Exercise, Sarcopenia, Cognition, and Mood

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Sarcopenia is the decline in muscle mass that occurs with normal aging. Sarcopenia is a major cause of frailty, disability, and loss of independence in the elderly [1]. It is not a disease and is seen even in master athletes as they age. However, exercise can reverse many of the effects of sarcopenia, and even make elderly people stronger than sedentary young ones. Exercise is also known to have beneficial effects on mood, which is often depressed in people with sarcopenia, and it may have psychological as well as physiological benefits in this population.

Prevalence and Characteristics of Sarcopenia

Although the decline in muscle mass and function with age is universal, for the purposes of epidemiological studies some cutoff must be established to define sarcopenia. Baumgartner et al. [1], using a cutoff of two standard deviations below the mean for healthy adults under age 30, found that the prevalence of sarcopenia rose from about 20% in the 7th decade of age to over 50% by the 9th decade.

An important characteristic of sarcopenia is that it seems to affect primarily type II muscle fibers, the anaerobic (white) fibers that are responsible for strength-requiring actions such as rising from a chair. In contrast, type I
Physiology of Sarcopenia

Sarcopenia is probably best thought of as the result of a gradual withdrawal of anabolic stimuli from muscle (Fig. 1). Many anabolic factors decline with age. Among the most important is likely to be the loss of alpha motor neurons from the spinal cord with age. By the 7th decade, healthy persons have lost a substantial number of motor neurons compared to persons in the 3rd decade [4]. At this time, this loss is irreversible. After age 30, growth hormone secretion by the pituitary begins to decline [5]. At menopause, women lose estrogen rather abruptly, while men lose androgen production over a longer and more poorly defined period termed the andropause [6].

An important cause of muscle loss in developed societies is the progressively more sedentary lifestyle of elderly people as they age. Physical activity in developed countries begins to decline in adolescence, strongly suggesting...
that prevention of sarcopenia must involve inculcating life-long habits of exercise and physical activity. Less physical activity means less total energy expenditure, but dietary energy intake usually fails to decline to an equal degree, so that a large portion of the population develops positive energy balance between ages 20 and 60. The result is weight gain, and the epidemic of obesity now being observed in the USA and elsewhere [7, 8]. Paradoxically, while weight gain protects against sarcopenia in the near term, because about 25% of the weight gained is lean mass, in the long term it probably promotes muscle loss. The reason for this is at least threefold: (1) obese persons are more sedentary than lean ones, and thus reduce one of the most important trophic stimuli to their muscle, that of physical activity; (2) obesity, especially with gain in the abdominal visceral fat, leads to insulin resistance, thus reducing another major anabolic stimulus to muscle, via insulin, and (3) adipocytes are known to produce tumor necrosis factor-α (TNF-α), a catabolic cytokine which can directly cause muscle atrophy and can also cause insulin resistance by interfering with the function of the insulin receptor [9].

Although positive energy balance and weight gain are the norm before age 60, after this age there is a tendency toward a slow loss of weight [10]. In addition, elderly persons are more likely than younger ones not to meet the recommended dietary allowance for protein. Inadequate protein intake can accelerate loss of muscle protein in the elderly, and it is not clear whether the recommended daily allowance for protein in the elderly is in fact adequate, as studies are evenly divided on this point [11]. Other dietary factors may also be important in preventing sarcopenia, such as vitamin D, antioxidants, and B vitamins [12].

In addition to the withdrawal of anabolic stimuli with age, it is not clear if there is an increase in catabolic stimuli to muscle as well. However, there is some evidence that production of the catabolic cytokines interleukin-6 (IL-6) and possibly interleukin-1β (IL-1β) are increased with age [13]. In the Framingham Heart Study, for example, production of IL-6 by peripheral blood mononuclear cells (PBMC) increased with age, and increased further in elderly persons with evidence of systemic inflammation, as determined by elevated levels of serum c-reactive protein (Fig. 2a). In addition, PBMC production of IL-1 receptor antagonist (IL-1Ra), a pure antagonist that is produced in response to the same stimuli that produce IL-1 and acts to prevent excessive IL-1 agonist activity, was increased fourfold in elderly adults compared to young healthy controls (Fig. 2b). Unlike the case with IL-6, however, IL-1Ra did not vary by cross-reacting protein status, suggesting that it may be increased as a result of age, and not inflammation. It is important to note that the increase in IL-1Ra was seen despite the absence of an increased production of either IL-1β or TNF-α, raising the unanswered question of what stimulates the IL-1Ra in the first place. However, these data suggest that there is a component of subclinical inflammation to aging, which may be an important factor in the
**Fig. 2.** Production of IL-6 **a** and IL-1Ra **b** by peripheral blood mononuclear cells (PBMC) from young healthy subjects and elderly subjects in the Framingham Heart Study. The elderly subjects are further subdivided according to serum C-reactive protein levels to indicate the presence of underlying inflammation (0 = undetectable, 1 = <1 µg/dl; 1–2 = <2 µg/dl; 2 = 2 µg/dl or more). From Roubenoff *et al.* [13] with permission.
development of sarcopenia. The role of catabolic cytokines in the development of sarcopenia remains to be elucidated.

**Exercise and Sarcopenia**

There is no question that progressive resistance exercise can reverse sarcopenia. Even in nonagenarians, muscle retains its plasticity and can be trained to be stronger [14]. However, the increase in strength – often on the order of 30–50% over 8–12 weeks – greatly exceeds the increase in mass that is seen with training, which rarely exceeds 5–10%. This discrepancy indicates that strength training has functional effects – at the level of the brain, peripheral nerve, neuromuscular junction, and myocyte – that exceeds its effect on simple muscle mass. Furthermore, although muscle mass is the main predictor of muscle strength, and decline in muscle mass and strength appear to occur in parallel, strength and mass are dissociated in response to training. In patients with HIV, for example, the increase in mass and increase in strength were each independent predictors of improvement in functional status after 8 weeks of exercise training [15].

In order for exercise to be effective against sarcopenia, it must be resistive, rather than aerobic, in nature; it must be intensive, with participants working at 60–80% of their maximal strength, and it must be progressive, so that as persons become stronger the amount of weight lifted is increased to maintain the intensity. It is not known whether routine physical activity, such as gardening, housework, or walking can effectively prevent or treat sarcopenia. However, it is clear that physical activity is a marker for successful aging, and persons who can be physically active are not frail.

**Sarcopenia, Mood and Cognition**

Sarcopenia often develops independently of psychological problems related to aging, such as depression and dementia. However, these conditions are often interrelated. Advanced sarcopenia, with its attendant frailty and loss of independence, is a clear cause of depression and grieving in the elderly. Conversely, dementia leads to reduced physical activity and dietary intake, and perhaps to elevations in resting metabolic rate, which in turn accelerate sarcopenia. Untreated depression, with its anhedonia and reduced physical activity, in many cases also accelerates sarcopenia.

**Effect of Exercise on Mood**

Both aerobic and resistance training methods have been tested as treatment for depression in the elderly in a small number of studies. Singh *et al.* [16]
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recruited 32 elderly adults with mild to moderate depression (mean age 71, mean Hamilton Rating Scale of Depression [HRSD] score of 12 out of a possible 52 points). Patients were randomly assigned to either resistance training or an attention-control group for 10 weeks. The training group exercised 3 times a week at a high intensity (75% of 1-repetition maximum), with emphasis on large muscle groups of the legs, buttocks, and trunk. This group had a mean increase in strength of 33 vs. –2% for the control group. The intervention group had an improvement in their HRSD of 7 vs. 2.5 points for the control group (p < 0.008; Fig. 3). Similar improvements were seen in other indices of mood and function. There was a significant association between the intensity of training (% of 1-repetition maximum at which patients trained) and their response in mood (r² = 0.617, p < 0.0002).

The study by Singh et al. [16] is the only one that has systematically evaluated strength training in the treatment of depression in the elderly. McNeil et al. [17] randomly assigned elderly adults (mean age 72) to 6 weeks of walking or an attention control group (social contact) or a wait-list control group (no intervention). Both the walking group and the social contact group improved compared to the wait-list group, suggesting (1) aerobic exercise may also help treat depression, and (2) this effect may at least partly be mediated by the social interaction inherent in exercise therapy. However, the strong association between exercise intensity and improvement in depression suggests that more intense exercise may be more effective and work through other mechanisms than socialization alone. In a younger population, Doyne et al. [18] also found both resistance and aerobic training to be effective. Martinsen et al. [19] found no difference between resistance and aerobic
training in treating mild to moderate depression, but this study was limited by the lack of an untreated control group.

A recent meta-analysis [20] examined the effect of exercise on anxiety and depression in patients with heart disease who participated in cardiac rehabilitation programs. Such programs traditionally use aerobic training almost exclusively, and details of each study were not given in the review. Furthermore, these patients were not all elderly, and no range of ages was provided, although one may expect that most of them were over age 60. A total of 13 studies on anxiety and 15 on depression were included in the meta-analysis. There was a significant effect of exercise on both conditions, with an effect size of 0.3 standard deviations for anxiety \( (p < 0.01) \) and 0.46 standard deviations \( (p < 0.001) \) for depression. However, the authors pointed out that these effect sizes must be considered moderate at best, and may be influenced by several biases, including publication bias. A notable finding of this review is that the effect size was inversely correlated with the sample size of the study, raising a warning about the ability of exercise to be used as a large-scale public health intervention. In defense of exercise, however, it should be pointed out that cardiac rehabilitation is not designed to treat depression per se, but rather to focus on improving cardiac function. Thus, the finding of any significant effect on depression speaks to the strength of exercise as a potential intervention.

**Exercise and Sleep Disorders in the Elderly**

In addition to its effect on depression, exercise training has been shown to improve sleep, in terms of duration, latency, and quality. Both aerobic and resistance training have an important effect on sleep (Fig. 4). This is of great potential importance in the elderly independent of depression, since the prevalence of sleep disorders increases dramatically with age. King *et al.* [21] studied 44 young-elderly adults (mean age 62) with moderate sleep disorders but without depression, cardiovascular disease, or physical limitations preventing exercise. They were randomly assigned to a low-impact aerobic program (30 min 4 times a week, twice in class and twice at home), to be done after dinner, or to a wait-list control group. The exercise group had significant improvements in sleep quality, fell asleep an average of 15 min earlier, and slept about an hour longer, as a result of the exercise program.

Singh *et al.* [22] also studied the effect of the above-mentioned resistance training program on sleep in a separate publication from the same study. The effects of resistance training were remarkably similar to those seen by King *et al.* [21] with aerobic training (Fig. 4), as overall sleep quality improved by 30\% \( (p < 0.006) \).

The effect of exercise on sleep has also been tested in elderly nursing home residents with incontinence, dementia, and requirement for physical
restraints [23]. In a second study [24], exercise was accompanied by improvement in the nursing home environment to foster better sleep, such as reducing noise, turning off lights, etc. The exercise program for these frail elderly subjects (mean age 85) consisted of increased transfers from bed to chair, increased walking with assistance or wheelchair propulsion, and structured exercises increasing the use of arms and legs. These exercises were carried out up to 4 times/day, 5 days/week. Physical activity alone did not have a significant effect on sleep, but combined exercise plus environmental intervention did improve sleep quality and duration.

**Exercise and Cognition**

Unfortunately, there is little information about the effect of exercise on cognitive disorders. In the nursing home studies discussed above, the mean cognitive function was poor (Mini-Mental State Examination score of 13.1 out of 30), and there is no discussion of change in this with the exercise [23, 24]. However, improvement in sleep after the intervention did lead to a 32% reduction in daytime agitation in this patient group \((p < 0.05)\). It cannot be determined if this is due to better sleep or the exercise *per se*. Thus, exercise may help with some symptoms caused by cognitive dysfunction, but it is unlikely to help improve the underlying disorder.
References

Discussion

*Dr. Meydani:* I was particularly interested in the data you showed with the different levels of cytokine expression in muscle. Have you looked at the protein level for these cytokines? You might get increased expression of the message but the protein level might do quite the opposite. For example, in the case of IL-6 we found that you might have a higher level of message but when you look at the protein level it does not change, while in other cases there is no message change but the protein level changes. I think you need to find a way of screening for the protein as well.

*Dr. Roubenoff:* We are going to start with *in situ* hybridization studies this year to do that.

*Dr. Burckhardt:* We are rather short of outcome data, and I wonder whether there will soon be any studies showing that exercise has an impact on health and morbidity. You showed a correlation but it was mostly cross-sectional. Also, on the graph where you showed all the different pathogenic factors that might have an effect, there was one that could be tested cross-sectionally, and that was hormones. There are many elderly women who take hormone replacement therapy, and I would be very interested to see whether that type of hormone supplementation makes a difference.

*Dr. Roubenoff:* As to the effect of exercise, there are many studies showing that exercise is beneficial in various different ways. The question of whether an exercise program would prevent nursing home admission has not been studied and I agree that is clearly something that needs to be done. In terms of the hormone replacement data, there is at least one study I know of that is looking at that now, but there are no results as yet. The results could be confounded by selection bias in the women who choose to go on to hormone replacement. The few data there are suggest that there is some maintenance of muscle, but this has not been studied in a systematic fashion and, you are right, it should be.

*Dr. Burckhardt:* I agree there will be confounding factors. I think that elderly women who take hormone replacement therapy have a more health-conscious lifestyle.

*Dr. Cottrell:* Is sarcopenia due to muscle fiber loss in numbers or in cross-sectional size?

*Dr. Roubenoff:* In fact it is both – they track each other quite closely and there is both hypoplasia and atrophy.

*Dr. Cottrell:* And how is the fiber lost? Is there a particular way?

*Dr. Roubenoff:* It is presumed to be by apoptosis and there is no evidence for an inflammatory mechanism, but there is no proof of that as yet. There are some studies showing increased apoptosis in muscle with age [1], but none showing that this is the mechanism of sarcopenia.

*Dr. Aihie Sayer:* It strikes me that looking at sarcopenia is very much about looking muscle loss, and I wonder what is known about how muscle loss relates to peak muscle function. How much work has been done looking at determinants of peak muscle function, in analogy to peak bone mass?

*Dr. Roubenoff:* There is very little about peak muscle function because the spread is so large. Unlike bone, muscle responds much faster to training or to the level of activity and then also detrains very quickly; you lose the effects in about 3 weeks. We don’t know much about mid-life function and late-life decline.

*Dr. Aihie Sayer:* I was wondering about earlier ages as well. In our data we showed that growth before birth relates to muscle function later in life. We also did work which we have not published yet looking at muscle size and function in childhood and found it to be related to birth size. I wondered whether these might track through to later life.
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Dr. Roubenoff: People who are physically active as children tend to remain active into adulthood, but at least in the USA physical activity falls precipitously after college. After the age of 22 or so, activity declines in the entire population and the people who maintain a high level of physical activity become a more selected population.

Dr. Aihie Sayer: But within any particular level of physical activity there will still be a range, and maybe the determinants of that range are relevant to outcome.

Dr. Folstein: Is there any work looking at bouts of exercise? In analogy to eating, are there factors that turn exercise on and others that turn it off? For example, we know that light can entrain activity in rats in the running wheel. Is there anything known about what turns on human exercise or what turns it off?

Dr. Roubenoff: Very little is understood about what makes one person become an athlete and another person not. There is some talk about endorphin levels and so on, and there are data on serotonin levels in athletes versus non-athletes, but these are cross-sectional data so you don’t know what is chicken and what is egg. There is a huge literature on the response to exercise in muscle, but not the other way round – in other words, what makes people begin exercising regularly versus not exercising. Data we have from the old people in our community-based studies suggest that they usually have no lifetime experience of exercise at all. The cohort of people who are now in their 60s and 70s spent virtually no time on exercise in school or after school, except for the very few elite athletes. What makes them respond to exercise is the result of the training program. The people who have the biggest response in terms of their self-efficacy scores are the ones who are most likely to continue, though why they are different we don’t know.

Dr. Jensen: In some cases sarcopenia appears to be a smoldering inflammatory state. We consider therapeutic interventions such as exercise and training, anabolic agents and so on, but is there any information about the use of anti-cytokines in situations characterized by loss of muscle, for example rheumatoid arthritis?

Dr. Roubenoff: We are doing a study now looking at TNF blockade, which has been clinically approved in the USA, and what that does to muscle and to insulin resistance. This is the first study of that kind that I’m aware of. There is evidence that non-steroidal anti-inflammatory agents do not affect the rate of sarcopenia, so whatever needs to be blocked has to be done at a more fundamental level in the immune cascade. Our data in the rat model show that to prevent the cachexia of arthritis we have to block both TNF and IL-1; neither one alone is sufficient. This suggests that a level of duplication is present in the system. While blocking either cytokine will reduce the arthritis at the clinical level, to obtain an effect on muscle requires blocking both.

Dr. Rosenberg: My strong plea is that the challenge to find pharmacologic agents for treating sarcopenia will not replace our zeal to determine the relation between exercise and muscle strength. I suppose that if you were aware of any large scale studies where exercise has been used at a public health level, with muscle mass and functional outcomes, you would have told us. There is one that I know of taking place in Chile, but I suspect it is too early to report any results. Maybe Dr. Bunout will comment on that. This is a hard kind of intervention to carry out. One needs all kinds of ‘social marketing’ to do so. Are you aware of any other countries or locations where this kind of thing is being undertaken?

Dr. Roubenoff: Most exercise studies show very powerful effects with the smaller studies but an inverse relation between the size of the study and the size of the effect – as the reach is broadened so you dilute the effectiveness. This may be an indication of our poor ability to do the study rather than a failure of the exercise per se. Secondly, in some of our HIV data we have looked at the cost of doing these interventions and compared them with the use of oxandrolone, an anabolic steroid. The costs work out to be very comparable – it costs about USD 1,800 to give somebody
oxandrolone for 12 weeks and about USD 1,200 to train them for that time, so it is not a 3-dollar intervention. Thirdly, Miriam Nelson and Jennifer Lane from our laboratory have been running community-based exercise programs in five states in the New England area over the past few years, and we are seeing substantial improvements in function. We have grass roots, home-based, and senior center-based exercise programs, with around 5,000 people who are regularly in training. With these kinds of community based programs, you don’t see huge changes in strength but you do see improvement in function, perhaps because it is easier to measure function in those people – and that is really what we care about: how they get better isn’t necessarily so important.

**Dr. Heseker:** I have a more practical question. How often and how long should elderly people train their muscles per week?

**Dr. Roubenoff:** We use a 3-times/week schedule of 20–40 min exercise, working the large muscle groups. These exercises can be done at home at very low expense and with low level technology – for example ankle and shoulder weights, a low chair for stepping on and off, and so on. There are many studies showing that if you train twice a week you get about 75% of the effect of a 3-times a week schedule, so it is good value – you get 75% of the effect for 66% of the effort. Once you have done this for 3 or 4 months, you can maintain fitness on a once-a-week schedule. You won’t make any further gains but you will not lose what has been achieved.

**Dr. Bunout:** Dr. Rosenberg referred to our study. It is not a really large scale study, but at least we are doing it in the community. We now have 18 months of follow-up. We planned for twice weekly exercises, but on an average the participants only came once a week to take part in the program. However, even with a once weekly training session we have been able to show changes in strength and in the activities of daily living. So even with rather poor compliance, we have obtained some good results.

**Dr. Roubenoff:** I think the biggest challenge in these longer term studies is compliance. We try to get people to keep records because that is how they see the benefit and it encourages them to continue. Miriam Nelson has published several books in which she outlines how to do this for the lay public. *Strong Women Stay Young* has been translated into 26 languages. So there are ways of communicating this to people around the world.

**Dr. Kehayias:** Could you comment on the value of the exercise in relation to obesity?

**Dr. Roubenoff:** One of the most striking benefits of exercise is that it reduces insulin resistance, which is one of the worst health effects of obesity. Sarcopenic obesity involves even more insulin resistance than plain obesity. The diabetes studies I described [Castaneda et al., unpublished observations] showed a marked improvement in glucose control with resistance training as well as with aerobic training, so you don’t necessarily need to have a complex regimen. It is much easier for obese people to do resistance training than aerobic training because that form of exercise doesn’t cause them to become short of breath, so they are willing to continue it. The other point to make in closing is that, in addition to the functional side of sarcopenia which we have been talking about, there is also a clinical side, which is that when people get sick they depend on the protein stores in their muscle to maintain a response to a catabolic insult. Thus the other value of exercise is to give them a larger protein store with which to enter hospital, if it comes to that.

**Reference**