THERAPY

Growth hormone supplementation: a silver lining for the aged?

Paul Lee and Ken K. Y. Ho

Previous randomized, controlled studies of growth hormone supplementation in the elderly have reported body-composition improvements but no beneficial effect on strength or physical function. The findings of a new study, however, hint at a potential benefit from the treatment for elderly individuals with functional decline.

A number of randomized, controlled studies have been undertaken to test the hypothesis that growth hormone supplementation reverses detrimental changes in body composition and function that accompany aging (Table 1); the most recent is by White *et al.*[1] All previous studies reported an improvement in body composition but no measurable gain in strength or physical function. By contrast, in addition to demonstrating body-composition improvements with growth hormone supplementation, White and colleagues provide the first evidence that this treatment improves physical function in the elderly. Can scrutiny of the differences between the study by White *et al.* and the other trials explain this new finding?

White and colleagues' study is notable for the selection of participants with physical impairment, the use of a growth hormone secretagogue and the large sample size. By recruiting individuals with evidence of frailty attributable to aging, the investigators may have avoided a ceiling effect that can prevent a measurable effect on physical function in healthy elderly individuals. In addition, White *et al.* used capromorelin, a ghrelin mimetic; therefore, effects of ghrelin other than those on the release of growth hormone might have contributed to improvement in the functional outcome measures.

Only one other study of growth hormone supplementation in the elderly used a ghrelin mimetic; in the study, Nass *et al.*[2] observed a trend towards an improvement in muscle strength which failed to reach statistical significance. This study included 65 participants, in contrast to the much larger group of 284 individuals evaluated by White *et al.* Indeed, the study by White and co-investigators is by far the largest of the controlled studies that have assessed growth hormone supplementation, which raises the possibility that a type II error could account for the apparent lack of growth hormone efficacy on function in previous studies.

Among several measures of physical function tested by White *et al.*, the investigators reported an improvement in power stair climb and in tandem walk speed in treated patients. Can these improvements be explained by the effects of growth hormone supplementation? Stair climb is a sensitive measure of lower limb power (which improves with resistance training) as well as a measure of cardiopulmonary fitness that is commonly used to predict patients' outcome after pulmonary resection. Tandem walk is an integrated assessment of neuromuscular function, which predominantly tests impairments that affect balance and coordination. However, lower limb strength contributes to postural stability. On the basis of the anabolic actions of growth hormone, the findings suggest that the functional improvements could occur from a gain in aerobic fitness or lower limb strength.

Evidence that growth hormone improves aerobic capacity or muscle strength in the elderly is poor. All previous growth hormone supplementation studies in the elderly have failed to demonstrate a positive effect on maximum oxygen consumption. A study in men with hypopituitarism reported that growth hormone inhibits the expression of genes in muscle that encode enzymes involved in oxidative metabolism of substrates, which suggests that growth hormone may inhibit aerobic capacity in muscle.[3]

None of the growth hormone treatment studies in the elderly has demonstrated a beneficial effect on muscle strength (Table 1). Taaffe *et al.*[4] administered growth hormone supplementation to patients after an initial period of resistance training; the training improved strength, but the growth hormone treatment had no additional beneficial effect on this parameter. Indeed, no evidence exists that growth hormone improves strength and aerobic capacity in athletes.[5] Intriguingly, White *et al.* did not measure strength as an outcome measure even though grip strength was used as a screening test for the detection of physical impairment at study entry. Thus, the improvements in stair climb and tandem walk tests after treatment with a growth hormone secretagogue stand in contrast to a lack of evidence that growth hormone improves aerobic capacity or muscle strength in individuals who are growth-hormone sufficient.

However, studies of growth hormone treatment have not as yet been undertaken in elderly individuals with functional decline. Until the effects of growth hormone treatment in this population are assessed, we cannot deduce whether the

Table 1 | Outcomes in major trials of growth hormone supplementation in the elderly

Reference	Treatment	Participants	Duration	VO_{2max}	Strength	Function
Papadakis *et al.*[8]	GH	52 healthy individuals	6 months	NA	NS	NA
Blackman *et al.*[9]	GH	60 healthy individuals[a]	6 months	NS	NS	NA
Taaffe *et al.*[4]	GH	18 healthy individuals	10 weeks	NA	NS	NA
Giannoulis *et al.*[10]	GH	32 healthy individuals[a]	6 months	NS	NS	NA
Nass *et al.*[2]	GHS	65 healthy individuals	1 year	NA	NS	NS
White *et al.*[1]	GHS	284 individuals with evidence of frailty	1 year	NA	NA	Improved

Body composition improved in all studies. [a]Only individuals who were randomly allocated to receive growth hormone and placebo are included. Abbreviations: GH, growth hormone; GHS, growth hormone secretagogue; NA, not assessed; NS, no significant effect; VO_{2max}, maximum oxygen consumption.

improvements seen after growth hormone secretagogue therapy are mediated by growth hormone. Could the improvements arise from ghrelin-mediated effects unrelated to growth hormone? Ghrelin has widespread biological functions, including actions on satiety, as reflected in the weight gain observed in participants in Nass *et al.* and White *et al.*'s studies. In addition to expression in the pituitary gland and the hypothalamus, the growth hormone secretagogue receptor is widely expressed in various parts of the brain.[6] Growth hormone secretagogues increase neural insulin-like growth factor I expression, exert a neuroprotective effect and prevent apoptosis of hypothalamic and cerebellar neurons.[7] These observations leave open the possibility that the improvements in physical function arise from a central action of ghrelin.

In conclusion, White *et al.* have undertaken a seminal study that demonstrates improvement of physical function in elderly individuals with evidence of frailty who were treated with an oral growth hormone secretagogue. Future trials of sufficient power should focus on elderly individuals with functional limitations to ascertain whether the benefits can be replicated with growth hormone alone. Despite some disappointing results from previous trials, this study puts forth a credible case for careful reappraisal of a potential role of growth hormone supplementation in selected older adults with functional decline.

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Competing Interests
The authors declare no competing interests.

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PITUITARY GLAND

Medical therapy for acromegaly: can we predict response?

Andrea Giustina and Teresa Porcelli

Response to medical therapy for acromegaly is highly variable, with few predictive factors available to help clinicians make informed treatment choices. Researchers in the UK now suggest that prior radiotherapy might influence an individual's response to secondary therapy with dopamine agonists or somatostatin analogs.

A group of researchers from the West Midlands region of the UK have examined factors that might potentially predict response to medical treatment for acromegaly. Sherlock *et al.*[1] retrospectively evaluated the effects of baseline prolactin status, prior neurosurgery and prior radiotherapy on response to medical therapy in 276 patients with acromegaly; they also assessed the relative efficacy of dopamine-agonist therapy versus somatostatin-analog therapy in their cohort of patients. The researchers found that the effects of dopamine agonists were independent of baseline prolactin concentrations. Prior radiotherapy, but not neurosurgery, was associated with distinct differences in the biochemical response to dopamine agonists (improved suppression of growth hormone [GH] levels) and somatostatin analogs (reduced suppression of insulin-like growth factor I [IGF-I] levels).

Therapies for acromegaly aim to reduce or control growth of the pituitary adenoma, inhibit hypersecretion of GH and normalize circulating levels of IGF-I.[2] Three approaches are currently available to treat this disease: neurosurgery, radiotherapy and medical management.[3] Neurosurgery is generally considered the first-line option for management of patients with acromegaly. By contrast, medical treatment with somatostatin analogs is often reserved for patients who fail to show an adequate biochemical response after neurosurgery; however, somatostatin analogs might also be considered as primary treatment for patients with a low likelihood of neurosurgical cure.[2] Finally, conventional radiotherapy, as well as use of the GH antagonist pegvisomant, is considered the third-line option in patients whose disease is not controlled by surgery and medical treatment with somatostatin analogs.[2]

The somatostatin analogs currently available in clinical practice (octreotide and lanreotide) decrease secretion of GH by the pituitary adenoma, predominantly through interaction with somatostatin receptor type 2.[3] These agents effectively control

Practice points

- Baseline prolactin level did not predict the biochemical response to treatment with dopamine agonists
- Prior radiotherapy was associated with improved suppression of growth hormone levels in response to dopamine-agonist therapy
- Prior radiotherapy was associated with a reduced suppression of insulin-like growth factor I levels in response to somatostatin-analog therapy