-body carbohydrate metabolism. In this review, we discuss the regulation of skeletal muscle glucose transport by muscular activity and inactivity. A large number of patients routinely seen by physical therapists exhibit some form of skeletal muscle insulin resistance. Therefore, we discuss how skeletal muscle insulin resistance can be localized to a relatively small muscle mass, or in other circumstances can affect a large proportion of the muscle mass leading to disturbances in whole-body glucose homeostasis. We review the mechanisms and regulation of skeletal muscle glucose transport as background for understanding how defects in this process may contribute to the underlying pathogenesis of insulin resistance. Research into the events regulating glucose entry into skeletal muscles has considerable impact on how physical therapy exercise prescriptions may benefit patients with disturbances in carbohydrate metabolism. With an understanding of the principles of proper exercise prescription, physical therapists can use exercise training as a primary therapeutic intervention to improve local muscle and whole-body glucose utilization, and thereby minimize insulin resistance. [Sinacore DR, Gulve EA. The role of skeletal muscle in glucose transport, glucose homeostasis, and insulin resistance: implications for physical therapy. Phys Ther. 1993;73:878–891.]

Key Words: Carbohydrate metabolism, Glucose, Insulin resistance, Skeletal muscle.

Physical therapists often focus on deficits in muscular functions while attempting to correct muscle weakness, improve endurance, or control inappropriate muscular movements. Unfortunately, physical therapists have largely ignored the role of skeletal muscle in the maintenance of glucose homeostasis and the deficits in skeletal muscle glucose metabolism that result from muscular inactivity.

The primary sources of energy for skeletal muscle are carbohydrates and fat. Uptake of glucose is important during exercise in order to supply fuel to the working muscles and after exercise for the replenishment of muscle glycogen stores. An overwhelming body of evidence now exists that acute muscle contractile activity and chronic exercise improve skeletal muscle glucose transport and whole-body glucose homeostasis.

The need for physical therapists to recognize, understand, and exploit the role of skeletal muscle in glucose homeostasis is underscored by the high prevalence of patients with underlying skeletal muscle insulin resistance. Resistance to the actions of insulin in these patients can be confined to isolated muscle groups (e.g., following immobilization of muscle groups by casting), or it can take on more severe proportions, such as that found in patients with impaired glu-
The purpose of this review is to examine the role of skeletal muscle in maintaining normal glucose homeostasis and in enhancing insulin’s action to promote the uptake and disposal of glucose. We discuss how skeletal muscle resistance to insulin-stimulated glucose transport is induced in a number of clinical conditions commonly encountered by physical therapists. Lastly, we summarize and review selected aspects of an appropriate exercise prescription, mainly for patients with IGT or NIDDM who are insulin resistant, and other factors that may influence glucose utilization by individual muscle(s) or the whole body.

Much of the discussion in this review is based on animal research. Our understanding of insulin action in normal and insulin-resistant states has been advanced tremendously by animal research. Although results from animal research can often be applied qualitatively to humans, quantitative differences (eg, in precise magnitudes or in the time course of events) often exist between animal studies and situations in humans. Exercise effects on adipocyte insulin action, liver metabolism, and pancreatic insulin secretion are beyond the scope of this review.*

### The Role of Skeletal Muscle in Glucose Homeostasis

Before addressing the importance of physical activity in maintaining glucose homeostasis, we will discuss the role of skeletal muscle in glucose metabolism and define some essential terminology. First, we will review the regulation of blood glucose. Next, we will describe the pathways for the transport of glucose into skeletal muscle. Finally, we will discuss the pathophysiology of insulin action in skeletal muscle and its contribution to disturbances of whole-body glucose metabolism.

### Regulation of Blood Glucose Levels

Blood glucose levels are ordinarily controlled within a very narrow range over a 24-hour period.1 In any nondiabetic population in the fasted state, blood glucose values generally vary between 3.4 and 6.2 mM (60-100 mg/dL). Although there may be some variations, several studies suggest that, within any given individual, normal blood glucose levels in the postabsorptive state (ie, the period between meals in which energy must be supplied by the body’s endogenous fuel stores) are strictly maintained within ±0.3 mM (5 mg/dL).2-3 Even postprandially (ie, after a meal), blood glucose concentrations increase only 1 to 2 mM, and rarely, if ever, exceed 7.8 to 8.4 mM (140-150 mg/dL).2 This strict maintenance of glycemia is normally achieved by a complex set of interactions between hormones that act in a coordinated fashion primarily on the liver, pancreatic β-cells, and skeletal muscles.4 Insulin-mediated glucose uptake and utilization by peripheral tissues (primarily skeletal muscle) play a pivotal role in these coordinated efforts to maintain normal glucose homeostasis (Table).

The maintenance of glycemia is dependent on the sensitivity of skeletal muscles to the actions of the polypeptide hormone, insulin. In the basal state, the pancreas normally secretes about 25 ng · kg⁻¹ · min⁻¹ of insulin.5 In the non-insulin-resistant state, fasting insulin levels may vary from 5 to 20 μU/mL.6 Postprandial levels may increase severalfold, with peak values reaching 100 μU/mL or higher.5-6 Insulin acts to promote the transport and disposal of glucose in insulin-sensitive peripheral tissues, specifically striated muscle and adipose tissue. Quantitatively, skeletal muscle is responsible for the vast majority of insulin-mediated glucose disposal.3-7-9 Insulin’s effects on the liver (eg, inhibition of hepatic glucose production from smaller precursors, or gluconeogenesis, and inhibition of glycogen breakdown, or glycogenolysis) also act to maintain euglycemia (normal blood glucose levels).

Under most conditions, the uptake and utilization of glucose by peripheral tissues is tightly balanced by hepatic glucose production and output, so as to strictly regulate glycemia while meeting fluctuating metabolic requirements. The rapid sensing of elevated glucose levels, subsequent increase in insulin secretion by β-cells, and insulin-mediated glucose transport and disposal into peripheral...
tissues are all critical steps for lowering blood glucose levels after a meal and establishing glucose homeostasis. It is not surprising that defects in all three sites (pancreas, liver, and skeletal muscle), singularly or collectively, have been implicated in conditions characterized by abnormal glucose homeostasis (eg, in NIDDM).4

The recognition that skeletal muscle can develop resistance to the actions of insulin has important consequences for physical therapists. Though rarely considered and even less often assessed, skeletal muscle insulin resistance is very prevalent in patients seen by physical therapists. Insulin resistance occurs after short periods of muscular inactivity, in denervation, or after inactivity due to bed rest. Most commonly, the insulin resistance is localized to individual muscles or small muscle groups, resulting in negligible effects on whole-body glucose metabolism. Disturbances in whole-body glucose homeostasis, however, may occur if insulin resistance develops in a large proportion of the muscle mass.

In conditions such as insulin-dependent diabetes mellitus (IDDM, or type I diabetes mellitus), NIDDM, and IGT,5 skeletal muscle insulin resistance contributes significantly to the overall disturbances in glucose homeostasis.3,4,10 Insulin resistance develops in obesity11 and is currently considered a prominent feature of chronic diseases such as hypertension, dyslipidemia, and atherosclerotic cardiovascular disease.12,13 For this review, however, we will focus on the insulin resistance that may occur in specific muscle groups and in patients with NIDDM and IGT, because we believe these individuals represent the majority of patients with insulin resistance seen by physical therapists.

**Glucose Transport Into Skeletal Muscle**

**Insulin-stimulated glucose transport.** The transport of glucose into skeletal muscles is the initial, and under many physiological conditions the rate-limiting, event in glucose metabolism (ie, the slowest step in the pathway that limits the overall rate of muscle glucose metabolism).14 Therefore, glucose transport is an event of major regulatory importance, as well as of potential disturbance, in glucose homeostasis. Despite the fundamental importance of skeletal muscle glucose transport, only recently have we begun to appreciate the complex molecular events leading to glucose entry into mammalian muscle cells. It has been recognized for decades that glucose entry, utilization, and disposal in resting skeletal muscles are greatly enhanced by insulin. The sequence of molecular events leading to insulin-mediated glucose transport is initiated at the muscle cell membrane by the binding of insulin to its plasma membrane receptor.15 Immediately upon binding, the insulin-receptor complexes internalize by receptor-mediated endocytosis to initiate several intracellular sequences of events, one of which is to facilitate glucose transport into skeletal and cardiac muscle and adipose tissue.

In the early 1980s, it was discovered that insulin rapidly mobilized carrier proteins from an intracellular pool and shuttled them to the plasma membrane.16,17 These carrier proteins allow glucose to be transported across the cell membrane, where it is rapidly phosphorylated by intracellular enzymes and used according to the cells' metabolic requirements. Soon after, a family of glucose transporter proteins was identified.18,19 The members of this family, which are specifically expressed in different tissues, are referred to as isoforms (ie, proteins that are similar, but not identical, in their amino acid sequences). The subtle differences in chemical composition allow for differences in functions between family members. Glucose transporter isoforms differ in properties such as their maximal rates of glucose transport, their ability to bind glucose, and the regulation of their activity by various hormones.19

Skeletal muscles contain at least three different isoforms of the glucose transporter. The GLUT1 isoform is a minor isoform that is located in perineural tissue and within muscle cells.20,21 The GLUT1 isoform's function is currently under debate, but it may mediate basal (ie, insulin- and contraction-independent) glucose transport.19 The presence of a GLUT5 isoform in skeletal muscle has recently been demonstrated.22 The GLUT5 isoform is present in low concentrations, and its function is unknown; it may actually be the major transport protein for fructose.22

The primary isoform, located almost exclusively in striated muscle and adipose tissue, is GLUT4.23-25 Insulin stimulates the rapid "translocation" of GLUT4, that is, the movement of GLUT4 proteins from intracellular membrane pools (inactive storage sites) to their sites of insertion into the plasma membrane.26,27 Once inserted into the plasma membrane, the transporters mediate glucose entry into the cell's interior. Many unanswered questions remain regarding the specific molecular events that occur between insulin binding and insertion of transporter proteins into the plasma membrane.

**Contraction-stimulated glucose transport.** Glucose transport in skeletal muscles can be activated by factors other than insulin. Muscle contractile activity itself is capable of stimulating glucose transport independently of insulin.28-30 Evidence for the existence of a contraction-activated pathway has been provided by a variety of experimental approaches, including the hind-limb perfusion technique and the incubation of isolated skeletal muscles. Increases in glucose transport can be induced by a bout of

---

exercise,31,32 by stimulation of muscles in situ,33 and by stimulation of isolated muscles in vitro.28,34 In addition to contractile activity, this pathway can be activated by hypoxia.35

Support for the existence of separate pathways comes from numerous studies demonstrating additivity of the maximal effects of insulin and exercise.28,31,32,34,36 That is, after glucose transport activity has been stimulated by a maximally effective concentration of insulin, increasing the insulin concentration further results in no greater increase in glucose transport activity. If an exercise stimulus is superimposed on the insulin stimulus, however, glucose transport can be further increased. Similarly, maximal effects of insulin and hypoxia are additive.35 In contrast, maximal hypoxic stimuli are not additive with effects of exercise or contractile activity.35 These findings suggest that muscle contractions and hypoxia activate a common pathway for glucose transport that is distinct from that stimulated by insulin.

The existence of a separate pathway from insulin for activating glucose transport has obvious functional consequences. Insulin released following a meal will stimulate glucose uptake into all skeletal muscles (albeit with magnitudes that differ among muscles). This glucose uptake is in accordance with insulin’s anabolic role for promoting energy storage. The presence of a contraction-mediated pathway allows for a selective increase in glucose uptake during exercise into working muscles.

The sequence of events by which muscle contractions and hypoxia stimulate glucose transport is incompletely understood. A great deal of indirect evidence, however, suggests that this pathway is activated by an increase in intracellular calcium (Ca++). Agents that increase intracellular Ca++ concentration stimulate glucose transport37-40 and inhibitors of sarcoplasmic reticulum Ca++ release prevent the activation of glucose transport.39,40 In contrast, insulin-stimulated glucose transport does not appear to be mediated by increases in intracellular Ca++.39,41

Although the events that initiate the activation of glucose transport through the insulin and contraction/hypoxia pathways are different, late steps in these pathways may be the same. Like insulin, contractile activity and hypoxia are known to stimulate the translocation of GLUT4 proteins from intracellular compartments to the plasma membrane.42,43 Whether insulin and contractions/hypoxia act on the same or different intracellular pools of transporters is not known.

Studies44,45 have demonstrated that maximal glucose transport varies between different muscles in proportion to the total concentration of GLUT4 protein. One recent study, examining skeletal muscles of different fiber type compositions, demonstrated that the relative contributions of the contraction/hypoxia and insulin pathways to total glucose transport activity differ between muscles.44 The significance of this finding is not fully apparent, but may indicate that muscles can regulate the activities of these two pathways in accordance with differing functional requirements.

**Skeletal Muscle as a Major Site of Insulin Resistance**

Historically, the contribution of skeletal muscle to glucose homeostasis in the postabsorptive and postprandial states has been underestimated. In large part, this has been due to the widespread belief that the maintenance of glycemia was the exclusive function of the liver.46 Also, until just over a decade ago, insulin deficiency resulting from pancreatic β-cell defects was still considered the primary pathogenetic factor responsible for the insulin resistance of NIDDM.3

Nearly 90% of insulin-mediated glucose uptake occurs in peripheral tissues rather than in the splanchnic bed (gut and liver).4 Skeletal muscle comprises 40% to 50% of the total body mass; therefore, it is quantitatively the major tissue responsible for insulin-dependent glucose utilization.4,8,9 Estimates of the total glucose uptake in adipose tissue are uniformly low (typically less than 5%).7,8,47 Furthermore, the overwhelming majority of glucose entering muscle cells in the postabsorptive state is stored as glycogen.48,49 Both the rate and extent of insulin resistance in skeletal muscle is now recognized as a prominent feature of NIDDM and perhaps several other chronic diseases.10,12 This belief is based on various observations. First, abnormally high circulating levels of insulin in the blood (ie, hyperinsulinemia) fail to maintain blood glucose levels, resulting in hyperglycemia. Second, studies with animal models of diabetes and humans with NIDDM or IGT have directly demonstrated the existence of skeletal muscle insulin resistance.13

Insulin resistance has been defined by the concentrations of insulin that are required to produce a desired biological response, such as the uptake of glucose into insulin-sensitive tissues.50 Studies have shown that insulin resistance can be present in the liver, adipose tissue, and skeletal muscle, though adipose tissue appears quantitatively less important than the liver or skeletal muscles.4

The concept of insulin resistance can be visualized by examining hypothetical dose-response curves for insulin action (Figure).50 The Figure shows that higher concentrations of insulin are needed to produce the same level of glucose transport when muscles are insulin “resistant.” When slightly higher physiological concentrations of insulin are needed to promote the same level of glucose transport, but maximal responses are still obtained, the muscle has decreased sensitivity to insulin action. When maximally effective concentrations of insulin result in diminished rates of glucose transport, however, the muscle has decreased responsiveness to insulin action.
Increased responsiveness

Normal

Increased sensitivity

Decreased responsiveness

Decreased sensitivity

LOG MOLAR INSULIN CONCENTRATION

MAXIMUM SKELETAL MUSCLE GLUCOSE TRANSPORT (%)

Figure. Hypothetical dose-response curves depicting resistance to insulin-stimulated glucose transport in skeletal muscle (rightward-shifted curves) and enhancement of insulin-stimulated glucose transport (leftward-shifted curves) from the "normal" curve. (Adapted from Kahn with permission from WB Saunders Co.)

Therefore, any rightward shift in the hypothetical normal curve will indicate a state of insulin resistance. Furthermore, any leftward shift in the curve signifies an enhancement of insulin action, in which less insulin produces the same or a greater biological response. The most common clinical indication of enhanced insulin action is enhanced glucose disposal with lower plasma insulin levels during a standard oral glucose challenge. Similarly, hyperglycemia in the presence of hyperinsulinemia identifies individuals exhibiting insulin resistance, and clearly characterizes the majority of individuals with NIDDM and IGT.

The presence of hyperglycemia or hyperinsulinemia, either alone or in concert, cannot precisely identify which tissue(s) are sites of insulin resistance, or which metabolic event is the primary pathogenic event. There have been numerous attempts to define the precise location and metabolic event(s) leading to insulin resistance in skeletal muscle. Defects could potentially occur in any one (or combinations) of the three general sites: prereceptor, receptor, or postreceptor. Prereceptor disturbances include defects prior to insulin-receptor binding such as circulating insulin antibodies or a defective insulin molecule. Receptor defects involve disturbances in insulin-receptor binding. Throughout the 1970s and early 1980s, numerous reports described decreases in the number or the affinity of receptors for insulin. These decreases diminish insulin binding and could potentially result in insulin resistance. Although prereceptor and receptor defects have been documented and contribute to some conditions of insulin resistance, the general conclusions from these studies are that the defects observed are not severe enough to account for all the disturbances in insulin action. Furthermore, the prevalence of prereceptor and receptor defects underlying clinical insulin resistance is low.

Recently, impairment of postreceptor events has been directly and indirectly implicated as a cause of insulin resistance. In skeletal muscle, the signaling and translocation of GLUT4 transporters to the sarcolemmal membrane may contribute to insulin resistance. Any defect in the expression, translocation, or intrinsic activity (average rate of membrane-transporting activity) of GLUT4 transporter proteins could potentially result in disturbances in glucose transport. Recent studies have demonstrated decreases in rodent skeletal muscle GLUT4 protein concentration in streptozotocin-induced diabetes. Furthermore, the diabetic state may affect fast-twitch muscle fiber types more than others, implying more selective defects in GLUT4 transporters in certain muscle fiber types. Muscles comprising predominantly fast-twitch glycolytic muscle fibers are known to possess lower GLUT4 protein concentrations. Although more recent data from humans demonstrate that total GLUT4 protein concentration is not significantly altered in NIDDM, impairment of the GLUT4 protein translocation process (decreased translocation efficiency) most likely contributes significantly to skeletal muscle insulin resistance and NIDDM.

Of practical relevance to physical therapists, among others, are recent reports that exercise training increases GLUT4 transporter concentration. The increase in the number of
proteins available for translocation, assuming a fixed percentage of GLUT4 proteins are available for translocation, may be the major mechanism underlying the observed improvements in glucose metabolism after exercise training. This possibility needs to be tested in future studies. An additional possibility is that exercise training of persons with diabetes could reverse the impairment in translocation efficiency.

**Regulation of Skeletal Muscle Glucose Transport by Activity and Inactivity**

Glucose transport into skeletal muscle is not a static process proceeding continuously at the same rate. Transport activity can be modulated acutely (ie, minutes to hours) by changes in the hormonal environment (eg, secretion of insulin after a meal) or by sudden changes in the level of physical activity. The glucose transport process also adapts to chronic changes in physical activity, for example, during prolonged bed rest or following a regular program of exercise (ie, training). In this section, we will discuss responses to specific alterations in physical activity.

**Inactivity**

Physical inactivity leads to a reduction in glucose tolerance.55-68 Bed rest is the primary model used for examining effects of inactivity of large muscle masses in humans. Bed rest or whole-body inactivity results in decreased whole-body insulin-mediated glucose disposal,69-72 which is due in large measure to impaired insulin-mediated skeletal muscle glucose disposal.71-73 The effects of inactivity are rapidly manifested. Peripheral insulin resistance is evident within just 3 days of absolute bed rest.74 In obese individuals, who were already insulin-resistant with compensatory hyperinsulinemia, 4 days of bed rest led to a further reduction in glucose tolerance.75 Insulin resistance appears to progress further with increasing duration of bed rest.67

The mechanism for the reduction in skeletal muscle insulin action with physical inactivity has been partially explained. The development of insulin resistance following bed rest appears to be independent of diminished gravitational stress, as evidenced by the finding that immobilization in the upright position also results in peripheral resistance.74 Furthermore, the effect of inactivity on skeletal muscle insulin action is not due to increases in hormones or metabolites that antagonize insulin action.69,72,73 Evidence suggests that the reduction in insulin-mediated glucose disposal following inactivity is due to a postinsulin receptor defect.

The reduction in glucose tolerance during bed rest is not associated with changes in insulin binding, at least in circulating monocytes.70,75 This finding is in accord with the results from immobilization studies. Inactivity results in decreased skeletal muscle insulin responsiveness,71,72 a condition associated with a postbinding defect.54,55 Studies in rats have shown that the decrease in skeletal muscle glucose uptake is due, at least in part, to a reduction in glucose transporter concentration.71 Future research should attempt to identify the specific transporter isoforms that are decreased following physical inactivity (cf, the effects of denervation).

Ambulation following a period of bed rest has long been known to improve glucose tolerance.55-67 The time required to normalize glucose tolerance depends on the amount of activity undertaken during the reambulation phase, as well as the duration of inactivity. In one study using 2 weeks of bed rest followed only by ambulation, without additional exercise, insulin action remained greatly diminished after 1 week of recovery and only partly restored by 2 weeks of recovery.75 Two studies using bed rest of 3 weeks or less followed by walking programs during the reambulation phase demonstrated a normalization of glucose tolerance to pre-bed-rest levels within 1 week of beginning ambulation.65,74 Thus, the addition of the exercise program during the reambulation phase accelerates the recovery of insulin action. When individuals are active during the bed-rest period, deterioration in glucose tolerance can be significantly diminished but not completely prevented.74,76 This effect may be independent of the type of exercise performed (eg, isotonic versus isometric) but is proportional to the total caloric expenditure.76 To completely prevent the hyperinsulinemia that develops during 2 weeks of bed rest, Dolkas and Greenleaf66 have calculated that at least 1,000 kcal of supplemental exercise must be expended per day. This amount of energy expenditure may be impractical in most clinical situations; however, lesser amounts of exercise could be encouraged.

**Immobilization**

In vitro77,78 and in vivo79,80 studies have shown that limb immobilization results in skeletal muscle insulin resistance for glucose uptake and glycogen synthesis. The impairment in glycogen synthesis is due to at least two factors: (1) impairment of insulin's ability to stimulate glycogen synthase activity and (2) reductions in the supply of glucose secondary to a decrease in transport activity.78 In humans, 1 week of lower-extremity casting combined with the use of crutches during non-weight-bearing ambulation resulted in a reduction in insulin-stimulated glucose uptake in the immobilized limb.80 Studies with animal models have demonstrated that insulin resistance for glucose transport can occur within the first day or two of immobilization.78,79 In mice that have had their hindlimbs casted, reductions in glucose transport have been noted within as early as 6 hours following immobilization; however, it is not clear whether the impairment in the early phase of this immobilization model is partly due to a stress response, with its accompanying increase in glucocorticoid concentrations.79 The insulin resistance observed within 1 day of immobilization was not due to a decrease in insulin binding or activity of the enzyme hexokinase (which phosphorylates glucose immediately after entry into
skeletal muscle); instead, a decrease in insulin responsiveness suggested a postbinding defect.78 Thus, inactivity leads to insulin resistance regardless of whether a large proportion of the body's musculature is inactive or whether the inactivity is localized to a small muscle mass.

In situations in which a small muscle mass is immobilized, glucose tolerance would not be expected to be impaired. Clinicians should recognize, however, that in addition to recovering strength, flexibility, and endurance in previously immobilized muscles, there needs to be a restoration of insulin-stimulated glucose transport and glycogen synthesis. The ability to replenish glycogen stores will in turn enhance muscle endurance performance in recovering muscles. Studies with animals suggest that exercise protocols that develop endurance would be sufficient to restore glucose transport activity following immobilization. Future research should be directed toward determining whether such exercise protocols will restore glucose transport activity following inactivity in humans.

**Denervation**

Denervation is known to induce severe insulin resistance for glucose uptake in skeletal muscles 81-84 In animal models, the onset of insulin resistance can be very rapid, with a reduction in glucose transport evident as early as 3 to 6 hours after denervation.82,84 The resistance continues to progress over the next several days.82,83 Insulin resistance can develop in fast-twitch and slow-twitch muscle fibers82 and also involves impairment of glycogen synthesis.82,83

The mechanism by which denervation decreases glucose transport appears to be complex. Analogous to the effect of immobilization, the initial defect induced by denervation is not mediated by a decrease in insulin binding,82,86 although this may occur following a prolonged period of denervation,80 nor is it due to an inability to phosphorylate glucose.82,83 A reduction in insulin responsiveness strongly implicates a postreceptor defect, as suggested by Burant et al.82 Furthermore, although most investigators have focused on the insulin pathway, denervation also results in reduced activity of the contraction-stimulated pathway for glucose transport.85 Initially, resistance to stimulated glucose transport occurs in the absence of changes in the concentration of GLUT4 protein,85,87 suggesting that the initial defect involves some aspect of the translocation process or more proximal steps in the signaling pathways.82,86 Within 3 days after denervation, however, GLUT4 concentration decreases; this reduction in GLUT4 protein may be responsible for the further deterioration in insulin action measured several days after denervation.85,87

**Single Bout of Exercise**

Exercise has different effects on skeletal muscle glucose transport activity depending on whether one is examining (1) the effects of a single bout of exercise in the untrained state or (2) the effects of repeated bouts of exercise (ie, exercise training). These two circumstances will be discussed separately. Unless stated otherwise, results from experiments using nondiabetic animals or individuals are presented.

A single bout of exercise has several effects on the transport of glucose into skeletal muscle. One effect is to directly stimulate glucose transport via the muscle contraction/hypoxia-activated pathway (ie, an enhancement of glucose transport activity measurable in the absence of insulin). A second effect is to enhance the insulin-stimulated pathway for glucose transport. These two effects of exercise have different time courses. The increase in transport activity measured in the absence of insulin generally reverses within a few hours after cessation of exercise.82,88 The increase in insulin action becomes apparent after the increase in glucose transport, measured in the absence of insulin, has partially or completely worn off.82,83,89,90

Individual bouts of endurance exercise of moderate intensity and 0.5 to 2 hours' duration increase insulin action in animals and in humans. Using a variety of different model systems (eg, in isolated muscles,82,91 in the perfused rat hindquarter,92 and in vivo93,94), a single bout of exercise increases insulin sensitivity and can also enhance insulin responsiveness for glucose transport. The exercise-induced increase in insulin responsiveness, however, persists for much shorter time periods than does the increased insulin sensitivity.90

When muscles are removed from the body and stimulated to contract in a defined incubation medium consisting of salts, glucose, and an appropriate buffer to maintain pH, glucose transport activity measured in the absence of insulin is enhanced to the same extent as that measured when muscles are removed after a bout of exercise.54,95 In contrast, when muscles are stimulated to contract in the same medium, insulin-stimulated glucose transport is not enhanced.95 These findings suggest that some factor(s) normally present in vivo is (are) required for the increase in insulin action that is induced by a single bout of exercise. This factor is not required for activation of the contractile activity/hypoxia pathway.28,34,35,94 Taken together, the experimental evidence reinforces the notion that a bout of exercise has two distinct effects on skeletal muscle glucose transport: (1) It activates the muscle contraction pathway, and (2) after a delay, it enhances the insulin-activated pathway.

The factors required for the exercise-induced increase in insulin action may be humoral factors or substances released from nerve terminals, such as sympathomimetic agents. When muscles from sedentary animals are stimulated to contract in situ, however, insulin sensitivity is increased by contractions.33 This finding suggests that changes in humoral factors (eg, changes in hormone concentrations) that normally occur during exercise are not necessary for the enhancement of insulin sensitivity. An important area of future research is to iden-
identify the essential factor(s). Insulin itself does not appear to be the factor, because one study has suggested that a permissive amount of insulin (i.e., a concentration of insulin that is not responsible for the effect by itself, but that must be present for exercise to exert its effects) does not need to be present during muscle contractions for the subsequent enhancement of insulin action.

Whatever the factor(s) required for the exercise-induced increase in insulin action, once this process has been activated, it can persist even in the absence of humoral or other factors present in vivo. When muscles are removed from animals immediately after exercise and then incubated in vitro for 3 hours before the measurement of glucose transport activity, insulin sensitivity is still greatly enhanced compared with that measured in muscles from sedentary rats.

Enhanced glucose uptake after exercise is not restricted to the insulin-stimulated pathway for glucose transport. A single bout of exercise also augments the effect of a subsequent submaximal hypoxic stimulus. This finding suggests that a prior bout of exercise also enhances the ability of muscle to subsequently activate glucose transport via the contractile activity pathway.

**Factors regulating reversal of enhanced insulin sensitivity after a single bout of exercise.** Maintenance of enhanced insulin action after a single bout of exercise is inversely related to the carbohydrate composition of the diet. When animals are fasted or fed a carbohydrate-free diet after a bout of exercise, insulin sensitivity remains markedly enhanced for at least 2 days. In contrast, with a carbohydrate-rich diet, the increase in insulin sensitivity reverses to values characteristic of the sedentary state between 3 and 18 hours after cessation of exercise.

The relationship between dietary carbohydrate content and reversal of enhanced insulin sensitivity can be understood by considering the effect of diet on muscle glycogen levels. Studies performed more than 25 years ago demonstrated that a single bout of glycogen-depleting exercise results in replenishment of glycogen stores to levels greater than those measured in the sedentary state (glycogen supercompensation). Carbohydrate loading to "supercompensate" muscle glycogen stores in individuals competing in long-distance events is a technique widely used.

More recent studies examining glucose transport have provided an explanation for this phenomenon. In muscles from animals deprived of carbohydrate after exercise, in which insulin action remains augmented, muscle glycogen levels remain far below the supercompensated level. Insulin action returns completely to values seen in sedentary rats only under conditions in which muscle glycogen stores are supercompensated. These findings suggest that the increase in insulin sensitivity after exercise, coupled with an adequate source of carbohydrate, is an important factor contributing to muscle glycogen supercompensation.

Studies examining the effects of dietary manipulation on insulin action after exercise cannot discriminate between a direct effect of carbohydrate uptake into muscle or indirect effects of carbohydrate feeding. When muscles are incubated in the absence of carbohydrates after exercise, insulin action remains greatly enhanced relative to that measured in muscles from sedentary rats. In contrast, incubation of muscles with glucose in the presence of insulin results in reversal of the enhanced insulin sensitivity. This finding suggests that glucose in combination with low concentrations of insulin can directly regulate the reversal of enhanced insulin sensitivity. Furthermore, the signal by which glucose and insulin down-regulate the elevated insulin sensitivity after exercise appears to be generated during intracellular metabolism of glucose rather than during the actual transport of glucose across the cell membrane. Thus, these studies provide an explanation for the mechanisms underlying the utility of the carbohydrate loading technique.

**Exercise Training**

Studies using animal models have demonstrated that endurance exercise training increases glucose transport into skeletal muscle. Exercise training increases insulin responsiveness and maximal glucose transport elicited by the combined stimuli of insulin and muscle contractions. Studies have shown little or no effect of training on basal glucose transport activity. In humans, both cross-sectional studies and longitudinal studies have shown increased insulin action for whole-body glucose disposal in endurance exercise-trained individuals. The training-induced increase in insulin action in humans also occurs in skeletal muscle.

As previously noted, GLUT4 makes up the vast majority of skeletal muscle glucose transporters. The GLUT4 concentration is closely correlated with maximal glucose transport capacity in different skeletal muscles, suggesting that GLUT4 concentration is an important determinant of a muscle's capacity for glucose transport. This relationship led investigators to examine whether the increase in glucose transport activity induced by training might be mediated by an increase in the concentration of muscle GLUT4 proteins. In animals, skeletal muscle GLUT4 protein concentration is increased by several different modes of exercise (i.e., by treadmill training, swimming, and wheel running). In contrast, GLUT1 protein concentration is not altered by exercise training. The increase in GLUT4 concentration is specific for muscles utilized during training activity and does not occur in response to a single bout of exercise. Studies utilizing isolated muscles have demonstrated that the relative training-induced enhancement of maximal glucose transport activity is directly proportional to the increase in GLUT4 protein concentration.
Thus, endurance exercise training, which increases the concentrations of enzymes involved in carbohydrate metabolism, also increases maximal insulin-stimulated glucose transport, total glucose transport capacity, and GLUT4 protein concentration. Furthermore, these increases can occur in the absence of any changes in muscle fiber type composition. Recent cross-sectional studies in humans have shown increased skeletal muscle GLUT4 protein concentrations in the trained state.

In most studies of the effects of training on glucose transport and GLUT4 protein concentrations, muscles containing predominately fast-twitch fibers were examined. A recent study demonstrated that treadmill and swimming exercise increase glucose transport and GLUT4 protein concentration in the soleus muscle, which is composed of predominately slow-twitch fibers. In this regard, it is interesting that a previous study utilizing wheel running found no increase in soleus muscle glucose transport activity or GLUT4 protein concentration when normalized to muscle mass. Wheel running is unique in that it induces hypertrophy of the soleus muscle, perhaps as a result of the stretch on this muscle during activity periods. Wheel running induced an increase in total glucose transport and total GLUT4 content in the soleus muscle, suggesting that glucose transport increases only in proportion to the increase in muscle mass. These results suggest that the induction of an increase in GLUT4 protein concentration by endurance exercise is inhibited by the presence of an accompanying hypertrophic stimulus. Muscles that do not undergo hypertrophy in response to wheel running show increases in glucose transport activity and GLUT4 protein concentration.

Further investigation is required to determine whether this relationship holds true with more conventional stimuli for muscle hypertrophy such as weight training. Few studies to date have examined the effects of weight training on glucose homeostasis. One recent study, however, suggested that repeated participation in activities involving a relatively high number of weight-lifting repetitions may improve glucose tolerance. The mechanism for the improvement in glucose tolerance is not known, but may be related to the increase in total muscle mass available for glucose disposal.

An apparent contradiction in the literature is that not all training studies in animals and humans have shown increases in all indexes of glucose homeostasis. One reason for many of these negative findings is probably that, in the absence of a significant reduction in body fat content, the effects of exercise training on glucose transport activity persist for only a few days. Initially, investigators assumed that training effects on glucose transport would persist for several weeks or even months, analogous to the effects of training on oxidative enzymes. The glucose transporter proteins, however, may have much shorter half-lives than the oxidative enzymes, resulting in a much faster loss of activity following cessation of training. Indirect evidence for this comes from detraining studies that have shown a deterioration of insulin action within 1 week after cessation of exercise (see "Detraining" section). The implication of these findings is that exercise must be performed on a regular basis in order to sustain beneficial effects on glucose disposal.

Utilization of blood glucose in the trained state. The effects of endurance training to increase maximally stimulated glucose transport activity as described might seem to be in contradiction with the well-known ability of exercise training to induce a shift toward greater fat utilization during exercise. Endurance training is known to reduce reliance on carbohydrates as an energy source during submaximal exercise. Training decreases the turnover of not only endogenous glycogen stores but also the turnover and oxidation of blood glucose.

This apparent contradiction can be understood by distinguishing between effects of training manifested at rest versus those manifested during exercise. During the intervening periods between exercise bouts, the training-induced increase in insulin-mediated glucose transport activity results in an enhanced ability of previously exercised muscles to replenish glycogen stores. When measured during exercise of the same absolute exercise intensity, however, the utilization of blood glucose and muscle glycogen is lower in the trained state, which in turn spares liver as well as muscle glycogen stores from excessive depletion. Thus, the training-induced increase in glucose transport activity evident at rest either is not manifested during exercise or is overridden by factors that shift the rate-limiting step for glucose uptake to some subsequent step in glucose metabolism.

Both effects of training act to minimize net reductions in muscle glycogen, improving the ability of individuals to tolerate repeated bouts of exercise.

Detraining

In well-trained individuals, 10 days of inactivity has been shown to result in a deterioration of glucose tolerance, with a concomitant increase in the plasma insulin response to oral glucose. Studies have also demonstrated that relatively short-term detraining (5–14 days) results in increased insulin secretion in response to a standardized glucose load and to a reduction in whole-body insulin-mediated glucose disposal. In one study, insulin action was greatly diminished just 5 days after the last bout of exercise. The reduction in whole-body glucose disposal after detraining is due in large measure to impaired insulin-mediated glucose disposal in skeletal muscle. Exercise training has several effects on glucose tolerance and insulin action. The first of these effects are mediated by the relatively rapid effects of acute exercise and exercise training on insulin sensitivity and responsiveness, as previously discussed. In addition, long-term exercise results in a reduction in body fat, particularly in central adiposity, which
most likely leads to an additional improvement in insulin action. This latter effect of exercise training is very important in the management of glucose intolerance in obese individuals, particularly those with NIDDM. Short-term detraining, which does not alter body fat, would be expected to result in loss of the rapid effects of exercise on glucose metabolism, but not in loss of longer-term adaptations resulting from reductions in central adiposity.

**Muscle Damage and Insulin Resistance**

Certain types of exercise, particularly those that involve eccentric contractions, can lead to muscle damage. Indexes of damage include muscle soreness, decreased range of motion, inflammation, and elevations in serum creatine kinase activity. Other studies have shown that exercise that induces muscle damage is also characterized by impaired glycogen resynthesis, which can occur in both slow-twitch and fast-twitch fibers. O'Reilly et al. showed that following exercise consisting of eccentric contractions, glycogen resynthesis can be impaired for prolonged periods (at least 10 days with their experimental protocol).

Costill et al. have demonstrated that changes in glycogen synthase activity cannot account for the entire impairment in glycogen resynthesis following eccentric exercise. Recent data indicate that insulin resistance of glucose transport may account for the impaired glycogen resynthesis after exercise that induces muscle damage. Ploug et al. showed that a single prolonged bout of exercise in untrained rats reduced insulin-stimulated glucose uptake in muscles containing high proportions of slow-twitch or fast-twitch muscle fibers. Another study using untrained rats showed a tendency for insulin resistance to develop in soleus muscles after a single 90-minute bout of treadmill exercise. The implication of these findings is that when untrained individuals begin to exercise, they should gradually increase exercise duration and intensity to avoid inducing muscle damage and the accompanying insulin resistance.

Kilman et al. recently examined the effects of downhill running in untrained individuals. Downhill running, which resulted in muscle soreness and elevated creatine kinase activity, also reduced the glucose disposal rate by about 40%. Neither hepatic glucose production nor basal glucose turnover was altered by the downhill run. In contrast, cycle ergometer exercise, an activity that did not induce muscle damage, did not induce insulin resistance. This study indicates that insulin-mediated glucose disposal, most likely into skeletal muscle, is impaired by eccentric exercise that results in muscle damage.

Thus, previous reports that exercise with eccentric contractions impairs glycogen resynthesis can be explained by the findings that muscle damage also impairs glucose uptake and disposal. Whether the impairment in glucose uptake can account entirely for the impaired glycogen resynthesis remains to be determined. The implication of these studies is that although most forms of exercise enhance insulin action in skeletal muscle, certain forms of exercise, particularly those that can lead to muscle damage, can actually induce insulin resistance in skeletal muscle. This insulin resistance in turn leads to impaired glycogen resynthesis, which can persist for prolonged periods. Thus, if eccentric contractions are at levels that may induce injury, they should probably comprise a minimal proportion of an individual's total activity pattern. The impairment of glycogen resynthesis that occurs with muscle damage can be partially overcome by ingesting a diet high in carbohydrates, although carbohydrate feeding does not completely offset the effects of muscle damage. Although less well studied, high-intensity, concentric weight training could, in some circumstances, result in muscle damage, especially if the exercise is novel. Therefore, insulin resistance may potentially increase following this form of exercise. The susceptibility for muscle damage may be increased in atrophied muscles, but this possibility needs to be examined.

**Exercise Prescription In Insulin-Resistant Individuals**

We believe there are direct implications regarding glucose uptake and disposal for practicing physical therapists. As a specific example of exercise prescription for the insulin-resistant state, we will discuss conditions of whole-body insulin resistance. Exercise prescriptions for conditions characterized by resistance in isolated muscle groups have not been adequately defined.

The exercise prescription should be thoughtfully constructed to maximize glucose utilization and enhance insulin action, yet minimize any potential risks to the patient. Among other factors, the exercise prescription must consider the severity of the diabetic state. In individuals with poorly controlled diabetes, exercise may actually worsen the diabetic state. An individual's diabetes, therefore, should be well controlled prior to the initiation of any exercise program. In addition, because persons with NIDDM, IDDM, or IGT have a much higher incidence of cardiovascular disease, it is imperative that these individuals be thoroughly evaluated prior to initiating an exercise program. Individual exercise prescriptions should be based on graded exercise test results along with the referring physicians' evaluation of the potential risks associated with exercise. Several important considerations in an exercise prescription for the insulin-resistant individual will be discussed including frequency, intensity, and duration of exercise.

As discussed previously, a growing body of evidence suggests that improvements in glucose homeostasis and insulin sensitivity are diminished rapidly (within a few days) after the last bout of aerobic exercise. If improvements are quickly lost and reversed after as little as 48 to 72 hours without exercise, then the maximum interval between exercise sessions should not exceed 48 to 72 hours.
Although it has not been adequately investigated, daily exercise training could conceivably be of greater benefit; in practice, however, many individuals may find it difficult to comply with a daily exercise regimen. Exercise prescribed on alternate days can be beneficial, assuming that the intensity and duration of exercise are adequate.

Exercise intensity is a critical component of the exercise prescription. The intensity of aerobic exercise must be optimized to induce positive changes, yet minimize potential complications such as hypoglycemia, hyperglycemia, or musculoskeletal injury. Exercise intensities ranging between 60% and 90% of maximal oxygen consumption ($V_{02\text{max}}$) have generally resulted in improved glycemic control in patients with IGT or mild to moderate NIDDM.

The results of these studies suggest that increasing the exercise intensity improves the likelihood of inducing a positive adaptation in glucose homeostasis. Few studies, however, have examined the dose responses for exercise training and adaptations in glucose homeostasis. This is a very important area that needs to be examined in greater detail.

As is common in clinical practice, when prescribing exercise intensity on the basis of age-predicted maximum heart rate or heart rate reserve, note that 60% of $V_{02\text{max}}$ corresponds to approximately 70% of age-predicted maximum heart rate. The therapist, therefore, should prescribe an exercise intensity based on the percentage of maximum heart rate that is high enough to induce positive adaptations in glucose homeostasis.

To enhance insulin’s action on glucose transport and glycogen resynthesis, the prescribed exercise should result in a reduction of muscle glycogen stores. The utilization of glycogen stores in an exercising muscle is directly linked to the intensity and duration of the exercise. In one study, in which bicycle ergometer exercise was performed at an intensity of 83% of $V_{02\text{max}}$, more than half of the stored glycogen was utilized within 1 hour.

As part of exercise prescription, the duration must be considered. Admittedly, less is known about how long exercise must be performed to derive optimal benefits. Because 80% to 90% of all patients with NIDDM have accompanying obesity, the duration of exercise should be long enough to allow a considerable caloric expenditure, which will in turn lead to a reduction in adiposity. A considerable body of evidence suggests that fat loss, independent of exercise, improves insulin action. Recent evidence indicates that reductions in abdominal fat may account for the observed improvements in insulin action following weight loss. Exercise programs that are combined with dieting for fat loss should therefore result in greater improvements in insulin sensitivity than either exercise or weight loss alone. The prescription for the duration of aerobic exercise should consider maximizing the total energy expenditure, because this is the most important factor influencing weight loss and indirectly insulin action.

Durations of as little as 20 to 30 minutes of continuous aerobic exercise have proven beneficial in improving glucose homeostasis, although 40 to 60-minute durations would expend twice as much energy and still be feasible to perform for many individuals on a daily or alternate-day program.

Conclusions

Skeletal muscles have a vital role in maintaining normal glucose homeostasis and in regulating whole-body glucose metabolism. Although rarely considered, skeletal muscle insulin resistance is a common condition in patients seen by physical therapists. Acute muscle contractile activity (exercise) and repetitive endurance exercise (training) appear to improve glucose metabolism through independent pathways for skeletal muscle glucose transport. Given the proper exercise prescription, individuals who are insulin resistant can enhance their sensitivity to insulin action within small groups of skeletal muscles or potentially improve whole-body glucose homeostasis.

More information is required in order to define specific protocols to ameliorate insulin resistance in small muscle groups. For example, it is very important for clinicians to know whether current protocols for improving muscle strength and endurance after inactivity are sufficient to recover glucose metabolism and to define the time course for such changes. Determination of whether protocols for electrical stimulation provide suitable means to ameliorate insulin resistance is also needed. Excessively forceful muscle contractions during the early phase of electrical stimulation could actually exacerbate insulin resistance due to transient muscle damage. In addition, more information is needed regarding the acute and chronic effects of resistance training. Thus, although our understanding of skeletal muscle glucose metabolism has advanced greatly over the past decade, more research is essential for the treatment of specific clinical conditions routinely encountered by physical therapists.

Acknowledgments

Dr Sinacore acknowledges the American Physical Therapy Association’s Section on Research and the Retreat Program Committee, particularly Lynn Snyder-Mackler, ScD, PT, and Stuart Binder-Macleod, PhD, PT, for providing support in the form of a graduate student stipend (to DRS) to attend the research retreat on “Muscle Function in Normal and Pathological States” held August 18-23, 1991, in New Hampton, NH.

References

3 DeFronzo RA, Ferrannini E, Koivisto V. New concepts in the pathogenesis of and treatment...


56 King PA, Horton ED, Hirschman MF, Horton ES. Insulin resistance in the Zucker rat (fa/la) skeletal muscle is associated with a failure of...
Localization of inactivity on tolerance of sugar. Cardiovascular risk factors, hemodynamics, during prolonged bed rest.

Rat Skeletal muscle. 

Seven days of bed rest decrease insulin action primarily in muscle. 

Expression of insulin-regulatable glucose transporter (GLUT-4) gene in human skeletal muscle. 

Evidence against altered expression of GLUT-4 in skeletal muscle of chronically streptozotocin-diabetic rats. 

Horn et al. 

Localization of glucose transporter in skeletal muscle of patients with non-insulin-dependent diabetic patients. 

Bourey et al. 

Expression of GLUT-4 in skeletal muscle of rats with diabetes. 

Richter EA, Buse MG. Insulin resistance of skeletal muscle in patients with obesity or NIDDM. 

Forsayeth JR, Andersen PLysiol., EA, Dela P, Galbo H. Increased glucose responses during bed rest with isotonic and isometric exercise. 

Richter EA, Ploug T, Galbo H. Increased muscle glucose uptake after exercise: no need for insulin during exercise. 

Dietz and physical performance. 

Effects of exercise training on in vivo insulin action in individual tissues of the rat. 

Dietz and physical performance. 

Effects of exercise training on in vivo insulin action in individual tissues of the rat. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Effect of endurance training on glucose transporter expression in rat skeletal muscle. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


Insulin action in trained athletes: association with inactivity during decreased physical activity in man. 

Insulin and glucose responses during bed rest with isotonic and isometric exercise. 

Effects of exercise on insulin action in human thighs after one-legged immobilization. 


