Resistance training, insulin sensitivity and muscle function in the elderly

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Abstract

Ageing is associated with a loss in both muscle mass and in the metabolic quality of skeletal muscle. This leads to sarcopenia and reduced daily function, as well as to an increased risk for development of insulin resistance and type 2 diabetes. A major part, but not all, of these changes are associated with an age-related decrease in the physical activity level and can be counteracted by increased physical activity of a resistive nature. Strength training has been shown to improve insulin-stimulated glucose uptake in both healthy elderly individuals and patients with manifest diabetes, and likewise to improve muscle strength in both elderly healthy individuals and in elderly individuals with chronic disease. The increased strength is coupled to improved function and a decreased risk for fall injuries and fractures. Elderly individuals have preserved the capacity to improve muscle strength and mass with training, but seem to display a reduced sensitivity towards stimulating protein synthesis from nutritional intake, rather than by any reduced response in protein turnover to exercise.

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Introduction

Getting older and ageing is associated with an increase in life-style related metabolic diseases as well as with a loss in overall function. Intimately linked to these events is on one side a reduction in insulin sensitivity that plays a major role in the development of the metabolic syndrome and diabetes, and on the other side a reduction in the skeletal muscle mass that plays a major role for the decrease in functional performance (Figure 1). For both metabolic and functional impairment with ageing it is not clear to what extent this can solely be explained by the age-associated reduction in activity levels. It is clear that ageing has an influence upon skeletal muscle loss, but it is also clear that metabolic impairment and functional losses can be largely counteracted by physical training especially of a resistive nature. With increasing age the amount of skeletal muscle is decreasing due both to a reduction in the number of muscle fibres and due to a reduction in the protein content and thus cross-sectional area of individual muscle fibres. Interestingly, the loss of muscle fibres and area is more pronounced in fast contracting type II fibres compared with the slower oxidative type I fibres, and therefore decreased ability to generate fast movements (maximal muscle power output or force over the first 100–200 ms) is more pronounced (around 3%/year after the age of 60) than the loss in maximal force (peak force generation independent of time; around 1%/year). In addition to loss of muscle fibres, a loss in spinal motor neurons, a reduced axon conduction speed in the remaining neurons and a reduced excitability of the remaining motor neurons contributes to the loss of force and power.

The loss of muscle protein with ageing is not fully explained, but can result in sarcopenia which is defined as: muscle mass/height² that is more than two standard deviations below the standard value for young individuals. Using this definition, it is found that approximately 20% of people over 70 years

Skeletal muscle

Altered morphology and metabolism
Insulin resistance
Fibre type shift
Sarcopenia (ageing-muscle loss)

Metabolic syndrome
Type 2 diabetes
Obesity

Morbidity
Mortality

Loss of function
Falls and fractures

Morbidity
Mortality

Figure 1. Schematic representation of how reduced physical activity together with ageing reduces both metabolic quality of skeletal muscle but also reduces the capacity to perform functional daily activities. Both these effects will lead to increased morbidity and mortality.
and 50% of all over 80 years are classified as sarcopenic. The implications of being sarcopenic is that the muscle mass drops below the critical value needed to perform everyday activities, which causes elderly people to become less independent, and rely on help from others in their daily life. With increasing adiposity in ageing, and thus increase in body weight due to fat, the function in sarcopenic elderly subjects will worsen. In addition to these functional implications associated with loss of muscle mass, both reduced activity and shift in muscle fibre characteristics from II to I will contribute to a reduced insulin-mediated glucose uptake in skeletal muscle of elderly subjects.

Resistance training has the overall aim to improve muscle strength and power for use either in relation to competitive performance, recreational sports or in a more clinical setting where increased muscle strength results in increased functional capacity as a part of rehabilitation after disease or injury. Especially in elderly subjects, resistance exercise has become increasingly important in order to avoid functional decline and disability. Resistance exercise results in both a net increase in muscle protein synthesis and thus a rise in muscle fibre cross-sectional area, as well as in an increased ability to activate motor units in a more synchronized way. Together these changes contribute to increased force output after training.

Resistance training and insulin sensitivity in the elderly

The headline may imply that insulin resistance is a natural development that inevitably follows ageing. This is not the case. With ‘healthy’ ageing, i.e. maintenance of a physically active lifestyle and avoidance of obesity, insulin-mediated glucose uptake rates in skeletal muscle does not necessarily decrease with age. When insulin resistance is so often associated with ageing, it is mostly due to a marked decrease in daily physical activity, decreased muscle mass, increased intramyocellular lipid deposits and accumulation of adipose tissue. For obvious reasons no longitudinal, randomized studies of this have been carried out, but studies of glucose tolerance and skeletal muscle biochemistry in master athletes [1–3] as well as measurements of muscle glucose uptake rates in elderly and young healthy subjects [4] support this notion.

Nevertheless, it is a fact, that with advancing age the prevalence of glucose intolerance and insulin resistance (type 2 diabetes) is increased, and for these patients non-pharmacological treatment should be the first ‘drug of choice’. Life-style modifications, focusing on changing dietary habits and energy restriction, have proved to be difficult and are often perceived as a limitation (i.e. disallowing a behaviour). In contrast, when prescribing exercise as a tool to prevent glucose intolerance developing into overt type 2 diabetes or even to treat established insulin resistance, this is perceived as adding an element, not taking something away or prohibiting a behaviour. However, as with any other treatment a successful intervention requires that the individual is motivated and quickly experiences a solid effect of the personal efforts. Thus an important task
for the health care professional is to visualize and explain such effects, e.g. by simple measurements of blood glucose, strength or aerobic capacity [5].

Apart from the positive effect on insulin resistance, exercise training also has wholesome effects on all of the other conditions associated with the metabolic syndrome (e.g. hypertension, dyslipidaemia, obesity and atherosclerosis), which is also seen more frequently with advanced age. In patients with diagnosed type 2 diabetes, and in pre-diabetic states such as impaired glucose tolerance, an increase in daily physical activity has been shown to prevent type 2 diabetes, improve insulin-mediated glucose uptake rates, glucose tolerance and the insulin response to glucose. The majority of intervention studies have used endurance/aerobic training programs and the effects of such programs on insulin sensitivity are undisputed. However, aerobic training may be difficult for many of the patients, due to the existence of co-morbidities or simply because the majority of the patients are overweight if not severely obese. For these patients, resistance exercise represents an attractive alternative.

The number of studies on the effects of resistance training on glycaemic control and insulin sensitivity in middle aged to elderly healthy subjects and patients with insulin resistance has increased substantially in the past 15 years. We have identified 25 such studies, but the limitations of the present chapter do not allow for a detailed review of these studies. However, in a review from 2003 [6] several of them are described. In general, the interpretation and individual comparison of intervention studies using resistance training is to some extent difficult, because there is no uniform agreement in how the exercise intervention is described in terms of intensity and/or number of repetitions. Some studies merely report that the used workload was e.g. 8RM, whereas others report the number of repetitions at a given percentage of max. workload. Furthermore, some studies describe in detail the use of progressive resistance training, while others do not give this kind of information. Therefore, a clear dose–response relationship between the training intensity and the effect on strength is difficult to obtain in these studies. Furthermore, a clear dose–response relationship as regards insulin sensitivity cannot be deduced from the published studies, but from a biological point of view it is difficult to imagine that such a relationship should not exist, at least up to a yet undefined maximum. In those studies where insulin sensitivity has been measured, the majority have shown a significant effect. With some uncertainty the percentage of maximal workload can be calculated from given data on RM, and by doing so it appears that resistance training at an intensity range of 45–80% of maximal load results in approx. 30% (range 10–75%) increase in strength and approx. 28% (range 15–48%) increase in insulin sensitivity. The duration of the intervention is in most studies more than three months, but as little as six weeks of training have shown marked improvements in insulin sensitivity [7].

The mechanism by which resistance training improves insulin action is not merely a function of increased muscle mass [8]. Several proteins increase
in abundance and/or activity, and below is given a short overview of the key players. Minor discrepancies may exist between effects of strength and endurance training, but in general the effects are similar and therefore a discrimination between the two training regimens is not made (Figure 2).

Insulin binding to the IR (insulin receptor) is not affected by training in rats [9] or humans [10]. The number of IRs has been shown to increase with training in rats [11] and in humans [7], to decrease in humans [12] and in rats [13] or remain unchanged in humans [14]. Insulin receptor kinase activity seems unchanged with training in humans [10,14]. Insulin receptor substrate-1 protein has been shown to decrease [13] in rats whilst remaining unchanged in humans [7].

The protein levels of the regulatory subunit, p85, of the phosphatidylinositol 3-kinase (PI3K), is not changed with training [7], whereas activity of the catalytic subunit, p110, has been shown to increase with training in rats [13,15]. Further along the pathway leading to GLUT4 (glucose transporter 4) translocation, protein kinase C λ/ζ activity increases with training [15]. One of the most robust findings is the training induced increase in GLUT4 protein and mRNA levels in humans [10,16]. Akt (protein kinase B) protein levels also

Figure 2. Key players in strength and/or endurance training induced improvements in fat- and carbohydrate metabolism in skeletal muscle

The depicted signals and pathways are not representing the complete picture. Rather the most important proteins and enzymes in relation to physical training are shown. See text for details.

ACC, acetyl-CoA carboxylase; FABPpm, fatty acid binding protein in the plasma membrane; GSK-3, glycogen synthase kinase-3; HK, hexokinase; HSL, hormone sensitive lipase; IRS-1, insulin receptor substrate-1; LPL, lipoprotein lipase; PDK 1/2, phosphoinositide-dependent kinase 1/2; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; NEFA, non-esterified fatty acid; TG, triacylglycerol.
increase with training in rats [13] and in humans [7] as does Akt activity in rats [15]. Akt inhibits glycogen synthase kinase-3, which in turn, has an inhibitory effect on the GS (glycogen synthase) enzyme. Thus, an increase in Akt may ultimately lead to a stimulation of GS and glycogen formation. Another robust finding is the training induced increase in GS activity [7].

As glucose enters the cytoplasm of the muscle cell, it is rapidly phosphorylated into glucose 6-phosphate by the enzyme, hexokinase. The third robust finding in training studies, is an increase in the activity of hexokinase [17].

In addition to the above-mentioned training effects on carbohydrate metabolism in skeletal muscle, it is well-known that physical training (in particular endurance training) increases the β-oxidative capacity (e.g. by enhancing the activity of hydroxy-acyl-CoA-dehydrogenase). More recently, it has been found that the maximal activity of CPT 1 (carnitine palmitoyltransferase 1), which is the rate-limiting step for mitochondrial oxidation of long-chain fatty acids, is increased with training [18]. In addition, these authors also found that training diminished the sensitivity of CPT 1 to inhibition by malonyl-CoA [18]. The fatty acid translocase, FAT/CD36, has now been found to be present in mitochondria [19], and furthermore, it co-immunoprecipitates with CPT 1 and this association increases with training [20]. Further up-stream of this pathway (Figure 2), the contents of FAT/CD36 and the fatty acid binding protein in the plasma membrane has been shown to increase with training [21–23]. All of these effects on proteins involved in the transport of fatty acids to the mitochondria form the basis for the increased capacity for fatty acid oxidation. One might expect that also the activity of the hormone sensitive lipase is increased with training, but so far this has not been shown [24]. In contrast, lipoprotein lipase activity increases with training [23,25,26], again improving the overall capacity for trained muscle to metabolize fatty acids at the expense of carbohydrates.

AMPK (AMP-activated protein kinase) plays a key role in regulating fuel combustion in skeletal muscle, and the amount of this protein is also highly influenced by the training status of the individual. Thus, AMPKα1 and AMPKβ2 protein expression increases, whilst AMPKγ3 protein and gene expression decreases with training [27,28]. Activation of AMPK by e.g. exercise, will cause a drop in malonyl CoA, which in turn will facilitate fatty acid transport into mitochondria and stimulate fatty acid oxidation. The effect is mediated via inhibition of acetyl-CoA carboxylase, which also increases in expression with training [27].

Recently, a study compared the mechanisms behind comparable increases in insulin-mediated glucose disposal after aerobic and resistance training in older men [29]. The authors reported a significant increase in skeletal muscle glycogen synthase activity only in the aerobically trained men, but a significant increase in muscle mass, muscle glycogen content or citrate synthase activity could not be demonstrated in any of the groups [29], which normally is a characteristic finding after training programs. With aerobic training for months,
an increase in capillary density is a common finding in both healthy and insulin resistant humans. This increase facilitates diffusion of glucose from the capillaries into the muscle cells, and is therefore also a part of the mechanism behind the increase in insulin action seen after aerobic training. Capillary density is normally not increased by resistance training, so the mechanisms behind the enhancement of insulin action with the two different training regimens are not completely identical, but most likely the mechanisms differ only in minor details. Further studies may clarify this issue.

Resistance training, muscle hypertrophy and function in the elderly

Cross-sectional data on elite master athletes demonstrate that regular strength training throughout life can preserve a last part of the muscle mass from a young age. Intervention studies on a variety of groups of elderly individuals from around 60 and up to 100 years of age has shown that improvements in both muscle strength and muscle volume can be achieved by resistance training. This beneficial effect of training is seen not only in healthy elderly individuals, but also in frail elderly, and older individuals with co-morbidities [30]. The main question is, to what extent elderly individuals can counteract their skeletal muscle loss, and what role training and nutrition plays. Trained elderly individuals often have the strength of young untrained individuals, and intervention with strength training often show a ‘strength-rejuvenation’ of 20–30 years. Strength training studies demonstrate an improvement in everyday functional abilities like chair rising and stair climbing.

The regulation of muscle growth in the elderly is not completely understood. Synthesis of myofibrillar protein in relation to exercise has been shown to be either lower or identical to young individuals, and similarly degradation of muscle protein has been found to be similar to or somewhat higher than in younger counterparts [31,32]. If the findings of reduced synthesis and increased breakdown should be true the muscle loss in the elderly would be larger than is actually seen. It is clear that the mTOR pathway involving p70 S6 kinase phosphorylation in elderly individuals is active, and interestingly this pathway can also interact synergistically with high amino acid concentrations [33]. Interestingly, it is known that elderly individuals when compared with younger counterparts do not respond as efficiently in using nutritional supplementation like amino acids [34]. This implies that the elderly possess anabolic insensitivity and that the ability to benefit sufficiently from their food intake is reduced. Ingestion of food will be associated with an increase in circulating insulin levels, which activates the insulin signalling cascade all the way down to p70 S6 kinase and 4EBP1. After resistance training this stimulating effect of insulin is enhanced by a mechanism that is not fully understood. The lower anabolic response to nutritional intake in the elderly can be shown both with ingestion of relatively small amounts of protein/amino acids and with
the combination of carbohydrate and protein administration. The latter finding is at least suggestive for the idea that elderly individuals have a reduced anabolic action of insulin. This could be due to an impaired capacity of insulin to stimulate the protein signalling pathway, but could also be due to a reduced capacity of insulin to stimulate muscle perfusion and thus amino acid availability to the skeletal muscle. Resistance training is known to cause an increased expression and protein synthesis of GH (growth hormone), IGF-1 (insulin-like growth factor-1) and the IGF-1 isoform entitled MGF (mechano growth factor), which has been suggested to be specific for skeletal muscle [35], but recently has been shown also to be up-regulated by exercise in connective tissue such as tendon [36]. The influence of IGF-1/MGF may result in a post exercise activation either via the insulin signalling pathway or via activation of satellite cells. Suggestions have also been made that the calcium/calmodulin dependent protein kinase plays a role in the acute effect of resistance exercise and the long-term adaptation and fibre type shift with resistance exercise. Amino acids can stimulate mTOR independently from insulin but also activate p70 S6 kinase and 4EBP1 independently from insulin. Whether these
pathways have a reduced capacity in elderly individuals compared with young counterparts is not known. Administration of GH to elderly individuals in amounts that double the circulating levels of IGF-1 did not enhance the muscle hypertrophy that was achieved by strength training alone [37]. In accordance with a reduced ability to benefit from nutritional supplementation in the elderly, administration of protein together with carbohydrate and fat in healthy elderly individuals after strength training resulted in an improvement in strength and muscle volume, only if supplementation was given immediately after training [38]. If given 2 h after training, the hypertrophy effect of strength training was abolished (Figure 3). Earlier classical studies have found varying results as to the effect of protein supplementation [30]. Although these reports all described the given dose, they did not report the timing for the administration, and this may be important. The exact mechanism behind the interaction between nutrition and strength training induced muscle hypertrophy is not elucidated, but it can be shown that in elderly individuals the protein balance is only positive if protein is taken, and that it is superior to carbohydrate intake.

Hormones like testosterone in elderly men and oestrogen in middle aged and elderly women have been shown to positively stimulate muscle growth [39]. In contrast, counteracting the age-related reduction in GH secretion (somatopenia) seen with ageing, does not improve muscle growth either alone nor in addition to strength training. A further factor that has been discussed in relation to ageing and skeletal muscle is the number and activity of satellite cells. In younger individuals its appreciated that satellite cells not only are active in the case of tissue injury and repair but also play a physiological role in providing new myonuclei as the muscle fibre grows in relation to strength training. Recently it has been shown that elderly individuals, independent of gender, increase their number of satellite cells in response to physiological strength training. This indicates that this pathway for forming new myonuclei is maintained in elderly individuals. What role nutrition may have in relation to satellite cells in the elderly is unknown.

Therefore, more studies are beginning to look at the response to training in individuals ‘at risk’ who typically have sub-optimal function and co-morbidities [40,41]. In such a study, elderly women who had experienced a fall injury (contusions but without fracture) were enrolled to either a training group or a non-training control group. After 6 months of strength training, women who trained improved their muscle strength significantly as well as their muscle power, evaluated as the ability to perform quick knee extensions in specialized and validated equipment. This increase in muscle power could indicate that training increased type II muscle fibre volume more than type I, but not all studies have been able to find a relative increase in type II to I fibre content as a result of training. An additional explanation for the increased muscle power could lie in the connective tissue. Although tendons of elderly individuals are thicker compared with younger individuals, they are also weaker, and interestingly it has been shown that strength training makes the
Ageing human tendon stiffer. This would cause less extensibility in the tendon during muscle contraction and thus result in a more rapid force transmission. The better muscle force and power in the frail elderly women after fall injury following training also resulted in improved everyday function. Interestingly, the maximal walking speed of these individuals was identical to the required speed which you need to have in order to be able to cross a street with traffic lights, and after resistance training the relative load to perform this task was lowered to 80–85% of maximal walking speed.

Low muscle mass is correlated with not only lower functional capacity, but is associated with a higher risk of falls, fractures and mortality. Low grip strength is associated with higher mortality, and low knee extension strength is related to incidence of early mortality after hip fracture. It was shown that those individuals with the highest knee extension strength had an almost 10-fold reduction in the mortality in association with a hip fracture compared with those individuals who had the weakest knee extension strength. Such a study is too small to detect whether strength training can not only influence factors of importance for falls but can also prevent *de facto* falls and injuries. Large scale studies comparing exercise training with vision control and managing of home hazards showed that exercise was the only intervention that had a significant effect upon fall frequency. Furthermore, looking at the larger studies within this area has shown that strength training in the elderly at risk from falls can reduce both frequency of falls as well as frequency of injuries with fractures by about a third. Thus there is good evidence that strength training, both supervised in a hospital setting as well as home-based exercises, is effective in counteracting falls and fractures.

In several groups with chronic diseases it has been shown that strength training can improve function (Figure 4). In patients with severe chronic obstructive lung disease increases in both muscle strength and in muscle volume after strength training was accompanied by a marked improvement in walking speed, stair climbing and activity of daily living. Furthermore, both in heart disease, osteoporosis and arthrosis it has been demonstrated that strength training will improve symptoms and function. Finally, in regards to depression, sleep pattern and mental well-being, strength training has been shown to be beneficial in elderly individuals. Training studies in patients vary often, but seem to be closely related to the compliance of the participants, rather than to detailed differences in the training pattern.

Strength training has been shown to play a positive role following surgery. With severe hip osteoarthritis, post-operative treatment with strength training was superior to electrical stimulation and standard mobilization regimens [42]. The increase in muscle strength that was obtained with strength training resulted in a neutralization of the side-to-side difference in strength that was observed prior to surgery, which is important considering that a difference in leg strength is a major risk factor for falls in the elderly. In addition to these improvements, with strength training, the functional performances improved
and correlated with the rate of force development of the thigh muscle. In addition the period of rehabilitation before the patients were discharged was reduced. Although these findings cannot be generalized to all surgical interventions it does show that training, in association with surgery is beneficial, and helps with restoring both muscle strength and functional performance [42].

Conclusions

Despite the fact that ageing is associated with a decreased muscle oxidative capacity and a reduced muscle function, a major part of this decline can be counteracted by physical activity, especially by resistance training. It is interesting that resistance training improves insulin sensitivity beyond the effect of just adding muscle mass, and this raises the question of whether heavy loading of muscle in the elderly causes similar effects on muscle that endurance activities would also create. The studies on protein turnover in skeletal muscle in the elderly are still not comprehensive enough to explain the mechanisms, and especially methods for the study of muscle protein degradation are not sufficiently accurate to draw major conclusions. Thus, adequate and timely nutrition support should accompany physical resistance training in elderly, and this advice should be followed whilst the mechanism behind the effect of exercise and nutrition is further investigated.
Summary

• Muscle mass and strength is lost with ageing both due to muscle fibre atrophy and loss of motor units.
• Resistance training can improve insulin sensitivity not only due to development of more muscle but also due to improved muscle quality.
• Improvement of strength and especially of power through resistance training prevents falls and injury in elderly people.
• Patients with chronic disease or who are post-operative can benefit from strength training and improve muscle strength as well as daily function.
• Elderly and young people respond to resistance training with a similar increase in muscle protein synthesis, but elderly people have a reduced nutrition-induced increase in protein synthesis.

References


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