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EDITORIAL COMMENT

Keeping the Genie in the Bottle

Growth Hormone and Cardiovascular Disease*

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Anabolic hormone use is increasingly common and includes replacement in patients with hormone deficiencies, questionable uses in those with borderline-low levels, and clear abuses among athletes aiming to gain a competitive advantage. Recently, direct-to-consumer marketing touting the benefits of "low T" treatment has led to increased testosterone use among middle-aged and older men, despite inadequate cardiovascular safety data. Although the Testosterone in Older Men Trial showed improvements in strength among treated patients, it was prematurely halted due to increased cardiovascular events in the treatment arm (1). Additionally, observational studies have demonstrated an association between testosterone prescription and increased myocardial infarction rates (2), as well as associations between testosterone therapy and adverse cardiovascular outcomes including all-cause mortality, myocardial infarction, and ischemic stroke (3). Recently, the U.S. Food and Drug Administration (FDA) announced an investigation of the safety of testosterone use, emphasizing that testosterone is only approved for use in men with low levels who have an associated medical condition (4).

The other anabolic hormone with clear treatment indications, as well as a potential for "indication creep" and abuse, is growth hormone (GH). GH is only approved for adults with proven deficiency, acquired immune deficiency syndrome wasting syndrome, or short bowel syndrome, and the Federal Food, Drug, and Cosmetic Act prohibits GH use for off-label indications. Among adults with GH deficiency, replacement improves body composition (5), exercise performance (6), and bone density (7). Additionally, GH replacement was shown to improve surrogate cardiovascular disease markers, including lipids (5) and inflammatory markers (8). Whether GH replacement improves cardiovascular morbidity or mortality in this population remains unknown.

Beyond these indications, athletes have used high-dose GH for performance enhancement. Additionally, low-dose GH in combination with other hormones, including testosterone, has been marketed by anti-aging clinics. Following the 1990 publication of a small study that demonstrated improvements in body composition among older men following GH supplementation, the use of GH as an antiaging therapy expanded rapidly and continues to increase (9,10). Despite no projected change in the prevalence of GH deficiency, the global market for GH is expected to increase from $3.5 billion in 2011 to $4.7 billion by 2018 (11). This is not unexpected, as previous data demonstrated that up to 30% of GH prescriptions in the United States were prescribed for off-label indications (10).

Despite high rates of unapproved GH use for performance enhancement and anti-aging, there are limited efficacy data to support improvements in physical status. Although GH administration increased lean body mass in a study of healthy, young individuals, it had no effect on strength or exercise capacity (12). A meta-analysis evaluating GH treatment in elderly individuals found improvements in body composition, but no changes in cholesterol, maximal rate of oxygen consumption, bone density, or blood glucose (13). Additionally, high rates of adverse events were noted in treatment groups, most commonly soft tissue edema, carpal tunnel

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syndrome, arthralgia, and gynecomastia (13). There are no clinical trials evaluating the long-term cardiovascular safety and efficacy of GH therapy in healthy individuals.

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In this issue of the *Journal*, Hallengren et al. (14) report an interesting epidemiological study that may provide additional insights into the cardiovascular effects of GH. They measured GH with a novel high-sensitivity (hs) assay in 4,323 healthy participants in the Malmö Diet and Cancer study and evaluated the associations between GH concentrations and cardiovascular risk factors, as well as incidence of coronary artery disease, stroke, congestive heart failure, and all-cause and cardiovascular mortality (14). Although no direct comparisons with a standard GH assay were performed, the hs-GH assay used by Hallengren et al. (14) likely captures a full range of values below the detection limits of standard assays, allowing the investigators to explore cardiac associations with physiological and not pathological levels of the hormone. Although individuals with higher GH levels had more favorable body composition and lipid profiles, similar to observations from studies of GH replacement (5), they also had higher rates of coronary artery disease, stroke, congestive heart failure, and all-cause and cardiovascular mortality (14). These findings have potential implications for the use of hs-GH as a biomarker in the general population, as well as implications for the appropriate use of GH in those with a diagnosed deficiency and for those using GH inappropriately.

Although hs-GH levels were statistically associated with adverse cardiovascular endpoints in the Malmö study, the magnitude of the association was modest and led to only a very small improvement in the C-statistic (14). For biomarkers to be useful for risk assessment in the general population, the magnitude of association will need to be larger and associated with improvements in discrimination and/or clinical metrics of risk classification, such as net reclassification improvement (15,16). Moreover, GH is probably too difficult to measure to be useful as a routine biomarker. As highlighted by the authors (14), GH secretion is pulsatile and may differ based on sleep patterns, time of day, and food intake (17). For these reasons, we do not believe it is likely that hs-GH will emerge as an important biomarker for cardiovascular risk assessment. However, well-performed biomarker studies, such as the present one, may have therapeutic implications and contribute to our understanding of disease processes, even if the magnitude of association of the biomarker with outcomes is modest. In this case, the findings raise preliminary concerns about the potential for adverse cardiovascular safety with GH treatment or illicit use.

Several caveats need to be mentioned. First, the application of the results of this analysis to the treatment of adults and children with diagnosed GH deficiency is unclear, because there may be important differences between endogenous GH levels and GH replacement. Indeed, the associations reported here appear to counter those seen in studies of GH replacement. The same difficulty in applying these results to GH-deficient patients exists when we consider their application to individuals who use exogenous GH for antiaging or performance-enhancing purposes.

This interesting study by Hallengren et al. (14) should be considered hypothesis-generating and should prompt additional study of the effects of GH on the cardiovascular system. Thus far, the data are conflicting, with some studies showing protective effects and others (including the present study) suggesting potential hazards. It is imperative that the cardiovascular safety of GH in adults at risk for or with cardiovascular disease be determined *before* the "genie gets out of the bottle" and GH use expands even further. The current situation with testosterone, where cardiovascular safety concerns are now emerging *after* the "genie" was released, should serve as a cautionary tale. Additionally, patients who are using GH for indications beyond those that are U.S. Food and Drug Administration–approved should be informed of the uncertainty regarding benefits and the potential for harm.

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REFERENCES

1. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109–22.

2. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014;9:e85805.

3. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829–36.

4. U.S. Food and Drug Administration. Testosterone products: drug safety communication—FDA investigating risk of cardiovascular events. 2014.

Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm384225.htm?utm_source=rss&utm_medium=rss&utm_campaign=testosterone-products-drug-safety-communication-fda-investigating-risk-of-cardiovascular-events. Accessed July 22, 2014.

5. Maison P, Griffin S, Nicoue-Beglah M, et al., Metaanalysis of Blinded, Randomized, Placebo-Controlled Trials. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a Meta-analysis of Blinded, Randomized, Placebo-Controlled Trials. J Clin Endocrinol Metab 2004;89:2192–9.

6. Widdowson WM, Gibney J. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. J Clin Endocrinol Metab 2008;93:4413–7.

7. Gotherstrom G, Bengtsson BA, Bosaeus I, et al. Ten-year GH replacement increases bone mineral density in hypopituitary patients with adult onset GH deficiency. Eur J Endocrinol 2007;156:55–64.

8. Sesmilo G, Biller BM, Llevadot J, et al. Effects of growth hormone administration on inflammatory and other cardiovascular risk markers in men with growth hormone deficiency. A randomized, controlled clinical trial. Ann Intern Med 2000;133:111–22.

9. Rudman D, Feller AG, Nagraj HS, et al. Effects of human growth hormone in men over 60 years old. N Engl J Med 1990;323:1–6.

10. Vance ML. Can growth hormone prevent aging? N Engl J Med 2003;348:779–80.

11. Wang SS. Scientists warn of risks from growth hormone. March 24, 2014. Available at: http://online.wsj.com/news/articles/SB10001424052702304179704579459290223091978. Accessed July 22, 2014.

12. Liu H, Bravata DM, Olkin I, et al. Systematic review: the effects of growth hormone on athletic performance. Ann Intern Med 2008;148:747–58.

13. Liu H, Bravata DM, Olkin I, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med 2007;146:104–15.

14. Hallengren E, Almgren P, Engström G, et al. Fasting levels of high-sensitivity growth hormone predict cardiovascular morbidity and mortality: the Malmö diet and cancer study. J Am Coll Cardiol 2014;64:1452–60.

15. Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. Circulation 2007;115:949–52.

16. Hlatky MA, Greenland P, Arnett DK, et al., American Heart Association Expert Panel on Subclinical Atherosclerotic Diseases and Risk Factors and the Stroke Council. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:2408–16.

17. Goldenberg N, Barkan A. Factors regulating growth hormone secretion in humans. Endocrinol Metab Clin North Am 2007;36:37–55.

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