Optimizing the therapeutic benefits of exercise in Type 2 diabetes

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Praet SF, van Loon LJ. Optimizing the therapeutic benefits of exercise in Type 2 diabetes. J Appl Physiol 103: 1113–1120, 2007. First published July 26, 2007; doi:10.1152/japplphysiol.00566.2007.—Other than diet and medication, exercise is considered one of the three cornerstones of good diabetes treatment. Nevertheless, current clinical guidelines on Type 2 diabetes provide no detailed information on the modalities of effective exercise intervention in the treatment of Type 2 diabetes. Based on a review of currently available literature, exercise modalities are being identified to maximize the benefits of exercise intervention in the treatment of different Type 2 diabetes subpopulations. Both endurance and resistance types of exercise have equal therapeutic strength to improve metabolic control in patients with Type 2 diabetes. When applying endurance-type exercise, energy expenditure should be equivalent to ~1.7–2.1 MJ/exercise bout on 3 but preferably 5 days/wk. In sarcopenic or severely deconditioned patients with Type 2 diabetes, focus should lie on the implementation of resistance-type exercise to attenuate and/or reverse the decline in skeletal muscle mass and strength. Before choosing the most appropriate exercise modalities, the patient’s disease stage should be well characterized, and an ECG-stress test should be considered. Based on baseline aerobic fitness, level of co-morbidities, body composition, and muscle strength, patients should be provided with an individually tailored exercise intervention program to optimize therapeutic value. A multidisciplinary individualized approach and continued exercise training under personal supervision is essential to enhance compliance and allow long-term health benefits of an exercise intervention program.

Type 2 diabetes; exercise; energy expenditure; body composition; sarcopenia; neuropathy

ESTIMATES OF GLOBAL DIABETES PREVALENCE and most recent projections for the future indicate that diabetes now affects 246 million people worldwide and is expected to affect some 380 million by 2025, representing as much as 7.1% of the global adult population (58). The increase in Type 2 diabetes prevalence can only partly be attributed to the changing population demographics, since epidemiological data show diabetes prevalence to increase progressively in young and middle-aged people (2). The latter implies that, in the near future, Type 2 diabetes-related complications, like nephropathy, retinopathy, neuropathy, myocardial infarction, stroke, and even death, will be experienced more frequently and at a much earlier age (94). The greater incidence and prevalence of overt clinical complications in a vastly expanding diabetes population will impose an enormous burden on our healthcare system and on the quality of life of the Type 2 diabetes patient (2, 16). Much effort is currently put into the discovery of novel pharmacological solutions that might improve metabolic control and prevent diabetes-related comorbidities. Although intense blood pressure and blood glucose-lowering therapy has been shown to reduce (microvascular) complications in Type 2 diabetes (120, 124), enhanced glycemic control with either sulphonylureas, glitazones, or exogenous insulin therapy does not necessarily prevent the number of cardiovascular events (87, 124).

Apparently, further reductions in glycosylated hemoglobin (HbA1c) levels and blood pressure are needed to improve long-term cardiovascular outcome. The Steno-2 study provides good evidence that this can only be achieved through multifactorial intervention, consisting of both well-structured lifestyle and pharmaceutical measures (46). Also, in populations at risk for developing Type 2 diabetes, it is now well established that increased physical activity levels and long-term weight loss reduce the prevalence of metabolic syndrome (49, 63, 90) and prevent or delay the progression toward Type 2 diabetes (67, 73, 91). In accordance, lifestyle intervention programs consisting of regular exercise with (35, 73) or without (35, 122, 128) dietary modulation and/or oral blood glucose-lowering medication (11, 65) have proven an effective therapeutic strategy in Type 2 diabetes. As such, the current increase in Type 2 diabetes incidence and concomitant cardiovascular comorbidities can only be reversed by dramatic lifestyle changes. Current guidelines from the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), or the American College of Physicians (ACP) all firmly recognize the therapeutic strength of exercise intervention (5, 84, 114). The ADA states that “to improve glycemic control, assist with weight maintenance, and reduce risk of cardiovascular disease, at least 150 min/week of moderate-intensity aerobic physical activity is recommended and/or at least 90 min/week of vigorous aerobic exercise . . . distributed over at least 3 days/week and with no more than 2 consecutive days without physical activity” (5). Since 2006, the ADA

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Invited Review
guidelines explicitly mention and recognize that “in the absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance exercise 3 times a week, targeting all major muscle groups, progressing to 3 sets of 8–10 repetitions at a weight that cannot be lifted more than 8–10 times” (114). However, these clinical guidelines generally do not include detailed information on the preferred type and intensity of exercise that should be applied to maximize the benefits of exercise for different subgroups of patients with Type 2 diabetes.

More than 20 years ago, it was already reported that there is an urgent need to define the characteristics of appropriate exercise prescription in chronic metabolic disease (106). The present review aims to identify the exercise modalities that define an effective interventional strategy in the treatment of different Type 2 diabetes subpopulations.

RESISTANCE- VS. ENDURANCE-TYPE EXERCISE

Both a single bout of endurance- (31) as well as resistance-type exercise (43, 101) have been shown to improve whole body insulin sensitivity and/or oral glucose tolerance. Therefore, both types of exercise are of therapeutic use in an insulin-resistant state (116). The acute effects of exercise on skeletal muscle insulin sensitivity are attributed to the prolonged activation of the skeletal muscle glucose transporter system (48), depletion of muscle and liver glycogen stores (96, 103), and/or increased skeletal muscle blood flow following the cessation of exercise (13). The glucose-regulatory benefits of either type of exercise training is represented by the sum of the effects of each successive bout of exercise. In addition, more prolonged exercise training is accompanied by a more structural adaptive response. Apparent differences exist in the long-term adaptive response to endurance- or resistance-type exercise training. Prolonged endurance-type exercise training has been shown to improve insulin sensitivity in both young (28), elderly (60), and/or insulin-resistant subjects (27, 29, 97, 107). The latter is attributed to the concomitant induction of weight loss, the upregulation of skeletal muscle GLUT4 expression, improved nitric oxide-mediated skeletal muscle blood flow (76), reduced hormonal stimulation of hepatic glucose production (112), and the normalization of blood lipid profiles (17). Long-term resistance-type exercise interventions have also been reported to improve glucose tolerance and/or whole body insulin sensitivity (33, 43, 54). Other than the consecutive effects of each successive bout of exercise, resistance-type exercise training has been associated with a substantial gain in skeletal muscle mass, thereby improving whole body glucose-disposal capacity (43). Besides the attenuation of the loss of muscle mass with aging, resistance-type exercise training also improves muscle strength and functional capacity, thereby allowing a healthier, more active lifestyle. Some studies report even greater benefits of resistance- as opposed to endurance-type exercise training on glycemic control and insulin sensitivity in long-standing patients with Type 2 diabetes (19). As such, it has been firmly established that both endurance- and resistance-type exercise training can be applied to improve metabolic control and quality of life in patients with Type 2 diabetes (116).

In most lifestyle intervention programs, the focus generally lies on the implementation of endurance-type exercise activity.

The latter can be explained by the fact that endurance-type exercise has been known for its efficacy to reduce body fat mass and its subsequent effects on whole body insulin sensitivity. Since many patients with Type 2 diabetes suffer from muscle weakness (6, 108, 129), cardiovascular comorbidities (117, 130), and reduced exercise tolerance (42), it has been proven difficult to engage patients with Type 2 diabetes into adhering to strict endurance-type exercise intervention programs (34, 111). Alternatively, endurance-type exercise combined with resistance (i.e., intermittent intensity-type exercise) forms a lower cardiovascular challenge (81) and improves functional performance capacity to a similar extent (79). Therefore, the combination of endurance- and resistance-type exercise is preferred since it augments the diversity and, as such, the adherence to the exercise intervention program. To maximize the benefits of exercise intervention, the emphasis to apply either more endurance- or more resistance-type exercise should be tailored to the level of comorbidity present in a specific diabetes subpopulation (see below).

INTENSITY VS. DURATION OF EXERCISE

Clinical practice guidelines on the application of exercise intervention in Type 2 diabetes do not provide much detail regarding the duration and/or intensity of exercise that should be applied to maximize subsequent health benefits for different subpopulations (5, 57). As exercise intensity is increased, muscle glycogen becomes a more important substrate source (61). The depletion of muscle glycogen stores and subsequent postexercise muscle glycogen resynthesis is coupled to the postexercise improvement in glucose tolerance and/or insulin sensitivity (48, 126). Therefore, when considering the more acute glucoregulatory effects of exercise, higher exercise intensities should theoretically be more effective to stimulate insulin sensitivity and improve glucose homeostasis. However, data from a limited number of studies (32, 66, 71, 72, 127) are inconclusive, and several factors, such as release of counter-regulatory hormones (66), training status (64), and exercise performed either in the postabsorptive (66) or postprandial state (72), may explain these contradictory findings. Nevertheless, the energy equivalent of the exercise bout appears to represent the major determinant of the exercise-induced changes in glucose homeostasis (71, 72). Therefore, a lesser exercise intensity should be compensated for by an increase in exercise duration.

Although less evident for resistance-type exercise, energy expenditure for endurance type exercise can be estimated by using metabolic equivalent tables (1). Endurance-type exercise programs should entail at least 3 exercise sessions/wk in which the energy equivalent of each exercise bout should represent \( \sim 1.7 \text{ MJ (} \sim 400 \text{ kcal)} \), or rather 4–5 sessions/wk with an energy equivalent of \( \sim 2.1 \text{ MJ (} \sim 500 \text{ kcal)} \) per exercise bout (52, 56, 88). In the average overweight/obese patient with uncomplicated Type 2 diabetes, this minimum of 5 MJ/wk (\( \sim 1,200 \text{ kcal} \)) would be equivalent to a minimum of 170–200 min or \( \sim 19 \text{ km of brisk walking per week} \) (20, 59, 115).

When applying resistance-type exercise, strength improvements tend to follow a linear dose-response relationship, at least in healthy subjects (47, 98). If the therapeutic aim of resistance-type exercise is to stimulate muscle glycogen storage depletion and net muscle mass gain, both exercise intensity
and volume should be kept high (21, 68). However, studies assessing the impact of exercise intensity in resistance-type exercise interventions in patients with Type 2 diabetes remain lacking. It has been established that progressively intensified moderate- to high-impact resistance training over a period of 6 wk (3 × 30 min exercise/wk) upregulates the activity of key proteins in the insulin-signaling cascade, resulting in enhanced insulin-stimulated blood glucose disposal in muscle (54). In accordance, resistance-type exercise training has been shown to reduce blood HbA1c levels with 0.4–0.8% in patients with Type 2 diabetes (116). Until more information becomes available, it is advised to implement resistance-type exercise training with exercise volume and intensity being progressively increased toward three sets of 8–10 repetitions performed at 70–80% of 1 repetition maximum per muscle group (114).

Many patients with Type 2 diabetes experience some musculoskeletal (6, 100, 108, 129) and/or cardiorespiratory deconditioning (42). Therefore, exercise intensity, duration, and volume should be gradually increased over a period of 6–12 wk. In addition, endurance- and resistance-type exercise of the same muscle group on the same day should be avoided to reduce the risk of overuse injuries and subsequent dropout.

**FREQUENCY AND TIMING OF EXERCISE**

The enhanced insulin sensitivity following an acute bout of exercise has been reported to persist for a period ranging from 2 (83), 4–6 (132), 12–16 (31, 89), 24 (24, 110), and to up to 48 h following the cessation of exercise (83). As such, the benefits of exercise on glycemic control may largely be attributed to the cumulative effects of each successive bout of endurance- or resistance-type exercise rather than the structural adaptive response to prolonged exercise training (110). In fact, long-term training effects on glycemic control must be lost entirely 6–14 days after cessation of training (27, 53). Therefore, it is preferred to perform exercise everyday. The ACP guidelines prescribe an exercise frequency of at least three times per week with no more than 2 consecutive days without physical activity (4). Indeed, the ADA (5) now recognizes that these guidelines need to be considered a minimal therapeutic dose and, therefore, a less than optimal therapy.

Furthermore, current guidelines on exercise prescription as therapeutic strategy (3, 5) do not consider an optimal timing of a daily exercise routine. In this respect, it is interesting to note that, in patients with Type 2 diabetes, hyperglycemic episodes during the day are most predominant in the morning in the postprandial state (51, 102). This so-called “dawn-phenomenon” (15) seems to be related to the diurnal variation in endogenous glucose production (104). Since moderate-intensity exercise suppresses endogenous glucose production, it might be advantageous to schedule moderate-intensity endurance exercise sessions in the morning, preferably in the postprandial state. More research is warranted to assess the impact of timing of exercise and nutrition on daily hyperglycemia in patients with Type 2 diabetes (71, 101).

**STAGE OF DISEASE AND COMORBIDITY**

The prolonged application of either endurance or a combination of resistance- and endurance-type exercise training has been shown to increase whole body glucose tolerance and/or insulin sensitivity (56) and can prevent the development of Type 2 diabetes (67, 123). The implementation of resistance- and endurance-type exercise improves glycemic control (11, 74, 75, 121), blood pressure (11, 74), body composition (11, 23, 74), and blood lipid profile (11, 75). Furthermore, exercise training has been reported to modify the progression of peripheral neuropathy (10) and attenuates the progressive increase in blood glucose-lowering medication requirements (11). However, when implementing endurance- and resistance-type exercise intervention in the treatment of Type 2 diabetes, we also need to consider the stage of the disease, body composition, and the presence of comorbidities. In recently diagnosed, obese patients with Type 2 diabetes, the main therapeutic target of lifestyle intervention should be a durable reduction in fat mass and a concomitant improvement in aerobic fitness and whole body insulin sensitivity (5), a conclusion well in line with exercise recommendations for normoglycemic obese subjects (50). As such, obese patients with Type 2 diabetes would benefit most from a program mainly consisting of moderate-intensity endurance exercise, aiming for an energy expenditure of at least 5 MJ (~1,200 kcal) (56, 88) but preferably >8.4 MJ (~2,000 kcal) per week (52). In these patients, endurance-type exercise should be combined with dietary restriction (14, 62, 133). To prevent the loss of lean body mass due to the energy intake restriction, at least one resistance exercise session should be included per week (25).

Another expanding Type 2 diabetes subpopulation is formed by the long-standing, insulin-treated patients with Type 2 diabetes (30). These patients generally suffer from severe exercise intolerance due to low oxidative capacity (42), neuropathy-related muscle weakness (6, 100, 108, 129), sarcopenia (18), and/or micro- and macrovascular disease (37, 100). Since generic exercise intervention programs are too demanding for most of these patients, it is of utmost importance to implement intermediate exercise intervention programs. Such intermediate programs are needed to bring patients to a level at which they are able to participate in more generic diabetes intervention programs. Such intermediate programs should implement short, relatively high-intensity exercise bouts applied in an intermittent fashion with the intention to increase muscle strength and functional performance. These so-called short “in-and-out” exercises do not produce feelings of dyspnea or discomfort and have been proven safe and effective in cardiac (79, 80) and insulin-treated patients with Type 2 diabetes (101) with a high-cardiovascular risk profile. The efficacy of such intermediate programs remains to be established, since exercise intervention studies have generally excluded long-standing, insulin-treated patients with Type 2 diabetes.

Another vastly expanding diabetes subgroup is formed by the elderly (>70 yr) patients with Type 2 diabetes. Aging is associated with the loss of skeletal muscle mass and represents one of the main factors responsible for the increase in Type 2 diabetes incidence at an advancing age (95). The loss of muscle mass is proportionally related to the reduction in blood glucose disposal capacity and the decline in muscle strength (92). The latter prevents many elderly diabetes patients from participating in lifestyle intervention programs. Although even low-impact endurance-type exercise has been reported to improve glycemic control in elderly patients with Type 2 diabetes (70, 121), it has been suggested that the insulin-sensitizing response
to exercise is attenuated with an advancing age (82, 113). Since Type 2 diabetes patients show an accelerated decline in muscle mass and strength with aging (93), it would be preferable to focus more on increasing skeletal muscle mass and strength when designing exercise intervention programs for the elderly patients with Type 2 diabetes (26, 131). Effective exercise intervention programs for the elderly patient with Type 2 diabetes should include resistance-type exercise, with exercise volume and intensity being progressively increased toward three sets of 8–10 repetitions with intensities ranging from 50 to 80% 1 repetition maximum for 7–10 exercises and/or muscle groups (9, 33, 43, 55). Dietary cointerventions might further improve the benefits of resistance-type exercise training in elderly patients (38, 69).

Furthermore, when prescribing exercise intervention in patients with Type 2 diabetes, it should be noted that long-term adherence to an exercise intervention program may vary with the presence of comorbidities, the level of deconditioning, and/or orthopedic limitations (7, 92). Therefore, a multidisciplinary team should consider the level of impaired exercise tolerance and individualize the exercise intervention program to prevent dropout and empower the patient to adhere to such lifestyle changes (34, 73, 111).

SAFETY ASPECTS

Before exposing patients with Type 2 diabetes to more vigorous exercise programs, the ADA and US Preventive Services Task Force recommend exercise testing for silent myocardial ischemia (SMI) if 10 years’ cardiovascular risk exceeds 10% (45, 114). Cardiac dysfunction (41) and SMI are estimated to be present between 6 and 22% (130) of the patients with Type 2 diabetes, with cardiac autonomic dysfunction, disease duration, and male gender being the best predictors for SMI (130). Moreover, poor physical fitness (78), scintigraphy abnormalities (39), diabetic retinopathy (39), and an advancing age >60 yr (125) in combination with the traditional cardiovascular risk factors also represent good predictors for the likelihood of a cardiac event. The UKPDS Risk Engine version 2.0 (available free of charge at http://www.dtu.ox.ac.uk/) can be of help to calculate an individual patient’s risk for coronary heart disease (118). Although arbitrary, the UKPDS Risk Engine indicates that ECG stress testing in Type 2 diabetes is useful in most patients with >2 cardiovascular risk factors, in middle-aged patients with a diabetes duration >5 yr, as well as in elderly patients >70 yr of age. Although a stress ECG is not the most sensitive diagnostic tool to detect...
SMI (86) and predict coronary events (85), it is still the most cost effective when trying to minimize the risk of a coronary event (22). In case SMI is expected, more sensitive diagnostic tests such as myocardial perfusion scintigraphy (12), electron beam computerized tomography (109), and/or coronary angiography (8) should be considered before more vigorous exercise is prescribed. Even in the absence of SMI, a stress test will detect chronotropic incompetence (36) as well as exercise-related hypertension and provide more objective information on the individual fitness level (42). This information should be used to further tailor an exercise program for the individual (Fig. 1).

CONCLUSION AND RECOMMENDATIONS

In the present review, we have identified the modalities of effective exercise intervention in the treatment of Type 2 diabetes. Before choosing the most appropriate exercise modalities, the patient’s disease stage should be well characterized, and an ECG-stress test should be considered. Based on baseline aerobic fitness, level of comorbidities, appendicular skeletal muscle mass, and strength, patients should be provided with a fitting exercise intervention program to optimize its therapeutic value. Recently diagnosed obese patients with Type 2 diabetes will benefit most from daily, intense moderate-intensity endurance training in combination with energy intake restriction. The latter should be combined with at least one resistance-type exercise session per week to prevent the loss of fat-free mass. Long-standing, insulin-treated patients with Type 2 diabetes, in whom comorbidities generally prevail, should be prescribed with an exercise program containing intermittent, relatively high-intensity resistance- and endurance-type exercise. After substantial improvement in muscle strength and functional performance, more generic exercise intervention programs (with more intense endurance-type exercise training) should be considered. In an expanding population of elderly onset patients with Type 2 diabetes, focus should lie on the implementation of resistance-type exercise to attenuate and/or reverse the decline in skeletal muscle mass and strength. When applying endurance-type exercise, energy expenditure should be equivalent to 1.7–2.1 MJ (≈400–500 kcal) per exercise bout on 3 but preferably 4–5 days/wk, since many of the benefits of exercise are temporarily. More vigorous exercise in uncomplicated insulin-resistant states will further improve glycemic control and enhance cardiorespiratory fitness and microvascular function. Most patients with Type 2 diabetes find it difficult to adhere to structural exercise intervention programs. Compliance to an exercise intervention program can be enhanced by a multidisciplinary approach and continued exercise training under strict personal supervision.

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Invited Review

EXERCISE AND TYPE 2 DIABETES


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EXERCISE AND TYPE 2 DIABETES


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