



# The relationship between serum IGF-1, handgrip strength, physical performance and falls in elderly men and women

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In August 2018, in the volume 179, issue 2 of the *European Journal of Endocrinology* van Nieuwpoort *et al.* (1) addressed the role of IGF-1 on muscle function and clinical implications of this relationship, i.e., in term of risk of falls, in community dwelling elderly.

IGF-1 is one of the most important anabolic hormones with a broad spectrum of action, including the modulation of muscle mass and activity. A recent systematic review identified a pattern of 47 genes that regulates muscle hypertrophy, but gene encoding for IGF-1 was not among the top 10 of genes highly expressed in skeletal muscle, although this hormone is secreted by muscle tissue (2). Moreover, in a very interesting study, Willems *et al.* (3) investigated the genetic determinants of variation in handgrip strength reporting a causal effect of higher genetically predicted muscle strength on lower fracture risk, but no evidence for a causal association between IGF-1 and handgrip strength. On the other hand, Verbrugge *et al.* (2) reported that many of the muscle hypertrophy-regulating genes belong to three signaling pathways, including the IGF1-Akt-mTOR pathway. Furthermore, transcriptome analysis revealed that IGF-1 expression in human muscle changes significantly (>10%) after strength training, supporting its role as hypertrophy-inducing factor (4). Beyond its muscle-specific anabolic effects, IGF-1 seems to modulate skeletal muscle function through paracrine actions on peripheral motor neuron axons (5), although underlying mechanisms are not yet well understood. These biological findings result in conflicting clinical implications of serum IGF-1 levels, particularly in terms of skeletal muscle function.

The paper of van Nieuwpoort *et al.* (1) investigated the association between age-related changes in serum IGF-1 and handgrip strength and physical performance, which are key outcomes for the identification of frailty and sarcopenia, defined in the geriatric field as the “new giants” (6). These conditions result in decline of the functional performance status of the affected individuals, with consequent falls, fractures, institutionalization and death. Indeed, it would be more appropriate to refer to sarcopenia rather than frailty, considering that muscle strength and physical performance are two of the three key outcomes to identify sarcopenia, according to different international recommendations (7,8).

In particular, in the clinical paradigm proposed by the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project (8), the assessment of physical performance is the first step for the diagnostic path for sarcopenia followed by the handgrip strength test, and finally by the measurement of appendicular muscle mass. On the other hand, recently the European Working Group on Sarcopenia in Older People (EWGSOP) (7) proposed the measurement of handgrip strength as the first diagnostic step to diagnose sarcopenia, followed by the measurement of muscle mass. Finally, the assessment of physical performance allows defining the severity of this condition. Evidence drawn from van Nieuwpoort *et al.* (1) are rather controversial, particularly about the paradoxical finding of reduced risk of falls in older, low active males with low serum IGF-1. Moreover, a gender difference is reported, because recurrent falls were more prevalent in older, more active females with low serum IGF-1. Indeed, higher levels of physical activity may justify the increased risk of falls in

the more active patients, regardless of serum IGF-1 levels.

Furthermore, it should be noted that IGF-1 has growth-promoting effects on many tissues and it is difficult to isolate its effects on skeletal muscle mass and function. Indeed, several hormones, cytokines and pathways are involved in structural and functional changes occurring in musculoskeletal system during aging (2).

Many studies investigated the association between muscle strength, physical performance and the risk of falls, fractures and even mortality.

Although lower limbs play a key role in physical performance, the measurement of handgrip strength by a handheld dynamometer is viable and recommended for the assessment of overall muscle strength, particularly in sarcopenic patients (7).

According to Van Ancum *et al.* (9), lower handgrip strength seems to be associated with increased falls in older patients in both pre- and post-hospitalization period, but only in males. However, authors claimed that the lower variation in muscle strength measures may account for the non-significant risk of falls reported in female patients. Furthermore, other risk factors may contribute to a gender specific pattern of risk of falls, including multi-morbidity and polypharmacy (10).

Low handgrip strength seems to be significantly associated with an increased risk of incident fracture over 10 years (+55%) (11). Moreover, a recent study suggests that muscle weakness is an independent risk factor for post-fracture mortality in elderly patients (12). In particular, each standard deviation (SD) (5 kg/m) lower height-adjusted post-fracture knee extensors strength was associated with an 18% and 43% increase in post-fracture mortality risk in older women and men, respectively. Measurement of handgrip strength is a simple, inexpensive risk-stratifying method for all-cause death. A 5 kg reduction in grip strength increased risk for all-cause mortality and non-cardiovascular mortality of 16% and 17%, respectively (13). Another study confirmed these findings, reporting a slightly stronger association between higher handgrip strength and lower risk of all-cause mortality in women (-40%) than men (-31%) (14). On the other hand, Steihaug *et al.* (15) investigated if sarcopenia could change post-operative physical performance in patients with hip fracture, demonstrating that muscle deconditioning did not predict change in mobility at 1 year follow-up. However, in a previous study we investigated the role of prevalent fragility fractures on muscle function, reporting a 2.46-fold increased risk to develop the dysmobility syndrome

(a clinical condition characterized by at least 3 parameters among low bone mineral density and muscle mass, muscle weakness, poor physical performance, obesity, history of falls) in older patients with osteoporotic fractures versus those without fractures (16). This finding points out that also fragility fractures might contribute to poor skeletal muscle function.

A reduction of 1 SD in physical function test results up to 21% higher risk of fall and up to 31% higher risk of becoming a recurrent faller, according to findings of the Swedish Osteoporotic Fractures in Men (MrOS) study (17).

A proper assessment of physical performance is also required to better define fracture risk. For instance, community-dwelling older adults who performed poorly on timed up and go test (TUG) or unipedal stance test (UST) experience a higher risk of fractures (+21%), particularly at hip (+80%) (18). Finally, poor physical functioning is associated with high mortality risk not only in older people, but also in late mid-life patients (19).

One of the criticisms of the paper authored by van Nieuwpoort *et al.* (1) is not having considered some important confounding factors. When discussing about the relationship between muscle function and falls, it is important to refer to other two hormones that have a considerable role in this field, such as vitamin D and PTH. In fact, it is widely demonstrated that patients with vitamin D deficiency and those with secondary hyperparathyroidism have significant reduction of both muscle strength and physical performance along with an increased risk of falls. Vitamin D exerts its action binding the vitamin D receptor (VDR), expressed also in human skeletal muscle (20). Vitamin D might affect muscle contraction through a short-term mechanism by regulating calcium-mediated second messengers (21). In previous studies, we demonstrated that vitamin D deficiency is significantly associated with low handgrip strength and physical performance in older people (22), and that women with hypovitaminosis D were 3-times more affected by dynapenic skeletal muscle function deficit (SMFD, a condition characterized by muscle weakness, slow gait, and normal muscle mass), versus those with normal serum 25(OH)D3 ( $P < 0.001$ ) (23). Furthermore, it is noteworthy that the prevalence of sarcopenia is significantly higher (more than 6-times) in people with vitamin D insufficiency and secondary hyperparathyroidism [serum 25(OH)D  $< 20$  ng/mL and serum PTH  $> 65$  pg/dL] (24).

In conclusion, we are sure that IGF-1 plays a role in muscle function, but to date clinical evidence suggests that

it is uncertain whether this pleiotropic hormone might be appropriate for assessing key functional outcomes in elderly, including risk of falls and fractures.

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## References

- van Nieuwpoort IC, Vlot MC, Schaap LA, et al. The relationship between serum IGF-1, handgrip strength, physical performance and falls in elderly men and women. *Eur J Endocrinol* 2018;179:73-84.
- Verbrugge SAJ, Schönfelder M, Becker L, et al. Genes Whose Gain or Loss-Of-Function Increases Skeletal Muscle Mass in Mice: A Systematic Literature Review. *Front Physiol* 2018;9:553.
- Willems SM, Wright DJ, Day FR, et al. Large-scale GWAS identifies multiple loci for hand grip strength providing biological insights into muscular fitness. *Nat Commun* 2017;8:16015.
- Vissing K, Schjerling P. Simplified data access on human skeletal muscle transcriptome responses to differentiated exercise. *Sci Data* 2014;1:140041.
- Gonzalez E, Messi ML, Zheng Z, et al. Insulin-like growth factor-1 prevents age-related decrease in specific force and intracellular Ca<sup>2+</sup> in single intact muscle fibres from transgenic mice. *J. Physiol* 2003;552:833-44.
- Morley JE. The New Geriatric Giants. *Clin Geriatr Med* 2017;33:xi-xii.
- Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2018. [Epub ahead of print].
- Studenski SA, Peters KW, Alley DE, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci* 2014;69:547-58.
- Van Ancum JM, Pijnappels M, Jonkman NH, et al. Muscle mass and muscle strength are associated with pre- and post-hospitalization falls in older male inpatients: a longitudinal cohort study. *BMC Geriatr* 2018;18:116.
- Hayakawa T, Hashimoto S, Kanda H, et al. Risk factors of falls in inpatients and their practical use in identifying high-risk persons at admission: Fukushima Medical University Hospital cohort study. *BMJ Open* 2014;4:e005385.
- Balogun S, Winzenberg T, Wills K, et al. Prospective Associations of Low Muscle Mass and Function with 10-Year Falls Risk, Incident Fracture and Mortality in Community-Dwelling Older Adults. *J Nutr Health Aging* 2017;21:843-8.
- Pham HM, Nguyen SC, Ho-Le TP, et al. Association of Muscle Weakness With Post-Fracture Mortality in Older Men and Women: A 25-Year Prospective Study. *J Bone Miner Res* 2017;32:698-707.
- Leong DP, Teo KK, Rangarajan S, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet* 2015;386:266-73.
- García-Hermoso A, Cavero-Redondo I, Ramírez-Vélez R, et al. Muscular Strength as a Predictor of All-Cause Mortality in an Apparently Healthy Population: A Systematic Review and Meta-Analysis of Data From Approximately 2 Million Men and Women. *Arch Phys Med Rehabil* 2018;99:2100-13.e5.
- Steihaug OM, Gjesdal CG, Bogen B, et al. Does sarcopenia predict change in mobility after hip fracture? a

- multicenter observational study with one-year follow-up. *BMC Geriatr* 2018;18:65.
16. Iolascon G, Moretti A, Giamattei MT, et al. Prevalent fragility fractures as risk factor for skeletal muscle function deficit and dysmobility syndrome in post-menopausal women. *Aging Clin Exp Res* 2015;27 Suppl 1:S11-6.
  17. Cöster ME, Karlsson M, Ohlsson C, et al. Physical function tests predict incident falls: A prospective study of 2969 men in the Swedish Osteoporotic Fractures in Men study. *Scand J Public Health* 2018. [Epub ahead of print].
  18. Chun SH, Cho B, Yang HK, et al. Performance on physical function tests and the risk of fractures and admissions: Findings from a national health screening of 557,648 community-dwelling older adults. *Arch Gerontol Geriatr* 2017;68:174-80.
  19. Keevil VL, Luben R, Hayat S, et al. Physical capability predicts mortality in late mid-life as well as in old age: Findings from a large British cohort study. *Arch Gerontol Geriatr* 2018;74:77-82.
  20. Olsson K, Saini A, Strömberg A, et al. Evidence for Vitamin D Receptor Expression and Direct Effects of  $1\alpha,25(\text{OH})_2\text{D}_3$  in Human Skeletal Muscle Precursor Cells. *Endocrinology* 2016;157:98-111.
  21. Boland RL. VDR activation of intracellular signaling pathways in skeletal muscle. *Mol Cell Endocrinol* 2011;347:11-6.
  22. Iolascon G, de Sire A, Calafiore D, et al. Hypovitaminosis D is associated with a reduction in upper and lower limb muscle strength and physical performance in post-menopausal women: a retrospective study. *Aging Clin Exp Res* 2015;27:S23-30.
  23. Iolascon G, Mauro GL, Fiore P, et al. Can vitamin D deficiency influence muscle performance in postmenopausal women? A multicenter retrospective study. *Eur J Phys Rehabil Med* 2018;54:676-82.
  24. de Souza Genaro P, de Medeiros Pinheiro M, Szejnfeld VL, et al. Secondary hyperparathyroidism and its relationship with sarcopenia in elderly women. *Arch Gerontol Geriatr* 2015;60:349-53.

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