Optimal Exercise Intensity for Individuals With Impaired Glucose Tolerance

David C. Wright, MS, and Pamela D. Swan, PhD, FACSM

Abstract

Impaired glucose tolerance (IGT) is a transitory state between normoglycemia and frank diabetes. One in three individuals with IGT will develop type 2 diabetes within 10 years if left untreated. A strong rationale exists for the implementation of strategies designed to reverse or stabilize the deterioration in glucose homeostasis in individuals with IGT.

Recent physical activity guidelines from the Centers for Disease Control and Prevention and the American College of Sports Medicine have suggested that intermittent moderate-intensity exercise is beneficial and can improve the health status of these individuals. Specifically, the guidelines recommend that every American should accumulate 30 min of moderate-intensity physical activity per day.

The current guidelines are based predominantly on epidemiological data, and very little clinical evidence exists that this level of physical activity can significantly improve glycemic status. More intense exercise prescriptions would appear to be needed to improve glucose tolerance and insulin action. Although higher exercise intensity is a key determinant for improvements in glucose homeostasis, it may produce mechanical and oxidative damage that can result in transitory impairments in insulin action and glucose tolerance. Therefore, the optimal exercise intensity for an individual with IGT appears to lie between these two extremes.

The pathogenesis of type 2 diabetes is not fully understood. However, there appears to be an intermediate state between normoglycemia and type 2 diabetes. This transitory condition is known as impaired glucose tolerance (IGT). From a clinical standpoint, the American Diabetes Association has classified IGT as a fasting blood glucose concentration between ~6–7 mmol/l or 110–125 mg/dl.[1]

Those with IGT have a one-in-three chance of developing type 2 diabetes within 10 years. Therefore, a strong rationale exists for the implementation of adjunctive therapeutic modalities designed to stabilize or reverse impaired carbohydrate metabolism in those with IGT.

Exercise is often prescribed as an initial therapy to control elevations in blood glucose. However, guidelines that specifically address the use of exercise in controlling blood glucose in individuals with IGT have not been developed.

Recently, the American College of Sports Medicine (ACSM), the Centers for Disease Control and Prevention (CDC), and the Surgeon General (SG) have issued statements regarding the recommended quantity and quality of exercise required to improve health status.[2] Specifically, they have suggested that every American should accumulate 30 min of moderate-intensity exercise on most, if not all, days of the week. Walking briskly (3–4 miles per hour), gardening, and general home-care activities have been classified as moderate-intensity exercise. From a clinical perspective, the new activity guidelines define moderate intensity as between three and six METS (metabolic equivalents) or ~11–21 ml/kg/min oxygen.

The current activity guidelines are based primarily on epidemiological data that suggest that those who perform 30 min of moderate-intensity exercise per day have lower morbidity and mortality rates than those who are habitually inactive. Leon et al.[3] examined the relationship between leisure time physical activity and the

Address correspondence and reprint requests to: David C. Wright, MS, Human Performance Laboratory, Ball State University, Muncie, IN 47306-0280.

occurrence of coronary heart disease and overall mortality in middle-aged men. During a 7-year follow-up study, they found that moderate amounts of leisure time physical activity were associated with 63% as many fatal coronary heart disease events and sudden deaths and 70% as many total deaths when compared with those who performed low levels of leisure time physical activity. Interestingly, the type of activity that was reported was intermittent in nature. The work of Leon and others[3–6] demonstrates a clear inverse linear relationship between physical activity and morbidity.

Although a wealth of epidemiological data support the current guidelines, little clinical evidence exists that would suggest that intermittent moderate-intensity exercise by itself would be beneficial in improving glycemic status. More intense exercise would appear to offer greater therapeutic benefit to those with IGT than the current recommendations, in part because of the pattern of substrate utilization. The more intense a given exercise session, the greater the reliance on intramuscular glycogen as a fuel source.[7]

Studies utilizing both animal and human models have demonstrated that glycogen depletion may be one of the predominant factors leading to an increased insulin action following exercise cessation.[8–12] The postexercise improvement in insulin action from a functional standpoint is necessary for the replenishment of muscle glycogen levels.

It appears that changes in GLUT4 may be one of the primary variables responsible for improvements in insulin action. GLUT4 is an intracellular protein that moves to the cell membrane in response to both insulin and noninsulin stimuli, such as contractile activity and hypoxia. GLUT4 enables the facilitated diffusion of glucose down its concentration gradient into the cell.[8] Exercise is believed to increase not only the number of GLUT4 proteins on the plasma membrane, but also the intrinsic activity of the transporter.[8] The greater the intensity of exercise, the greater the intramuscular glycogen depletion and subsequently the greater the postexercise GLUT4 concentration and turnover rate resulting in improvements in insulin action and glucose tolerance.

Short-Term Exercise

Traditionally, improvements in the glycemic state following exercise and diet interventions have been associated with training-induced adaptations, such as weight loss and increased aerobic capacity. However, significant improvements in glucose tolerance and insulin action can occur independent of weight loss following exercise interventions as short as 1 week in duration.

Research has indicated that at least a portion of the favorable change in glucose metabolism following exercise may reflect the cumulative effects of the most recent exercise sessions. Several recent investigations have demonstrated that exercise performed in excess of 50 min at ~70–75% of maximum heart rate reserve (MHRR) for 7 consecutive days can improve insulin sensitivity and glucose tolerance by as much as 35% in obese and glucose-intolerant populations.[13–15]

Unpublished observations from our laboratory (Arizona State University) indicate that exercise intensity is a key predicator of improvements in insulin action as measured by a modified short-term insulin tolerance test. Seven consecutive days of exercise performed for 30 min at 70–75% of MHRR resulted in a 36% improvement in insulin action in subjects with IGT, while 1 week of intermittent moderate-intensity exercise did not result in similar improvements.

Further evidence supporting the importance of exercise intensity comes from investigations in which the total caloric expenditure in high- and low-intensity exercise sessions was equal, i.e., eucaloric. Kang et al.[14] found that insulin action increased to a greater extent following high-intensity exercise than it did after a eucaloric low-intensity exercise session. That is, less intense exercise performed for a longer duration, resulting in an energy expenditure equivalent to that of a more intense exercise session, did not result in similar improvements in glucose metabolism in obese subjects.

More intense exercise prescriptions, performed in a semi-acute fashion, can significantly improve insulin action and glucose metabolism. The current guidelines, although not specifically designed to elicit acute changes in health-related physiological variables, do not appear to significantly affect glucose homeostasis after 1 week. The strength of the current recommendations may lie in a preventive role. Chronic, life-long utilization of intermittent moderate-intensity exercise may reduce the incidence of diabetes, obesity, and other diseases thought to be lifestyle-related.

Chronic Exercise Interventions

Numerous chronic exercise interventions have indicated that exercise can result in significant weight loss and subsequent improvements in glucose homeostasis.[16–18] Because of the study designs of many long-term investigations, it is difficult to determine whether improvements in glycemic status are a result of the direct effects of exercise or whether exercise mediates improvements in glucose metabolism through weight loss. In other words, are the benefits derived from exercise because of the "process" (exercise) or "product" (weight loss)? The acute effects of exercise would seem to suggest that the initial improvements in insulin action appear to be the result of an exercise-induced adaptation independent of weight loss, while the long-term improvements may be reliant on both weight loss and acute adaptations.

Exercise is often prescribed as a weight loss modality. Everything else being equal, the more intense the exercise prescription, the greater the caloric cost of the exercise bout. Moreover, the more intense the exercise, the greater the postexercise caloric cost. That is, following exercise cessation, the body's metabolic rate will be elevated, thus increasing energy expenditure. By increasing the intensity of any given exercise, one will increase caloric expenditure not only during exercise, but also following the exercise session. This may affect glycemic status both acutely, through effects independent of weight loss, and chronically by increasing daily energy expenditure and subsequent weight loss if a negative energy balance is imparted.

The current guidelines (ACSM, CDC, and SG) suggest that the accumulation of 30 min of moderate-intensity exercise should result in an energy expenditure of approximately 150–200 kcal daily. When projected chronically, it is unlikely that this would result in significant weight loss unless simultaneous changes in diet also occurred.

Few studies have directly explored the effects of long-term, intermittent, moderate-intensity exercise on glucose tolerance and insulin sensitivity. Snyder et al.[19] reported that after 32 weeks of intermittent, moderate-intensity exercise (10 min, three times/day, 5 days/week, 50–65% maximum heart rate), fasting insulin and glucose levels did not change. Interestingly, Donnelly et al.[20] found that after 18 months of an intermittent exercise program (two times/day, 15 min/session, 50–65% MHRR, 5 days/week), the insulin area under the curve decreased significantly compared with baseline during an oral glucose tolerance test (OGTT) in moderately obese females with slightly elevated fasting glucose levels. Not surprisingly, there were no changes in body composition after the 18 months of training, suggesting that improvements in insulin action occurred independent of weight loss.

These results would seem to suggest that the ACSM/CDC guidelines may be effective in improving insulin action. It should be noted, however, that the intensity of exercise prescribed by Donnelly et al.[20] is much more intense than the recommendations put forth in the current physical activity guidelines.

Little clinical research would seem to support the contention that intermittent, moderate-intensity exercise is optimal for improvements in glucose homeostasis. Further long-term studies using the specific guidelines established by the ACSM, CDC, and other organizations should be completed before any definitive statements are issued regarding the efficacy of this particular form of exercise prescription for individuals with IGT.

Both acute and long-term exercise interventions indicate that the primary determinant of changes in insulin action is exercise intensity. The more intense the exercise stimulus that one prescribes, the greater the acute benefit will be. Moreover, more intense exercise will result in a greater caloric deficit increasing the likelihood of long-term weight loss. The relationship between exercise intensity and the benefits associated with exercise can be best represented by a dose-response curve (Figure 1).

The ACSM and CDC guidelines suggest that the largest relative benefits in health status can be achieved from moving from a sedentary state to one in which moderate-intensity physical activity is employed. Current research would seem to suggest that those with IGT might improve insulin action to the greatest extent by the incorporation of more moderately intense exercise prescriptions.

Contraindications

Research using both chronic and acute exercise has demonstrated that the prescription of relatively intense physical activity can improve insulin action and glucose tolerance in individuals with abnormal carbohydrate metabolism. The prescription of relatively intense exercise (>75% $V_{O_{2max}}$) can, however, lead to transitory impairments in insulin action.

There are several mechanisms that have been postulated to be responsible for the attenuation of glucose tolerance following intense exercise. King et al.[21] demonstrated that after the cessation of a 5-day exercise regimen (45 min/day, 73% $V_{O_{2max}}$), both the insulin and glucose responses to an OGTT were significantly elevated immediately postexercise when compared with baseline. It was hypothesized that the attenuation of glucose tolerance was the result of an elevation in counterregulatory hormones, namely catecholamines. Plasma free fatty acid levels measured during an OGTT were significantly elevated immediately postexercise when compared with a carbohydrate challenge 1 day after the cessation of exercise, suggesting that the hormonal milieu following intense exercise may be contributing to the attenuation of glucose tolerance.

The human body naturally produces oxygen free radicals (O_2, nitric oxide, etc.) as products of aerobic metabolism. Free radicals are highly reactive molecules or fragments of molecules that readily oxidize various tissues of the body, such as cell membrane lipids.[22] The oxidation of cell membrane lipids leads to a series of reactions within the cell membrane called lipid peroxidation. This leads to structural alterations in the cell membrane, which may inhibit cell function.

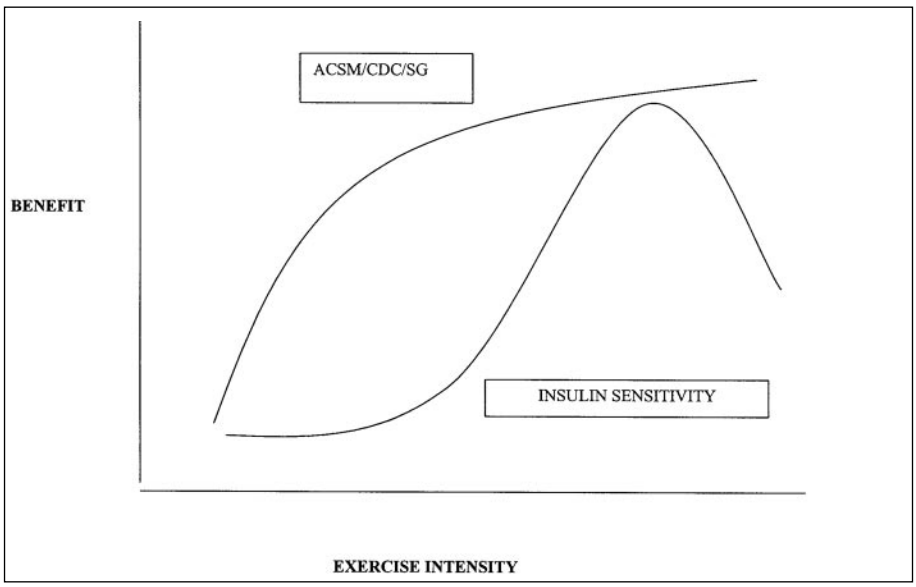

Figure 1. Dose-response curves representing the relationship between excercise intensity and health benefits as proposed by the ACSM/CDC/SG and the hypothesized relationship between exercise intensity and insulin action in individuals with IGT.

During intense exercise, high levels of free radicals are produced, which may result in oxidative tissue damage. Recent research from our laboratory has demonstrated that supplementation with vitamin E, an antioxidant, decreases the attenuation of glucose tolerance following vigorous circuit training exercise (unpublished data).

Evidence exists to suggest that increases in both counterregulatory hormones and free radicals may contribute to the transitory glucose intolerance following intense exercise. Eccentric muscle contractions (forced lengthening of the muscle while under a load) have also been implicated in impairments in glucose tolerance following exercise. Downhill running[23] and resistance training[24] have both been shown to lead to significant increases in creatine kinase, a marker of muscle damage, and subsequent decreases in insulin sensitivity immediately after exercise. Schell et al.[25] found that the insulin response to a glucose load was significantly greater after a single bout of resistance exercise when compared with a single session of treadmill running. These results indicate that the increased eccentric damage associated with resistance exercise leads to the decrease in insulin action.

The intensity of exercise is a key determinant of how an individual may respond to a given exercise regimen in terms of improvements in glucose tolerance. If the exercise intensity is too low, the maximal benefits of exercise will not be realized. Conversely, high-intensity, damaging exercise may lead to a transitory impairment in glucose tolerance and a decrease in the benefit derived from exercise.

Exercise Prescription

Type 2 diabetes is associated with a host of disease states that are contraindicated for exercise. Those with IGT, however, may not suffer from many of the disease complications associated with frank diabetes because of the state of disease progression. Therefore, the prescription of relatively intense exercise may be warranted unless other comorbidities that preclude intense exercise are present.

We hypothesize that 7 days of exercise can lead to significant improvements in insulin sensitivity. However, from a programmatic standpoint, advising one to exercise every day, at least initially, would not be conducive to optimal exercise adherence. Each component of an exercise prescription (frequency, intensity, time, and type) should be designed and evaluated based on the current health status, background, and goals of the individual involved.

Frequency. At the onset of an exercise program, delayed-onset muscle soreness may be a concern, especially at higher intensities. Allowing for adequate recovery between each exercise bout is important not only from a physiological standpoint, but also from a psychological one. Initial exercise prescriptions should encourage activity three to four times per week with 24 h of rest between exercise sessions.

Intensity. As mentioned previously, exercise intensity appears to be the key determinant in improvements in insulin sensitivity. Exercise intensity can be quantified by demonstrating to patients how to measure resting and exercise heart rates and subsequently determining the percentage of maximum heart rate or percentage of MHRR. Although they may be cost-prohibitive, heart rate monitors often simplify the quantification of exercise intensity. Exercise should be performed between 70 and 75% of maximum heart rate.

Time. A tradeoff exists between exercise intensity and exercise duration. The higher the intensity, the shorter the duration of exercise, and vice versa. Thirty to sixty minutes of exercise should be performed continuously. If a patient cannot perform 30 min of exercise continuously, allow a short break before continuing exercise.

Type. The mode of exercise should employ the large muscle groups of the body. Stair climbing, walking/jogging, and stationary cycling are all excellent exercise modalities. Treadmills are especially useful because they enable the intensity of exercise to be controlled by increasing not only the speed of the belt but the incline of the tread as well.

Motivational and Practical Suggestions

Although starting an exercise program may be intimidating for individuals with IGT, there are several key points that can help enhance motivation and maintain interest in a regular exercise program. Changes in insulin sensitivity and glucose tolerance occur rapidly and initially independent of changes in body composition. Patients can receive rapid positive feedback following the initiation of an exercise program. Although an OGTT or other clinical measures of glucose tolerance or insulin sensitivity may be too time-consuming, a simple finger stick to determine the fasting blood glucose concentration can provide positive feedback. Another tool to improve motivation and adherence to exercise is to introduce several modalities of exercise from which the patient can choose. The more forms of exercise to which patients are exposed, the more likely it is that they will find one that fits their lifestyle.

Summary

The CDC, ACSM, and SG have recently advocated the use of intermittent, moderate-intensity exercise. The use of this form of exercise is supported by epidemiological evidence. Those who accumulate 30 min of moderate-intensity physical activity on most, if not all, days of the week will have lower rates of mortality and morbidity than those who are inactive.

If followed at an early age and performed chronically, the guidelines may offer a preventive benefit. However, clinical investigations both chronic and semi-acute do not support the efficacy of the guidelines acting as a rehabilitative modality. Specifically, exercise performed in excess of 70% of maximum heart rate improves insulin sensitivity to a greater extent than intermittent, moderate-intensity physical activity, if performed semi-acutely or chronically.

While there are many disease complications associated with type 2 diabetes that may be contraindicated for vigorous exercise, those with IGT are often free of complications. If contranindications are not present, we recommend that vigorous exercise programs be encouraged for individuals with IGT.

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David C. Wright, MS, is a doctoral research fellow at the Human Performance Laboratory at Ball State University in Muncie, Ind. Pamela D. Swan, PhD, FACSM, is an associate professor in the Department of Exercise Science and Physical Education at Arizona State University in Tempe.