



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 point 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 criticism 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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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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