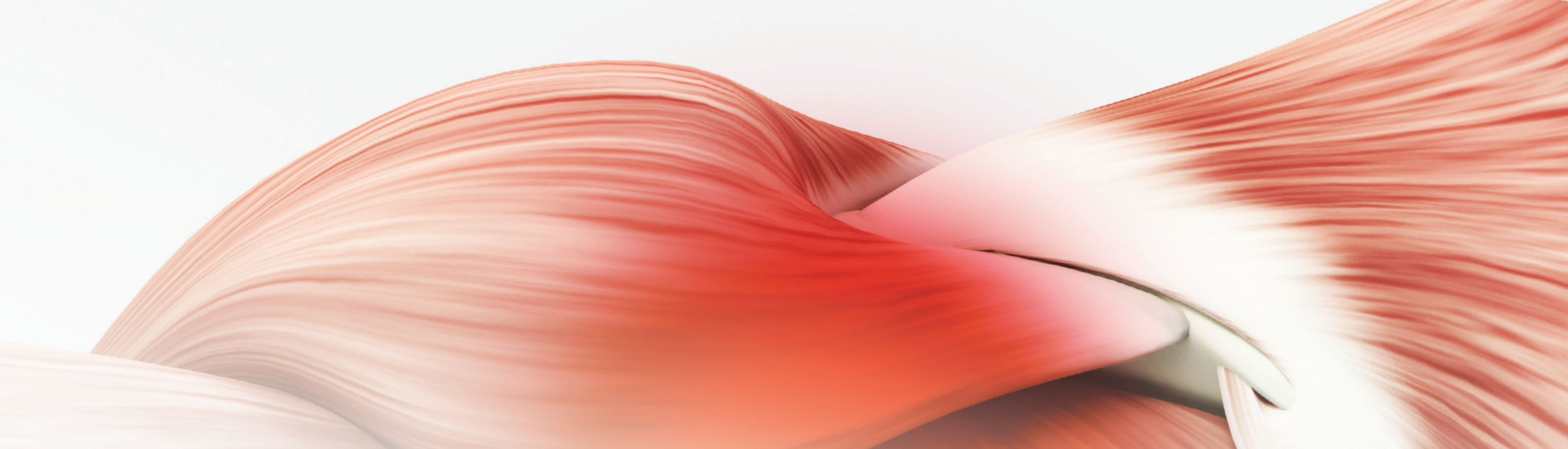

Vitamin D and Protein for Muscle Health

Insights from recent research

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I hate to be the bearer of bad news but none of us are getting any younger. In fact, you're aging as you read this and by 2050, over 20% of the world's population will be over 60 years old.[1] While living longer is great (and is directly related to improvements in global nutrition, hygiene and health care... yay science), many would argue "what's the point?" if you're not healthy too. Which brings up the importance of health-span, or healthy lifespan, the years someone lives free of chronic disease and disability. That's another story entirely as health-spans aren't increasing as quickly as lifespans.[2] Take Japan, a country with some of the longest-lived people in the world, as an example. There, from 1990 to 2010, the life expectancy of men increased by 3.3 years but the healthy life expectancy only increased by 2.2 years.[2] So we're seeing a global trend of living more years but not necessarily healthy years.

When people think about health as they age, they may think about things like heart disease, diabetes, frailty and risk of falls, and they often think of these conditions as some sort of inevitability. Not everyone ages the same way and looking for trends amongst those that age better might help us reduce the negative effects of aging in others. One factor that seems to be associated with better health-span is muscle, something that still doesn't get enough discussion time when talking about long term health. As we age, we tend to progressively lose both muscle mass or size, muscle quality and muscle function. This is called sarcopenia and has some major direct effects on our health and quality of life.[3, 4] To give you an idea of how big an issue this is, up to 40% of the mass of some muscles can be lost from our twenties to eighties.[5] While muscle mass is relatively easy to observe in some people, we also know there is an even bigger drop in muscle strength, which is called dynapenia, and both the loss in muscle strength and size are related to many of the chronic diseases seen in aging like type 2 diabetes mellitus (T2DM)[6] cardiovascular disease (CVD)[7] and cognitive decline,[8] as well as lower quality of life[9] and all-cause mortality.[10]

It surprises many people to know that muscle can have such a major effect on health so it's important to understand why. One major reason is that skeletal muscle is the largest insulin-sensitive tissue in the body which means low muscle mass and quality can make it more difficult to dispose of glucose properly after we eat. This drop in insulin sensitivity can increase the risk of developing T2DM[6] which is well known to be a major contributor to the risk of CVD.[11] Reduced muscle function and strength also can make it difficult for people to move around and be active which means you often see increased body fat (particularly abdominal adipose tissue) in people with sarcopenia. This is known as sarcopenic obesity (SO), which can also lead to an increased risk of heart disease. The accumulation of body fat in SO can lead to a vicious cycle of muscle dysfunction, with the build-up of fat within muscle tissue making movement even more difficult, reducing physical activity further and making muscle loss even more likely.[12] A reduction in muscle mass, which is known to produce many anti-inflammatory cytokines, and an increase in body fat, which is associated with pro-inflammatory cytokines, can lead to an overall state of low-grade chronic inflammation and add to the risk of cardiometabolic disease.[13]

This is why maintaining muscle mass as we age is so important for health and there are a number of possible strategies to help deal with this.[14] One of the most commonly recommended ways to manage sarcopenia is protein supplementation. Current research tells us that older adults may need much higher doses of protein of 1.2-1.5 g/kg/d, in order to maintain muscle size and strength.[15, 16] This is because older people experience anabolic resistance, meaning their bodies don't react as well to anabolic stimuli like exercise and protein. In the UK, 35% of older adults don't even consume 0.75 g/kg/day of protein (the reference nutrient intake for the general adult population) and fewer than 15% consume the recommended 1.2 g/kg/day.[17] To better understand the efficacy of protein, our research group recently published a systematic review and meta-analysis of the effects of protein supplementation in older adults, in the American Journal of Clinical Nutrition.[18]

With our paper we wanted to see how beneficial protein interventions could be without the use of other substances that are known to have potentially anabolic effects such as creatine, vitamin D and even hormonal therapy. We also wanted to see how important the role of resistance exercise (where muscles work against a weight or force) was in these interventions. This is because the mechanical loading of skeletal muscle plays a key role in stimulating muscle growth in all age groups.[19] In fact, just one session of resistance exercise can increase the anabolic response to eating protein, for up to 24 hours after that exercise[20] so it's role in maintaining muscle mass can't be overstated.

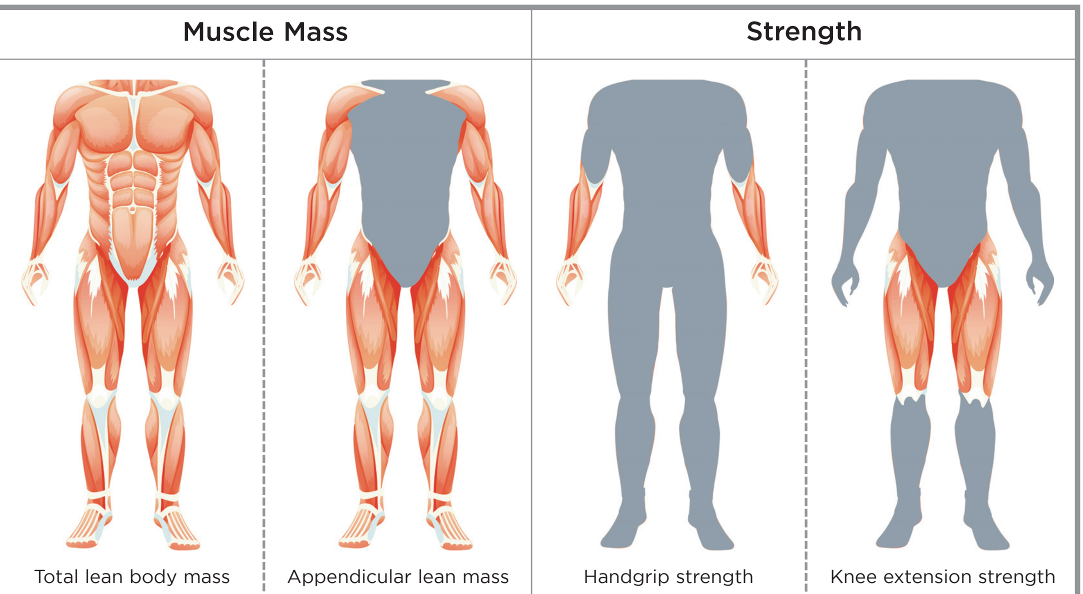
Using the results from 20 different randomised control trials, we performed meta-analysis looking at the effects of protein supplementation, with or without resistance exercise on 4 different outcomes: total lean body mass (LBM), appendicular lean mass (ALM), hand-grip strength and knee extension strength. It's worth mentioning why we chose these outcomes. While total LBM often gets a lot of attention, it represents all the non-fat mass in the body which includes muscles, bones, ligaments, tendons, and internal organs so not just muscle mass. Appendicular lean mass on the other hand refers only to the muscle tissue in the arms and legs. It's an important difference because we know that resistance exercise specifically helps increase ALM; i.e. when we do exercise with our arms and legs, it increases muscles in our arms and legs, funnily enough. In terms of strength, handgrip strength has been used very extensively in population studies as a proxy for upper body muscle strength and associates very well with metabolic health and longevity. Finally, knee extension strength is a good proxy for lower body strength in general, which may also be a useful indicator of strength and potentially long-term health.

What we found goes somewhat against the common knowledge relating to the effects of protein. Our meta-analysis revealed that extra protein, without exercise, had no effect on muscle mass or strength. However, in interventions that did use resistance exercise, adding protein did have a beneficial effect in terms of increasing ALM and handgrip strength. We also did a subgroup analysis of the studies and found that the effect was significant in frail or sarcopenic populations. That means that the populations that are suffering most from muscle loss are also those most likely to benefit from interventions using resistance exercise and protein, which is promising. Our results also highlight the importance of exercise for maintaining muscle mass. Protein on its own had no benefit on increasing muscle mass or strength despite the fact that there are many blanket recommendations for the elderly to just eat more protein. Our results show that extra protein can only be beneficial for increasing muscle size strength and if done together with exercise, which is the primary stimulus for muscle growth. See **Figure 1**.

Figure 1: Protein intake, exercise and changes in muscle

Populations
- Men & women
- Mean age >50 years
- Healthy, frail or sarcopenic

Interventions
- Higher vs. lower protein intakes
- NO isolated amino acids, vitamins, steriods or supplements known to induce hypertrophy
- With or without resistance exercise



Do HIGHER vs. LOWER protein intakes affect muscle mass or strength?		Total lean body mass	Appendicular lean mass	Handgrip strength	Knee extension strength
	WITHOUT resistance exercise	No effect	No effect	No effect	No effect
	WITH resistance exercise	No effect	↑ *only in frail/ sarcopenic populations	↑ *only in frail/ sarcopenic populations	No effect

Adapted from Kirwan, et al (2021).[18]

Now, something worth pointing out whenever we speak about meta-analyses in nutrition science is that there is often a huge amount of heterogeneity, meaning there is a lot of variation in the different study designs which makes teasing out results a lot more difficult. For example, some studies used protein shakes, some used high protein foods and some high protein diets. Some studies used whey protein, some casein, some soy and some collagen. The frequency of protein supplementation varied hugely from twice a week to 3 times daily as did the protein dose from 5 g to 40 g. All of these different factors make elucidating the real effects of protein more difficult which is why the results of meta-analyses (which were originally designed for combining the results of tightly controlled pharmaceutical studies) in nutrition science should always be taken with a pinch of salt.

Besides protein, another common intervention to try and improve muscle mass and strength is to supplement with vitamin D3. Vitamin D is a prohormone with a multitude of functions in every cell in the body. Vitamin D intake from our diet is limited and as most of us spend very little time in the sun, we don't produce much vitamin D in our skin. Up to 40% of the European population suffers from vitamin D insufficiency and deficiency, making it a serious health concern.[21-23]

A major issue with traditional nutrition science is that it can be very difficult to determine causality. In population studies, because of their cross-sectional nature, we can only determine associations and randomised controlled trials are very limited by the length of time they can be run for and depriving one group of an essential nutrient like vitamin D is ethically, let's just say, questionable. That's where the relatively new science of Mendelian randomisation analysis comes in. Named after the father of genetics, Gregor Mendel, Mendelian randomisation (MR) uses variation in genes as a natural experiment that we can use to investigate the potentially causal relations between a risk factors and different types of health outcomes. Basically, we use huge databases or combinations of databases with information on the genes that can affect a specific risk factor and with information on health outcomes. It allows us to use observational data for assessing potential causal relationships. It also allows us to have massive statistical power while doing it and avoid problems like reverse causality and confounding that we see in much of observational research.

If you haven't heard of MR before, don't worry, it's still relatively new on the research scene but it's a powerful tool for understanding how certain risk factors can affect health. That's why our research group recently carried out and published an MR analysis in the Journal of Nutrition Health and Aging,[24] looking at the effects of vitamin D on muscle mass. We used data for 6 single nucleotide polymorphisms (SNPs) related to serum vitamin D levels, specifically 25-hydroxy vitamin D, each of these SNPs has an effect on vitamin D levels and we looked at the association for someone's genetic vitamin D level and total fat-free mass, trunk fat-free mass and arm and leg fat-free mass.

What we found is that serum vitamin D has a positive effect of total, trunk and arm fat-free mass. While clinically, the effect is quite small, we can say that vitamin D has a potentially causal effect in increasing muscle mass. One of the big surprises is that we didn't find a positive effect on lower body (leg) fat-free mass. While this seems a little odd, we did find some examples of this in other research. In a study of elderly people in Holland, higher vitamin D levels were associated with total ALM but not with leg lean mass.[25] Another cross-sectional study also reported a stronger association between serum vitamin D and muscle strength in the arms compared to the legs.[26] A possible reason might be the distribution of the vitamin D receptor (VDR) in type 2 muscle fibres[27] which have a higher percentage in the upper body compared with lower body muscle.[28-31] We know that vitamin D affects both the size and the number of type 2 muscle fibres, which are especially important for the elderly, as they help with the explosive movements needed for maintaining balance and preventing falls.[32, 33] The presence of more VDR on muscle cells has been shown to stimulate growth through increased muscle protein synthesis.[34]

As I mentioned earlier, vitamin D deficiency is common and dietary sources are rare. Considering the mounting evidence for the importance of vitamin D in musculoskeletal health, ensuring adequate serum vitamin D levels is a realistic, low-cost and easy win for many older (and younger) individuals. Combine that with resistance exercise and adequate protein intake and people may be well on their way to improving their quality of life and reducing their risk of a number of common, chronic diseases of aging.

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