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Myostatin: A Powerful Biomarker for Sarcopenia and Frailty?

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Dear Editor,

Arrieta et al. [1] investigated whether circulating myostatin concentrations were associated with physical fitness and frailty. They selected male and female long-term nursing home residents without dementia or needing ambulatory assistance. Serum myostatin was indeed associated with lean body mass, physical performance, and non-frail status, and in men with upper and lower limb strength and endurance. However, opposite to the authors' expectations, the direction of the association was positive, and myostatin increased following their physical exercise intervention.

Biomarkers of sarcopenia and/or frailty, especially those related to pathogenetic mechanisms and therapeutic targets, would be highly useful for several reasons. Firstly, as an accessible tool for office-based diagnosis and screening, and secondly, for prognosis, for example, to identify elderly who are (or in the case of myostatin, may not be) at risk for developing (severe) sarcopenia and might benefit most from physical exercise or pharmacological interventions.

Myostatin acts as a chalone: a counter-regulator of muscle mass, as evidenced by the marked muscle hypertrophy in "mighty" myostatin knock-out mice, Belgian blue cattle, whippet dogs, and rare human cases [2]. Previous studies have shown that myostatin restrains the response to anabolic stimuli like testosterone [3]. Considering this background of myostatin that it limits further muscle hypertrophy in those who already have sufficient muscle mass, the higher myostatin serum concentrations in fitter, less frail individuals may not be so paradoxical or counterintuitive after all. Whether the association with muscle power only in male subjects observed by Arrieta et al. [1] represents a truly gender-specific effect possibly related to androgens [3], rather than a consequence of gender differences in muscle mass, clearly deserves further investigation.

The findings by Arrieta et al. are convincing, but clearly more work is needed and several questions remain before serum myostatin can enter the clinic. Firstly, sarcopenia and frailty often coincide but are still separate disorders: the association of myostatin with each condition independent of the other needs to be clarified [4]. Secondly, the biological relevance of circulating versus autocrine/local hormone effects of myostatin need to be better understood. Here, we can learn from recent studies on sclerostin, a Wnt inhibitor produced by osteocytes also acting as a chalone for bone mass. Circulating sclerostin appears to correlate with total body bone mass (i.e., the number of osteocytes), and levels are higher in men than in women [5]. Furthermore, several studies show a poor correlation between circulating sclerostin versus expression in bone [6]. Thus, one explanation for higher myostatin levels in fitter, less frail individuals might be its known (although moderate) correlation with total muscle mass [7].

Thirdly, preanalytical aspects of circulating myostatin (e.g., influence of renal function, fasting as well as comorbidities such as obesity, insulin resistance, and arthritis [8]) need to be investigated. Furthermore, myostatin presents a particular analytical challenge because it circulates as a complex with inhibitory binding proteins, and immunoassays may be confounded by the closely related GDF11 (growth and differentiation factor 11), which plays an adverse role in ageing [9]. Follistatin is another counter-regulator of myostatin [10], and perhaps a myostatin:follistatin ratio has to be considered. In any case, a mass spectrometry assay simultaneously measuring these proteins, such as the one developed by Bergen et al. [6], is strongly recommendable. Analytical issues may help explain contradictory findings on basic issues, such as age and gender differences in myostatin, like those recently reported by Fife et al. [10]. Finally, pretreatment biomarkers, such as myostatin, should be measured in clinical trial intervention and control groups to determine whether they predict outcomes and response to therapy. Unbiased proteomics approaches may then be used to investigate the clinical usefulness of these and other potential biomarkers.

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References

1 Arrieta H, Hervás G, Rezola-Pardo C, Ruiz-Litago F, Iturburu M, Yanguas JJ, et al. Serum myostatin levels are higher in fitter, more active, and non-frail long-term nursing home residents and increase after a physical exercise intervention. Gerontology. 2018 Nov;21:1–11.

2 Schuelke M, Wagner KR, Stolz LE, Hübner C, Riebel T, Kömen W, et al. Myostatin mutation associated with gross muscle hypertrophy in a child. N Engl J Med. 2004 Jun;350(26):2682–8.

3 Dubois V, Laurent MR, Sinnesael M, Cielen N, Helsen C, Clinckemalie L, et al. A satellite cell-specific knockout of the androgen receptor reveals myostatin as a direct androgen target in skeletal muscle. FASEB J. 2014 Jul;28(7):2979–94.

4 Gielen E, Verschueren S, O'Neill TW, Pye SR, O'Connell MD, Lee DM, et al. Musculoskeletal frailty: a geriatric syndrome at the core of fracture occurrence in older age. Calcif Tissue Int. 2012 Sep;91(3):161–77.

5 Mödder UI, Hoey KA, Amin S, McCready LK, Achenbach SJ, Riggs BL, et al. Relation of age, gender, and bone mass to circulating sclerostin levels in women and men. J Bone Miner Res. 2011 Feb;26(2):373–9.

6 Bergen HR 3rd, Farr JN, Vanderboom PM, Atkinson EJ, White TA, Singh RJ, et al. Myostatin as a mediator of sarcopenia versus homeostatic regulator of muscle mass: insights using a new mass spectrometry-based assay. Skelet Muscle. 2015 Jul;5(1):21.

7 Sinnesael M, Laurent MR, Jardi F, Dubois V, Deboel L, Delisser P, et al. Androgens inhibit the osteogenic response to mechanical loading in adult male mice. Endocrinology. 2015 Apr;156(4):1343–53.

8 Dankbar B, Fennen M, Brunert D, Hayer S, Frank S, Wehmeyer C, et al. Myostatin is a direct regulator of osteoclast differentiation and its inhibition reduces inflammatory joint destruction in mice. Nat Med. 2015 Sep;21(9):1085–90.

9 Schafer MJ, Atkinson EJ, Vanderboom PM, Kotajarvi B, White TA, Moore MM, et al. Quantification of GDF11 and Myostatin in Human Aging and Cardiovascular Disease. Cell Metab. 2016 Jun;23(6):1207–15.

10 Fife E, Kostka J, Kroc Ł, Guligowska A, Pigłowska M, Sołtysik B, et al. Relationship of muscle function to circulating myostatin, follistatin and GDF11 in older women and men. BMC Geriatr. 2018 Aug;18(1):200.