TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 16
Number 2 *Spring 2023*

12-18

2023

Is Growth Hormone the Fountain of Youth?

David Youlus

Is Growth Hormone the Fountain of Youth?

David Youlus

David Youlus graduated with a Bachelor of Science degree in Biology in January 2023.

Abstract

Finding the cure for aging has been a sought-after quest for as long as the world has existed. Growth hormone has been shown as a possible treatment to negate the phenotypic effects of aging. Growth hormone is released from the adenohypophysis in response to sleep, exercise and stress. This in turn stimulates insulin-like growth factor-1 (IGF-1) secretion from the liver. Growth hormone circulation decreases in volume during aging. Studies on growth hormone therapy have indicated youth-like benefits, such as the reversal of sarcopenia, improved cognitive function, and boosted immunity. However, creating an imbalance of growth hormone and insulin-like factor-1 also has its detriments. IGF-1 has been linked to cancer and diabetes. The purpose of this study was to determine if there is sufficient evidence of growth hormone's anti-aging effects to consider it as an effective age-reversal therapy. Based on the health risks, insufficient degree of positive results, and the benefits of low insulin-like growth factor-1 for evading cancer, growth hormone is likely not the anti-aging drug being sought.

Introduction

Aging is by far the most considerable risk factor for chronic diseases and their related deaths worldwide. Commonly recurring conditions like cardiovascular disease and cancer, are known to occur at a much higher rate among the aging. In fact, beginning at midlife, the incidence of mortality from chronic disease doubles nearly every 7-8 years (Rae et al., 2010). This presents an important dilemma for a world population that is getting increasingly older, with a higher population density of those aged 60 or over every year. Without any intervention, this could cause a major problem for hospitals and healthcare infrastructure as they attempt to keep up with the higher demand for medical care. Some of the negative impacts of aging are the result of cellular and molecular damage inflicted by the dysfunction of human body systems and other environmental factors over time. This can lead to conditions such as organ hypertrophy, sarcopenia, and a compromised immune system. Much research has been done on this subject, with anti-aging interventions performed on both animals and humans, yielding some promising results (Weindruch & Walford, 1988). Reversing aging could positively impact both longevity and health span, giving the elderly more "youthfulness" and a higher quality of life in their later years. In specific, Growth Hormone (GH) treatments have been identified as a possible solution to the aging crisis. With aging, GH pulsation decreases in both frequency and quantity and becomes almost nonexistent in some. Human Recombinant Growth Hormone (hRGH) therapy has been shown to increase the body's muscle to adipose ratio in younger subjects with growth hormone deficiency (Elbornsson et al., 2013) and could possibly counteract the effects of sarcopenia. It is hypothesized that GH would also cause organ growth, including the thymus which is very important for immunity-providing T cells. However, side effects of GH treatment must also be considered, with the increased ability of cancerous growths to proliferate. Another negative effect of GH therapy to examine is diabetes mellitus. This can occur as the result of over targeting on the GH/IGF1 axis, leading to dampened insulin sensitivity. Overall, it must be determined if GH is a worthy treatment for aging prevention, at what dosage is it most affective, and if it could be combined with other drugs known to combat its side effects.

Methods

Databases including Google Scholar, PubMed, EBSCO, and ProQuest were used to search for peer-reviewed articles and journals with relevant scholarly information. Articles were reviewed and analyzed for both accurate contemporary content as well as any conflict of interest. Keywords used for searching included "Growth Hormone", "Aging", "GH-IGF-1 axis", and "Somatopause."

Discussion

What is Growth Hormone?

Human growth hormone (hGH), or somatotropin, is the most abundant hormone in the adenohypophysis, accounting for up to 10% of the total weight of the pituitary gland (Devesa & Devesa, 2020). This small proteohormone is originally stimulated by growth hormone releasing hormone (GHRH) from the hypothalamus in the brain. Stress, exercise, and sleep stimulate the release of GHRH to the adenohypophysis and the resulting GH secretion by somatotrophs into the bloodstream. As its name suggests, growth hormone was initially discovered for its growth inducing properties on longitudinal bones in children. However, the effects of GH were quickly recognized to be much greater than just longitudinal growth. One of the earliest pioneers of GH treatment wrote, "Pituitary growth hormone is distinctive in causing growth of almost all tissues…" (Raben, 1962). We now know that growth hormone increases the growth of most cells by increasing amino acid uptake, and that it also regulates metabolism through lipolysis in fat tissue (Tresguerres et al., 2022). Therefore, GH plays a large role not just in children and adolescents, but also in adults that have "ceased" growing.

GH circulation levels reach their maximum soon after birth and remain high throughout the early stages of life. After reaching the full growth potential of adulthood,

there is a slow decline in GH levels caused by less hypothalamic GHRH production. Measuring GH levels in the body has long been a problem for researchers, because of its nature of pulsatory secretion. The highest GH levels are always found during sleep and fluctuate greatly throughout the day. As a result, new tests to indirectly detect GH have been developed, with the most common way being the measurement of plasma IGF-1 (Insulin-like growth factor-1). This method was proven by measuring IGF-1 levels in the aging to see that they closely resembled the downward curve of GH levels (Rudman et al., 1990). IGF-1 levels directly correspond to those of growth hormone since IGF-1 acts as a GH mediator and regulator in the GH/IGF-1 axis.

The GH/IGF-1 Axis

Once GH is secreted from the pars distalis, it travels through the bloodstream to target tissues. These include the muscle, adipose tissue, and liver. The adipose tissue then decreases as it undergoes lipolysis. On the other hand, an increase of protein and amino acid uptake results in growth of muscle tissue. When GH reaches the liver, the liver secretes IGF-1 which acts as a mediator to affect both chondrocytes and the body's organs. GH affects nearly all cells in the body, either directly or through IGF-1 secretion. However, since IGF-1 closely resembles insulin's chemical structure, this results in competition for insulin binding sites and a dampened insulin sensitivity, which can lead to hyperglycemia (LeRoith, 2007). The regulation of GH occurs on both the hypothalamic and pituitary levels. Somatostatin is released by the hypothalamus and inhibits both growth hormone and GHRH activity. IGF-1 acts to increase somatostatin and inhibits GH both directly and indirectly, through GHRH inhibition. So, in essence, GH regulates itself. Sleep, exercise, and trauma act as stimulants for GH. Ghrelin, sometimes called the hunger hormone, which is produced in the gastrointestinal tract, also acts as a stimulant for GH. This is the well-known GH/IGF-1 axis for regulating growth hormone activity, especially in the longitudinal growth which occurs in children.

Growth Hormone Deficiency (GHD) in Children and Adults

In 1985, the FDA approved the use of hRGH (human recombinant growth hormone) as a treatment for children suffering from GHD. Growth hormone deficiency is characterized by a dysfunction of the hypothalamus or pituitary gland which results in an inadequate amount of circulated GH. The causes of this dysfunction can be either congenital or etiological, with its effects seen in children as well as adults. GHD in children is sometimes referred to as pituitary dwarfism and is easily identified by a lack of growth and short stature. GH treatment in children has shown overwhelming success rates in dose-dependent increase of growth and stature (Chatelain et al., 1994). GH has become somewhat standardized for children with small-stature as a result of GHD. In adults however, GHD diagnosis becomes much more complicated. Adult patients may present with obesity and a lack of lean muscle, but this is not always apparent. Hypoglycemia often accompanies GHD since it causes dysregulation of the GH/IGF-1 axis, although there can be many other causes of low blood sugar levels. Additionally, measuring GH levels requires constant and persistent testing using GH/IGF-1 assays to obtain accurate results (Melmed, 2019). Diagnosis can often only be made after putting together the entire picture. GH treatment for adults with GHD was FDA-approved in 1996 and patients immediately showed major improvements in body composition and bone health, as well as a self-reported increase in quality of life in both male and female cohorts (Attanasio et al., 1997).

Is GH Treatment Safe?

The effects of GH therapy have been monitored over the past 30 years, in thousands of patients, to determine that it is generally safe for children and adults. The risk of developing cancer both for children and for adults is not affected by GH treatment. Cancer recurrence also seems to be unaffected in children, while more data is still necessary to determine the risk of recurrence in adults. However, increased IGF-1 levels have been linked to several types of neoplasms including prostate and colon cancer. Additionally, it is likely that the anabolic effects of GH and IGF-1 would aid cancerous growth once a malignant growth is already present (Jenkins et al., 2006). The incidence of type 2 diabetes mellitus has also been shown to be unchanged after GH treatment, even though insulin sensitivity is a common concern when increasing the GH/IGF-1 axis. Moreover, it can be hypothesized that risk of cardiovascular disease actually decreases, since levels of LDL cholesterol are decreased when compared to GHD. Growth Hormone has been known to cause peripheral edema, arthralgias, and carpal tunnel syndrome in older patients (Hersch & Merriam, 2008). There are several other rare cases of illness, including intracranial hypertension, scoliosis, and sleep apnea, although direct relation to GH therapy has not been confirmed (Allen et al., 2016).

Acromegaly and Excess GH Secretion

On the other hand, immoderation of GH secretion, which is generally caused by a pituitary adenoma, also yields negative results. Gigantism results when excess growth

hormone is secreted before the long bones have fused. When left untreated, patients commonly develop diabetes and arthritis. Acromegaly, which is the consequence of increased GH production in adults, carries a greater risk for hypertension and cardiomyopathy. These health risks result in morbidity rates of up to three times that of their age group (Adelman et al., 2013). Although, since the cause of this disorder is hypersecretion due to adenoma, there can be many other hormones that will also be present in excess which can also contribute to adverse effects.

GH/IGF-1 Axis in Centenarians

Centenarians are perhaps the closest model you can find for a healthy and delayed aging process. The ability of these long-lived people to thrive in old age can usually be attributed to their success in avoiding and outlasting major illness, like cancer, cardiovascular disease, and diabetes mellitus. There are several factors that affect healthy aging, with genetics playing a large role in avoiding disease entirely. In fact, several aging associated diseases, including Alzheimer's and cardiovascular disease, are practically nonexistent in extremely old individuals (Zhang et al., 2020). Therefore, studying the long-lived and their offspring can likely yield insight for anti-aging techniques.

There have been several studies documenting the GH/IGF-1 axis in long-lived individuals, but the results appear controversial. Many studies found an incidence of decreased levels of plasma IGF-1 among centenarians (Bonafe et al., 2003;Van der Spoel et al., 2015). On the other hand, one study showed that low IGF-1 levels in centenarians predicted impendent mortality (Arai et al., 2008). Some even reported no change in the GH/IGF-1 axis of centenarians when compared to those over the age of 65 (Paolisso et al., 1997). There are several factors that could influence the effectiveness of these studies. It is hard to determine the role of GH/IGF-1 in aging based on this data, especially when taking into account the normal age-related decline in GH secretion. Additionally, other important longevity factors include socioeconomic situations and exceptional genetics when it comes to predisposition for certain illnesses. Accordingly, it is likely that more research is necessary to accurately determine a pattern of GH levels in centenarians. Studying the offspring of these individuals could be a better option for obtaining enough data, since it can be difficult to find and test centenarians due to a small sample size, as well as their physical limitations of old age.

GH Therapy as An Anti-Aging Drug

The idea that growth hormone could be used in an aging prevention capacity is based on established knowledge of growth hormone's functional properties in metabolism and growth. It is well documented that GH secretion declines with age starting from as early as 30 years old. After that point GH secretion decreases about 15% more every decade of life (Garcia, et al., 2000). With this progressive loss of growth hormone circulation, it is hypothesized that this deficiency plays a large role in several aging processes. Firstly, changes in body composition in the aging favor a higher ratio of adipose tissue and less lean body mass. Additionally, hypertrophic processes are reflected in many organs such as the liver, spleen, and bone. GH replacement could be used to prevent and reverse this aging decline, much like we see its effectiveness regarding the adipose to muscle ratio in GHD patients.

In a landmark study, GH replacement therapy was introduced to 21 men over the age of 60. After a 6-month treatment period, the results showed major improvements, increasing muscle mass by 8.8 percent and skin density by 7.1 percent, and decreasing the mass of adipose tissue by 14.4 percent. Bone density also showed a marginal increase. This data indicated that GH is indeed responsible at least partially for the aging phenotype. GH therapy could be a breakthrough in the treatment of aging decline, as well as common age-related conditions like sarcopenia (Rudman et al., 1990). Additionally, the fact that there were practically no side effects in this cohort indicated that GH could be used safely in aging patients if given at low/replacement doses.

This study though, was only a small representation of GH success. The sample size was 21 patients, and the treatment period was only 6 months. More research would be required to identify long-term anti-aging improvements and any adverse effects. One such concern was that although GH therapy could reverse the effects of aging by inducing growth of internal organs, maybe it would also aid cancerous growths. Although, research in children and adult GHD has shown no such risk, there is not much data on older adults where the incidence rates of cancer are already heightened. Additionally, the side effects found in the test group included hypertension and hyperglycemia. Over longer periods of treatment, it is likely that insulin sensitivity could decrease and lead to diabetes mellitus. Other adverse effects reported from GH administration at therapeutic levels (although the muscle to adipose ratio increased greatly) included peripheral edema, carpal tunnel syndrome, and arthralgia, which occurred in up to 46% of patients in one study (Blackman et al., 2002). In replacement therapy though, these symptoms were not seen, other than a low incidence of joint pain. It is important to consider that when looking through the lens of health span rather than longevity, maybe such a

treatment would be worth the risk. The ultimate goal is to delay aging, in the sense of a longer feeling of youthfulness, rather than merely extending life after aging. However, because of the great possibility of serious illness, additional research would be necessary before declaring the unearthing of the fountain of youth.

A better way to measure effectiveness of GH could be by using epigenetic clocks in place of chronological age. Epigenetic aging clocks are a type of biological clock which measures DNA methylation levels. DNA methylation is a type of DNA modification that increases with age and plays a role in proper gene expression and function. Since this methylation is a dynamic process, it can accurately predict biological age in regard to many health risks (Field et al., 2018).

A study was conducted showing the impact of GH on thymic involution and immunity from an epigenetic aging perspective. The shrinking of the thymus is a common effect and a key factor in many aspects of aging. The reduction of the functional mass of the thymus, the thymic fat free fraction (TFFF), results in decreased t-cell production and a compromised immunity from major illnesses like cancer and pneumonia. Lack of t- cells can also result in inflammation and can lead to pain and atherosclerosis. Growth hormone replacement therapy combined with DHEA (dehydroepiandrosterone) and metformin, was administered to 9 patients in 2 separate trials. The results, as seen by MRI imaging, showed rejuvenation of the thymic fat free fraction of the thymus, indicating greater immunity t-cell production. The purpose of using DHEA and metformin with the GH was to counter the possible effects of hyperinsulinemia on thymic growth. Hyperinsulinemia is often caused by insulin resistance which could be caused in this case by elevated IGF-1 levels. Immunophenotyping confirmed a higher lymphocyte-monocyte ratio and an increase in recent thymic emigrant t cells, which is associated with better outcomes in 8 different cancers. Most importantly, the epigenetic age of both cohorts increased by a mean of 2.5 years when tested using 4 of the most accurate epigenetic clocks, DNAm, Pheno, Hannum, and GrimAge. (Fahy, 2019). This discovery indicates that GH treatment confers an important immunity boost, which could potentially offset the increased risk of cancer caused by its growth properties. Additionally, the use of a combination of treatments to counter side effects could possibly be useful when trying to combat negative effects of growth hormone treatment including diabetes mellitus. Overall, a reduction in biological age is a strong indicator of GH efficiency in the reversal of aging processes.

Another less studied effect of GH therapy is regarding memory function. The association between GH therapy and memory gain has already been established in studies of GHD children and adults. Researchers have determined that memory will predictably decline in growth hormone deficient patients when compared to a similar control group. When treated with GH however, these patients experienced cognitive improvements in relation to their previous state when deficient in growth hormone (Maruff & Falleti, 2006). The precise mechanism for this link between GH/IGF-1 and memory is not currently known, but we do know that GH does have the ability to cross the blood-brain barrier. It has been speculated that GH could affect the dopamine concentration in the hippocampus, thereby increasing memory and cognition (Arwert et al., 2005). However, we must consider that this improvement in cognitive behavior was mostly seen in younger adults with child onset GHD. Another possible explanation for this phenomenon is the development and maturation of the human brain in early adulthood. More research in older patients must be conducted in order to determine if GH indeed boosts cognitive functioning.

Although GH therapy promotes many age-reversal effects, one study found low GH/IGF-1 levels in the elderly to be a conservation process extending longevity. In a group of 184 subjects above the age of 90 (93 with low IGF-1 levels and 91 that exhibited high IGF-1 levels when compared to the median), it was found that females in the low IGF-1 group survived two times as long as those with high IGF-1 levels. Interestingly, male subjects with low IGF-1 tested the same as those above the median. When comparing both males and females who had a history of malignancy, the survival rate increased to nearly 2.5 times longer for both males and females with low IGF-1 than that of the control group (DeVito et al., 2022). This suggests that GH and IGF-1 decline in aging may in fact be the body's way of self-preserving especially when there is a history of malignancy. One mechanism for this phenomenon could be the increased activity of IGF-1 binding proteins leading to an imbalance in protein homeostasis. For the aged, such an imbalance to homeostasis could mean an inefficient response of the cells to stress, in addition to major health implications on cellular maintenance, causing a decrease in longevity.

GH Treatment and Moderation in Animal Studies

For years it has been known that mice that have a pituitary deficiency of GH have a much longer lifespan than their ordinary siblings (Brown-Borg et al., 1996). Ames dwarf mice, for example, which are deficient in GH, thyroid stimulating hormone, and prolactin, lived a median of 50 percent longer for both males and females. However, when these mice were treated with recombinant GH immediately

after birth, their median survival decreased by 22 percent when compared to a control group, proving the association between growth hormone modulation and longevity (Sun et al., 2017). Interestingly, in the same study normal mice that were injected with GH did not exhibit any change of lifespan compared to untreated controls. A possible explanation for this is that small doses of GH are more tolerable in the early stages of life, given that GH levels are already at maximum.

To better study GH modulation in mice, two laboratories genetically modified mice so that one group had a disruption in the growth hormone receptor (GHR) gene and the other had a modification in the GHRH gene. In both cases there was a major extension of life in both genders (Sun et al., 2017). One of the purposes of this experiment was to better show that GH was responsible for lengthening life, even when all other hormones such as TSH and prolactin are functioning normally. Additionally, this showed that it is possible to create a genetic GH/IGF-1 modulation system without any previous history of GHD. If this could be replicated in humans, it could possibly lead to extended longevity, although the appropriate time for such a change to low GH/IGF-1 would likely have to take place during adulthood to prevent child GHD issues.

GHR Disruption and Laron Syndrome

It is of worthy mention that the longest-lived mouse, winner of the Methuselah prize for longevity in laboratory mice, was a genetically modified growth hormone receptor knockout (GHRKO) mouse that survived almost 5 years. This was an important discovery since the GHRKO gene correlates greatly with patients who have Laron Syndrome (LS). In cases of LS, patients are also found to have a low serum IGF-1 while exhibiting high levels of GH (Duran-Ortiz, 2021). IGF-1 is linked to cancer, with effects on cell proliferation, angiogenesis, apoptosis, and metastasis. Increased IGF-1 has even been thought to cause resistance to chemotherapy treatments (Jenkins et al., 2006). People with LS often live to normal life expectancy or longer and are even immune to certain types of cancer. In one study of LS with 222 patients, not one of them developed cancer while there was a cancer prevalence of 8-24 percent among relatives (Shevah & Laron, 2007). This supports the idea that low IGF-1 levels are associated with longevity in humans. Indeed IGF-1 blockers are currently under investigation as a possible chemotherapeutic agent (Zhang & Douglas, 2004).

Conclusion

Growth Hormone therapy in the aging has shown many of the positive effects that we have seen in GHD children and adults. However, it seems that excess GH/IGF-1 can also act as a detriment to longevity. Cancer proliferation seems more likely with high levels of IGF-1 and the development of diabetes mellitus from acquired insulin insensitivity remains a concern. Furthermore, animal studies have shown that low GH and IGF-1 levels are strong indicators for longevity. To declare GH as an anti-aging drug would require more research into these health risks. The results of GH therapy have not indicated that they are worth the risk of adverse effects. Perhaps testing other doses of GH could reverse aging more, or using a combination of medications could limit negative results. At this point it is impossible to determine if growth hormone is the fountain of youth, or merely the body's way of protecting itself from age-related diseases.

References

Adelman, D. T., Liebert, K. J., Nachtigall, L. B., Lamerson, M., & Bakker, B. (2013). Acromegaly: the disease, its impact on patients, and managing the burden of long-term treatment. International Journal of General Medicine, 6(31). doi:10.2147/IJGM.S38594

Allen, D. B., Backeljauw , P., Bidlingmaier , M., Biller , B. M., Boguszewski , M., Burman , P., . . . Thorner, M. (2016, February). GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. Eur J Endocrinol, 174(2), 1-9. doi:10.1530/EJE-15-0873

Arai, Y., Takayama, M., Yasuyuki, G., Inagaki, H., Yamamura, K., Nakazwa, S., & Hirose, N. (2008). Adipose endocrine function, insulin-like growth factor-1 axis, and exceptional survival beyond 100 years of age. The Journals of Gerontology: Series A, 63(11), 1209-1218. Retrieved from https://doi.org/10.1093/gerona/63.11.1209

Arwert, L., Deijen, J., Muller, M., & Drent, M. (2005). Long-term growth hormone treatment preserves GH-induced memory and mood improvements: a 10-year follow-up study in GH-deficient adult men. Hormones and Behavior, 343-349. doi:10.1016/j.yhbeh.2004.11.015

Attanasio, A. F., Lamberts, S. W., Matranga, A. M., Birkett, M. A., Bates, P. C., Valk, N. K., . . . Strasburger, C. J. (1997, January). Adult Growth Hormone (GH)-Deficient Patients Demonstrate Heterogeneity Between Childhood Onset and Adult Onset Before and During Human GH Treatment. The Journal of Clinical Endocrinology & Metabolism, 82(1), 82-88. doi: https://doi.org/10.1210/jcem.82.1.3643

Blackman, M., Sorkin, J., Munzer, T., Bellantoni, M., Busby-Whitehead, J., & Harman, M. (2002). Growth Hormone

and Sex Steroid Administration in Healthy Aged Women and Men. Journal of the American Medical Association, 288(18), 2282-2292. doi:10.1001/jama.288.18.2282

Bonafe, M., Barbieri, M., Marchegiani, F., Olivieri, F., Ragno, E., Giampieri, C., . . . Paolisso, G. (2003, July 1). Polymorphic variants of insulin-like growth factor I (IGF-I) receptor and phosphoinositide 3-kinase genes affect IGF-I plasma levels and human longevity: cues for an evolutionarily conserved mechanism of lifespan control. The Journal of Clinical Endocrinology & Metabolism, 88(7), 3299-3304. Retrieved from https://doi.org/10.1210/jc.2002-021810

Brown-Borg, H. M., Borg, K. E., Meliska, C. J., & Bartke, A. (1996, November). Dwarf mice and the ageing process. Nature, 384, 34. doi:10.1038/384033a0

Chatelain, P., Job, J. C., Blanchard, J., Ducret, J. P., Oliver, M., Sangard, L., & Vanderschueren-Lodeweyckx, M. (1994, June 1). Dose-dependent catch-up growth after 2 years of growth hormone treatment in intrauterine growth-retarded children. Belgian and French Pediatric Clinics and Sanofi-Choay (France). The Journal of Clinical Endocrinology & Metabolism, 78(6), 1454-1460. doi:https://doi.org/10.1210/jcem.78.6.8200949

Devesa, J., & Devesa, P. (2020). Hormona de crecimiento. Fisiología Humana. doi:https://doi.org/10.1016/j.medcli.2009.10.017

DeVito, L., Barzilai, N., Cuervo, A., Niedernhofer, L., Milman, S., Levine, M., . . . Campisi, J. (2022). Extending human healthspan and longevity: a symposium report. The New York Academy of Sciences, 1507(1), 70-83. Retrieved from https://doi.org/10.1111/nyas.14681

Duran-Ortiz, S. L. (2021). Extending lifespan by modulating the growth hormone/insulin-like growth factor-1 axis. Pituitary.

Elbornsson, M., Götherström , G., Bosæus, I., Bengsston, B., Johannsson , G., & Svensson , J. (2013). Fifteen years of GH replacement improves body composition and cardiovascular risk factors. European Journal of Endocrinology, 168(5), 745-753. doi:10.1530/EJE-12-1083

Fahy, G. M. (2019). Reversal of epigenetic aging and immunosenescent trends in humans. Aging cell.

Field, A., Robertson, N., Wang, T., Havas, A., Ideker, T., & Adams, P. (2018, September). DNA Methylation Clocks in Aging: Categories, Causes, and Consequences. Molecular Cell, 71(6). Retrieved from https://doi.org/10.1016/j.molcel.2018.08.008

Garcia, J., Merriam, G. R., & Kargi, A. (2000). Growth Hormone in Aging. South Dartmouth (MA): MDText.com, Inc.

Hersch, E. C., & Merriam, G. R. (2008). Growth hormone (GH)–releasing hormone and GH secretagogues in normal aging: Fountain of Youth or Pool of Tantalus? Clinicaln Interventions in Aging, 3(1), 121-129. Retrieved from PMID: 18488883; PMCID: PMC2544358.

Jenkins, P., Mukherjeet, A., & Shalett, S. (2006). Does growth hormone cause cancer? Clinical Endocrinology, 64, 115-121. doi:10.1111/j.1365-2265.2005.02404.x

LeRoith, D. (2007). The growth hormone/insulin-like growth factor-1 axis in health and disease [Video file]. In The Biomedical & Life Sciences Collection. Henry Stewart Talks. Retrieved November 11, 2022, from https://hstalks.com/bs/498/

Maruff, P., & Falleti, M. (2006). Cognitive Function in Growth Hormone Deficiency and Growth Hormone Replacement. Hormone Research in Paediatrics, 64(Suppl 3), 100-108. Retrieved from https://doi.org/10.1159/000089325

Melmed, S. (2019, June 27). Pathogenesis and Diagnosis of Growth Hormone Deficiency in Adults. The New England Journla of Medicine, 380, 2551-2562. doi:10.1056/NEJMra1817346

Paolisso, G., Ammendola, S., Del Buono, A., Gamardella, A., Riondino, M., Tagliamonte, M. R., & Varricchio, M. (1997). erum levels of IGF 1 and IGFBP3 in healthy centenarians: relationship with plasma leptin and lipid concentrations, insulin action and cognitive function. Journal of Clinical Endocrinology and Metabolism, 2204-2209.

Raben, M. S. (1962). Growth hormone-physiological aspects. New England Journal of Medicine.

Rae, M. J., Butler, R. N., & Campisi, J. (2010). The demographic and biomedical case for late-life interventions in aging. Science Translational Medicine, 2(40). doi:10.1126/scitranslmed.3000822

Rudman, D., Felle, A., Nagraj, H. S., Gergans, G. A., Laplitha, P. Y., Goldberg, A. F., & Mattson, D. E. (1990). Effects of human growth hormone in men over 60 years old. New England Journal of Medicine, 1-6.

Shevah, O., & Laron, Z. (2007). Patients with congenital deficiency of IGF-I seem protected from the development of malignancies: a preliminary report. Growth Horm IGF Res, 17(1), 54-57. doi:10.1016/j.ghir.2006.10.007

Sun, L., Fang, Y., Patki, A., Koopman, J., Allison, D., Hill, C., . . . Bartke, A. (2017). Longevity is impacted by growth hormone action during early postnatal period. eLife, 6. doi:10.7554/eLife.24059

Tresguerres, J. Á., Fernández-Tresguerres, I., Viña, J., Rancan, L., Paredes, S. D., Linillos-Pradillo, B., & Vara, E. (2022). Effects of GH on the Aging Process in Several Organs:. International Journal of Molecular Sciences, 14.

Van der Spoel, E., Rozing, M. P., Houwing-Duistermaat, J. J., Slagboom, P. E., Beekman, M., de Craen, A. J., . . . van Heemst, D. (2015). Association analysis of insulin-like growth factor-1 axis parameters with survival and functional status in nonagenarians of the Leiden Longevity Study. Aging, 7(11), 956-963. doi:10.18632/aging

Weindruch, R., & Walford, R. L. (1988). Retardation of aging and disease by dietary restriction. Charles C. Thomas.

Zhang, H., & Douglas, Y. (2004). The therapeutic potential of agents targeting the type I insulin-like growth factor receptor. Expert Opinion on Investigational Drugs, 13(12), 1569-1577. Retrieved from https://doi.org/10.1517/13543784.13.12.1569

Zhang, Z. D., Milman, S., Lin, J. R., Wierbowski, S., Yu, H., Barzilai, N., . . . Vijg, J. (2020, July 27). Genetics of extreme human longevity to guide drug discovery for healthy ageing. Nature Metabolism, 2, 663-672. Retrieved from https://doi.org/10.1038/s42255-020-0247-0