Factors contributing to the variability in muscle ageing

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Ageing is accompanied with a progressive loss of muscle mass and force generating capacity. Ultimately, the muscle wasting and weakness may dramatically impact on mobility and the quality of life, where the elderly has increasing problems with performing activities of daily life, such as rising from a chair or climbing stairs. The rate of structural and functional deterioration of muscle appears to vary considerably between people. Part of the variation in the 'rate of muscle ageing' is attributable to genetic factors, the timing of changes in circulating hormones and the presence or absence of chronic low-grade systemic inflammation. Where an individual cannot change much in his or her genetic constitution, circulating hormones and systemic inflammation, (s)he can still significantly slow the rate of muscle ageing by an adequate dietary intake and regular physical activity. Finally, it is suggested that age-related alterations in the capillary bed may negatively affect muscle mass.

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1. Introduction

While muscle properties are quite stable up to the age of about 40, there is a progressive loss of muscle mass and slowing of movement beyond this age [1,2]. Both factors lead to a considerable loss of maximal force generating capacity and muscle power [3]. The muscle weakness and slowing of movement is accompanied by mobility deficits and causes increasing difficulties to perform tasks of daily life such as climbing a stair and rising from a chair. The muscle weakness and slower contractile properties could also greatly increase the risk of falls [4] and bone fractures. These effects and the observation that loss of mobility is one of the main factors that contributes to the inability to live independently, and thus leads to social isolation, shows the importance of maintaining muscle function to ensure a high quality of life even at old age. Thus, the challenge is to develop strategies that attenuate the age-related loss of muscle mass and 'performance', particularly as the proportion of elderly people is rising steadily in the Western World. To do so, we must first obtain a good understanding of the causes and mechanisms of muscle wasting and weakness. Although it is

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common knowledge that the ‘rate of ageing’ varies enormously between individuals, this observation has received relatively little scientific attention. Yet, this variation may hold some clues on how to develop strategies of ‘successful muscle ageing’. This is the subject of the current review.

2. Age-related changes in skeletal muscle structure and function

In previous reviews we have discussed in more detail the age-related changes in skeletal muscle structure and function [5]. Briefly, the age-related decrease in muscle mass is a consequence of both a reduction in fibre number and size, where the fibre atrophy is particularly evident in type II fibres [6,7]. There is a large variation in fibre sizes within and between young individuals that may be even larger in both old men [8] and rats [9]. This increased range of fibre sizes at old age maybe a reflection of the ongoing denervation–reinnervation process [6] where denervated fibres atrophy and innervated fibres develop compensatory hypertrophy. A side-effect of this increased variability in fibre sizes can be an increase in the heterogeneity of capillary spacing, as capillaries can only be located at the edge of fibres [9]. The heterogeneity of capillary spacing is rarely assessed, but an increase in the heterogeneity of capillary spacing may negatively affect tissue oxygenation [10]. In addition to a higher heterogeneity of capillary distribution capillary rarefaction [11] would further diminish tissue oxygenation and supply of substrates to the muscle fibres, and hence viability of the muscle. In fact, there is evidence in heart failure that capillary rarefaction precedes muscle fibre atrophy [12] and a similar situation might apply to the ageing muscle. The impact of age-related changes in the microcirculation on skeletal muscle mass and function has, however, received only limited attention.

3. Inter-individual variation in sarcopaenia

Individuals of identical age do not have an identical muscle mass. This is graphically illustrated in scatter plots of cross-sectional ageing studies, such as those in [2,7]. While men in general have larger muscles than women, about 50% of the variation in skeletal muscle mass in both men and women is related to differences in body mass [2] and height [13]. This shows that it is important to take at least body mass into account when assessing sarcopaenia, by using parameters such as appendicular muscle mass height$^2$ [13]. The usefulness of this parameter is reflected by its correlation with functional impairment and disability [13], but even this parameter shows quite some variation in relative muscle mass between individuals of a given age. It should be noted that body mass and height change during life. Bone size, however, is largely determined by muscle size and does not change much after adolescence [14] and this ratio thus might provide an indication of the intra-individual age-related loss of muscle mass [15]. However, despite some reduction in the variation when taking into account bone size, body mass or height, considerable variation remains indicating that the ‘rate of muscle ageing’ does indeed vary greatly between individuals.

4. Between and within muscle variation of sarcopaenia

The rate of muscle ageing not only varies between people, but also between muscles of a given individual. Most noticeable is that the loss of muscle mass is somewhat larger in leg than arm muscles [2], which might be due to a larger extent of reduced use in the leg than in the arm muscles. There is also some evidence that the age-related loss of muscle mass and function is greater in the dominant than in non-dominant side. The asymmetrical strength deficits in the lower limbs could play some role in mobility limitation and falls in older people. Even at the level of an individual muscle fibre there may be variation in the size of the fibre, where thinner parts of the fibre are associated with mitochondrial abnormalities [16].

5. Factors that might contribute to the variation in sarcopaenia

There are many factors that may contribute to the wide inter-individual variation in sarcopaenia, such as inter-individual differences in genotype, circulating hormone levels, chronic low-grade systemic inflammation, nutrition and physical activity levels [5,6]. Here some of these factors will be discussed.

5.1. Genetic influences

Even in rats there is a differential rate of muscle ageing. The animals with the most severe degree of sarcopaenia were also the animals in which muscle regeneration capacity was highest, suggesting that the regenerative capacity of even the most severely sarcopaenic muscles is maintained [17]. It was suggested by the authors that the rate of sarcopaenia was at least partly genetically determined [17]. The comparison of frailty in twins indicates that also in humans part of the variability in frailty between individuals is genetically determined [18]. In fact, it has been suggested that up to 52% of variance in muscle strength might be explicable by genetic factors [19]. The variation in strength may be related to differences in fibre number that may also have a genetic origin [20], but it is difficult if not impossible to pin-point the variation to specific polymorphisms among others because muscle strength and size is determined by more than one gene [19]. The observation that handgrip strength at 56–68 years of age and longevity of the mother are strong predictors of longevity [21] further suggest that genetic background plays an important role in longevity and hence the rate of ageing. There is, however, no correlation between longevity of the father and longevity [21]. This discrepancy may be reconciled when one considers that mitochondrial genes are maternally inherited. It is thus possible that mitochondrial genes play an important role, which is supported by variants of mitochondrial genes predisposing for longevity [22]. An age-related decrease in the impact of the genetic background [19] suggests that other factors, like the environment, become increasingly important for muscle size and strength with increasing age.

5.2. Hormones

During ageing there are profound changes in the profile of circulating hormones [23] that may have an impact on skeletal muscle structure and function. In post-menopausal women, for instance, the force generating capacity of the muscle was less than that of pre-menopausal women with similar activity levels. This lower force generating capacity was not only due to muscle atrophy [24], but also a sudden decrease in specific tension (force per muscle cross-sectional area) during menopause [24,25]. The reduction in specific tension was at least to some extent attributable to an increased fat infiltration in the muscle of post-menopausal women [24] and a reduction in single fibre specific tension [26]. In men the decline in specific tension is more gradual [25], which could be a reflection of the more gradual decline in free circulating testosterone in comparison to the relatively abrupt changes in oestrogens during menopause [23]. The importance of peri-menopausal changes in the hormonal environment for the decrement in force generating capacity is reflected by the prevention of this phenomenon by hormone replacement therapy [25,26], where also in men hormone replacement therapy may attenuate
or reverse some of the age-related muscle wasting [27]. The large inter-individual variability in the levels of oestrogen and testosterone of men and women of a given age [23] may thus be another factor that contributes to the variation of the rate of muscle ageing.

The impact of e.g. oestrogens may well be modulated by thyroid hormone [28]. This is important as thyroid hormone levels do also decrease with age [23]. Thyroid hormone not only has important effects on metabolism, but also induces the expression of fast myosin isoforms even in old rats [29] and lowered levels of this hormone may contribute to the observed age-related slowing of muscle contractile properties. Many elderly people also suffer from vitamin D deficiency which is associated with muscle weakness. Vitamin D supplementation does, however, only appear to have a significant positive effect on muscle strength if circulating vitamin D levels are below 25 nmol L\(^{-1}\) [30]. Finally, circulating insulin-like growth factor I (IGF-I) decreases with age [23]. In the elderly the level of IGF-I positively correlates with muscle strength, indicating that at least part of the variation in muscle function between the elderly is related to circulating IGF-I levels [31].

5.3. Inflammation

Many elderly people suffer from chronic low-grade systemic inflammation that may well contribute to the age-related muscle wasting and weakness [5]. It is noticeable that not all elderly people suffer from systemic inflammation and it has been observed that individuals with IL-6 and tumour necrosis factor-\(\alpha\) (TNF\(\alpha\)) levels above 2 and 3 pg ml\(^{-1}\), respectively, had smaller and weaker muscles than age-matched individuals with low levels of IL-6 and TNF\(\alpha\) [32]. Although it might be tempting to provide IGF-I supplementation to people suffering from muscle wasting, this should be done with care as at least in cell culture studies IGF-I in the presence of low levels of TNF\(\alpha\) enhances cell death, rather than stimulating cell growth [33]. Interestingly, the positive relationship between circulating IGF-I and muscle force generating capacity was absent in the presence of high levels of circulating IL-6 [31], suggesting that also in vivo IGF-I supplementation may not always be helpful.

5.4. Nutrition

While one cannot do much about his or her genetic constitution, the age-related changes in the circulating hormone profile and the development of low-grade systemic inflammation, there are still many opportunities to modify the rate of ageing. One of them is food intake and diet. It has been shown that elevated levels of TNF\(\alpha\) are associated with a lower food intake and carcass mass in rats [34]. It is thus possible that the low-grade systemic inflammation, together with reduced physical activity levels and an increased proportion of fat at old age may result in a reduced food intake, which in turn may cause a reduced micronutrient intake and consequent deficiencies and development of muscle weakness and frailty. At first glance this appears at odds with the increase in life-expectancy that accompanies (life-long) caloric restriction. However, caloric restriction is not without risk and care should be taken that nutrient intake is adequate [35]. Given an adequate micronutrient intake caloric restriction does slow the rate of ageing. While ageing is associated with an increased expression of genes involved in the stress response and a lower expression of genes involved in protein turnover and energy metabolism in muscle, these changes are prevented by life-long caloric restriction [36]. This is significant as a lower protein turnover may result in an increased abundance of misfolded and post-translationally modified proteins that could result in a reduced catalytic activity of enzymes. Glycation, for instance, does slow the velocity at which actin filaments are propelled by myosin in in vitro motility assays [37], and the increased glycation of myosin at old age [38] may thus contribute to the age-related slowing of type I and IIa fibres [39]. Protein glycation may not only be enhanced as a result of slower protein turnover at old age, but be further aggravated when mitochondria produce excessive reactive oxygen species [40]. It is therefore tempting to speculate that an enhanced protein turnover and a reduced generation of reactive oxygen species by mitochondria during caloric restriction [41] attenuate the occurrence of glycation and thereby improve muscle (fibre) function at old age. The latter mechanism may also explain the attenuated loss of motoneurons during caloric restriction [42]. This and the observation that anti-oxidant supplementation reduces circulating TNF\(\alpha\) levels, improves muscle strength and attenuates sarcopenia [43] suggest that inflammation-induced oxidative stress may be an important contributor to age-related muscle wasting.

Aging is characterised by a diminished hypertrophic response to exercise, or anabolic blunting. Part of this may be a consequence of the inflammatory environment that is not conducive for development of hypertrophy. It appears that combination of exercise and a leucine rich diet are most effective in inducing hypertrophy in the elderly [44], and additional benefits may be gained with an omega-3 rich diet [45]. What all these examples show is that differences in dietary intake between individuals may greatly influence the rate of muscle ageing.

5.5. Physical activity

Aging is associated with a progressive reduction in physical activity levels in all sorts of organisms including humans [46]. Physically inactivity maybe the most important factor accelerating the rate of ageing and it is thus no surprise that physical activity has been considered the most important factor in slowing the age-related decline in many physiological functions [47]. Part of the benefits of exercise on muscle at old age may be realised by the reduction of the chronic low-grade systemic inflammation [5] and reversal of anabolic resistance as observed in sedentary young individuals [48]. Regular exercise has, however, also direct beneficial effects on skeletal muscle that may be even more significant than the reduction in systemic inflammation and anabolic resistance. A possible explanation for the larger age-related decline in size of leg than arm muscles [2] may be a reduction in locomotor activity with age [46] that results in leg muscles experiencing a greater reduction in use than arm muscles. In support of a role of differential disuse is that the rate of decline in muscle force generating capacity between 75 and 85 years was less in physically active than sedentary people [49] where resistance exercise in the elderly also causes a reduction in intra-myocellular fat [50]. The latter may contribute to the maintained specific tension in master sprinters, though they still had a slowing of the type I fibres and fibre atrophy [51], while normally ageing is associated with a reduction in specific tension [39].

In addition to maintained fibre function, regular physical activity may also attenuate the loss of motor units. Master endurance runners, for instance, had a similar number of motor units in the tibialis anterior muscle as young controls, while the number was lower in old sedentary age-matched controls [52]. Following the suggestion that the hypertrophic response might be related to the number of available fibres [53] the maintained number of motor units, and thus possibly fibres, in the master endurance athletes may give them a better reserve for hypertrophy than their age-matched peers, even though they are weaker.

With ageing there can be a reduction in the number of satellite cells per fibre, which may result in an impaired regenerative capacity at old age [54]. However, both resistance and endurance exercise can induce an increase in the number of satellite cells [55]. While the amount of hypertrophy that could be obtained after resistance exercise was largest in those individuals with the largest accretion
of new myonuclei, or satellite cell proliferation and differentiation, which in turn was positively related to the basal number of satellite cells [56], a recent study on mice shows that satellite cell recruitment is not required for the development of exercise-induced hypertrophy [57]. Here we suggest that capillary proliferation is essential for the development of hypertrophy. This is supported by the almost identical time course of capillary proliferation and hypertrophy during overload in rats [58]. While diminished hypertrophy after irradiation has generally been ascribed to abolishment of the mitotic capacity of satellite cells [59], it is ignored that during irradiation also capillary proliferation is precluded. Clearly, this contention deserves further investigation, but in light of this review it should be realised that regular exercise had a strong impact on the density of the capillary network. Overall, it appears that a difference in physical activity between individuals is a major factor that contributes to the observed variation in age-related muscle wasting and weakness.

6. Conclusion

There is a large variability in the rate of skeletal muscle ageing between individuals. This is determined both by factors that cannot be modified, such as genetic constitution, changes in the levels of circulating hormones and development of low-grade systemic inflammation. There are, fortunately, also some factors that one may control and that will have a significant effect on the rate of ageing. For instance, and adequate dietary intake and even more important, regular physical activity, do significantly slow the rate of muscle ageing [47]. Future studies should also address the role of the microcirculation in maintenance of skeletal muscle mass during ageing.

Contributors

Dr Hans Degens conceived the idea of the outline of the review and wrote the first draft. Dr. Marko Korhonen has made additional suggestions and made comments on the pre-final manuscript.

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References


