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Growth Hormone and Aging

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Aging is associated with a significant decline in secretion of growth hormone. This in turn leads to reduced circulating IGF-I and changes in IGF-binding proteins. Growth hormone replacement to growth hormone-deficient individuals has been shown to improve quality of life, enhance bone and muscle mass, and reduce cardiovascular risk. However, studies with growth hormone therapy in the elderly have been somewhat disappointing with minimal changes in lean body mass, musculoskeletal function, and overall quality of life. Moreover, recent evidence suggests that high normal serum IGF-I levels may be associated with a greater risk of several neoplastic disorders. Hence, there is less enthusiasm for reversing the changes of the "somatopause" with recombinant growth factors. An overview of these issues and the prospects for the future will be discussed in this article.

Key Words: Growth hormone; IGF, Aging.

Introduction

Aging is associated with profound changes in numerous organ systems of all mammals. Central nervous system atrophy and degeneration, accelerated atherogenesis, neoplastic transformation, cardiac failure, osteoporosis, sarcopenia, immune dysfunction, and endocrine hypofunction are all consistent characteristics of the aging phenotype. Recently, tremendous insight has been gained from observational and interventional studies in humans especially in respect to age-related atrophy of the musculoskeletal system. At the tissue and molecular level, genetic programs that define cellular senescence and/or programmed cell death have partially been elucidated, owing in part to studies in models such as the fruitfly and earthworm. The conclusions drawn from these investigations have resulted in numerous hypotheses regarding the pathogenesis of aging in humans. The growth hormone (GH)/IGF-I system is no exception. It has been the focus of numerous postulates in relation to several tissues including the heart, bone, muscle, and brain. Some investigators have proposed that the obvious and consistent musculoskeletal atrophy so characteristic of aging is a result of a "somatopause," i.e., a decline in growth hormone secretion. Others have suggested that there is a peripheral resistance to growth hormone leading to lower levels of IGF-I. Alternatively, scientists have suggested that resistance to somatomedins such as IGF-I results in musculoskeletal atrophy and impaired functional status. These tenets have resulted in several large intervention trials of elderly men and women administered recombinant peptides including rhGH, rhIGF-I, and the combination. In experimental animals, IGF-I has been introduced via specific viral vectors into muscle and has been shown to transiently increase muscle function and mass.

In sharp contrast to those efforts designed at "replacing" growth hormone or growth factors, recent observations have raised the specter that enhancing growth hormone, or IGF-I, may not necessarily be in the best interest of the organism. For example, in inbred and mutant mice with growth hormone abnormalities, studies have revealed that lifelong low levels of IGF-I are associated with greater longevity and lower likelihood of neoplasms *(1)*. Dietary restriction has long been noted to prolong life in experimental animals, and recently this has been tied to changes in the IGF-I axis *(2)*. Yet almost paradoxically, expression of the type I IGF-I receptor on various cells confers significant protection against programmed cell death *(3)*. And, high "normal" levels of IGF-I in two very large cohort studies have been strongly associated with greater prostate and breast cancer risk *(4,5)*. Recent in vitro studies also suggest that stimulatory signals for mammary tumor growth, including estrogen, work through intracellular networks including the insulin-like growth factor/IRS-I/Stat/Map kinase system *(6)*. Furthermore, IGF-binding proteins such as IGFBP-3, with very strong affinity for IGF-I, have been shown to have IGF-I independent effects on cell proliferation *(7)*. Indeed, the discovery of a p53 regulatory element in the IGFBP-3 gene suggests that this tumor suppressor may work through the IGF regulatory system *(8)*.

The fundamental paradox inherent in defining the role of the growth hormone/IGF-I system in aging serves to

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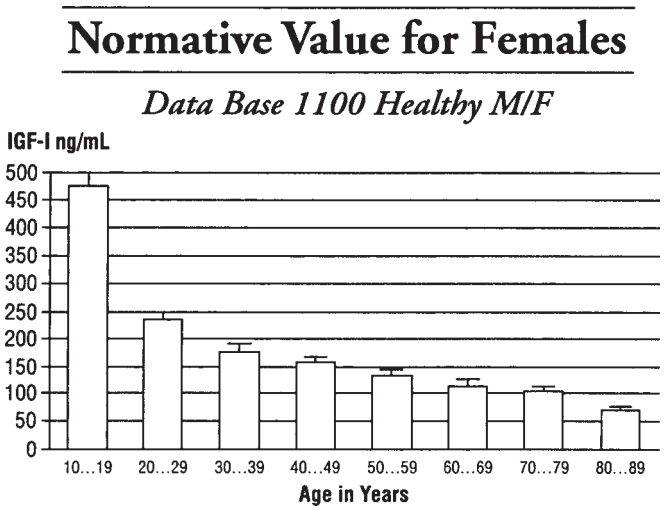

Fig. 1. Age related changes in serum IGF-I in healthy women from ages 10 to 90. These data are based on assays performed in one laboratory over seven years in multiple cohorts from around the world. There is an age-associated regression for serum IGF-I ($r = –0.56$, $p < 0.0001$).

exemplify how physiologic complexities in this ubiquitous network can lead to disparate conclusions. Moreover, as more regulatory elements and targets are defined for these peptides, it is likely that greater insight will be gained into their role in the aging process. Clearly, the overly simplistic hypotheses of the late 1980s linking growth hormone deficiency to frailty are likely to fade, only to be replaced by a more sophisticated appreciation for cellular senescence. In this paper, I will review how aging affects components of the growth hormone/IGF-I axis, and then examine these perturbations in relation to functional aspects. I will focus principally on the musculoskeletal system in part because most studies have been conducted to examine that end point.

Age-Related Changes in the GH/IGF-I System in Mammals and its Implications

Measurement of Growth Hormone Dynamics in the Elderly

From "north to south" alterations in the GH/IGF-I system have been documented in older individuals. But, each diagnostic tool for defining the status of growth hormone release or secretion has inherent limitations as well as value. In addition, it is critical for the clinician to define the purpose of the test as much as the type of measure. For example, although GH secretion wanes with age, and serum levels of IGF-I and IGFB P-3 decline over time (*see* **Fig. 1**),this does not mean all elders are growth hormone-deficient *(9)*. To ascertain a true growth hormone-deficient (GHD) state in order to consider "replacement" therapy, dynamic testing is essential. On the other hand, screening for age-related changes in GH responsiveness using serum IGF-I, IGFBP-3, acid labile subunit, or other combinations, does not constitute a strong rationale for treating elders with rhGH.

There are a variety of measures that have been utilized to test for GHD. For assessment of the status of hypothalamic releasing factors (GHRH) or hypothalamic inhibitory peptides (somatostatin), perturbations in the downstream effectors can be detected through provocative studies such as GHRH or other secretagogs (arginine, insulin, clonidine, L-dopa, or any combination thereof) *(10)*. For assessment of pituitary reserve, a similar array of tests is available along with deconvolution analyses of periodic GH concentrations sampled over 24 h *(11)*. While deconvolution analysis may provide the best assessment of basal physiologic GH secretion in a given individual, it is laborious and not well-suited for clinical assessment. Similarly, insulin-induced hypoglycemia can define GH status both accurately and precisely, but is potentially dangerous in the very old, and can also be expensive *(12)*. Serum measurements of IGF-I, IGFBP-3, the ratio of these two, or determination of the acid labile subunit (ALS), which combines with IGFBP-3 to carry IGF-I, are also utilized clinically although both sensitivity and specificity are reduced compared to the insulin tolerance test *(12)*.

Regardless of the method, it has been estimated that there is a 14% decline in GH secretion per decade after age 20 *(13)*. This results in a consistent age-related drop in serum IGF-I. Figure 1 shows the per decade mean serum IGF-I concentrations in women performed in our laboratory from a database accumulated in studies from around the world in nearly 1100 healthy men and women *(14)*. The assay is a double antibody RIA performed after extraction of nearly all the IGF binding proteins *(14)*. It should be noted that serum concentrations of IGF-I are fairly consistent in subjects after age 60, where one standard deviation is 36 ng/mL compared to a one standard deviation value of 75 ng/mL in younger individuals (ages 20–40). This is also illustrated in **Fig. 2** in which individual serum IGF-I levels are noted for several different cohorts of elderly individuals, some who were healthy and some who were frail. Despite the relative consistency among groups with different backgrounds, the "normal" concentration of serum IGF-I in elderly individuals still varies by nearly a factor of 10 (e.g., 30–300 ng/mL). Overall, it is clear that the age-associated drop in GH secretion noted by deconvolutional analysis matches up with a decline in serum IGF-I. But in studies comparing dynamic indices with serum IGF-I, the correlation is not strong. This bespeaks the nature of IGF-I as an integrative measure of several factors. Moreover, it would imply that there must be significant variance for the relative decline in GH secretion by an individual over time.

Regulation of IGF-I

Several regulatory factors besides GH affect serum IGF-I concentrations, and these variables can be more pro-

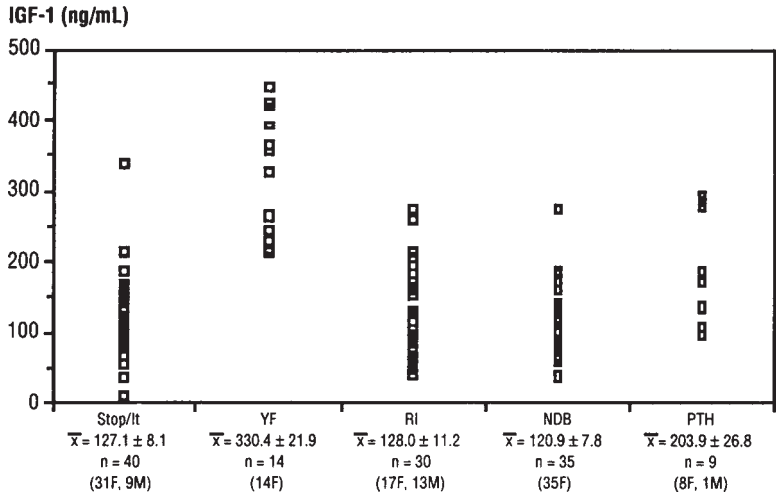

Fig. 2. Serum IGF-I from various cohorts of women measured in the same assay. YF- represents young females from a cohort in Oregon; NDB represents 70-yr-old white females residing in northwestern Maine; STOP/IT represents a cohort of women from the Boston area over age 65; RI represents older frail women from Rhode Island recruited for a growth hormone trial; CT represents a healthy elderly cohort involved in an exercise program; PTH represents middle-aged women with primary hyperparathyroidism. There were no differences in serum IGF-I among similarly aged elderly women regardless of their functional status. Young females had significantly higher serum IGF-I levels than did their elderly counterparts.

nounced in the elderly. Protein calorie undernutrition, for example, depresses the expression and production of IGF-I in the liver *(15,16)*. In chronic malnutrition, GH secretion is high but GH receptors are down-regulated and signal transduction is impaired leading to a significant decline in serum IGF-I. At least two IGFBPs that are inhibitory in nature, IGFBP-1 and IGFBP-4, are increased in the circulation of malnourished individuals *(17)*. Insulin deficiency similarly leads to a significant decline in IGF-I and a markedly increased serum IGFBP-1 level *(17)*. Acute catabolic stress, surgery, trauma, hip fractures, and infectious diseases can also set up a state of relative growth hormone resistance leading to low levels of serum IGF-I. Conversely, protein supplementation for 6 mo in elderly individuals after a hip fracture markedly increases serum IGF-I and reduces rehabilitation time *(18)*. Finally, exogenous glucocorticoids and estrogens can reduce serum IGF-I by 20–50% *(19)*. But, even considering these other factors, there remains a wide variance in serum IGF-I. One possibility is that heritable determinants could be responsible for intra-population differences in serum IGF-I.

The large variance in serum IGF-I in the elderly has also led investigators to consider whether differences in serum IGF-I can be related to various functional limitations so characteristic of the aging phenotype. This thesis was first advanced in the mid-1980s and was supported by preliminary cross-sectional studies in older men, individuals with previous poliomyelitis, and some institutionalized patients. Interest in this hypothesis was most pronounced after publication of a now-famous study in the *New England Journal of Medicine* in 1990 *(20)*. In that nonrandomized nonplacebo controlled trial, rhGH–0.1 mg/kg/d, was administered to 18 older men with low serum IGF-I levels. After 6 mo, serum IGF-I rose dramatically and skin texture improved, as did bone mineral density in one of nine sites. The popular press and others concluded that rhGH was a safe and effective way of restoring some element of youth to older individuals. In the span of this last decade, more data have been generated from observational and longitudinal studies calling into question the results of that study and the relationship of the somatopause to age-related frailty.

Evidence Concerning the Relationship Between IGF-I and Functional Status

Several lines of evidence, both cross-sectional and longitudinal, have raised questions about the predictive value of serum IGF-I for defining functional status in older individuals. Kiel et al. demonstrated that serum IGF-I in elderly and frail individuals did not correlate with functional status, bone mass, muscular strength, or overall health status *(21)*. Papadakis et al. administered GH to older men and were unable to show functional improvement despite significant increases in serum IGF-I and a very modest rise in spine bone mineral content *(22)*. On the other hand, several cross-sectional and cohort studies have shown that there is a relationship between IGF-I and bone mass or fractures in elderly people. In a recent evaluation of women from the Framingham Heart Study, the highest serum IGF-I by quartiles could be related to the highest bone density at the spine, hip, and wrist *(23)*. Moreover, in the Study of Osteoporotic Fractures, the lowest quartile of serum IGF-I was associated with a nearly twofold greater risk of hip fracture even after controlling for bone mineral density

(24). Clearly, further prospective studies will be required to define the precise relationship between this peptide and fracture risk. Yet despite these findings, there is little evidence that IGF-I can be used to predict functional outcomes in the elderly.

Ironically there are now very convincing data from several large clinical trials of rhGH in patients with documented GH deficiency, suggesting that replacement of GH has a beneficial effect *(25–28)*. On the other hand, trials with rhGH and IGF-I in elderly patients either with primary osteoporosis or frailty have been disappointing. Although exogenously administered GH and IGF-I can raise serum IGF-I levels and increase markers of bone formation, changes in bone mass are relatively small and in the best of studies, only comparable to those seen with antiresorptive therapies such as alendronate or estrogen *(22,29–31)*. In part, this can be attributed to the capacity of skeletal IGF-I to stimulate both bone resorption and bone formation, thereby causing little change in overall bone mineral density. Rosen et al. recently completed a large 12-mo prospective randomized trial of rhGH with or without exercise in frail elders *(32)*. They reported that among the 132 men and women randomized to various doses of rhGH ranging from 2.5 to 10 μg/kg/d, markers of bone turnover increased in a dose-dependent manner, but changes in bone mass were minimal (i.e., <1% above baseline) at best *(32)*. More studies will have to be undertaken to define how GH or IGF-I can be utilized, if at all, in osteoporotic states. Most importantly, such trials will have to be of longer duration in order to refute or confirm earlier trials. However, it is clear that there will remain a significant cost–benefit issue for using rhGH in elders, since the recombinant peptide is relatively expensive and there can be major side effects, such as gynecomastia, glucose intolerance, and carpal tunnel syndrome.

Other Issues Surrounding "Replacement Therapy" with GH or IGF-I.

Although it has been known for several decades that acromegalics have an increased propensity for colonic neoplasms, interest in the association between serum IGF-I and cancer risk has increased with reports that individuals with high IGF-I levels (or low IGFBP-3 levels) within the broad normal range between acromegaly and GH deficiency have increased risk of prostate, colon, and breast cancer *(4,5,33)*. In the one study, Chan et al. demonstrated that among a nested cohort of men in the Physician's Health Study, the highest quartile of plasma IGF-I levels was associated with a 4.3-fold relative risk of prostate cancer compared to the lowest quartile *(4)*. This association was independent of baseline PSA levels and suggested that IGF-I might be an independent predictor of prostate cancer risk. The major findings of this study were subsequently confirmed by Wolk et al. *(34)*. In a separate study of similar design utilizing women in the Nurses Health Study, Hankinson et al. noted that among premenopausal women less than age 50, there was a 4.5-fold relative risk of breast cancer in the highest quartile of plasma IGF-I compared to the lowest quartile *(5)*. Adjustment for IGFBP-3 increased the predictive value of IGF-I in two of these studies *(4,5)*. Indeed IGFBP-3 was shown to be inversely related to risk, while IGF-I was positively related to risk. This relationship was particularly strong in a study concerning predictive value of IGF-I and IGFBP-3 with respect to colon cancer *(33)*.

The inverse relationship of IGF-I to IGFBP-3 with respect to risk of neoplasia deserves comment. Normally both IGFBP-3 and IGF-I are regulated by GH and, therefore, these two peptides exhibit a strong and direct correlation in the serum. Conceivably, certain individuals may have polymorphic variations in the promoter regions of the genes encoding IGF-I and/or IGFBP-3 that result in a lack of coordination of expression of IGF-I and IGFBP-3, and such variants might be linked to high IGF-I/IGFBP-3 ratios, increased cellular proliferation, and hence, to increased accumulation of somatic cell mutations and cancer risk. Acromegalics may have subtle (rather than extreme) increased cancer risk because in this condition, both IGF-I and IGFBP-3 are elevated, and changes in the IGF-I/IGFBP-3 ratio are subtle.

Other studies, some of which have utilized antineoplastic drugs, have provided further indirect evidence that the IGF regulatory system is involved in the pathobiology of neoplasia, in terms of both risk of cancer and behavior of cancers. Only a few of many examples are listed here. With respect to risk, it is highly relevant that a positive correlation between GH level (or IGF-I level) and breast epithelial cell proliferation was seen in an aged rhesus monkey model *(35)*. With respect to neoplastic behavior, tumor growth in IGF-I deficient mice has been shown to be reduced relative to control mice *(1)*. Furthermore, it has recently been shown that fenretinide, a synthetic retinoid with antitumor activity, reduced plasma IGF-I levels and increased IGFBP-3 concentrations, especially among premenopausal women *(36)*. Also, tamoxifen has been shown to decrease IGF-I serum level and to down-regulate IGF-I induction of tyrosine phosphorylation of the IGF-1R and inhibit IRS-1 signaling in MCF–7 cells *(37)*. Dunn et al, utilizing a p53 deficient mouse model, demonstrated that as expected, dietary restriction lowered serum IGF-I, and that this was associated with increased apoptosis, and decreased tumor progression *(38)*. Furthermore, IGF-I administration to these diet restricted mice increased cell proliferation and blocked the inhibitory effect of dietary restriction to tumor growth. Taken together, these and other experimental data suggest that the IGF-I system is involved in tumor development and progression. However, there are many unanswered questions. For example, it has not been

established that the relationship between IGF-I levels and cancer risk is causal. Perhaps dietary factors are critical, and influence both IGF-I and risk. More work is also needed to reconcile the observations that while IGF-I levels appear to be related to risk of cancer, in advanced cancers autocrine IGF-II loops are common and may render circulating IGF-I irrelevant (and invalid as surrogates for IGF bioactivity) *(39)*.

Conclusions

There is very strong evidence that the growth hormone IGF-I axis is dampened during the aging process. Whether this is an epiphenomena, a result of changes in body composition, or the cause of musculoskeletal frailty, remains to be defined. But it is known that changes in somatostatinergic tone, growth hormone releasing hormone secretion, growth hormone receptor number, and IGF-I can produce a state of relative GH deficiency. Still, the full implications of these events in the life of an organism have not been clearly defined. We have certainly reached an era where use of "substitution" therapy for growth hormone deficiency states is becoming routine. More questions, however, continue to be raised about "pharmacologic" rhGH or rhIGF-I treatment to prevent or reverse age-associated changes in body function. Indeed, IGF-I is a trophic growth factor, capable of stimulating neoplastic proliferation and preventing programmed cell death, raising a whole new set of issues surrounding efficacy of treatment. Hence, trials designed to answer safety and effectiveness will still need to be performed in order to delineate the precise role of growth hormone and/or IGF-I treatment to forestall or even reverse some of the devastating effects of the aging process.

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