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Does the liver accelerate ageing: Talking muscles and liver?

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Despite what the general media would like us to believe, we live in a time of unparalleled health. People are living longer; the increase in longevity has been driven by a decline in early life mortality as a result of improved hygiene and nutrition in the early 20th century, with the advent of new drugs delivering a decline in late life mortality in the 21st century [1]. As a consequence of our success in ageing, we are now facing a new problem, how to live *well* as well as *longer*.

Ageing is not programmed but results from a gradual, lifelong accumulation of damage to cells and tissues of the body over time. Consequently, there is no single cause for ageing, but spans (not exclusively) the accumulation of mitochondrial DNA mutations, aberrant epigenetic markings, nuclear genome instability and telomere erosion caused by chronic inflammation, metabolic stress and oxidative stress/redox imbalance amongst others [1]. This accumulation of cellular damage drives the ageing process and results in the development of frailty and chronic age-related diseases. Crucially, however, we know that many of the factors involved in the ageing process can be attenuated by lifestyle factors and accelerated with poor lifestyle choices [2] and also with some classes of drugs (such as chemotherapy [3] or anti-retroviral drugs [4]). This creates a disconnect between an individual's biological age and their chronological age – some people age quicker and some people age slower.

Ageing is characterized by loss of muscle, which can ultimately result in a loss of physical function and is then termed sarcopenia. Despite our best efforts the loss of muscle mass with age cannot be prevented, but loss of muscle is accelerated with loss of insulin sensitivity and poor glucose control, which is not surprising as insulin itself has a powerful effect on muscle growth. Our most recent understanding of muscle suggests that muscle peptides and cytokines released from muscle also have endocrine and paracrine effects [5]. As such, a decline in muscle mass not only has an effect on physical function, the loss of muscle mass can directly affect other physiological systems in the body (and indeed, *vice versa*).

What is new?

The paper from Koo and colleagues in the *Journal of Hepatology* describes the prevalence of sarcopenia in 309 people with biopsy proven healthy liver, non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) [6]. They conclude that as liver disease worsens, the prevalence of sarcopenia rises, with 1 in 4 people with NASH having sarcopenia *vs.* 1 in 10 for people without liver disease. Multivariate analyses controlling for age, gender, body mass index (BMI), hypertension, diabetes, and smoking status reveal an odds ratio of 2.8 (95% CI, 1.21–4.30). Odds ratio for having sarcopenia was even elevated after controlling for insulin resistance (OR, 2.05; 95% CI, 1.01–4.16). Although other cohorts have examined links between liver and sarcopenia, the current study applied improved methods for the detection of sarcopenia and also liver health.

Sarcopenia *per se* is a pathological disorder characterized by a generalized loss of skeletal muscle mass; low muscle mass is associated with weakness (low muscle strength, also referred to as "dynapenia"), but both measures should be related to body shape, i.e., BMI. The Sarcopenia Project of the Foundation for the National Institutes of Health (NIHSP) defined the cut-points for low lean mass and muscle strength on the basis of 9 large community-dwelling elderly cohorts, based on appendicular lean mass adjusted for BMI (ALM_{BMI}) and maximal grip strength adjusted for BMI ($GSMax_{BMI}$) in men and women [6] (Table 1). The whole analysis was based on lean mass measured from total body scans using dual-energy X-ray absorptiometry (DXA), where appendicular lean mass was the sum of lean mass from both arms and legs, and grip strength was measured by a hand-held dynamometer. The cut-points of weakness and low appendicular mass defined by NIHSP proved useful for epidemiological and clinical purposes [7,8], both predicting increased likelihood for 10-year incident mobility impairment, independently of each other, not 10-year mortality risks [9].

Several points remained however unsolved. Weakness and low reduced muscle mass, although frequently associated, do not necessarily identify the same population or an identical risk [10,11]. In general, muscle strength seems more predictive of mobility impairment and long-term mortality [9], but is less commonly measured in clinical practice. Secondly, segmental bioelectrical impedance analysis of the bilateral upper and lower limbs [12] has gained popularity to measure sarcopenia in more

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Table 1. Recommended cut-points for weakness and low muscle mass for men and women, proposed by International agencies.

Cut-point	Men	Women
Grip strength adjusted for BMI (GS_{BMI}) [3]	<1.00	<0.56
Appendicular lean body mass adjusted for BMI (ALM_{BMI}) [4]	<0.789	<0.512
Skeletal muscle index adjusted for weight (SMI_{weight}) [9]	<29.0	<22.9

GS_{BMI} and ALM_{BMI} cut-points were identified by the National Institutes of Health (NIH) Sarcopenia Project. SMI_{weight} cut-points have been defined by bioelectrical impedance analysis as SMI values below 2 standard deviation of a normal healthy population, where SMI% = total appendicular skeletal muscle mass (kg)/body weight (kg) × 100.

recent epidemiological studies. In this case, sarcopenia is defined by the skeletal muscle index (SMI) [13], i.e., the appendicular skeletal muscle mass adjusted for body weight, but how does it compare with DXA? In a sensitivity analysis, Koo and colleagues provide evidence that the two measurements give similar results [6], which is reassuring, but do they parallel in other populations? Finally, are cut-offs valid for all populations, and what about their use outside the elderly or in morbid obese populations? The cut-points for dynapenia and low muscle mass were derived considering a usual gait speed <0.8 m/sec, which may be challenging in severely obese persons. The NIHSP concluded that we still need a lot of information on the effects of sarcopenia on patient-reported outcomes, as well as longitudinal observational and intervention trials before to define the measures of weakness and muscle mass that best identify clinical problems [14].

What this means?

The paper from Koo and colleagues provides a unique insight into the relationship between age-related loss of muscle mass, metabolic control and liver disease. We have known the relationship between metabolism, abdominal adiposity and liver health for some time [15]. Although previous reports have shown that sarcopenia relates to NAFLD, it is the extension of this to NASH, independently of insulin resistance, which is of most interest. There are several important questions that remain unanswered; which comes first – sarcopenia or NASH? Are sarcopenia and NASH both organ-level presentations of a more systematic factor (transplanted NASH patients develop NASH again, suggesting that there is something beyond the liver influencing fibrosis). Indeed, obesity affects liver by increasing inflammation and tumourgenesis via elevated IL-6 and $TNF\alpha$ [16]. Pro-inflammatory cytokines can drive cellular senescence and limit regenerative capacity in regions around it. This cellular cross-talk could be a 'butterfly effect' of cellular senescence. In this context, NASH could be viewed as the livers response to accelerated ageing. Finally, loss of muscle mass has been known for decades to be common in advanced liver disease, namely in cirrhosis [17], with a negative effect on disease progression [18], and sarcopenia improves the prediction of mortality independent of etiology [19]. In the study of Koo et al., sarcopenia was associated with severe fibrosis ($\geqslant$F2) [6], which raises the possibility of an independent effect of poor liver function. However, cirrhosis was rare in the population (only 7% of cases), and sarcopenia was present throughout the histological spectrum of NAFLD. It is very likely that the altered metabolic milieu of NAFLD (obesity and diabetes) may significantly contribute to accelerate the loss of muscle mass.

Moving forward, prospective cohorts will teach us more about which comes first, sarcopenia or NASH, and the mechanisms underpinning this. However, there are important implications for clinical care today. Sarcopenia carries with it significant individual burden, whether or not a patient has NASH. The ability to move is essential for the maintenance of independence and also for the prevention of secondary disease. The excess risk of falls and frailty alongside negative impact on quality of life with sarcopenia [20] mean that care teams should be actively considering functional wellbeing whilst clinically managing NASH. These data highlight the pressing need for multi-disciplinary teams to support patients. Whilst effective therapies for NASH are limited, or in early development, helping patients maintain muscle function through diet and exercise (and possibly pharmacotherapies), may be the most potent therapy available to us. Whilst we are reaping the benefits of living longer, the paper by Koo and colleagues is a stark reminder that we need to focus on ageing well, and treating the patient as a whole, not just the liver.

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