Mini-Review

Skeletal Muscle and Metabolic Health: How Do We Increase Muscle Mass and Function in People with Type 2 Diabetes?

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Abstract

Background: Whilst skeletal muscles' primary role is allowing movement, it has important metabolic roles, including in glycemic control. Indeed, evidence indicates that low muscle mass and function are associated with an increased risk of type 2 diabetes, highlighting its importance in the development of metabolic disease.

Methods: In this mini-review, we detail the evidence highlighting the importance of muscle in type 2 diabetes and the efficacy of resistance exercise in improving glycemic control alongside our approach to increase uptake of such exercise in people with type 2 diabetes. This summary is based in the authors' knowledge of the filed supplemented by a Pubmed search using the terms "muscle," "glycemic control," "HbA1c," "type 2 diabetes," and "resistance exercise."

Results: The main strategy to increases muscle mass is to perform resistance exercise and, although the quality of evidence is low, such exercise appears effective in reducing Glycated Haemoglobin (HbA1c) in people with type 2 diabetes. However, to increase participation we need to improve our understanding of barriers and facilitators to such exercise. Current data indicate that barriers are similar to those reported for aerobic exercise, with additional resistance exercise specific barriers of looking to muscular, increase risk of cardiovascular event, having access to specialized equipment and knowledge of how to use it.

Conclusions: The development of simple resistance exercises that can be performed anywhere, that use little or no equipment and are effective in reducing HbA1c will be, in our opinion, key to increasing the number of people with type 2 diabetes performing resistance exercise.

Key Words: muscle, type 2 diabetes, strength, resistance exercise

Metabolic Importance of Skeletal Muscle

The primary role of skeletal muscle is to allow body movements via the generation of force. The importance of this is highlighted in conditions where muscle mass is lost, such as in sarcopenia—the age-related loss of muscle mass and function (1–3). This process begins from 30–40 years of age (4–6), even in healthy adults, and results in an increased risk of falls, disability, loss of functional abilities, and a reduction in the quality of life (7). Not only does this loss of muscle mass have deleterious consequences to the individual, but there are also large financial costs. The first study to investigate the economic consequences of sarcopenia estimated that the direct health care costs of sarcopenia in the United States in 2000 were $18.5 billion (~1.5% of total annual health care costs), with excess health care costs of ~$900 per individual with sarcopenic (8). More recent data from the UK indicated that excess health and social care costs of muscle weakness were £2707 per person per year, with an estimated annual excess cost of £2.5 billion (9).

The loss of skeletal muscle is also accelerated in several disease states, including type 2 diabetes. Differences in skeletal muscle mass and function between people with and without diabetes have been clearly demonstrated in older adults with type 2 diabetes in the Health, Aging, and Body Composition Study. In this study of 485 older adults with diabetes and 2133 older adults without diabetes, it was shown that while arm and leg muscle mass was higher (leg muscle mass was 4.6% higher in men and 11.1% higher in women, while arm muscle mass was 5.8% higher in men and 9.5% higher in women) in people with diabetes (due to being larger in size), muscle strength was 3% to 6% lower in men, but not in women, and muscle quality (strength per unit of muscle mass) was 7% to 8% lower in both men and women with diabetes (10). Differences in muscle mass between people with type 2 diabetes and those without are more apparent when looking at muscle mass relative to weight or height (2), with the risk of having low relative muscle mass being 2- to 4-fold higher in people with type 2 diabetes (11). On top of this, the loss of muscle mass, strength, and quality with age occurs at a faster rate (between 28% and 33% faster) in older adults with type 2 diabetes (both diagnosed and undiagnosed) relative to older adults without type 2 diabetes. The loss of muscle mass is particularly an issue in women with type 2 diabetes where the decline in thigh muscle cross sectional area was twice as fast as seen in women without diabetes (12, 13). It is perhaps not surprising, therefore, that physical functional limitations are prevalent in people aged >55 years with type 2 diabetes, with a higher odds of physical function limitations (odds ratio 1.46–1.93) compared with people without diabetes (14).

As well as having a clear functional role, skeletal muscle is also a strong marker, and in some cases perhaps a determinant, of general health (15–18). Indeed, in our recent work, we have demonstrated this in approximately half a million participants from the UK Biobank, where we found that low grip strength was associated with an increased risk of death from all-causes (39% and 67%), cardiovascular disease (CVD; 44% and 84%), respiratory disease (73% and 89%), and cancer (22% and 34%) for women and men, respectively (19). Furthermore, we have recently shown that the addition of grip strength can improve CVD risk prediction scores to a similar extent, as seen with other blood biomarkers such as C-reactive protein or lipoproteins (20). Relevant for type 2 diabetes, we have also demonstrated that the excess risk of all-cause and CVD mortality in people with type 2 diabetes is attenuated in those with high grip strength (21). At this point, using this observational data one cannot infer a causal relationship between muscle and health outcomes, but they do clearly indicate that muscle strength may be a useful predictive tool to identify those at the highest risk of poor health outcomes and that low muscle strength may contribute to the poorer health outcomes in people with type 2 diabetes.

On top of skeletal muscles' functional role, it has other important, and often underappreciated, roles in health and disease (22). One example of this is that skeletal muscle is the primary protein store in the body. In the fasted state, it has been known for many years that muscle protein is the primary reservoir used to replace circulating amino acids taken up by other tissues, such as skin, liver, heart, and brain, ensuring protein synthesis is in balance with protein breakdown—a continuous process in these tissues (23, 24). Maintenance of protein content of these tissues is essential for survival. In addition, these amino acids can also be used for hepatic gluconeogenesis (25). The importance of these physiological roles of muscle are apparent during starvation, after severe burns, and in chronic conditions

such as AIDS, heart disease, and cancer where a higher muscle mass is associated with improved survival (26–30). Focusing on type 2 diabetes, skeletal muscle is the primary site for glucose disposal, with ~80% of glucose being taken up into muscle in the postprandial state (31–33). A larger mass of muscle, therefore, should more effectively maintain normoglycaemia, particularly postprandially.

It is worth noting, however, that the importance of muscle goes beyond simply the amount of muscle mass, and indeed insulin resistance of muscle has been suggested to be the primary defect in the development of type 2 diabetes (34). Furthermore, as mentioned previously, muscle mass is actually higher in people with type 2 diabetes until body size is accounted for—and even then differences are subtle, with muscle glucose uptake around 60% lower in people with type 2 diabetes (35). This supports our assertion that the importance of muscle goes beyond simply size and that other muscle-related mechanisms, indicative of muscle quality, can account for the importance of muscle for metabolic health.

Muscle Mass and Function and Risk of Type 2 Diabetes

Several studies have demonstrated that high muscle mass, high muscle/fat mass ratio, and high muscle strength are associated with lower insulin resistance in a variety of populations (36–39). On top of this, it has been demonstrated in several studies that low muscle strength is associated with a higher prevalence and severity of type 2 diabetes in a broad range of ethnicities (40–45). Interpretation of such data are, however, limited due to their cross-sectional nature. More recently, this literature has been extended with several studies investigating the prospective associations of muscle mass and strength with the incidence of type 2 diabetes. Beginning with muscle mass, for example, in a study of ~200 000 men and women from Korea, who were free of type 2 diabetes at baseline, it was demonstrated that the skeletal muscle index (muscle mass/bodyweight *100), as a measure of relative muscle mass, was negatively associated with incident type 2 diabetes in a dose-response manner (46). In this study, there was a 96% and 121% higher risk, in men and women respectively, of incident type 2 diabetes in the lowest relative to the highest quartiles of relative muscle mass. There are, likely due to its relative ease of measurement, more studies that have looked at the association of muscle strength with incident type 2 diabetes.

These studies have mixed findings (15, 47–55) and have recently been pulled together in a meta-analysis from Tarp and colleagues (56), where it was demonstrated that, when controlling for adiposity, each standard deviation higher muscular strength was associated with a 13% lower risk

of type 2 diabetes, and 24% lower risk of type 2 diabetes when not controlling for adiposity. While this may indicate that much of the relationship between strength and risk of type 2 diabetes is related to larger body size, this is further complicated by data also indicating that when strength was normalized to body weight, effect sizes were general larger than when looking at absolute strength. Further work is, therefore, needed to establish whether relative or absolute muscle strength (and indeed muscle mass) are more important in predicting the risk of type 2 diabetes. These data, therefore, demonstrate that high muscle strength is associated with a lower risk of type 2 diabetes incidence—although, again, whether this relationship is causal cannot be determined from these observational data.

There are, however, some data to indicate that this relationship may be causal. Mendelian randomization (MR) studies use random allocation of genetic material at conception as a form of randomized comparison, and therefore provide stronger unconfounded causal inference than traditional observational studies (57). While an early MR study found no association of grip strength with diabetes (58), a more recent MR study indicated that a higher muscle mass and grip strength may be causally related to a lower risk of diabetes, although the data were far from conclusive (59). The divergence in findings between these 2 studies likely reflects the greater number of alleles (130 vs 2 Single Nucleotide Polymorphisms [SNPs]) included in the latter study increasing the variance in grip strength explained by these alleles. It is worth noting at this point that, as noted earlier, type 2 diabetes results in a more rapid loss of muscle mass and function (11–13); indeed, insulin resistance can drive a decrease in muscle protein synthesis (60), highlighting that this relationship is bidirectional. This bidirectional relationship was observed in the latter MR study published (59).

Strategies to Maintain or Increase Muscle Mass and Function, and Improve Glycemic Control in People with Type 2 Diabetes

This evidence provides a clear rationale to investigate strategies to increase muscle mass and function for the prevention and treatment of type 2 diabetes. While nutritional strategies are frequently suggested as approaches to increase muscle mass and function, it is clear that in the absence of concomitant exercise, data supporting the efficacy of these strategies, such as increasing protein intake, are lacking (61). Although they may be of benefit on top of resistance exercise (61, 62).

The most effective strategy to increase muscle mass and function is resistance exercise, which is efficacious across the lifecourse, even in nonagenarians (63). It is, at

this point, worth noting that resistance exercise will elicit a number of physiological and metabolic changes, in addition to increasing muscle mass and strength. Determining, therefore, the relative contribution of increases in muscle mass/function and the various other physiological/metabolic changes to the benefits of resistance exercise is challenging and beyond the scope of this review. The effects of resistance exercise on cardiometabolic health in adults have recently been summarized in a meta-analysis from Ashton and colleagues (64). In this analysis of 173 randomized, controlled trials, it was shown that resistance exercise training results in reductions in systolic blood pressure (-5 mmHg), diastolic blood pressure (-5 mmHg), fasting insulin (-0.59 µU/mL), fasting glucose (-2.39 mg/dL), and Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) (-1.22), as well as increases in cardio-respiratory fitness. There was also some indication of improvement in blood lipids, although data were less clear. It is worth noting that for all outcomes, the Grading of Recommendations, Assessment, Development and Evaluation summary noted that quality of evidence was low or very low and heterogeneity was moderate to high. In general, larger absolute improvements were seen when analyses were restricted to older adults and those at higher cardiometabolic risk. For this reason, alongside the improvements in muscle function, it is therefore not surprising that resistance exercise is recommended twice per week in the current World Health Organization physical activity recommendations (65) for the general adult population and has recently been given greater prominence in recent UK guidelines (66). Due to the metabolic effects and metabolic roles of skeletal muscle, it is also clear why such exercise may be of benefit for people with type 2 diabetes in improving glycemic control.

Indeed, while there are not as many studies on the effects of resistance exercise on glycemic control in patients with type 2 diabetes, as is the case for aerobic exercise, the available data does indicate that resistance exercise is effective at improving glycated haemoglobin (HbA1c) in people with type 2 diabetes. In the first meta-analysis on this topic, Umpierre et al (67) looked at randomized, controlled trials of at least 12 weeks and found that in people with type 2 diabetes, resistance exercise training was associated with a 0.57% decrease in HbA1c, relative to control. This was in comparison with reductions of 0.67% with aerobic exercise and 0.51% with the combination of resistance and aerobic exercise. In a further meta-analysis of resistance exercise alone in older people with type 2 diabetes, resistance exercise was associated with a 0.50% reduction in HbA1c (68). It was also noted that although adverse events were not reported in all trials, the only adverse event frequently observed was transient muscle soreness. In the most recent meta-analysis of exercise in patients

with type 2 diabetes, compared with the control group's resistance exercise (-0.30%), aerobic (-0.30%), and combined resistance and aerobic exercise (-0.53%), all resulted in reductions in HbA1c (69). While these results are all notable, the heterogeneity of results was high and trial quality was often low, and the number of studies and patients included were low, and this is clearly, therefore, an area where further high-quality trials are needed. However, on the basis of the available trial data, they do indicate that resistance exercise is safe and efficacious in reducing HbA1c in people with type 2 diabetes to a clinically meaningful degree (70), along with the other functional, health, and quality of life benefits of such exercise; as noted earlier, resistance exercise is recommended (71).

As noted earlier, the importance of muscle for metabolic health is not simply related to muscle size, and this is confirmed when looking at the effects of resistance exercise on muscle mass and muscle glucose uptake. While we will not review this literature in detail, it has been demonstrated that 6 weeks of resistance exercise training increases muscle mass by 2.3% in people with type 2 diabetes, while leg glucose clearance increased by ~20% (72). This suggests that much of the improvement in glycemic control is not simply due to increases in muscle size, but that other mechanisms such as increases in mitochondrial function (73) and vascular structure and function (74) are involved, although further work is needed in this area.

Increasing Participation of People with Type 2 Diabetes in Resistance Exercise

However, participation in resistance exercise is generally much lower than that for aerobic exercise in the general population (75), with no data specifically in people with type 2 diabetes. A review looking at the barriers to regular exercise, not specifically resistance exercise, in adults either at high risk of developing type 2 diabetes or diagnosed with type 2 diabetes reveal a lack of studies in this area. Barriers to exercise in general for people with type 2 diabetes included feelings of discomfort, lack of time, weather conditions, lack of motivation, and health problems, which are broadly similar to barriers reported in other populations (76). To our knowledge, there has been only 1 study investigating the specific barriers to resistance exercise in people with type 2 diabetes. In a recent randomized controlled trial, people with type 2 diabetes were randomized to 3 different intervention groups: aerobic exercise, resistance exercise, or combined. Participants from the resistance exercise group and combined exercise group self-reported higher levels of improvement than the aerobic exercise group only; these included improvements in wellbeing, fitness, and

higher levels of enjoyment. The barriers reported were similar across all groups: for example time, work, illness/injury, weather, vacations, tiredness, boredom, and family commitments (77). Data from older people, not specifically with type 2 diabetes, indicate that barriers to resistance exercise are like those reported for aerobic exercise. However, some specific resistance exercise barriers were reported, including looking too muscular and concerns about an increased risk of heart attack, stroke, or death. Furthermore, another key barrier specific to resistance exercise is that access to specialized equipment and knowledge of how to use the equipment is generally required (78, 79). This is a particular problem for resistance exercise, as many aerobic exercise activities, such as walking/jogging, freely accessible to all without any training or complex equipment.

It is clear, therefore, that a detailed understanding of the barriers to participation in resistance exercise is needed in patients with type 2 diabetes. With input from social scientists, exercise physiologists, exercise specialists, and diabetologists, we need to overcome these barriers and facilitate participation in resistance exercise. For example, we need to develop an effective way to overcome the requirement for complex and expensive equipment by developing exercises, with co-creation a potentially useful strategy to adopt (80), that can be performed with little or no equipment such as resistance band exercises, squats, lunges, press-ups. On a positive note, resistance exercises are generally easier to perform for people who are overweight/obese (as many people with type 2 diabetes are) compared with aerobic activities, which are

often hard to perform for people with high body mass (81). Instruction will still be required in how to safely perform such exercises, and we envisage that advances in mobile technology and the use of online video instruction may help to facilitate this in a pragmatic way.

The design of the exercise program can also be simplified considering new understandings of the mechanisms underlying gains in muscle strength and mass, which can simplify the recommendations that are made. Current recommendations from organizations such as the American College of Sports Medicine give detailed advice for the number of sessions per week, repetitions, rest periods, and the load lifted (expressed as 1-repetition maximum [1RM]) (82). However, not only has the evidence supporting these recommendations recently been challenged (83), but our opinion is that the complex nature of these recommendations is a barrier to people taking part in such exercise, alongside their focus on exercises that must be performed in a gym facility (ie, by recommending loads based on 1RM, which can only be measured on gym equipment). Indeed, counter to most recommendations, which suggest that a relatively high load is required for gains in muscle mass and strength, recent advances indicate that the load at which the exercise is performed does not determine the magnitude of the effects of resistance exercise on muscle, when exercise is performed to voluntary failure, with the majority of benefit coming from a single set of exercise performed per week (84–86, 87, 88).

This allows for a relatively simple exercise prescription, with our suggestion for people with type 2 diabetes to focus on performing a single set of each exercise to target major
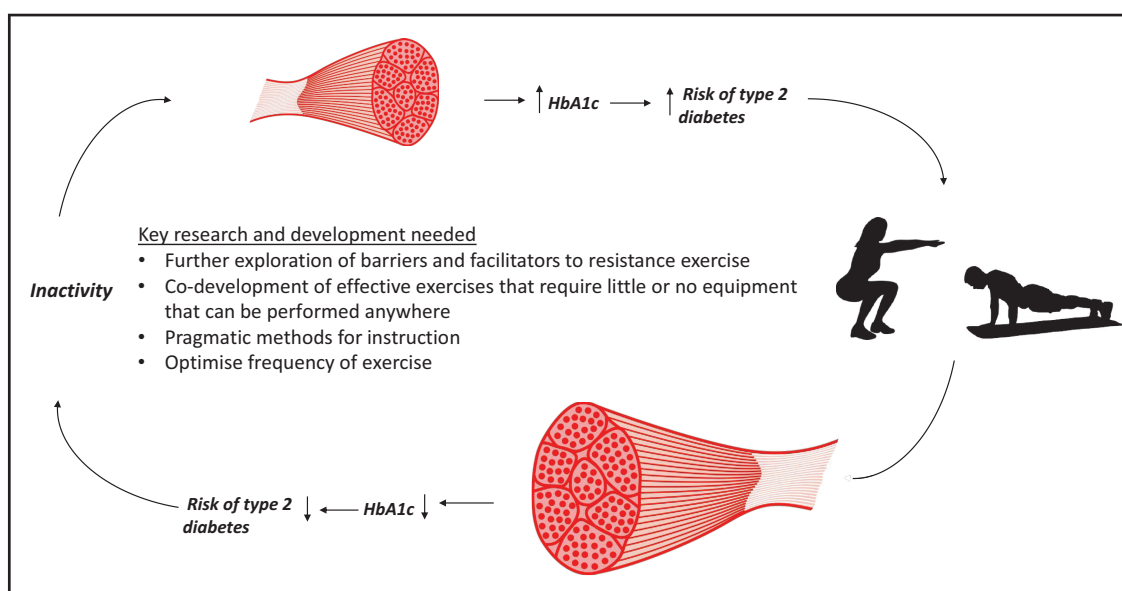
Figure 1. Some of the key research and developmental work needed to increase the uptake of resistance exercise and optomize its effectivness in people with type 2 diabetes. Abbreviation: HbA1c, Glycated Haemoglobin.

muscle groups per week and self-selecting a load that leads to fatigue and that they find most enjoyable. This only requires a short time commitment and also removes the requirement for exercises to be performed at specific percentages of 1RM, allowing for the prescription of home-based exercises, such as resistance band exercises, squats, lunges, and press-ups, to be carried out in a simple manner. Each of these exercises can easily be adapted and progressed depending upon the participants baseline strength and ability, ie, progressing from a lighter to heavier resistance band or progressing from press-ups against the wall before moving to the floor. It is worth noting that we still need to determine the effectiveness of such an exercise program in improving glycemic control in people with type 2 diabetes.

Conclusions

In conclusion (Fig. 1), this review of current evidence gives us a great deal of hope and we believe that resistance exercise has the potential for implementation in people with type 2 diabetes due to its relative time efficiency, its efficacy in improving glycemic control, and the fact that such exercises can be relatively easily performed by people with type 2 diabetes. With the right developmental research, we think that resistance exercise may, therefore, be easier for people with type 2 diabetes to adhere to, or it simply be an alternative accessible form of exercise. Strategies are needed to allow such exercise to be performed at adequate levels in a pragmatic and sustainable fashion.

Additional Information

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    Disclosure Summary: The authors have nothing to disclose.
    Data Availability: Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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