ACE inhibitors for sarcopenia—as good as exercise training?

Sarcopenia is a major health problem for older people. Progressive impairment in muscle strength and loss of muscle mass are key contributors to falls, fractures and reduced physical function, is a key risk factor for death, and for the need for assistance with activities of daily living [1, 2]. Finding effective ways to prevent and reverse sarcopenia, therefore, has great importance as a way of attempting to reduce falls and immobility, avoid institutionalisation and enhance healthy ageing.

No consensus threshold for diagnosing sarcopenia has yet been arrived at, but the pathophysiological hallmarks of the condition are becoming better defined. Reduced cross-sectional muscle area, fibre loss and reduced muscle quality all play a part; mitochondrial dysfunction occurs together with preferential loss of type II (fast twitch) fibres and changes in calcium handling by the sarcoplasmic reticulum [3]. These changes lead to reductions in maximal muscle strength, affecting predominantly explosive power but also leading to increased fatigability.

The biological mechanisms underlying the pathophysiological changes of sarcopenia are still not well understood, but basic science and epidemiological studies have given us important insights in the last few years. Satellite cells in muscle, which usually provide the substrate for muscle regeneration, are lower in number in older people [4]. Chronic inflammation is linked to sarcopenia, with proinflammatory cytokines, including IL-6 and TNF alpha, thought to have deleterious actions on muscle [5]. Hormonal

changes are also thought to play a role, and there are emerging links between the metabolic syndrome and sarcopenia [6]. Finally, a number of lines of epidemiological evidence now link the renin-angiotensin-aldosterone (RAAS) system to skeletal muscle function. Individuals with the II genotype of the ACE gene have greater endurance and greater skeletal muscle trainability in some studies [7]; hypertensive patients taking ACE inhibitors have greater cross-sectional muscle mass and a slower decline in walking speed than those taking other antihypertensives in epidemiological studies [8].

What works in sarcopenia? The best evidence to date is exercise. Both endurance and resistance exercise improve skeletal muscle function and cross-sectional area, even in very old patients [9]. These benefits are not simply abstract but can translate into an enhanced ability to perform activities of daily living [10]. However, as many older people are unwilling or simply unable to engage in exercise training other avenues need to be explored. The appealing prospect of a pill which might confer improved exercise capacity has led to a number of pharmacological interventions being evaluated. These include testosterone [11], which shows moderate effects on muscle strength in older men, growth hormone, which is expensive, shows only modest effects and has problematic side-effects [12], and vitamin D [13], which has shown improvements in muscle function in some, but not all studies.

Following on from recent observational data suggesting a beneficial effect of ACE inhibitors, we recently reported results from a randomised controlled trial of ACE inhibitors on physical function involving 130 older patients with impairment of daily activities [14]. Patients were all aged 65 years and over, and were excluded if they had concurrent heart failure or LV systolic dysfunction. At baseline, patients had a wide range of comorbid conditions and had significant impairment of physical function—the baseline six-minute walk distance was only 300 metres and the median baseline timed-up and go time was 13 seconds. The intervention group received 4 mg of perindopril daily for 20 weeks; the control group received placebo. The intervention group achieved a 31 m improvement in the six-minute walk distance compared to placebo (p = 0.046), and there was a nonsignificant improvement in the timed-up and go time (1.3 seconds, p = 0.08). The improvement in exercise capacity recorded is equivalent to that reported after six months of exercise training [15], and the intervention was well tolerated with nonsignificantly fewer falls in the treatment group.

What remains less clear from these results is the mechanism of action. ACE inhibitors are known to have effects on cardiac function, and it is possible that they improved cardiac output, and hence, muscle blood supply—many patients in this study had cardiovascular disease, and a high proportion of older people display disturbances of diastolic cardiac dysfunction even in the absence of an overt diagnosis of heart failure. ACE inhibitors are also known to improve endothelial function, muscle glucose uptake, increase potassium levels and modulate other hormonal systems including IGF-1, all of which could contribute to improved skeletal muscle function. Finally, ACE inhibitors could of course be mediating a direct effect on skeletal muscle structure and function; they are known to have trophic effects on myocardial tissue.

What does this mean for the treatment of older people? Firstly, it should give us reassurance that older people treated with ACE inhibitors for other cardiovascular conditions are very unlikely to suffer from worsening physical function as a result of therapy. More excitingly, it promises to reinvigorate attempts to find pharmacological approaches to the difficult problem of sarcopenia. More work is now needed to understand the precise mechanisms underlying the observed clinical effect, to test how best to combine interventions such as exercise and ACE inhibitors for treating sarcopenia, and to explore whether other interventions suggested by observational work and basic science might have beneficial effects on this problem that afflicts vast numbers of older people.

What does this mean for the treatment of older people?

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References