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INVITED COMMENTARY

Growth Hormone and the Fountain of Youth

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The quest for vitality and youth, going back centuries to the writings of Herodotus (5th century BC), has surged on to the scene of modern medicine. While Ponce de Leon and his mythical search for such waters landing him in modern-day Florida may be one of the more popular legends, the search for sacred, restorative waters dates back to thousands of years ago. The idea of rejuvenation and anti-aging has found myriads of ways for creeping into medical science and the search for the "hormonal fountain of youth" has been under investigation since Brown-Sequard tried to rejuvenate himself with testicular extract. What has transpired since that time is a booming industry of anti-aging clinics that offer hormone treatment for the promise of rejuvenation. There is a great deal of basic science research that has developed the pathways of how these hormones interact at the cell level, but at the time of this writing, the clinical literature of hormonal rejuvenation is scarce and of poor quality. Cost considerations add another complicated dimension to the field as treatments, almost always out-of-pocket fees, can cost thousands of dollars. Most physicians in the anti-aging business are not endocrinologist and the ethics behind the various offered treatments are often unclear. As an example, human growth hormone (HGH), one of the main prescriptions in the anti-aging cocktail, has very few indications and is considered illegal to distribute for anti-aging and rejuvenation purposes.

Anti-aging clinics have made waves through the popular press after the death of a 54-year-old woman. A marathon runner who was nervous about not being in peak physical shape sought help from a so-called anti-aging medicine center. The clinic she found was run by a radiologist who proceeded to prescribe HGH. Tragically, the marathoner was found deceased 6 months later with liver tumors. The *New York Times* has highlighted the illegal use of growth hormone (GH) through a story of one physician who reports excellent personal results while taking HGH at the same time to promote his new anti-aging clinic.[1] Cost considerations in reports are often overlooked as most are out-of-pocket expenses with great variation among different clinics. With injections of HGH costing upward of $12,000 per year, the industry was expected to gross $291 billion worldwide by 2015.[2] A 2010 article in a local Florida newspaper reported initial evaluation and laboratory work costs of approximately $4,000 (or higher depending on the tests performed). In addition, patients were asked to pay a variable monthly "consultation fee" depending upon the specifics of their treatment plan and ranging between $700 and $1,000.[3] 8 Years later and with no breaks in the frenzy to maintain youth, it is likely that these costs are even higher today.

Researchers in the field have evaluated different domains adversely affected by the aging process and have attempted to isolate pathways for potential restoration. The domains that are of the most interest for rejuvenation lie within the areas of memory and cognitive function, bone and skeletal health, and functional status. The purpose of this article is to review the scientific merit in some of these areas in order to better assess the rejuvenation claims of the involved clinics and health care practitioners.

GROWTH HORMONE

GH, also known as somatotropin, is a single-chain polypeptide secreted from the anterior pituitary gland that is known for stimulating growth, cell production, and cellular regeneration. It has been shown to decrease in an age-dependent manner after a peak in adolescence,[4] an entity termed "somatopause." Elderly men may produce as little as 50 μg/d compared with pubertal boys who produce 1.0−1.5 mg/d.[5] Insulin-like growth factor (IGF)-1 mediates the action of GH, and its concentration reflects the circulating concentration of GH. The half-life of IGF-1 is 18 hours, which makes it more appropriate to follow rather than GH, which has a 3− to 4-minute half-life.[6] No one cut-off point of IGF-1 has been used as diagnostic of GH deficiency, but the largest study determined a cut-point of 84 μg/L (11 nmol/L), which yielded a positive predictive value of 96 and 94% specificity.[7] IGF-1 determination is variable as it is based upon other hormones as well as nutritional status. Also, many assays have yet to be validated. At this time IGF-1 can be used for screening and further tests, such as GH stimulation test in combination with clinical symptoms, may be necessary for accurate diagnosis.

In 1990 a study by Rudman et al[8] followed up older men with low circulating levels of IGF-1 who were supplemented with GH for 6 months. The authors observed that men supplemented with GH showed an increase in lean body mass, decrease in adipose density, and increase in skin thickness.[8] This article has been referenced as the source supporting the use of GH to reverse the aging process, although it has been criticized for its

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lack of control group, its rather heterogenous population, and inability to prove a cause-and-effect relationship.

The most debilitating side effect of aging is sarcopenia, which is associated with increased rates of disability, poor mobility, frailty, and hospitalization. Sarcopenia has also been directly associated with osteoporosis, which is identified as a known risk of skeletal fracture.[9] Determining who will sustain a fracture is of the upmost important because of the associated morbidity and mortality. Sarcopenia and bone mineral density is one part of fracture risk but there are risk assessment tools that can be used to determine high-risk patients. Algorithms presented by Kanis et al[10] have shown the 10-year risk of facture in men and women with variable risk factors. It has been demonstrated that IGF-1 plays an essential role in the development of the growing skeleton and in the maintenance of bone mass during late adulthood and aging. The response of bone mineral density is bi-phasic in response to GH replacement: an initial increase in resorption followed by an increase in bone mineral density has been observed. A randomized study included 32 men with somatopause were randomized to GH replacement vs placebo. Patients had normal growth and development and were diagnosed with GH deficiency after 18 years of age. The GH replacement group increased bone mineral density in the lumbar spine by a mean (±SD) of 5.1% ± 4.1% and bone mineral density in the femoral neck by 2.4% ± 3.5%. There was also an observed significant increase in bone turnover proteins as well as lean body mass, but a significant decrease in percentage body fat.[11] Changes in lean body mass have also been observed in GH replacement. This is well documented in animal studies and has been confirmed in multiple human studies.[12–15] Lange et al[16] assigned healthy elderly men (mean age 74 years) to GH, GH and exercise regimen, placebo, or placebo and exercise regimen. What they observed was similar to other studies: GH supplementation caused a significant increase in lean body mass and a decrease in fat mass. While anthropometric data improved, there was no change in power or strength in muscles.[16] The studies investigating the association of GH and elderly frailty are difficult to compare. The sample sizes are frequently small, GH dosing is variable, and the studies frequently use different function tests. Despite consistent evidence that bone health and lean muscle mass increase, the clinical significance of these observations remains questionable.

IGF-1 is synthesized locally in neuronal tissue and systemic IGF-1 is known to cross the blood-brain barrier. Blood levels of IGF-1 have been directly related to cognitive performance. In human beings, IGF-1 plasma levels of healthy elderly were positively associated with Mini Mental State Examination scores.[17] Treatment with GH has shown conflicting reports for improving cognition.[18] IGF-1's role in cognition is still unclear and some recent studies using GH-releasing hormone (GHRH) peptides have shown some promise in the cognitive domain; this will be discussed later in this review.

Studies relating GH to longevity are inconsistent as to whether there is a benefit in having increased or decreased GH levels. This is represented in the Laron syndrome patients with short stature who have a GH gene deletion. This population exhibits a typically long life span, reaching ages 80—90 years. In one study of this population, 222 patients with short stature had no malignancies compared to up to 24% of family members.[19] This is in stark contrast to an Ecuadorian population with GH receptor mutation and IGF-1 deficiency who have a shorter life span and two thirds die by 65 years of age.[20] One of the concerns related to GH supplementation is that IGF-1 has been linked with multiple different cancer lines including prostate and breast cancer.[21,22] Importantly, studies that show an increased risk of cancer are usually representative of those with sustained elevated circulating hormone. Risks of cancer from intermittent use of GH maintained at physiologic norms have not been demonstrated.

The side effects of GH treatment include increased insulin levels, swelling in the extremities, joint and muscle pain, gynecomastia, cardiovascular disease, and possible increase risk of certain cancers. The Safety and Appropriateness of GH Treatments in Europe study followed European children treated with exogenous GH and observed a 30% increase in expected mortality in children taking GH.[23] At this time GH therapy in adults is limited to a few indications that include GH deficiency in childhood, documented hypopituitarism, AIDS wasting syndrome, and short bowel syndrome.

GHRH ANALOGS, SERMORELIN

GHRHs such as sermorelin simulate the patient's own pituitary gland by binding to specific receptors to increase production and secretion of endogenous GH. Similar to GH secretagogues, these agents increase endogenous GH secretion controlled by a negative feedback loop and return GH levels to normal rather than supra-physiologic values. GHRH will also cause secretion in a more pulsatile pattern rather than sustained dosing as seen with injected GH.

GHRH has been shown to increase IGF-1 levels and lead to improved body composition. In one study, twice-daily subcutaneous administration of a GHRH for 3 months led to elevated GH and IGF-1 concentrations in postmenopausal women, reduced abdominal visceral fat mass, increased total body water, improved certain measures of physical performance, and elicited significant local skin reactions.[24] These authors also noted that woman on estrogen replacement saw a blunted effect that has been demonstrated by estrogens inhibitory effects of GH. Similar effects were seen in healthy older men given 1 or 4 mg GHRH sub-cutaneously twice daily for 3 months, who responded with elevated GH and IGF-1 concentrations and dose-dependent changes in body composition.[25] GHRH has also shown benefit in the cognitive domain of aging. 6 Months of GHRH treatment resulted in significant improvement in cognitive functions, particularly those that involve problem solving and psychomotor processing and working memory of both healthy older men and women.[26] Another study that