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EDITORIAL

Maintaining Muscle Strength in Crohn's Disease: Can a Vitamin D Daily Keep Muscle Loss Away?

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Background

Intact skeletal muscle strength and function are underappreciated aspects of normal human functioning. Moreover, it is widely accepted that muscle strength is a predictor of physical disability in patients with chronic diseases similar to inflammatory bowel disease (IBD, comprising Crohn's disease and ulcerative colitis) such as rheumatoid arthritis [1], but also in normal ageing where healthy persons with a greater reserve in muscle function appear to have longer life spans [2]. Despite the intuitive importance of skeletal muscle in daily living, and the recent interest in the characterization of disability in patients with IBD [3], hitherto there are few studies examining muscle dysfunction in IBD [4].

In this issue, Salacinski et al. [5] have objectively demonstrated reduced lower limb muscle strength in subjects with Crohn's disease (CD) compared to healthy controls, confirming the work of previous studies [6, 7]. However, the study was unable to show that this reduced strength was directly attributable to lower vitamin D (25-(OH) or vitamin D3) levels in CD subjects as originally hypothesized. This exemplifies the complexity of teasing out potential causative and/or contributing factors in the reduced muscle strength and performance seen in CD.

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Delving Further into Vitamin D

Both anecdotally and based on the available literature, it is widely accepted that vitamin D deficiency is commonly seen in patients with CD, putatively due to "direct" effects of the pro-inflammatory milieu on absorption and binding, malabsorption secondary to small bowel mucosal disease or surgical resection, as well as "indirect/illness" effects such as reduced sunlight exposure, physical inactivity, and reduced dietary intake [8] (Fig. 1). Hence, given the low side-effect profile and the widespread promotion of vitamin D supplementation for bone health and multiple other less evidence-based health benefits, testing for and treating vitamin D deficiency/insufficiency has become commonplace in IBD management, contiguous with the broader healthcare sector.

Thus, studies in this field, such as that by Salacinski et al. in this issue, are likely hampered by an inability to differentiate vitamin D concentrations in healthy and CD populations given this widespread supplementation, which has leveled out comparison. For instance, the mean 25-(OH) vitamin D level was not significantly different between the CD and healthy control groups (mean 80 vs. 87.5 mmol/l, $p = 0.31$). Moreover, approximately 47 % of the patients with CD and similarly, 37 % healthy controls, had vitamin D levels <75 mmol/l respectively.

Furthermore, the measurement and lack of standardization of the 25 (OH)D assays used worldwide remains a vexing issue. Salacinski et al. appropriately used a high-performance liquid chromatography technique that is considered the gold standard for measurement of total 25 (OH)D. However, it remains uncertain whether total serum 25(OH)D is truly an accurate representation of vitamin D's intracellular, end-organ effects (including in muscle), which are thought to be dependent on vitamin D-binding

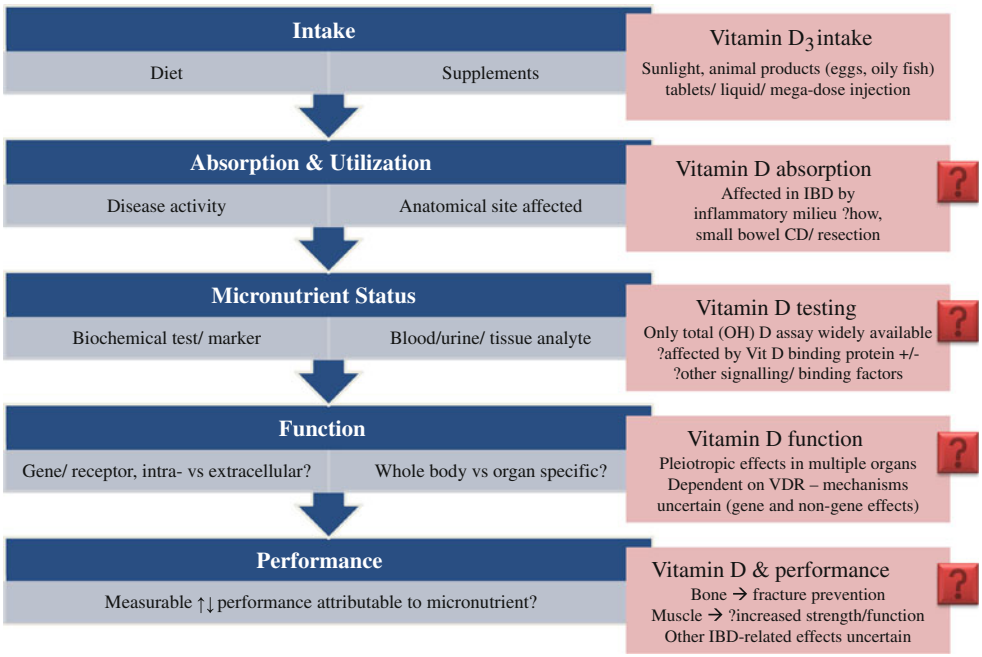

Fig. 1 Schematic exemplifying the complexity of the analyte measurement, ascertainment of end-organ effects, and resultant perturbations of human function/performance of micronutrient deficiencies. Clearly, the pathophysiology of IBD may influence much of this multistep process, resulting in multiple possible causes for micronutrient deficiency/ies. Vitamin D is a typical example—yet the question marks represent the lack of knowledge/evidence of each respective step in the process, especially relating to IBD

protein (up to 90 % of 25(OH)D is bound to this protein in the circulation) [9]. For instance, in a small series of 49 young adults, bone mineral density (BMD) was positively correlated with only free and bioavailable 25(OH)D, not total 25(OH)D, and BMD inversely correlated with D binding protein concentrations [10]. Furthermore, although a circulating half-life of 25 (OH)D is approximately 10–15 days, its release from tissue stores (especially muscle and adipose tissue) effectively lengthens half-life to 2–3 months, further complicating interpretation of a one-off serum measurement, especially within a relapsing-remitting disease like IBD. Further studies are therefore required to ascertain the most appropriate serum and end-organ tests, which may be more relevant to vitamin D effects than standard total 25(OH)D assays (Fig. 1).

Nevertheless, investigating a potential link between vitamin D and neuromuscular (dys)function in CD remains appealing for many reasons. Firstly, from an intuitive viewpoint, skeletal muscle is a major reservoir for vitamin D (as 25 (OH)D) [10], and secondly, the vitamin D receptor is abundantly expressed in muscle cells and thought to be a critical mediator of myogenesis and contractility [11]. Thirdly, as the authors Salacinski et al. alluded to, muscle dysfunction and decreased vitamin D concentrations in CD theoretically share similar pathogenic pathways to sarcopenia (the process of muscle loss in healthy ageing) and lower vitamin D levels, as seen frequently in the elderly. In this population, however, albeit primarily in observational studies, there are considerably more data supporting a correlation between vitamin D concentration and muscle function [12].

Importantly, Salacinski et al. showed in all participants (CD and healthy controls) that those with higher vitamin D levels (>100 mmol/l or 40 ng/ml) exhibited a 53 % greater extension peak torque normalized to body weight than those with lower levels (<80 mmol/l or 32 ng/ml). This implies that although vitamin D insufficiency may not be the root or sole cause of reduced muscle strength in CD, vitamin D remains likely to be one of many contributors to muscle integrity in healthy and diseased groups alike, which is amenable to change with a favorable risk:benefit ratio.

Summary and Future Directions

Although the authors of Salacinski et al. were unsuccessful in confirming their hypothesis of a primary role for vitamin D in reduced neuromuscular function in CD, this study is one of the first to investigate putative mechanisms underpinning muscle dysfunction in this population. This is an important new step—it is now reasonably well established that muscle strength and function in CD is reduced—future studies must next concentrate on further understanding the complex multifactorial etiologies of muscle dysfunction in CD before realizing the ultimate objective of identifying

effective approaches to prevent and/or restore muscle loss. Similarly, further mechanistic understanding of the myriad of postulated positive effects of vitamin D in IBD is needed. Meanwhile, although vitamin D daily appears not to be enough to keep muscle loss away in its own right, it nevertheless remains an important part of optimizing musculoskeletal health in IBD.

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