Exercise and the Treatment of Diabetes and Obesity

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• Exercise • Skeletal muscle • Insulin resistance
• Substrate metabolism • Gene expression • AMPK

Lifestyle intervention programs encompassing exercise and healthy diets are an option for the treatment and management of obesity and Type 2 diabetes and have long been known to exert beneficial effects on whole-body metabolism, in particular leading to enhanced insulin-sensitivity. As evident from other articles in this issue, obesity is associated with increased risk of several illnesses and premature mortality. However, physical inactivity is itself associated with a number of similar risks, independently of body-mass index,[1] and is an independent risk factor for more than 25 chronic diseases, including Type 2 diabetes and cardiovascular disease.[2] Because obesity, with or without overt Type 2 diabetes, and physical inactivity very often coexist in the same individual when being discussed,[3] there has been debate recently regarding the relative effects of physical exercise itself and the effect of exercise-induced weight loss.

EXERCISE INTERVENTION PROGRAMS

In obese individuals, a low level of physical fitness is a better predictor of all-cause mortality than cholesterol levels, smoking status, or blood pressure and is similar to having had a previous cardiovascular event.[4] Exercise training has many cardiovascular and metabolic benefits, including decreased blood pressure,[5] plasma lipoprotein and triglyceride levels,[6] and improvements in glycemic control,[7] insulin sensitivity,[8] vascular structure, and endothelial function.[9] The goal of exercise and lifestyle modification programs is to combine education, dietary awareness, supervised physical activity, and social support to assist participants in making permanent lifestyle

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changes.[10] Exercise training increases insulin sensitivity[8] and results in lower fasting insulin concentrations. Studies using the hyperinsulinemic-euglycemic clamp demonstrate that for the same circulating insulin concentration, glucose disposal rates are higher and endogenous glucose production rates are lower in exercise-trained subjects.[11,12] This benefit can be maintained in those who exercise throughout their lifespan, as master athletes have a similar glucose and insulin response to an oral glucose tolerance test as young athletes, and a significantly better insulin response than young sedentary subjects. Therefore, exercise training has a positive impact on insulin sensitivity, glucose disposal, and insulin secretion in normal glucose-tolerant subjects.

Exercise training also increases whole-body insulin-mediated glucose disposal in obese Type 2 diabetic patients.[13] The clinical profiles of subjects with impaired glucose tolerance,[14–17] or with relatively newly diagnosed diabetes[18] have been successfully improved using exercise intervention programs. In larger studies however, patient compliance is a major challenge, especially as the obesity itself—as well as other common associated ailments—make regular exercise programs both difficult and unsafe.[19] One hurdle for exercise programs is that successful implementation of exercise and lifestyle-modification programs in patients with long-standing disease or complications has been more challenging.[20,21] However, lifestyle modifications can be successful in subjects with more long-standing disease. The authors have shown that a 31-week residential lifestyle-modification program significantly improved several clinical parameters in overweight Type 2 diabetic subjects, with significant improvements in glycemic control, oxygen uptake, blood pressure, and cholesterol.[22] At the same time, average weight loss was modest (2 kg–3 kg reduction from an average starting weight of approximately 100 kg). Importantly, subjects also reported increased well being and reduced stress.[22] Participants were referred to the program by their physicians and were not volunteers who would perhaps be more likely to comply with dietary and exercise advice. Instead, most of these patients had not responded to previous lifestyle advice and pharmacologic interventions. Thus, lifestyle-modification programs are a powerful treatment option to reduce risk factors associated with obesity and diabetes, even in patients who have not responded to conventional therapy.

EXERCISE-MEDIATED EFFECTS IN SKELETAL MUSCLE

Exercise and muscle contraction per se leads to alteration in skeletal muscle metabolism and alters the metabolic capacity of the muscle. Contraction may also lead to the release of circulatory factors from the muscle, which could exert influence on other organs. In response to exercise training (that is, several repeated exercise bouts) muscle growth is increased.[23] There are also accompanying changes in the metabolic profile of the muscle, such that there is an increased reliance on lipid oxidation, even under higher work-loads. Another well-characterized response to exercise and contraction is enhanced skeletal muscle insulin sensitivity. These changes are reversible, and thus the opposite effects are noted in response to inactivity. A section later in the this article discusses some of the molecular changes in skeletal muscle following exercise and contraction, and which may be important in mediating the beneficial exercise effects.

Metabolic Response to Exercise

Exercise is a metabolic stress that acutely increases the demand for energy production. While lipid and carbohydrate oxidation are both increased during exercise, the limitation of oxygen availability favors carbohydrate as the preferential substrate. Skeletal muscle glucose uptake is increased during exercise and blood-glucose

concentrations are maintained by hepatic glycogenolysis and gluconeogenesis and indirectly by an increased rate of muscle glycogen utilization. Prolonged or high-intensity exercise has been shown to deplete both liver[24] and muscle glycogen,[25] resulting in reduced carbohydrate oxidation and blood-glucose concentration. The after-exercise period is characterized by an increased rate of glucose uptake to replenish muscle glycogen concentrations.[26]

Lipid oxidation is especially important during prolonged low-intensity exercise where oxygen availability is sufficient for β-oxidation, when carbohydrate stores are depleted, and in the after-exercise recovery. Exercise training also results in an increase in the relative contribution of lipid to total oxidation during submaximal exercise.[27] The regulation of lipolysis and the relative contribution of plasma nonesterified fatty acids (NEFA), plasma triglycerides, and intramuscular triglycerides (IMTG) to skeletal muscle fat oxidation are also influenced by the exercise conditions. Exercise training improves the insulin sensitivity of lipolysis[28] and increases the rate of glycerol and NEFA appearance at rest.[29] However, during low-intensity exercise, the rate of lipolysis does not change following exercise training,[11,30] and as the rate of NEFA appearance exceeds that of fat oxidation,[31,32] it is likely that the increased lipid oxidation following training is caused by IMTG oxidation.[30,33,34] Endurance exercise training increases the accumulation and turnover of IMTG.[33,34]

Immediate Effects of a Single Bout of Exercise

An acute bout of exercise leads to an immediate increase in glucose transport in skeletal muscle, mediated via an insulin-independent translocation of glucose transporter (GLUT)-4 to the cell surface.[35–38] The work performed by the muscle leads to a reduction of ATP relative to AMP levels, leading to the activation of the AMP-sensitive protein kinase (AMPK).[39] Activation of AMPK stimulates glucose uptake and lipid oxidation to produce energy, while turning off energy-consuming processes, including glucose and lipid production, to restore intracellular energy balance. AMPK activation is also central in mediating some of the long-term effects of exercise, as discussed below.

Exercise and Substrate Oxidation in Obesity and Type 2 Diabetes

Impairments have been noted in skeletal muscle glucose and fatty acid metabolism in obesity and Type 2 diabetes in the resting state.[40–43] This is evident by impaired post-receptor insulin signaling, reduced glucose uptake, and rates of glycogen synthesis.[44,45] Abnormal fatty acid metabolism leads to increased accumulation of IMTGs[46] and decreased lipid oxidation during fasting and insulin-stimulated conditions.[47] Thus, exercise-mediated enhancement of substrate oxidation is especially important in the treatment of obesity and Type 2 diabetes, as these conditions are associated with impaired skeletal muscle lipid utilization. An acute bout of exercise increases lipid oxidation in overweight and obese subjects, but it is not clear if total lipid oxidation is less than[48] or greater than lean controls.[49] Glucose disposal and plasma NEFA oxidation during 60 minutes of exercise at 50% VO_2peak has been found to be similar in lean and obese subjects, although the contribution of muscle glycogen was reduced in obese subjects, with the balance presumably coming from an increase in nonsystemic lipid oxidation.[49] It has been challenging to clearly understand the response of obese subjects to exercise because of the inherent heterogeneity of this group. Phenotypic differences may partly explain the variable response, as plasma lipid availability is reported to be greater in men with visceral adiposity compared with those with subcutaneous adiposity,[50] and exercise training has a greater impact on fat oxidation in subjects with upper body but not lower

body obesity.[51] It is also important to note that, while weight gain is associated with insulin resistance, the degree of insulin resistance varies greatly and can subsequently influence substrate selection. For example, total carbohydrate oxidation and muscle glycogen utilization has been found to be lower in overweight insulin-resistant women as compared with insulin-sensitive women, consistent with a greater contribution of lipid oxidation to energy production during exercise.[52]

The effect of exercise training on substrate oxidation is not as clear in obese and Type 2 diabetic populations, as in lean populations. While resting fat oxidation may not change in obese subjects after training at either low or high intensity (40% or 70% VO_{2max}), fat oxidation during exercise increases at lower intensity.[53] In this study, the absolute rate of fat oxidation was similar in both high- and low-intensity training groups after training, the respiratory exchange ratio for the high-intensity group was greater before training, giving a high basal fat oxidation rate and a lower training adaptation.[53] In studies that have combined energy restriction with exercise training, the exercise is associated with increased resting fat oxidation,[27] insulin sensitivity[27,54] and mitochondrial adaptations.[55,56]

The accumulation of IMTG in obesity is most likely caused by a reduction in lipid oxidation with similar or increased NEFA uptake. Energy restriction and exercise training do not decrease IMTG in obese subjects,[57] though an increase in IMTG turnover could contribute to enhanced insulin sensitivity. The inconclusive results for training-related changes in lipid oxidation for obese individuals may be related to subject heterogeneity, as explained previously, or study design. In many exercise intervention protocols the exercise intensity is relatively low, and training frequency is usually 3 to 4 days per week. This leads to a total increase in energy expenditure of approximately 1,000 kcal per week. This is significantly less than a typical energy restriction protocol of 500 to 1,000 kcal per day. Recent evidence, which will be discussed later, indicates that weekly energy expenditure in excess of 2,000 kcal may be required to prevent weight gain and even more may be necessary for weight loss. It is also possible that the lipid oxidation rates may not increase following training because there may be an upper limit of skeletal muscle fat oxidation.[53] In line with this, maximal oxygen uptake increased in young obese—but not young obese Type 2 diabetics—following a 12-week exercise training program.[58] Thus, intrinsic factors in the muscle that regulate oxidation may not be responsive to exercise training in some populations; whether this is a disease-related factor or reflects underlying genetic differences in exercise response is discussed below.

Carbohydrate oxidation rates appear to be similar in lean, obese, and Type 2 diabetic groups during exercise.[59,60] However, if excess lipid availability alters substrate utilization in obese subjects, the combination of elevated glucose and lipid levels in Type 2 diabetes leads to further metabolic difficulties. In response to one-legged aerobic exercise training in subjects with Type 2 diabetes or nondiabetic controls, glucose oxidation tended to decrease in both groups during exercise, while increased fat oxidation was only noted in the nondiabetic group.[61] Sixteen hours after the last training bout, the rate of carbohydrate oxidation had increased in both groups, but significantly more in the nondiabetic group, thus indicating an impaired exercise response in subjects with Type 2 diabetes.[61] Furthermore, in normo-glycemic insulin-resistant offspring of Type 2 diabetics, carbohydrate oxidation rates were proportionally decreased, and there was no increase in response to an acute bout or 6-weeks of exercise training.[62] Based on the current literature it is difficult to draw conclusions regarding substrate utilization in obese and Type 2 diabetes subjects; however, it is likely that the elevated fasting glucose and lipids result in different metabolic responses than in lean controls. These changes may result in altered exercise

response, differential regulation of the insulin-signaling cascade, and regulation of gene expression and protein synthesis.

MOLECULAR MECHANISMS UNDERLYING EXERCISE EFFECTS IN SKELETAL MUSCLE

Insulin Resistance and Metabolic Dysfunction in Skeletal Muscle

Evidence suggests that decreased insulin-mediated glucose transport is a primary defect in skeletal muscle.[63,64] Insulin resistance is characterized by decreased insulin receptor and insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation, and decreased phosphatidylinositol 3-kinase (PI3-kinase) activity following insulin stimulation.[65] A potential mechanism for the down-regulation of the insulin-signaling cascade involves the regulation of lipid metabolism. The accumulation of IMTG is correlated with insulin resistance and is thought to be related to a decrease in mitochondrial oxidative activity[66] resulting from a reduction in the activity of oxidative enzymes[67] and the electron transport chain.[68] Accumulation of IMTG may be the result of a decrease in mitochondrial fatty acid oxidation, resulting in an increase in cytosolic long-chain fatty acyl CoA (reviewed in Lowell and Shulman[69]). Diacylglycerol (DAG) accumulation also occurs and is associated with an increase in the activity of protein kinase C ϵ and θ isoforms, which are known to increase the serine phosphorylation of the insulin receptor and IRS-1. Reduced expression of DAG kinase delta has been noted in skeletal muscle from Type 2 diabetic subjects,[70] which could contribute to an increased DAG accumulation. Interestingly, exercise leads to enhanced skeletal muscle expression of DAG kinase delta.[71,72]

Although it is probable that many different factors underlie and contribute to the disturbances in metabolism, altered mitochondrial function would affect both lipid and glucose metabolism. Skeletal muscle is highly dependent on oxidative phosphorylation for energy production. Reduced expression of enzymes important for mitochondrial oxidative phosphorylation have been found in skeletal muscle from obese subjects.[73] Alternatively, the decrease in mitochondrial oxidative phosphorylation in insulin resistance could be because of changes in mitochondrial structure. The size and number of mitochondria are decreased and there is evidence of degenerated mitochondria in insulin-resistant conditions, such as obesity and Type 2 diabetes.[68] Thus, recent evidence points to a strong association between insulin resistance and mitochondrial dysfunction in skeletal muscle. The identification of mechanisms that increase mitochondrial biogenesis, oxidative enzyme activity, and glucose transport have important implications for increasing substrate utilization and insulin sensitivity.

Skeletal Muscle Contraction and the Regulation of Gene Expression

Muscle contraction is known to produce a multitude of physiologic adaptations, including an increase in insulin-mediated glucose disposal,[38] and therefore provides a novel model for identifying cellular and molecular mechanisms of insulin resistance. In addition to the many physiologic adaptations, exercise training increases skeletal muscle mitochondria size and number[74] in an intensity-dependent manner.[75] This is coupled with an increase in Krebs cycle, β-oxidation, and electron transport-chain activity, facilitating a shift in cellular substrate utilization toward greater free fatty acid oxidation.[74] Interestingly, a lifestyle modification involving both weight loss and increased physical activity in previously sedentary obese subjects led to an increase in both mitochondrial size and number.[76] The changes noted in mitochondria were also associated with improvements in insulin resistance.[76] This indicates that reduced mitochondrial number associated with obesity is reversible.

Thus skeletal muscle contraction not only increases energy expenditure but is also a key regulator of gene and protein expression. The impact on protein synthesis extends beyond the mitochondria to include a broad range of proteins involved in carbohydrate metabolism (GLUT-4, hexokinase, glycogen synthase), lipid metabolism (lipoprotein lipase, CD36, carnitine palmitoyltransferase I) insulin-signaling intermediates (PI3-kinase activity), and angiogenic regulators.[61,77–82] As a corollary, the absence of regular physical activity will lead to decreased rates of protein synthesis and over time contribute to impaired metabolic function.

Recent work on the mechanisms responsible for enhanced NEFA oxidation suggest that exercise-mediated up-regulation of gene expression associated with peroxisome proliferator-activated receptor alpha and gamma (PPARα/γ) and PPARγ coactivator-1α (PGC-1α) may be responsible.[83,84] Short term exercise training increases lipid oxidation and this is associated with an increased expression of FAT/CD36, regulating NEFA uptake across the plasma membrane, and CPT-1, regulating mitochondrial NEFA uptake.[84]

Although there is compelling evidence for exercise-mediated regulation of mitochondrial function, it is also important to point out that the role of mitochondrial impairments in mediating the metabolic phenotypes associated with Type 2 diabetes and obesity has been challenged. In human subjects harboring mitochondrial mutations, diabetes often develops as a result of impairments in beta cell function, while peripheral insulin sensitivity is maintained and obesity rarely develops.[85] Mice with a targeted reduction in mitochondrial function are protected against diabetes and obesity, suggesting that the reduction in oxidative phosphorylation noted in the muscle of insulin resistant subjects could be a compensatory mechanism.[86]

Which Exercise-Regulated Pathways Mediate Changes in Muscle Metabolism?

The contractile process is an important mechanical stimulus for the regulation of cellular signals controlling gene expression and mitochondrial biogenesis. Mitochondrial biogenesis is a complex process requiring the coordinated expression of nuclear- and mitochondrion-encoded proteins and the import and assembly of these proteins into a functional organelle. There is strong evidence to suggest that intracellular calcium flux ($[Ca^{2+}]_i$) and ATP turnover (which leads to AMPK activation) are the major contraction-mediated signaling cascades contributing to changes in gene expression and mitochondrial biogenesis.[87,88]

The activation of these signaling cascades culminates in the expression and activation of transcription factors, including CREB and MEF2, and promotes PGC-1α gene expression.[89] Calcium binds to calmodulin (CaM) before activating Ca^{2+}/CaM-dependent kinases (CaMK). CaMKIV increases mitochondrial biogenesis via PGC-1α in mouse skeletal muscle[90] but is not expressed in human skeletal muscle.[91] Calcium signaling in human muscle may be mediated via CaMKII, which is activated in a dose-dependent manner by contraction.[91]

AMPK is required for mitochondrial biogenesis in skeletal muscle in response to chronic energy deprivation.[92] AMPK increases mitochondrial biogenesis by activation of NRF-1,[87,93] and by directly increasing gene expression by colocalizing to the nucleus.[93] However, the mechanism of AMPK-regulated gene expression is not fully understood as it increases the expression of some, but not all, mitochondrial enzymes.[94] AMPK also directly binds to, and phosphorylates, PGC-1α[95] and may have a more important role as a regulator of protein activation and function.

It has become clear that nuclear receptor-mediated transactivation requires interaction with coactivators. PGC-1α is a well-characterized coactivator of a wide array of transcription factors and, when over-expressed in myotubes, there is an increase in

oxygen consumption, the expression of genes in oxidative phosphorylation, and mitochondrial biogenesis,[96] all of which are characteristic adaptations associated with endurance exercise training. PGC-1α is believed to be a master regulator of metabolic gene expression as it regulates transcription factors involved in the expression of nuclear encoded mitochondrial proteins, mitochondrial DNA transcription, GLUT-4 biogenesis, and fatty acid oxidation (reviewed in Lin and colleagues[97]). PGC-1α expression is attenuated in obesity and diabetes, contributing to metabolic dysfunction, with decreased mitochondrial content, energy expenditure, and increased IMTGs and insulin resistance.[98–100] Obese Zucker rats have a greater rate of palmitate incorporation into IMTG and decreased expression of PGC-1α in comparison to lean controls.[101] The regulation of PGC-1α expression and the subsequent execution of cell-specific transcriptional programs are important for metabolic homeostasis.

Because many aspects of exercise-trained muscle are similar to properties associated with type 1/oxidative muscle fibers, including enhanced insulin sensitivity and increased number of mitochondria, the study of fiber-type determination using transgenic mice has been illustrative in identification of genes that are also important in response to exercise. For example, in transgenic mice, over-expression PGC-1α leads to an increased proportion of type IIA and type I skeletal muscle fibers.[102] Similarly in mice, transgenic expression of an activated form of PPARδ also increased the proportion of type I fibers.[103] The expression of a highly homologous receptor, PPARα, has been shown to be controlled by exercise and metabolic status in skeletal muscle.[104–106] Because PGC1 is a cofactor for both PPARδ and PPARα, there is collective evidence for the importance of these signaling events in regulation of muscle metabolic phenotype.

Expression of PGC-1α is increased 2 to 3 hours following an acute bout of exercise[107–111] and after exercise training.[107,112–114] There is a positive relationship between the expression of PGC-1α and maximal oxygen consumption, as well as oxidative phosphorylation activity in human skeletal muscle.[115] While there is strong evidence to support a contraction-mediated increase in PGC-1α expression following exercise, the regulation of PGC-1α target genes is less clear. NRF-1 expression is unchanged following an acute bout of exercise[108,116] and exercise training[112] despite an increase in PGC-1α. Therefore, it is important to consider the importance of PGC-1α activation, the role of other transcription coregulators, and muscle fiber characteristics in the regulation exercise-mediated mitochondrial biogenesis.

In addition to signals mediated via PPARα, PPARδ, and PGC-1α, expression and activity of the Ca^{2+} sensitive enzyme calcineurin has also been implicated as playing an important role in fiber-type transformation, using muscle-targeted expression of Calcinuerin Aα.[117–120] Compared to transgenic mice over-expressing PPARδ or PGC-1, the calcinuerin transgenic mice have a more modest increase in type 1 fiber content, suggesting that calcineurin activity alone is not sufficient to drive the slow-fiber phenotype.[118] Thus, data from transgenic mice and functional genomics implicate PPARα, PPARδ, PGC-1α, and Calcineurin as the basis of a signaling network controlling skeletal muscle fiber-type transformation and metabolism in rodents.

Given the substantial differences between rodent and human skeletal muscle,[74] in particular as regards skeletal muscle adaptation and fiber-type transformation, translational studies in human beings are important. Elite athletes have an increased 24-hour skeletal muscle metabolism, enhanced whole-body insulin sensitivity, and an increased proportion of type I fibers.[121] In contrast, following spinal cord injury, alterations in neuronal input are associated with changes in skeletal muscle phenotype, with decreased fiber size, increased percentage of mATPase type IIB fibers, and dramatic loss of type I fibers to near undetectable levels.[122,123] When comparing

these two groups to a group of age-matched healthy sedentary subjects, the authors could show that expression of PPARα, PPARδ, PGC-1α, but not Calcineurin Aα correlated with the exercise status and type I fiber content in skeletal muscle *vastus lateralis* biopsies, providing evidence for the relevance of these genes implicated in controlling skeletal muscle fiber-type transformation and metabolism in human beings as well.[124]

Genetic Variation May Determine Exercise Response

Although exercise exerts many positive effects in the majority of subjects, there is also a wide range of individual response to exercise. There is increasing evidence that an individual's genetic make-up will influence the subsequent response to exercise, and that some individuals may be inherently less able to respond to training. Differences in mRNA profiles in skeletal muscle have been mapped between groups of subjects who show marked difference in the improvement in glucose tolerance as a response to the same amount of 20-week exercise training, demonstrating the existence of "exercise resistance."[72]

A proline for alanine substitution at position 12 (Pro12Ala polymorphism) in the gene encoding PPARγ *(PPARG)* has been related with obesity directly, as well as physical activity level,[125] while variations at Gly482Ser predict exceptional endurance capacity.[126] Carriers homozygous for the Ser482 variants have been shown to be more capable of improving cardio-respiratory fitness when physically active, suggesting that Gly482Ser could explain some of the between-person variance in adaptation after exercise training.[127]

Exercise training leads to increased skeletal muscle expression of PPARδ in both animals[104] and human beings.[71] Up-regulation of skeletal muscle PPARδ protein expression has been linked to improvements in clinical parameters in diabetic subjects following an exercise intervention, such that subjects where there was no change in PPARδ did not experience the metabolic improvements observed in subjects where PPARδ increased.[71] A further indication that the ability to up-regulate PPARδ may be necessary for exercise to mediate positive effects on metabolism come from studies linking genetic variations at the *PPARD* locus with change in aerobic physical fitness and insulin sensitivity during lifestyle intervention. Genetic variation at the *PPARD*, *PPARGC1A*,[128,129] and *PPARG*[130] have also been linked to exercise response loci. Variations at *PPARD*, and *PPARGC1A* have both additive[129] and independent effects.[128,129] The association of genetic variation at the loci of the above genes with the ability to benefit from physical exercise further highlight PPAR-PGC1 regulated genes and pathways as key in mediating exercise adaptation.

EXERCISE RECOMMENDATIONS IN THE MANAGEMENT OF OBESITY AND TYPE 2 DIABETES

Physical inactivity is undoubtedly a major contributing factor to weight gain and the development of Type 2 diabetes. It has been argued that exercise is necessary to maintain normal metabolic function because of the important regulatory control on gene expression, mitochondrial biogenesis, oxygen consumption, and energy expenditure.[2] One of the challenges faced by clinicians and exercise specialists is to reintroduce physical activity into daily living, in place of sedentary behaviors adopted by advances in technology. In an attempt to encourage physical activity, the recommendations developed over a decade ago focused on the minimal amounts of physical activity required to maintain or improve cardiovascular health.[131] While this approach had many merits, the recommendations quickly became adopted as general guidelines for population health and the treatment of clinical conditions. It

has recently been proposed that these guidelines may not be adequate to prevent weight gain or optimize the use of exercise to treat clinical conditions. This has caused a certain amount of conflict between those who promote practical and achievable guidelines in a modern society and those who wish to optimize the therapeutic benefits of exercise.

There have been relatively few randomized, controlled trials to evaluate the impact of exercise on weight reduction.[132] Many of the published articles adopted an exercise protocol of approximately 150 minutes per week, based on an exercise recommendation of 30 minutes of physical activity on all or most days of the week.[131] This is equivalent to 150-kcal to 200-kcal energy expenditure per day or approximately 700 kcal to 1,000 kcal per week. Therefore, the magnitude of weight loss for exercise alone, or the additional benefit of exercise to an energy-restricted diet has been modest.[133] This is not surprising if one considers that energy-restricting protocols often result in a 500 kcal per day energy deficit, equivalent to 3,500 kcal per week. There have only been two studies that have matched the energy expenditure of exercise with that of an energy-restricting protocol. When 500 kcal[134] or 700 kcal[135] per day was expended by exercise, the magnitude of weight loss was similar to that of an isocaloric energy-restricting diet for 12 weeks. Therefore, exercise is an effective weight-loss strategy but the accumulated energy expenditure required for weight reduction may be greater than the general recommendations.

Recently, the United States Institute of Medicine (IoM) and the International Association for the Study of Obesity (IASO) have recommended that 45 to 60 minutes per day of physical activity may be required to prevent weight gain.[136,137] The IoM developed this recommendation from the evidence in their Doubly Labeled Water database, which indicated that those who maintained a normal body-mass index across the lifespan had a total daily energy expenditure that was 1.7 times their basal metabolic rate,[136] and the data indicated that 60 minutes of daily physical activity would be required for an individual to move from a sedentary to an active lifestyle. The IASO estimated that for a sedentary individual to become active they would require an additional 490 kcal of daily energy expenditure,[137] which is considerably more than the 150 kcal to 200 kcal per day accumulated with the general exercise guidelines. It is likely that this increased recommendation will pose difficulties for public health guidelines and for professionals who promote exercise adherence, but it is necessary to distinguish between general health and therapeutic benefits of exercise and to establish more specific strategies.

A more targeted approach has recently been taken for the role of exercise in the treatment of Type 2 diabetes. In a review of the evidence base for exercise modality, intensity and frequency, Praet and van Loon[138] have proposed exercise guidelines based on the clinical characteristics of the patient. In particular, they differentiate the exercise prescription on the basis of the duration of diabetes, the initial fitness of the individual, their body mass index, and the length of time they have been exercise training. They have also provided guidelines for endurance, resistance, and interval training, all of which have been shown to improve insulin sensitivity and glycemic control.[138] To advance the therapeutic use of exercise in the treatment of obesity and Type 2 diabetes, it will be necessary to conduct more randomized, controlled trials and to clearly differentiate between the general health and clinical benefits of exercise.

SUMMARY

An active lifestyle increases general health and is protects from a number of different conditions, including exercise and obesity. There is emerging evidence that exercise

by itself exerts clinically beneficial effects in both lean and obese subjects, even in the absence of effects on weight.[1] Recent results have brought an increasing understanding of the molecular mechanisms underlying the beneficial effects of exercise at the level of metabolism and changes in gene expression. There is a significant dose-response to the effect of exercise, and the current guidelines regarding exercise amount may need to be revised upwards. Furthermore, this treatment option should not be overlooked.

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