Spring 2019

More Than Growth? A Study of the Additional Functions of Growth Hormone in the Human Body

Damien Chance Hutchins

More Than Growth? A Study of the Additional Functions and Effects of Growth Hormone in the Human Body

An Honors Thesis

Presented to

The University Honors Program

Gardner-Webb University

7 May 2019

by

Damian Chance Hutchins

Accepted by the Honors Faculty

_____	_____
Dr. Meredith Rowe, Thesis Advisor	Dr. Tom Jones, Associate Dean, Univ. Honors
_____	_____
Dr. Don Olive, Honors Committee	*Dr. Anna Sieges Beal, Honors Committee*
_____	_____
Prof. Frank Newton, Honors Committee	*Dr. Christopher Nelson, Honors Committee*

Table of Contents

Abstract: Growth Hormone (GH) may have many more effects on the human body than those commonly known by the public. A study was conducted to determine what these additional functions may be, if these functions could necessitate the continued use of GH treatment for adults with Growth Hormone Deficiency (GHD), and how these effects might invite the additional usage of GH as a treatment for normal individuals. Research consisted of a literature review and a statistical analysis of 86 adult GHD reports regarding how GH treatment had affected various symptoms. Reports were analyzed for significance using one-way ANOVAs. Observed results support that GH impacts energy, cognition, the cardiovascular system, the integumentary system, thermoregulation, wound regeneration, and the immune system. Each of these observed effects support that GH treatment may be a requirement to maintain the health of adult GHD patients. Literature review results also support that GH could be a possible treatment for cognitive impairment and nervous tissue injury in normal individuals. Results also suggest that GH treatment may not adequately attenuate hypohidrosis or poor thermoregulation symptoms in GHD patients.

Introduction:

Growth Hormone (GH) is an important hormone produced and secreted from the pituitary gland. As its name suggests, it is most known for its role in the elongation of bones from infancy until adulthood. GH is often prescribed to children to treat known and idiopathic conditions that inhibit growth rates. The insistence on this titular role being the only important mechanism caused by GH secretion has been a majorly debated topic. Until the early aughts, most patients with GH deficiency (GHD) stopped receiving treatment when they were fully grown. It had been thought that there was no furthered need for the hormone supplementation as again the titular role was thought to be the only role, and secretions of GH in healthy adults were observed to decrease substantially. Hypersecretion of GH was also observed to be detrimental to the body. In tandem, it had appeared that GH treatment cessation for adults with GHD was the correct choice until these patients were studied over an extended period.

The shared symptoms of these patients invited furthered research on GH. As a hormone this molecule is secreted into the blood stream. It therefore is able to reach the surface of most human cells. Most cells of the body also have receptors for growth hormone (McKinley 674). These factors support that growth hormone could have many more important functions in the body. The following thesis studies the health and symptoms of 86 adult GHD patients and reviews the recent findings concerning these many possible GH functions. The primary focus was to evaluate the continued use of GH treatment for adult GHD patients and the possible use of GH to treat a number of other diseases.

Materials and Methods:

Literature collected for this study was found using the databases Proquest, Science Direct, Elsevier, Clinical Skills, and Access Medicine. Gardner-Webb's library database includes these databases in its search, so it was prominently used. Standard up to date undergraduate anatomy and cell biology textbooks were also used. All articles obtained were in a digital format. The author of this review read and annotated each article to truly understand the information held within each.

A survey was also conducted to evaluate whether patients' symptoms align with these recent literature findings. The survey follows current guidelines set by the American Psychological Association concerning the ethical treatment of humans. CITI training to conduct social and behavioral research was attained along with exempt IRB research approval prior (i.e. file number 18100301) to the uploading of the survey. The survey itself was created using the webtool Google Forms. It includes an informed consent document to be read by participants before they begin the survey. A debriefing statement is also included at the end of the survey for participants to read. The survey was posted on the Magic Foundation Adult GHD and Panhypopituitarism Facebook group. Members were invited to take the survey, but they could also scroll past the post if they did not wish to participate. Subjects were only at minimal risk. This is estimated based on the fact that individuals answered questions anonymously. Each subject attained a random number before survey was taken. This was accomplished by them clicking a link that redirects them to a random number generator and then them pasting the resulting number to their second survey question. No identifying factors were collected. Thus, not even the individual conducting the

study was able to identify any of the participants. The study was also conducted online which mitigates breaches of confidentiality by other subjects. Subjects were also asked to skip questions they found to be too personal. This was to reduce any emotional risks that may have arisen when someone took the survey. There are only two questions that must be answered in the survey. The first asks participants to confirm that they are 18 or older, have used GH treatment, have read the informed consent document, and are aware that they can ask questions or drop out (i.e. by emailing the researchers with their random number) at any time. The second forces participants to copy/paste the previously mentioned random number. The remaining questions concern the possible effects of GH and the demographics of the participants. Questions are worded in a manner that does not lead individuals to select specific answers. Results of the previously mentioned studies are also not specifically mentioned in the survey. There were also a plethora of answer choices available for each question. These factors allowed participants to answer in an honest manner. They also remove possible skewing of the data due to patients being persuaded to choose a particular answer choice. Demographics of the respondents can be found in Table 1.

Table 1: Demographics of Subjects That Participated in the Online Survey

Gender:	n Participants	Ethnicity:	n Participants	GH treatment duration:	n Participants
Male	14	Caucasian	74	t < 1 year	12
female	72	Asian	3	t > 1 year	7
		Other	9	t > 2 years	30
				t > 5 years	12
				t > 10 years	25
age:	n Participants	cause of GHD:	n Participants		
18-23	6	Removal of pituitary tumor during childhood	3		
24-29	3	Non-tumor derived childhood onset	9		
30-39	28	Congenital panhypopituitarism	6		
40-49	25	Congenital GHD	3		
50-59	15	removal of pituitary tumor during adulthood	26		
60+	9	other	39		

The survey was analyzed using one-way ANOVAs which accessed the significance of the variance between responses chosen for each question. ANOVAs were created using the program Graphpad Prism. Each possible response was designated as a single group. Groups included a set number of values corresponding to the total number of individuals who answered the survey question. Values were either 1 which signified that the participant had picked the response designated with that group or 0 which signified that the designated response was not picked by that participant. The one-way ANOVAs specifically analyzed variance among the resulting

means of values in each group for a given question. Variance where calculated p values were below 0.05 indicated that the prevalence of response choice was unlikely to occur due to random chance. This result would imply that variance seen among response groups is statistically significant. Once statistical significance was determined, response choice prevalence was used to support or oppose literary findings.

Chapter 1: Growth Hormone's Effects on Energy

One question asked in the survey conducted for this thesis was "Has GH affected your level of energy?" The possible answers choices were: yes, I feel much more invigorated than I used to; yes, I feel that I might have a bit more energy than I used to; no, I notice no change in my average level of energy to perform tasks; Yes, I feel more easily fatigued after beginning GH therapy; and Yes, my degree of fatigue is so great that I find it difficult to get out of bed on most days of the week. The percentage of responses chosen can be seen in Figure 20 (Appendix A). ANOVA analysis (Figure 1) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

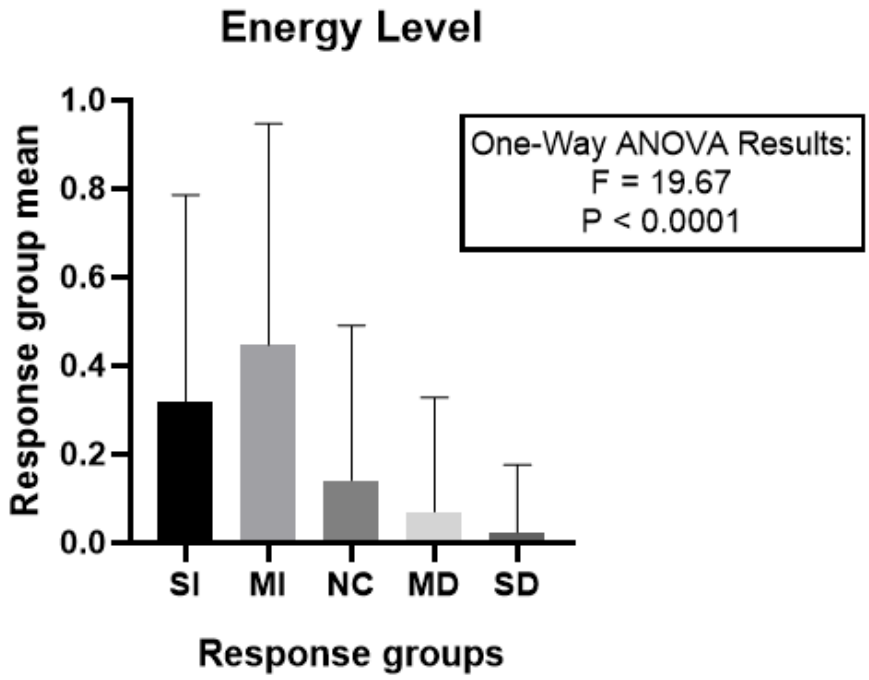

Figure 1. ANOVA results, response choice mean, and standard deviation for each response group from survey question 1 data. SI: strong increase; MI: moderate increase; NC: no change; MD: moderate decline; SD: strong decline.

Seventy six percent of those surveyed noticed improvement in their energy level after starting GH therapy. Nearly 32% of those surveyed said that their energy level had greatly increased. This subjective data supports that GH affects energy in some manner. The reasoning behind these effects will be discussed.

Metabolism:

GH might regulate energy through its effects on metabolism. GH is known to affect the storage and breakdown of lipids and proteins (Mckinley 674). Adenosine triphosphate (ATP) is commonly referred to as the energy chemical as it is often used to aid the occurrence of reactions in cells. These reactions must always be occurring, or the cell will die. Thus, ATP is a necessary chemical. It can be made using carbohydrates, lipids, and proteins. The storage and breakdown of these molecules is thus incredibly important for survival. A 2009 study in the Journal *Endocrine Reviews* mentions that GH may be the primary metabolic hormone while fasting. Carbohydrates (e.g. glucose, fructose, lactose, and sucrose) are the primary macromolecules used to make ATP in cells. When glucose is unavailable, the body is able to use the building blocks of proteins and lipids to make ATP. GH is theorized to be the primary metabolic actor during a fasting state because it has been observed to be the only anabolic hormone that has an increased serum concentration during this period. The scientists who wrote the previously mentioned 2009 study concluded from a review of research on GH's metabolic effects that GH increases lipolysis, decreases lipogenesis, and inhibits protein breakdown during a fasting state. This conclusion was supported by the fact that GH secretions during a fasting state caused serum concentration of free fatty acids (i.e. the fragments of fatty tissue used for ATP

production) to increase by 50%, caused a 50% reduction in urea production (i.e. a process caused partly by a need to remove nitrogen from proteins to make ATP), and caused a 50% reduction of protein breakdown in humans (Moller and Jorgensen 159-161). Untreated GHD patients often exhibit abdominal weight gain. This symptom appears to showcase an alteration in the metabolism of GHD patients. The increase in weight is theorized to occur due to a decreased breakdown of fats and an increased breakdown of lean muscle mass (Moller and Jorgensen 163). The body must use either lipids or proteins to make ATP in fasting conditions. Lipids are preferred over proteins because adipose tissue's primary function is to store energy for later use. Proteins have other uses, so they are often the last resort option to produce ATP in normal patients. The increased abdominal weight and decreased muscle mass in GHD patients seems to indicate that proteins from muscle are being used instead of fats to make ATP in a fasting state. GHD patients thus have a 50% increase in protein breakdown and a 50% decrease of lipid breakdown. Without GH, the body does not properly utilize lipids to make ATP. Instead the body breaks down muscle tissue and increases the amount of stored fats. This can cause the patient to feel fatigued due to muscle breakdown and make them more susceptible to becoming obese. One 2002 study in the *Journal of Clinical Endocrinology and Metabolism* researched how three years of GH treatment affected the body composition of 242 adult GHD patients. They found that GH treatment resulted in a significant increase in lean body mass of most GHD patients studied and a significant decrease in fat mass in the males with adult onset GHD (Attanasio et al. 1604). This indicates that GH could attenuate the effects of this abnormal usage of macromolecules seen in GHD patients. Thus, metabolism

research on GH suggests that GH treatment may be a necessary treatment to regulate the metabolism and energy level of GHD patients. Analysis of the survey conducted for this thesis will further evaluate whether GH can reverse these symptoms of muscle breakdown and weight gain due to lipid accumulation.

“Has your weight changed since you began GH therapy?” Available answer choices were: yes, I have lost more than 45 pounds; Yes, I have lost more than 15 pounds; No, my weight has not changed by more than 15 pounds; Yes, I have gained more than 15 pounds; and Yes, I have gained more than 45 pounds. The prevalence of response chosen for this question can be found in Figure 21 (Appendix A). ANOVA analysis (Figure 2) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

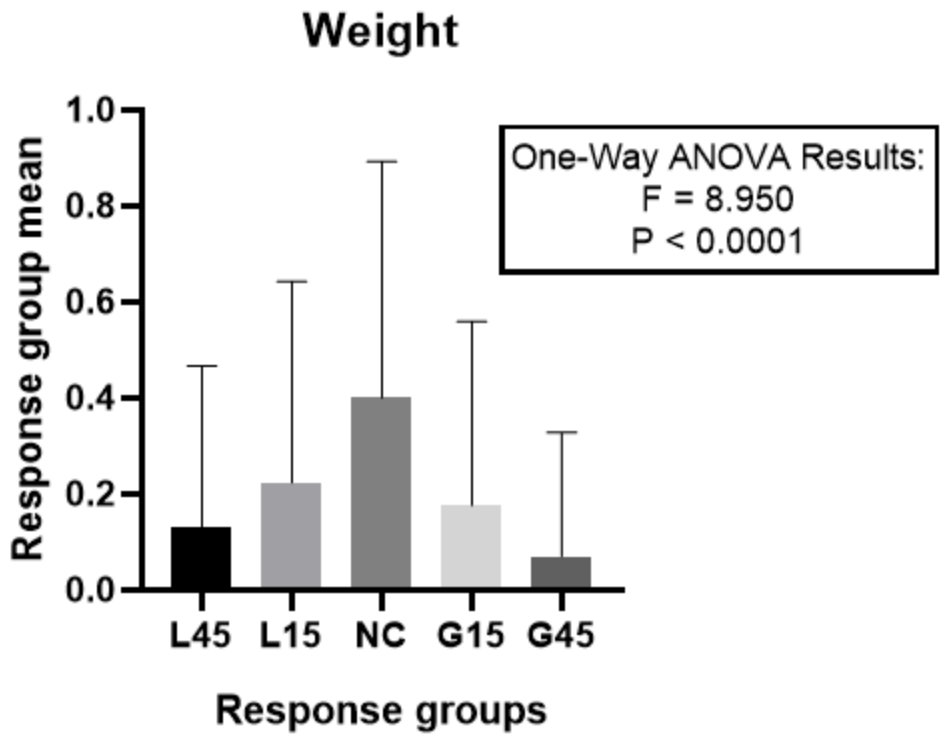

Figure 2. ANOVA results, response choice mean, and standard deviation for each response group from survey question 2 data. L45: weight loss of more than 45 pounds; L15: weight loss between 15 and 44 pounds; NC: no major change; G15: gained weight between 15 and 44 pounds; G45: weight gain of more than 45 pounds.

Nearly 13% of subjects said that they lost more than 45 pounds and 22.4% of subjects said they had lost between 15 and 44 pounds. Forty percent of subjects reported that their weight had not changed by more than 15 pounds. This large percentage may indicate that GH's effect of increasing lean muscle mass and decreasing fat might result in no major in overall weight in some GHD patients. More objective research is necessary to corroborate this hypothesis. The fact that 35.3% subjects reported notable weight loss does support that GH has some effect on metabolism.

“Has your level of muscle mass been altered since you began GH therapy?” available answers choices were: yes, I have more muscle mass and I have spent months trying to increase my muscle mass; yes, I have more muscle mass, but my level of physical activity would not warrant this increase; no, I have noticed no change in my muscle mass; yes, I have less muscle mass than I used to, but I no longer exercise or lift weights as much as I used to; and yes, I have less muscle mass than I used to and my exercise regime has not changed. The prevalence of responses chosen for this question can be found in Figure 22 (Appendix A). ANOVA analysis (Figure 3) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

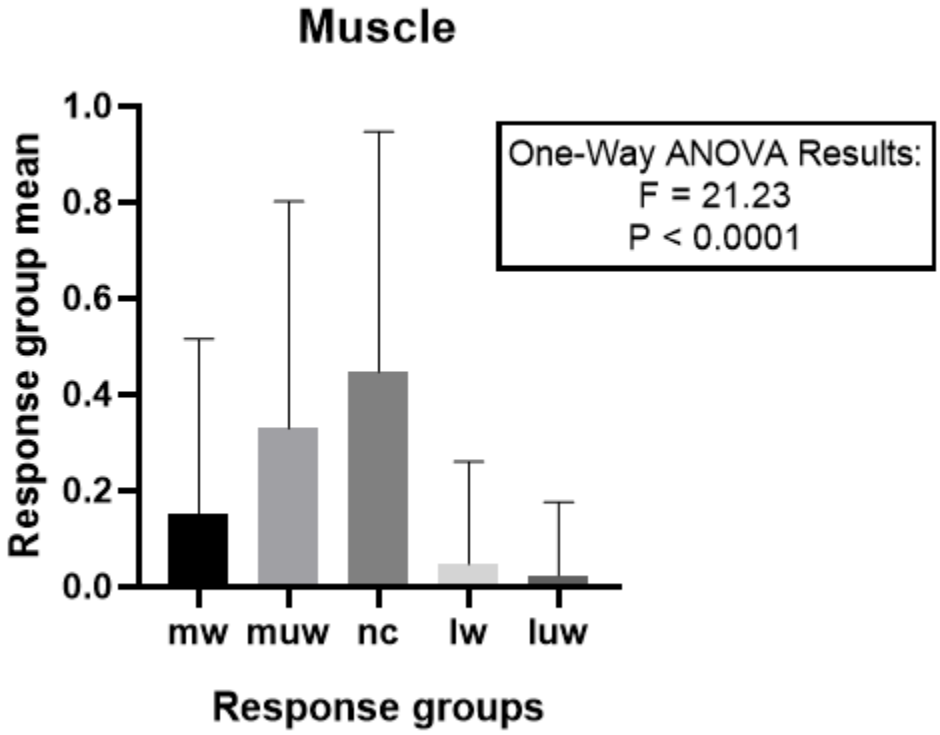

Figure 3. ANOVA results, response choice mean, and standard deviation for each response group from survey question 3 data. MW: warranted muscle mass increase; MUW: unwarranted muscle mass increase; NC: no change; LW: warranted loss of muscle mass; LUW: unwarranted loss of muscle mass.

This question was meant to evaluate whether GH treatment alone could increase muscle mass in GHD patients. Nearly 33% of those surveyed said that their muscle mass had increased after taking GH treatment even though they had not performed any exercises that might elicit this effect. This muscle mass increase is hypothesized to occur because their bodies have reduced the use of proteins to make ATP. This result supports that GH regulates metabolism through its effects on protein anabolism and catabolism.

Physical Capacity:

Endurance is another measurement of energy. GH might also affect an individual's ability to exercise. A 2008 metanalysis in the *Journal of Clinical Endocrinology and metabolism* mentions that GHD patients often have reduced physical endurance due to a decrease in muscle strength and a 27% decline in the ability to properly utilize oxygen during exercise (i.e. measured via VO_2 max test) (Widdowson and Gibney 4413). Fortunately, GH treatment appears to attenuate these symptoms. The same 2008 metanalysis reviewed data collected from over 268 GHD patients that received GH treatment. Their analysis revealed that GH treatment on average caused maximal power output to increase by 40% and maximal oxygen utilization to increase by 34% (Widdowson and Gibney 4415). These results support that GH may be a necessary treatment for adult GHD patients to possess a healthy capacity to exercise. It also suggests that GH might regulate energy level via its effects on endurance.

The survey conducted for this thesis also gauged subject endurance. "Has your physical endurance been altered by GH therapy?" The available answer choices were:

yes, I find that I am able to handle exercising for 30-75 minutes more than I did previously in one session; yes, I find that I am able to handle exercising for 10-25 minutes more than I did previously in one session; I notice no large difference in my level of physical endurance; yes, I find that I must exercise for 10-25 minutes less than my previous length of exercise in one session; and yes, I find that I must exercise for 30-75 minutes less than my previous length of exercise in one session. The prevalence of responses chosen for this question can be found in Figure 23 (Appendix A). ANOVA analysis (Figure 4) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

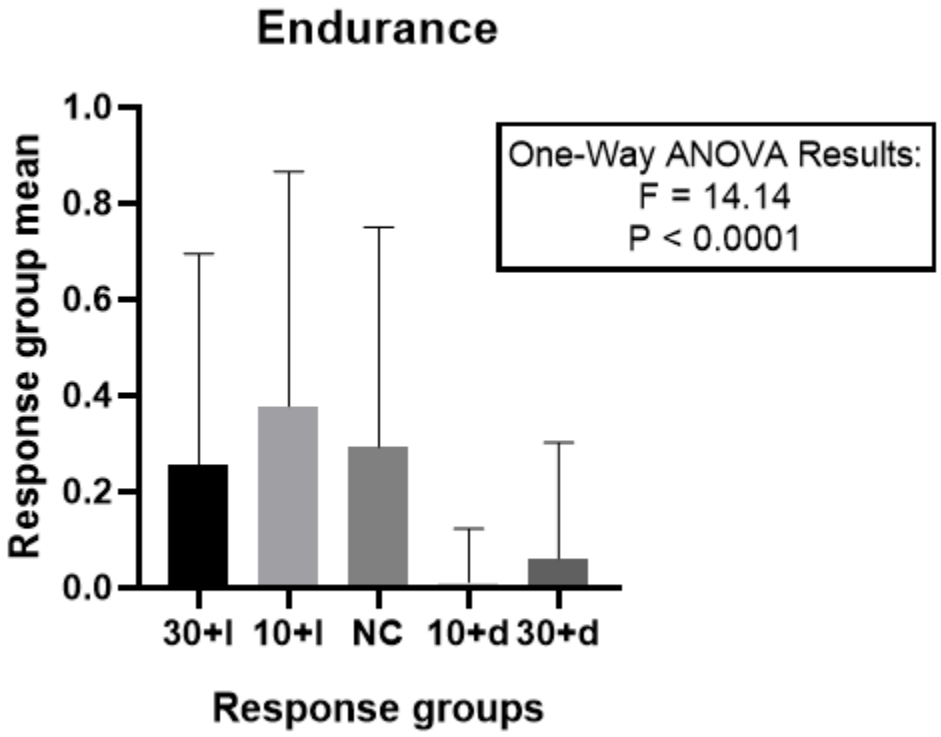

Figure 4. ANOVA results, response choice mean, and standard deviation for each response group from survey question 1 data. 30+I: 30 minutes or more increase; 10+I: 10-25 minute increase; NC: no change; 10+d: 10-25 minute decline; 30+d: 30 minutes or more decline.

Nearly 65% of those surveyed said that their exercise duration had increased by 10 or more minutes since they began GH therapy. Twenty five percent of those surveyed said that their exercise duration had increased by at least 25 minutes. These results support that GH may increase endurance in GHD patients.

Mental Health:

What has been discussed thus far has been a possible explanation for how GH might affect energy levels via its impact on both metabolism and endurance. Abnormal mental health can also affect energy levels. Many GHD patients report having depression, low Quality of Life (QOL), and anxiety when they are not on GH treatment. GH might also regulate energy through its effects on mental health. Three studies on this topic will be discussed.

A 2005 study in the *Journal of Hormones and Behavior* researched the effects of GH therapy on memory and anxiety in GHD patients studied over a 10-year period. They used the State-Trait Anxiety Inventory (STAI) to measure whether GH treatment might reduce symptoms of anxiety. The STAI has resulting scores between 20 and 80 where a higher score indicates more severe anxiety symptoms. A significant decline in scores from the baseline throughout the study indicated that, on average, GH treatment did reduce symptoms of anxiety (i.e. $p < 0.05$). The average baseline score was 35 and an average 6.4 point decrease was observed (Arwert et al. 347). This supports that GH treatment may attenuate anxiety symptoms in GHD patients. Further study on this topic should involve a larger sample size and the study of GHD patients with much higher STAI scores to determine whether GH could greatly reduce symptom severity in patients with more extreme anxiety.

If GH treatment can reduce anxiety in GHD patients, perhaps patients with GHD may be at an increased risk of having a mental disorder. A 2018 study published in the *Journal of Growth Hormone and IGF Research* evaluated whether children with GHD might be at an increased risk of having a mental health condition. The study reports that children with GHD may fail to mature psychologically, have a lack of self-confidence, have poor social skills, and exhibit depressive symptoms. The objective of the study was to investigate the relation between GHD, anxiety disorders, and depression in youth. 122 minors with GHD and 122 healthy minors (i.e. aged 7–17) were studied. 87 GHD patients received GH treatment and 35 did not. The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children was primarily used to evaluate whether subjects had a mental health condition. Additional diagnosis tools were the DSM-V, the Children's Depression Inventory (CDI), the State-Trait Anxiety Inventory for Children (STAI-C), and the Social Anxiety Scale for Children-Revised (SASC-R). Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) were significantly more common in children with GHD compared to the control group (i.e. there were 20 more diagnosed cases of GAD and 11 more cases of SAD in GHD patients than in the control group). Depression diagnoses were smaller in the GHD group, but this difference was not statistically significant (Akaltun et al. 25-26). These results indicate that anxiety symptoms may appear more often in untreated GHD patients. A similar analysis should be conducted on adults to determine if this increased prevalence continues in adulthood.

Since such a study does not yet exist, the next best thing is a subjective 2014 study that asked 43 GHD patients (from either Germany, the United Kingdom, or the

U.S.) to describe the effects of living without growth hormone. The researchers posit that psychological impairment was most mentioned by the subjects (Brod et al. 4). Prevalent symptoms were feelings of depression and anxiety. Subjects also said that their condition caused them to be less socially active. GH treatment seemed to have attenuated these symptoms (Brod et al. 6-7). It is unknown whether the improvements reported by the subjects was merely a placebo effect. This study may lack substantial evidence to back the claims of its subjects, but it does provide an idea of what some adults with GHD could be experiencing. This data invites continued research on the topic.

The survey conducted for this thesis also includes a question relating to mental health. “Has GH therapy affected your mental state? Select all that apply” The available answer choices were: yes, I once experienced anxiety, but I no longer experience those symptoms; yes, I once experienced sad feelings for months at a time, but those feelings have now ceased; no, I have a healthy mind and I have always had a healthy mind; I am not sure, I did have anxiety or clinical depression before starting GH treatment, but I take prescribed medications to attenuate those symptoms; yes, I have had increased anxiety since I began GH treatment; and yes, I have felt extreme sadness for a period lasting longer than a month since I began GH treatment. The prevalence of responses chosen for this question can be found in Figure 24 (Appendix A). ANOVA analysis (Figure 5) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

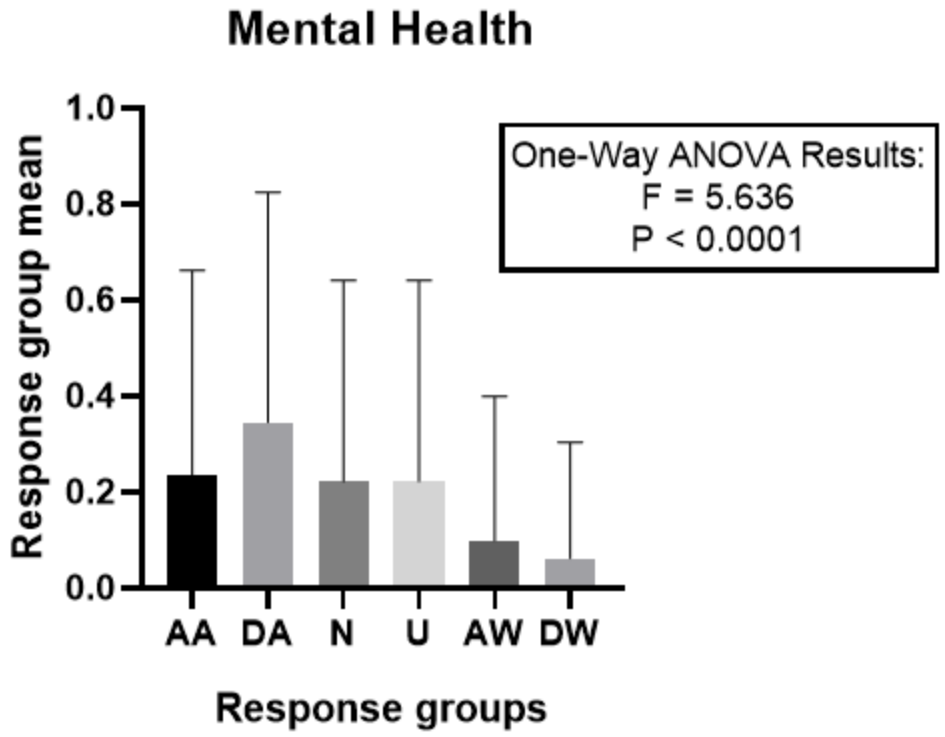

Figure 5. ANOVA results, response choice mean, and standard deviation for each response group from survey question 5 data. AA: attenuated anxiety; DA: attenuated depression; N: never experienced symptoms; U: unsure; AW: anxiety worsened; DW: depression worsened.

Thirty four percent of subjects said that their symptoms of clinical depression had ceased after taking GH, but 6.2% admitted to having clinical depression symptoms after starting GH. Twenty three percent reported a decrease in anxiety symptoms and nearly 10% reported an increase in anxiety. GH dosage differences among patients could account for this difference between patient reported symptoms, but that is only a hypothesis. As previously mentioned, the questionnaire had a very small sample size, so its results do not accurately reflect similar qualities on the total population of adult GHD patients. It does however, invite further investigation on how GH treatment may affect the mental health of adult GHD

patients. The results do support that GH could attenuate depression and anxiety symptoms in some GHD patients. Understanding if this is indeed the case with a larger study and a possible investigation into the mechanism for how low GH causes anxiety and depression will surely support furthered GH treatment use for adult GHD patients.

Sleep:

Tiredness is an antonym of energy. GH might also be a necessary treatment for adults with GHD because it regulates the secretion of Growth Hormone Releasing Hormone (GHRH). It is important to mention that the Growth hormone secretion pathway is regulated by a negative feedback mechanism. This mechanism begins when the hypothalamus is stimulated to secrete GHRH. GHRH signals the pituitary gland to secrete GH and then GH signals the liver to produce IGFs. When serum concentrations of GH and IGFs become sufficient, both hormones will signal the hypothalamus to stop secreting GHRH (McKinley 671-674). This mechanism is brought to the forefront of discussion currently because the lack of regulation of this pathway in GHD patients has been observed to disrupt sleep. A 2009 study in the *American Journal of Physiology* researched how GHRH affected non-rapid eye movement (NREM) sleep in rats. What they discovered was that GHRH injections in the preoptic area of the hypothalamus significantly ($p<0.001$) increased NREM durations and significantly ($p<0.001$) increased EEG slow wave activity during sleep. They also found that GHRH antagonist hormone injections in the same area exhibited an opposite effect (Peterfi et al. 149-150). This supports that GHRH secretion levels heavily impact NREM sleep in mammals.

GH directly inhibits GHRH secretion and GH is always secreted during the initial 3rd and 4th stages of NREM in normal humans (qtd. in Peterfi et al. 147). These two facts could also possibly explain why untreated GHD patients often feel fatigued. Tiredness instead of physical or mental fatigue might contribute to this phenomenon. A 2010 study in the *Journal of Endocrinology and Metabolism* researched differences in reported tiredness, sleep stage durations, and EEG wave activity during sleep among 30 normal individuals and 30 untreated GHD patients. Pituitary specific (i.e. GH deficiency due to an inability of the pituitary gland to produce and secrete GH) GHD patients were shown to have significantly increased durations of NREM stages and significantly increased EEG slow wave activity compared to the control group. The increases in these more objective values were also associated with a high prevalence of reported poor sleep quality and tiredness during the day in those patients (Copinschi et al. 2198-2201). This data supports that GHD patients have altered sleep activity possibly due to a lack of GHRH secretion regulation by GH.

The same group who conducted the 2010 human sleep study also published a study in the *European Journal of Endocrinology*. This secondary study researched whether 10 of those same pituitary specific GHD patients had improved sleep after they were given GH treatment for 4 months. Differences in reported tiredness, sleep stage durations, and EEG wave activity were similarly measured in this study. The measurements attained from the 10 treated pituitary specific GHD patients were compared with measurements taken from 10 saline treated pituitary specific patients (i.e. which were also examined in the previous study). Seven participants had to

leave the study. A significant decline in average total sleep duration and a significant decline in EEG slow wave sleep activity were observed in the remaining GH treated subjects. Sleep duration was, on average, an hour shorter in GH treated patients than placebo treated patients (Morselli et al. 767-8). This difference in total sleep duration was relevant because sleep duration is dependent upon the time it takes for slow wave activity to reach minimum levels. GH treated patients also reported being less tired. These researchers hypothesize from this resulting data that untreated GHD patients exhibit increased tiredness and longer sleep times because the signal to increase slow wave activity by GHRH is never turned off by GH. Thus, untreated GHD patients could feel fatigued because their brains are still in a deep sleep stimulating state.

The latter study has limited significance due to its small sample size. A sample size of 13 subjects is not nearly enough to properly represent the total population of GHD patients. The survey conducted for this thesis included questions relating to sleep to possibly corroborate these claims with a larger sample size.

“Have you noticed a change in your ability to sleep since you began GH therapy?” The available answers were: yes, once a week I will stay up for more than 24 hours because I cannot sleep; yes, biweekly I will stay up for more than 24 hours because I cannot sleep; yes, once a month I will stay up for more than 24 hours because I cannot sleep; yes, I often get less than 7 hours of sleep per night because I toss and turn and am unable to fall asleep in an average amount of time; no, I notice no change in my ability to sleep; yes, I find it much easier to fall asleep and I often get 7 hours of sleep per night; yes, I find it incredibly easy to sleep and I often

get 8-10 hours of sleep per night; and yes, I find that I sleep too much and yet I never feel rested. The prevalence of responses chosen for this question can be found in Figure 25 (Appendix A). ANOVA analysis (Figure 6) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

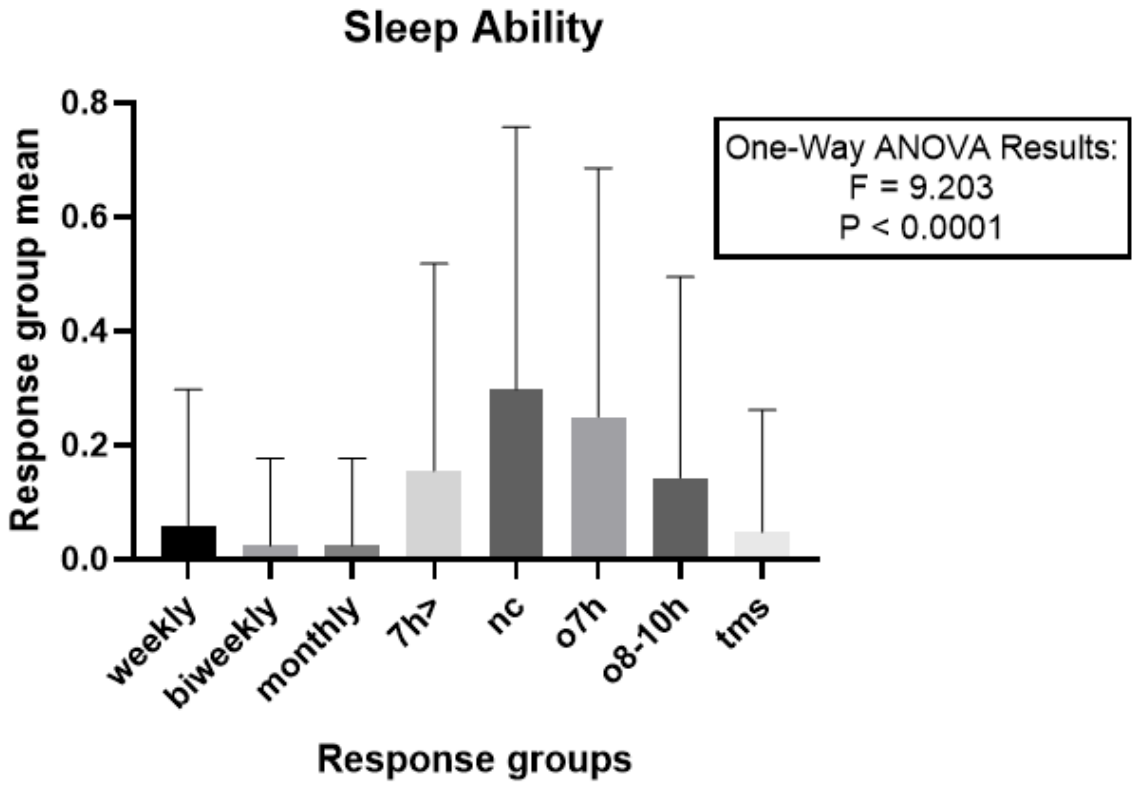

Figure 6. ANOVA results, response choice mean, and standard deviation for each response group from survey question 6 data. Weekly: one day without any sleep weekly; biweekly: one day without any sleep biweekly; monthly: one day without any sleep monthly; 7h>: often less than 7 hours; nc: no change; o7h: often 7 hours; o8-10h: often 8 to 10 hours; tms: too much sleep.

Nearly 40% of those surveyed reported that they can fall asleep easily and that they often get healthy amounts of sleep each night. Only 4 individuals reported that they sleep too often and yet never feel rested. These results support that GH therapy may be able to improve sleep ability and sleep quality in GHD patients.

Have you noticed any changes in your average sleep duration since you began GH therapy? The available answer choices were: yes, I find that I often wake up after an hour or 2 of being asleep; yes, I find that I often wake up after 3 to 4 hours of being asleep; no, I notice no changes in my average sleep duration; and Yes, I find it extremely difficult to wake up after going to sleep. This question is meant to gauge if GH therapy might reduce sleep time to such a degree that might be detrimental to GHD patient health. The prevalence of responses chosen for this question can be found in Figure 26 (Appendix A). ANOVA analysis (Figure 7) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

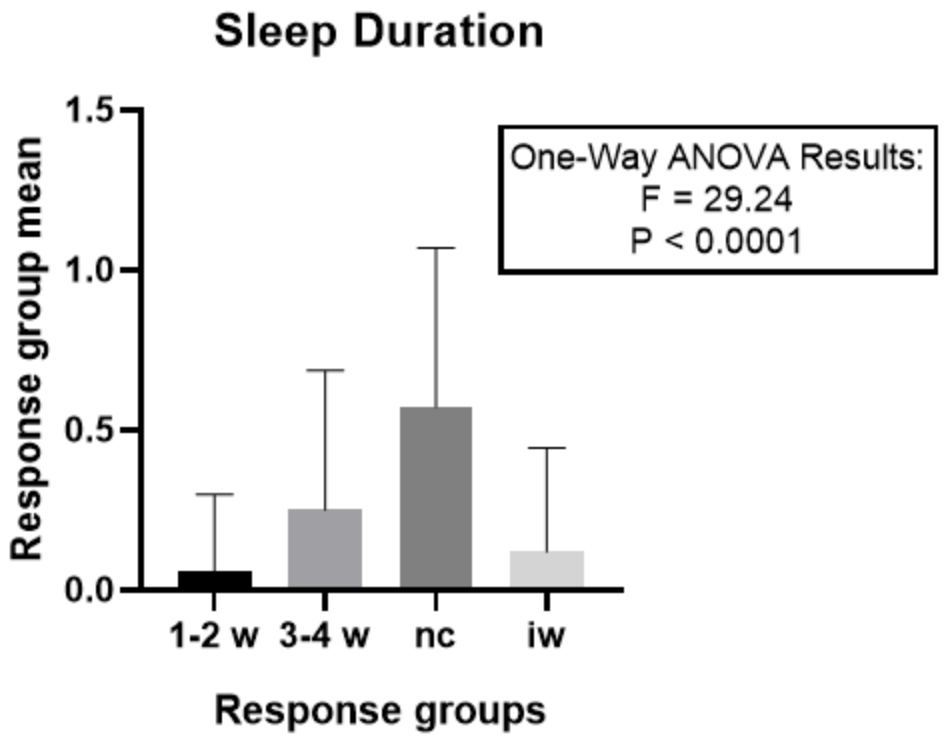

Figure 7. ANOVA results, response choice mean, and standard deviation for each response group from survey question 7 data. 1-2 W: wake up after 1-2 hours; 3-4 W: wake up after 3 to 4 hours. NC: no change; IW: impaired waking ability.

Fifty seven percent of those surveyed said they did not notice a change in their average sleep duration. Twenty five percent of subjects said that they often wake up after three or four hours. These results support that GH therapy could cause some GHD patients to have unhealthy sleep durations. More research is needed to determine if this might be a possible side effect.

Energy Conclusion:

GHD has been observed to reduce patient VO_2 max, physical strength, endurance, lean body mass, and the serum concentration of free fatty acids. GHD has also been observed to increase body fat and sleep duration. Patients with GHD

also may have a higher incidence of anxiety and depression than the normal population. These patients also report that they never feel well rested. Energy can be affected by mental health, metabolism, endurance, and sleep. The discussed survey results and the mentioned studies support that GH could regulate energy via these four factors. Results also support that these symptoms can be attenuated via GH treatment. It is surmised from this data that GH is a necessary treatment for GHD patients because it appears to have a major effect on energy. These factors alone indicate that GH treatment is integral to the health of adult GHD patients, but there is much more to discuss to truly delineate why GH is a necessity.

Chapter 2: Growth Hormone's Effects on Cognition

The possibility of mental health effects caused by GH are just the tip of the iceberg when it comes to the effects of GH on the brain. This section will examine how GH might affect human cognition. Scientists define cognition as an animal's ability to process information (Nyberg and Hallberg 357). Processing information could thus also be broken down into two sub categories: memory and intelligence. Intelligence is the scale of one's ability to understand a given topic in a certain amount of time and memory is the ability to retain that understanding for a given duration (Merriam-Webster.com). The definition of both concepts is generally understood though the actual mechanism for their action is currently being researched.

Memory:

Memory is easily quantifiable. One is either able to remember something or unable to remember that thing. This binary mutually exclusive aspect of memory makes it easy to detect changes in one's ability to retain memories. Scientists have not reached a consensus regarding how memories work though. The current theory states that memories are unlike files in a computer. Memories are not stored in a specific place nor are they an independent component of the brain. On the contrary, memories are patterns of electrical signals among multiple synapses between neurons (Nyberg and Hallberg 357-8). GH could regulate memory formation via its effects on synaptic plasticity.

Research on mice has shown that GH is able to stimulate synaptic plasticity (i.e. the ability of synapses to alter their membrane potential) (Molina). This stimulation of synaptic plasticity is said to activate long term potentiation (i.e. prolonged transmission between two synapses based on previous electrical patterns experienced by the neuron), which plays a role in learning and long-term memory storage (Nyberg and Hallberg 357-8). Said stimulation is believed to be transmitted via glutamate receptors. When bound to glutamate, these receptors signal calcium and sodium channels to open which signal synaptic plasticity and an action potential. GH is theorized to play a role in the formation of different subunits that make up the glutamate receptor N-Methyl-D aspartate (NMDA). The theorized mechanism is thought to involve the JAK-STAT pathway. The JAK-STAT pathway is a common cellular signaling pathway that is often activated by cytokines. This pathway has three components: a receptor on the surface of the cell that binds to ligands such as cytokines or hormones, Janus kinases (i.e. a type of protein that adds a phosphate group to another protein to activate that protein), and STATs (i.e. signal transducers and activators of transcription). A signal cascade caused by the JAK-STAT pathway involves a ligand binding to the receptor which signals Janus kinases to phosphorylate the receptor using ATP. The newly phosphorylated receptor phosphorylates STAT molecules. When STATS are activated through phosphorylation, they form dimers and relocate to the nucleus where they will then modify the transcription of genes which alters protein production in the cell. GH is said to bind to its receptor GHR which signals Janus Kinases to phosphorylate the receptor. This reaction causes the signal cascade mentioned above and causes

STAT dimers to then travel through the nucleus and bind to DNA to increase the transcription of genes associated with the NMDA receptor (i.e. GluN1, GluN2A and PSD-95). GH is also theorized to stimulate the binding of glutamate to NMDA (Nyberg and Hallberg 360-3).

GH may also play a role in synaptic plasticity through its effects on NF-kB activation. NF-kB has been theorized to play a role in the transformation of a short-term memory to a long-term memory (Kaltschmidt). One study showed that crabs with inhibited NF-kB expression had significantly impaired ability to form long term memories (Merlo). GH has not been proven to increase NF-kB activation in the brain, but there is evidence that it stimulates NF-kB activation in other areas of the body. Multiple studies have found that GH does regulate NF-KB activation in the lungs, in adipose tissue, in macrophages, and other somatic cells (Liu, Jeay, and Kumar). It is hypothesized that GH may also regulate memory formation via the activation of NF-KB. Further research to test this hypothesis is needed, but the fact that GH can activate NF-KB in other areas of the body and the fact NF-KB regulates memory formation may indicate that there are more GH mechanisms that are important to memory maintenance. GH thus may play a role in ensuring proper memory formation in the mammalian brain via its ability to increase synaptic plasticity by possibly regulating NMDA receptors and NF-KB secretions.

Intelligence:

Intelligence does not yet have a discernible marker in the brain. The intelligence quotient is often used to determine one’s intelligence, but scientists are not yet sure of what causes one person to be more intelligent than another

individual. It is hypothesized that intelligence may have something to do with the glial cells of the CNS. The primary example that can support this conclusion lies in a 1985 study on the genius, Albert Einstein's brain. This study found that Albert Einstein's brain only differed from other lower IQ brains in that it had more glial cells in a region of the brain that was believed to have a role in logic and mathematical reasoning (Diamond et al. 201-4). The following paragraphs will detail how GH might affect glial cells.

Scientists in Madrid, Spain discovered that GH may affect the development of astrocytes. They studied hypothalamus and hippocampus astrocytes. In this study they found that GH treatment on rat brains was found to increase the secretion of GFAP (i.e. a protein secreted specifically by differentiated astrocytes). This indicates that GH may cause immature astrocytes to differentiate. They theorized that GH played a role in the successful differentiation of these cells through its binding to plasma membrane GH receptors which signaled the activation of a PI3K/AKT pathway. The PI3K/AKT pathway is a cellular signaling pathway that is often activated by a growth factor ligand. Its signaling cascade involves a receptor tyrosine kinase, a phosphatidylinositide 3 kinase (PI3K), phosphatidylinositol 4,5-bisphosphate (PIP2), mTOR, pyruvate dehydrogenase kinase 1 (PDK1) and Serine/Threonine protein kinase (AKT). The pathway begins as a growth factor (e.g. growth hormone) binds to the cell surface portion of 2 receptor tyrosine kinases that have dimerized. The receptor complex stimulates the autophosphorylation of the cytoplasmic side of the receptor tyrosine kinases. PI3K then binds to the phosphorylated tyrosine kinases. The receptor tyrosine kinase then phosphorylates

PI3K which phosphorylates PIP2 (PIP2 becomes PIP3 which stands for phosphatidylinositol 3,4,5-triphosphate). AKT then binds to PIP3 and is phosphorylated by either a PIP3 bound PDK1 or an mTOR complex. Activated AKT then may cause the cell to alter glucose metabolism, inhibit apoptosis (programmed cell death), alter gene transcription, stimulate cell differentiation, signal cell proliferation, alter GABA receptor expression, or activate NF-kB which has been shown to play an important role in both synaptic plasticity and immune system regulation. In summary, GH may cause astrocytes to differentiate through this cellular pathway. Growth hormone releasing peptides were also shown to signal the astrocytes to multiply in number through the same PI3K/AKT pathway. These scientists corroborated their assumptions by preventing the ligand binding of GH and GHRPs to their receptors on the astrocytes and found the side effects mentioned above to be reversed. The same effect was observed when PI3k activation was blocked (Baquedano et al. 266-272). This supports that GH and the peptides associated with it, could play a role in the division and development of astrocytes.

Oligodendrocytes

A joint study between Wake Forrest University and University of Oklahoma found that GH helps regulate the production and survival of oligodendrocytes. Corpus callosum oligodendrocytes in rats with growth hormone deficiency were researched. These scientists found that the GH deficiency inhibited the creation of new cells. Two weeks after the cessation of GH treatment, the size of the newly created group of immature oligodendrocytes had been 25% fewer than past observed groups. GH deficiency was also found to inhibit the survival of new

oligodendrocytes. The two effects led to a 30% decrease in the total population of oligodendrocytes in the corpus callosum (Hua et al.1064-6). These results indicate that GH stimulates the proliferation and successful survival of oligodendrocytes in some manner. The scientists theorized that this drop in the oligodendrocyte population (i.e. due to a decrease in GH and IGF-1) might be a cause of the cognitive decline that occurs due to aging (Hua et al. 1068). GH secretion naturally declines as one ages, and thus the possible reduction in these myelinating agents would decrease the speed of signaling between neurons. This notion is supported by another study which found that normal elderly patients with the best cognitive ability out of those tested were shown to produce more GH than the other subjects (Quik et al.). GH thus may influence intelligence through its role in regulating oligodendrocyte proliferation and survival rate.

GH may regulate memory through its effects on synaptic plasticity, and GH may affect intelligence by stimulating the proliferation and differentiation of glial cells. What may be equally as important in discerning how GH affects cognition are studies on the clinical manifestations of the absence of and use of GH treatment in GHD patients in relation to cognitive functioning. The above list of possible mechanisms for how GH might affect cognition are somewhat meaningless without studies that examine whether cognitive function is even altered in GHD patients. Clinical testing for changes in intelligence and memory will now be discussed in the form of IQ and memory differences among GHD patients without GH treatment, GHD patient that receive GH treatment, and healthy individuals.

Clinical Manifestations:

A group of pediatric endocrinologists from the Netherlands endeavored to study children treated with GH due to them being vertically challenged. They endeavored to determine if GH had any additional functions besides increased height. Fifty-three children took an Intelligence Quotient examination throughout an 8-year GH treatment period. IQ was shown to increase at a statistically significant rate throughout the treatment with mean scores either coming close to or surpassing the average scores of the general population (Chaplin et al. 395-8) These results are promising, but more data is needed to truly determine if GH increases IQ in GHD patients. IQ does change slightly during childhood, which could skew the data they found. An adult study of the same nature is needed to truly determine if GH has the ability to increase IQ.

Members of the Neuropsychology department at the University of Amsterdam studied 30 GHD adults with an age range between 42 and 76. They tested the adults' working memory and learning ability. Low dose patients were found to have deteriorated memory and learning ability at the end of the four-year session. High dose patients had means higher than baseline in both aspects at the end of the four-year session (Deijen et al. 4) This difference may be because entrance of GH past the blood brain barrier is dependent on dosage (Nyberg and Hallberg 359). The large age range and small survey size limit what can be concluded from the study though.

The same group also studied 23 GHD adult men for a ten-year period. This study was previously mentioned because it also researched mental health in GHD

parents. These scientists also endeavored to learn about growth hormone's effects on mood memory in GHD patients. They found that the patients' short term memory began to improve after one year, while long term memory improved after two years. Both memory types were found to improve for the first five years of treatment. Memory tests were never similar, so patients could never prepare for said examinations. The scientists were forced to reduce the GH dosage administered during the final five years. The final tests at the end of the period showed memory scores below the fifth-year scores, but above the baseline and all other test scores (Arwert et al. 347). This result supports the previously mentioned dosage blood brain barrier theory. The Survey size might be too low to be representative of GH's effects on all GHD patients, but these results support that GH could play a prominent role in memory function.

A 2006 meta-analysis in the *Journal of Psychoneuroendocrinology* analyzed multiple studies that tested memory impairment difference between untreated GHD patients, treated GHD patients, and normal patients. Altogether the analysis studied more than 300 patients. What they found was that untreated GHD patients had much worse memory than those of the normal population. They also found that GH treatment typically attenuated these symptoms. Moderate improvement of memory was observed after 6 months of GH treatment, but the GHD treated patients were never observed to have equal memory capacity with those of the normal patients (Falleti et al. 685-9).

The survey conducted for this thesis also gauges the clinical manifestations of cognitive impairment in GHD patients. This was done by asking patients about how

they felt GH has affected their different cognitive abilities. “What is your highest level of academic achievement?” Available answer choices were: Less than a high school diploma, High school diploma, Some college, Associates, Bachelor’s, Master’s, Doctorate, and Post Doctorate. This question was meant to gauge intelligence. An IQ question would have been more quantitative, but it was doubtful that most subjects would be aware of their IQ. Intelligence is all about learning ability and those who learn better are more inclined to do well in their collegiate pursuits. The prevalence of responses chosen for this question can be found in Figure 27 (Appendix B). ANOVA analysis (Figure 8) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

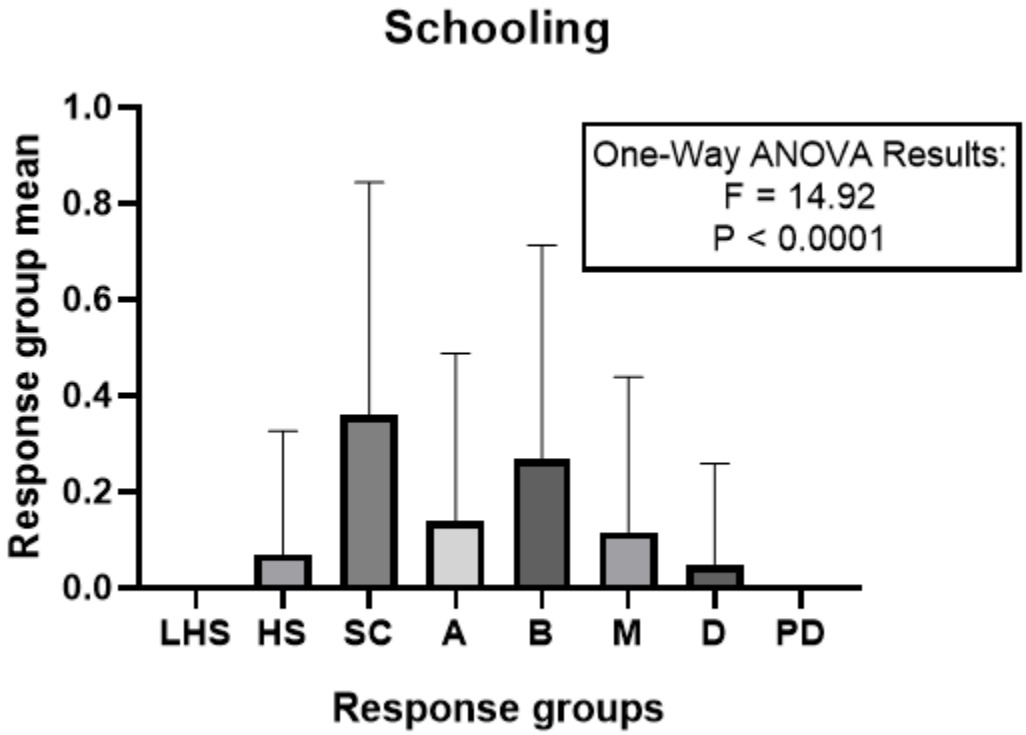

Figure 8. ANOVA results, response choice mean, and standard deviation for each response group from survey question 8 data. LHS: less than high school diploma; HS: high school diploma; SC: some college; A: associates degree; B: bachelor’s degree; M: master’s degree; D: doctorate; PD: post doctorate.

A 2010 Harvard University and Asian Development Bank study found that 6.7% of the global population had a college degree of some kind (Barro and Lee 32). The latest American census mentions that 33.4% of the American population has a bachelor's or higher degree (qtd. in Alonzo). Fifty seven percent of those surveyed have college degrees of some kind. Forty three percent of respondents attained a bachelor's or higher degree. A limitation of this question is that it does not establish if GH was taken during matriculation periods. The significance of these results is inhibited by this limitation. The results somewhat support previous findings that GH might increase intelligence. The next question delves further into how GH might affect school performance.

"If you are a student, do you feel that growth hormone treatment has affected your school performance?" Available answers choices were: yes, my grades have improved slightly since I began GH treatment; yes, my grades have improved significantly since I began GH treatment; I have witnessed no change in my academic performance since taking growth hormone injections; yes, my grades have declined slightly since I began GH treatment; and yes, my grades have declined significantly since I began GH treatment. This question has much fewer responses because only 30 of the 86 participants were currently in school. The significance of the results is minimal due to the small sample size but they do invite further testing regarding this topic. As was already discussed, GH seems to play a role in regulating memory formation and intelligence. It would be difficult to argue that each of these factors are not integral to getting good grades in school. Thus, the question can be used to subjectively assess the quality of those factors. The prevalence of

responses chosen for this question can be found in Figure 28 (Appendix B). 16 individuals reported no effect, 12 reported improvement, and 2 reported decline. ANOVA analysis (Figure 9) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

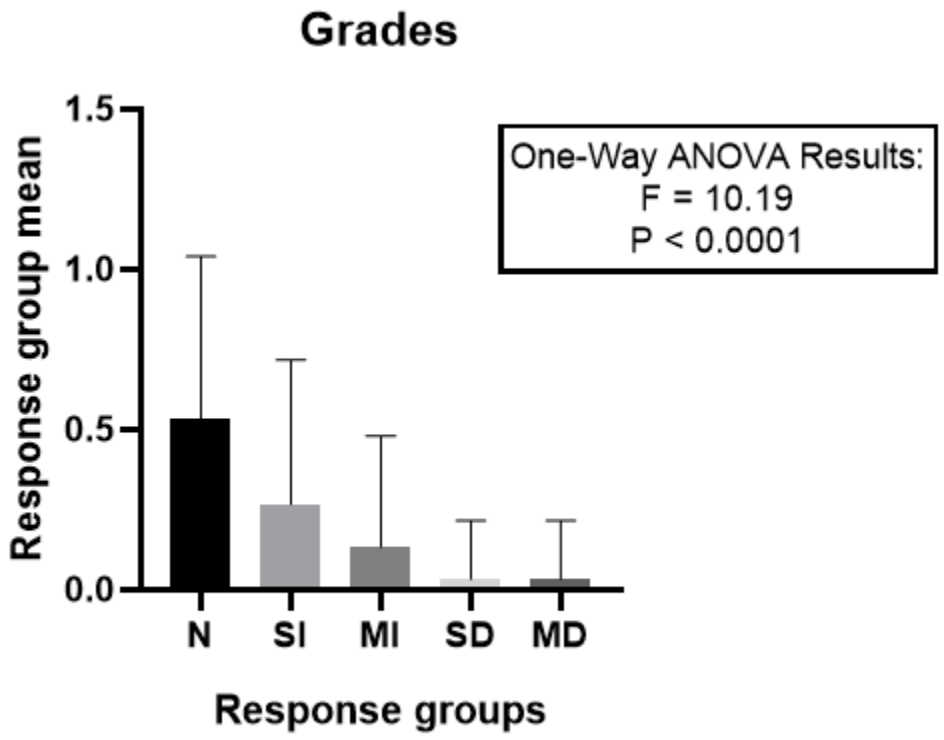

Figure 9. ANOVA results, response choice mean, and standard deviation for each response group from survey question 9 data. N: no change; SI: strong improvement; MI: moderate improvement; SD: strong decline; MD: moderate decline.

Forty percent of those who responded say that their grades improved. These results somewhat support that GH therapy can attenuate cognitive decline symptoms in GHD patients. The next question focuses specifically on memory.

“Has GH treatment affected your memory?” Available answers choices were: yes, GH has strengthened my short-term memory. I have an easier time memorizing

phone numbers and other lists of 7-10 letters and numbers after a couple of minutes; Yes, GH has strengthened my long-term memory. I have an easier time recalling concepts or scheduled tasks that I have tried to memorize and remember for a period lasting longer than 1 day; No, I have noticed no change in my ability to store and retain memories following the inception of my growth hormone therapy; Yes, GH has weakened my short-term memory. I find it difficult to memorize phone numbers and other lists of 7-10 letters and numbers after a couple of minutes; and yes, GH has weakened my long-term memory. I find it harder to recall concepts or scheduled tasks that I have tried to memorize and remember for a period lasting longer than 1 day. The prevalence of responses chosen for this question can be found in Figure 29 (Appendix B). ANOVA analysis (Figure 10) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

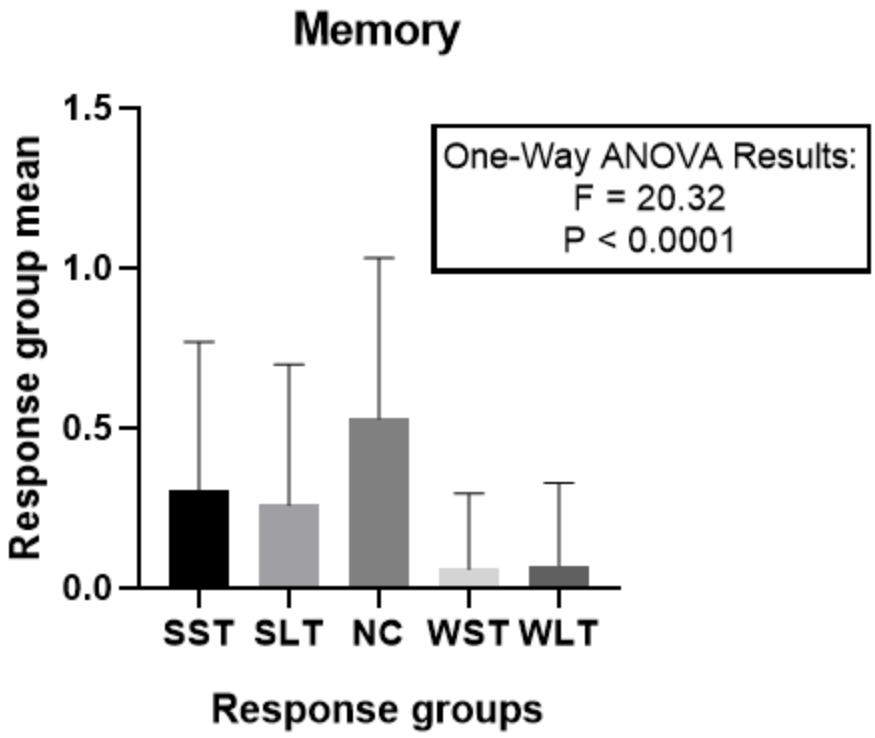

Figure 10. ANOVA results, response choice mean, and standard deviation for each response group from survey question 10 data. SST: strengthened short-term memory; SLT: strengthened long-term memory; NC: no change; WST: worsened short-term memory; WLT: worsened long-term memory.

More than 25% of those surveyed mention that GH has improved both their short-term and long-term memory. Less than 6% mentioned that their ability to form long-term and short-term memories had worsened after they started GH. Such a discrepancy without any prompting of the subjects supports that GH treatment might improve memory in GHD patients.

These discoveries on how GH effects cognitive ability in GHD patients have incentivized some scientists to test if GH could enhance cognitive recovery in the normal population. GH may also serve roles that directly affect neurons. Research shows that GH acts as a neurotropic factor. Neurotropic factors are peptides that stimulate the development and differentiation of neurons. These factors are also

believed to increase the survival of neurons. Their method of action is through tyrosine kinase (i.e. mostly receptor tyrosine kinases such as the one in the previously mentioned PI3K/AKT pathway). Neurotropic factors were also observed to stimulate the reparation of damaged neurons in vitro (Malenka 211-221). GH's use as a treatment for cognitive impairment in non-deficient patients is still being researched though. At present there are a few case studies and some murine experiments that indicate that GH can attenuate the symptoms of brain damage.

One murine study researched the use of growth hormone as a treatment to attenuate cognitive impairment in stroke (i.e. a condition characterized by the death of neural tissue due to a lack of blood flow to the affected area) induced mice. Mice were given GH for 28 days 48 hours after the stroke was induced. GH-treated mice had a better learning capacity over control groups. GH-treated mice were also observed to have significantly less neural tissue death. Other neurotropic factor populations were also raised in GH treated mice. Factors which indicate the creation of new synapses (i.e. Synapsin-1) and the remyelination (i.e. Myelin basic protein) of neurons were present in much higher numbers in the stroke affected tissue of GH treated mice. CD31 and collagen-IV which indicate the presence of vascular tissue were also higher in number and present in more areas of the stroke affected tissue in GH treated mice (Ong et al. 1257-1266). In summary, these scientists found that GH could be a potential treatment for stroke victims because it was observed to promote cognitive and neuronal recovery.

A human case study found that GH treatment was able to repair nerve damage in a 61-year old man (i.e. with a normal functioning pituitary gland) that

abused opioids. They found that GH was able to reduce the apoptosis of neural tissue and promote the regeneration of neurons in the patient (Rhodin et al. 760-3). As a case study these results provide insight into how GH treatment could benefit similar patients, but it does not indicate without a doubt that this same positive end result would be seen in similar patients.

Another human case study observed the effects of GH treatment in addition to neurorehabilitation techniques to improve the cognitive capabilities of a plane crash victim. The 18-year-old male patient was treated fifteen months after the incident and was observed to have a nearly destroyed right hemisphere. The man had a severe case of traumatic brain injury. Growth hormone was chosen as a treatment because it was previously shown to stimulate neurogenesis and angiogenesis in rats and it did not seem to have the negative effects generally associated with the use of other neurotropic factors. He received two years of treatment with a dosage of 1mg per day. Before treatment, he was unable to walk or speak. He was able to sign himself out of the hospital at the end of treatment. On a five-point scale, the patient was shown to have a 3-point increase in speech ability and a 4-point increase in mobility (Devesa et al. 30472-30480).

Another case study observed the effects of GH treatment accompanied by typical neuro rehabilitative techniques on a cognitively impaired child. The subject was a 10-year-old female who had acute perinatal asphyxia during her birth. The girl had normal pituitary function but was treated with GH to possibly improve her cognitive capabilities. She received a dosage of 0.5 mg per day for three months and later 1.2 mg every three days. Her traditional neurorehabilitation involved

occupational therapy, speech therapy, and auditive therapy. The study lasted 9 months. Following treatment, her IQ increased by 29 points. The research group observed that she was at her grade level in most subjects after completing the treatment (Devesa et al. 2-7).

Attention:

The above studies and survey results support that GH effects cognition and may be an effective treatment to attenuate cognitive decline. What has yet to be discussed is whether GH might affect abilities related to cognition. Untreated GHD patients may also have trouble focusing. The previously mentioned 2006 meta-analysis also gauged improvements in attention after GHD patients started GH. Data from more than 300 patients was analyzed. Attention capability was significantly worse in untreated GHD patients than in the healthy patients. The measured factor with largest discrepancy between the two groups was attention. The analysis also found that GH treatment had led to moderate or large improvement (after 6-9 months) in the attention capabilities of GHD patients (Falleti et al. 685-9). These results support that GH could regulate attention to some degree. The previously mentioned 2018 article in the *Journal of Growth Hormone and IGF Research* contradicts the meta-analysis findings though. It found no significant difference in the prevalence of ADHD in minors with GHD (Akaltun et al. 25-26). This would support that GHD does not cause ADHD.

Clinical manifestations of attention abnormalities in GHD patients yield inconclusive results. It may be better to discern the effect of GH on attention by looking at the mechanisms involved. A 2001 study found that attention can be

modified via NMDA receptors (Turchi and Sarter 103-117). The importance of GH regarding these receptors has already been discussed. It is possible that GH could regulate attention through its effects on NMDA receptors. GH secretion might also be altered by ADHD medication. A 2003 study in the *Journal of Child and Adolescent Psychopharmacology* researched how the ADHD medication guanfacine effects growth hormone secretion in children with ADHD. Eight children with ages ranging between 8 and 10 were studied. Patients either had ADHD with reading disabilities or only ADHD. Guanfacine treatment caused GH secretion amounts to significantly increase for both groups. Those with only ADHD had even higher GH secretions (Halperin et al. 287-291). The lower GH increase in patients with reading disabilities might further support that inhibition of GH secretion may contribute to cognitive abnormalities. The more novel result of the study is the fact that a medication for ADHD somehow affects the mechanism for GH secretion. Such a small sample size fails to represent the larger population of individuals with GHD, but it does support that there could be a relationship between GH and attention. The questionnaire attempts to further evaluate the clinical manifestations of these effects on attention.

The prevalence of responses chosen for this question can be found in Figure 30 (Appendix B). 15 of the 86 subjects reported being diagnosed with ADHD. The 2018 study mentioned above found 7 of the 122 GHD patients and 6 of the 122 healthy patients to have ADHD. When compared to the 2018 study, the survey responses support that there may be increased prevalence of ADHD in adults with GHD. The smaller sample size limits one’s ability to discern whether this is true of

the larger GHD population though. The next question gauges improvement of attention in those surveyed.

Increased focus duration should be directly caused by improvement in attention capability. The prevalence of responses chosen for this question can be found in Figure 31 (Appendix B). Thirty-five individuals reported having improvement in their ability to focus. Twelve of those 35 reported that their focus duration improved by two hours. Forty-four noticed no change and 5 reported decline in focus duration. ANOVA analysis (Figure 11) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

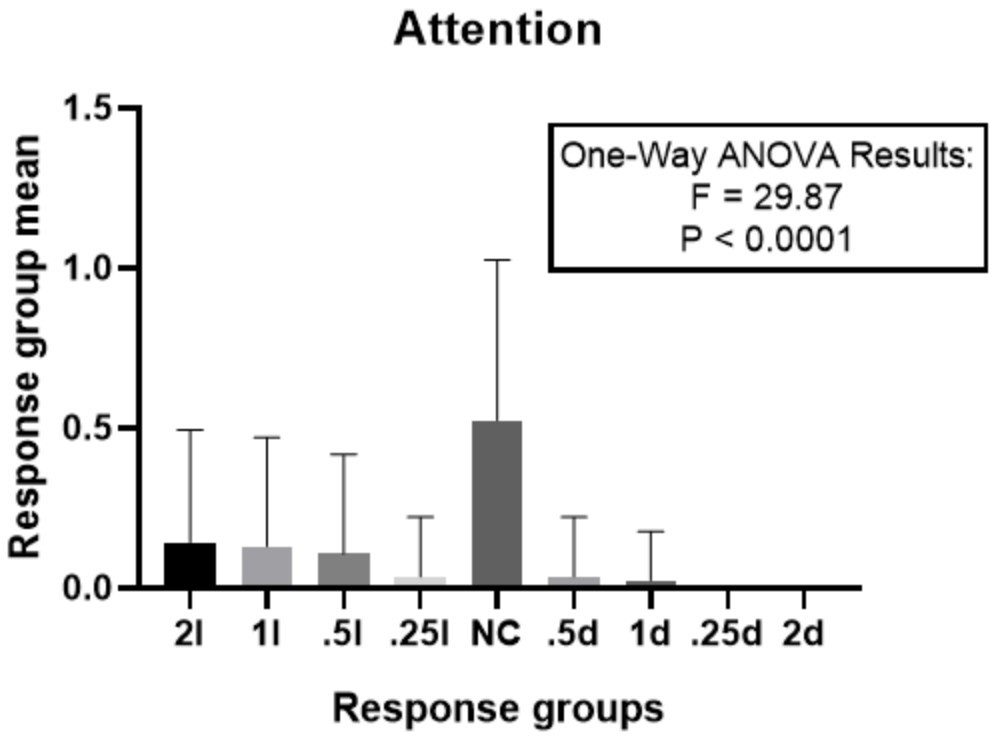

Figure 11. ANOVA results, response choice mean, and standard deviation for each response group from survey question 12 data. 2I: 2 hour increase; 1I: 1 hour increase; .5I: 30 minute increase; .25I: 15 minute increase; NC: no change; .5d: 30 minute decline; 1d: 1 hour decline; .25d: 15 minute decline; 2d: 2 hour decline.

It is possible that the effects noticed by these patients could have also been caused by the placebo effect. The likelihood of this being the case was combatted by the wording of the question. It was not asked if GH improved attention. Subjects were only asked to describe if there were any changes in attention. The 35 individuals that said they had improved attention were not in any way prompted to come to such a conclusion. The fact that 41.7% of subjects independently concluded that their attention span improved after taking GH supports the validity that GH affects attention in some manner.

Cognition Conclusion:

In tandem, there exist possible mechanisms for how GH might effect cognition; known examples of GHD patients without treatment being cognitively impaired; known examples of GH treatment improving cognitive capacity in both GHD patients and in patients with brain injuries; known examples of GH being used to repair nervous tissue, known examples that GHD patients appear to struggle with poor attention capabilities, and known examples that GH treatment can attenuate those low attention symptoms. This plethora of data was supported by the questionnaire responses. Growth hormone could be integral to nervous system functioning. Not all is known about how GH secretion affects nervous tissue, but available data does certainly provide just enough information to invite furthered study. GH must hold some importance, or the previously mentioned effects would not be reported. Evidence suggests that many GHD patients could exhibit cognitive decline without treatment. It is supported by previously mentioned data that GH can improve cognition in GHD patients. New research also suggests GH could be a treatment to restore nervous tissue function and attenuate cognitive impairment in normal patients. It could be argued that GH is more important for cognitive functioning than it is for bone elongation.

Chapter 3: Growth Hormone's Effects on Other Bodily Functions

GH might also have effects on other organ systems. Most organ systems contain cells with Growth Hormone Receptors (GHRs), so it possible that GH can regulate more unmentioned mechanisms. GH's possible effects on the cardiovascular system, the integumentary system, thermoregulation, wound regeneration, and the immune system will now be discussed.

Cardiovascular System:

Recent research supports that GH could affect cardiac structure and some aspects of cardiovascular function. GH may affect blood pressure via its regulatory effects on nerves. This is theorized because GHD patients have been observed to have overactive sympathetic nerve signaling to vasculature smooth muscles. Such an observation indicates that GH could lower blood pressure by decreasing peripheral resistance. This is further supported by recent findings that show that this symptom of overactive sympathetic nerve activity was observed to be attenuated after one year of GH treatment (Isgaard et al. 26). While this mechanism for how GH could affect blood pressure is credible, clinical manifestations of blood pressure alteration due to GH are inconclusive. Some studies indicate that GHD patients had hypertension that can be attenuated with GH treatment. Other studies found that GH did not affect blood pressure (Isgaard et al. 26). This indicates that more research is necessary to truly discern GH's effects on blood pressure.

The effects of GH on heart structure and function appear to be more conclusive. GHD patients without treatment were observed to have a smaller left

ventricular mass and decreased cardiac output (Isgaard et al. 27). Cardiac output was observed to be lower than normal patient control groups by an average of 17% while resting and by 29% during exercise in GHD patients younger than 40. GH treatment was observed to boost cardio-myocyte growth, improve systolic and diastolic cardiac function, increase stroke volume, increase heart rate, and increase left ventricular mass size (Isgaard et al. 28). Such observations support that GH may be necessary to maintain healthy cardiac function. Untreated GHD patients were also observed to have an average 40% increased risk of having a heart attack in a study with sample size of 1411 GHD patients. Another study with a sample size of 289 GHD patients observed that those treated with GH were at a lower risk of having a heart attack than normal patients (Isgaard et al. 29-30). Such observations support that GH may be necessary to maintain healthy cardiac function.

The survey conducted for this thesis also includes questions relating to the cardiovascular system. The first question asked patients to detail if they had a heart condition. Have you been diagnosed with any heart abnormalities? Available answer choices were: yes, I have some heart abnormalities and I was diagnosed with such conditions after being diagnosed with GHD; yes, I have some heart abnormalities and I was diagnosed with such conditions before being diagnosed with GHD; and I do not have any diagnosed heart abnormalities. The prevalence of responses chosen for this question can be found in Figure 32 (Appendix C). ANOVA analysis (Figure 12) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

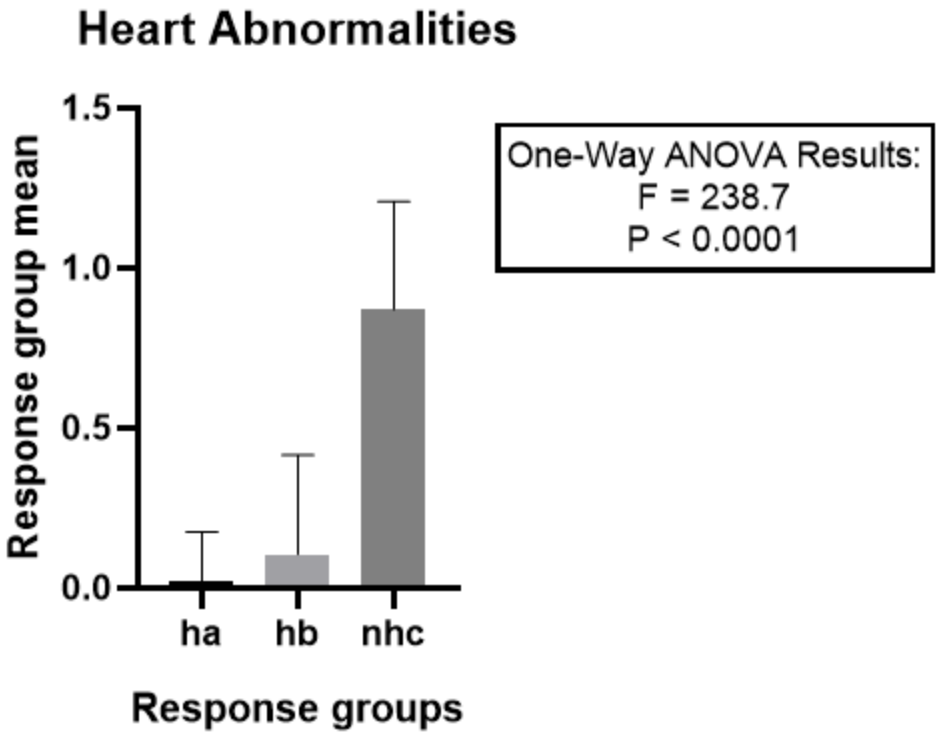

Figure 12. ANOVA results, response choice mean, and standard deviation for each response group from survey question 13 data. HA: have acquired after; HB: have acquired before; NHC: no known heart condition.

Eighty seven percent of those surveyed reported that they did not have any diagnosed heart abnormality. This result opposes that GHD patients have altered cardiac structure that contributes to major cardiac dysfunction.

The second cardiovascular question gauged how GH treatment affects cardiovascular vital signs. Has your heart rate or blood pressure changed significantly since you began GH therapy? Subjects were asked to select all answers that applied to their current condition. Available answer choices were: yes, my resting heart rate has increased by more than 20 beats per minute; yes, my systolic and diastolic blood pressure are both 20 mm Hg higher than they were before I began GH therapy; yes, I now have hypertension; no, there has been no change in

my heart rate; no, there has been no change in my blood pressure; yes, my resting heart rate has decreased by more than 15 beats per minute; yes, my systolic and diastolic blood pressure are both 20 mm Hg lower than they were before I began GH therapy; and yes, I now have hypotension. The prevalence of responses chosen for this question can be found in Figure 33 (Appendix C). ANOVA analysis (Figure 13) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

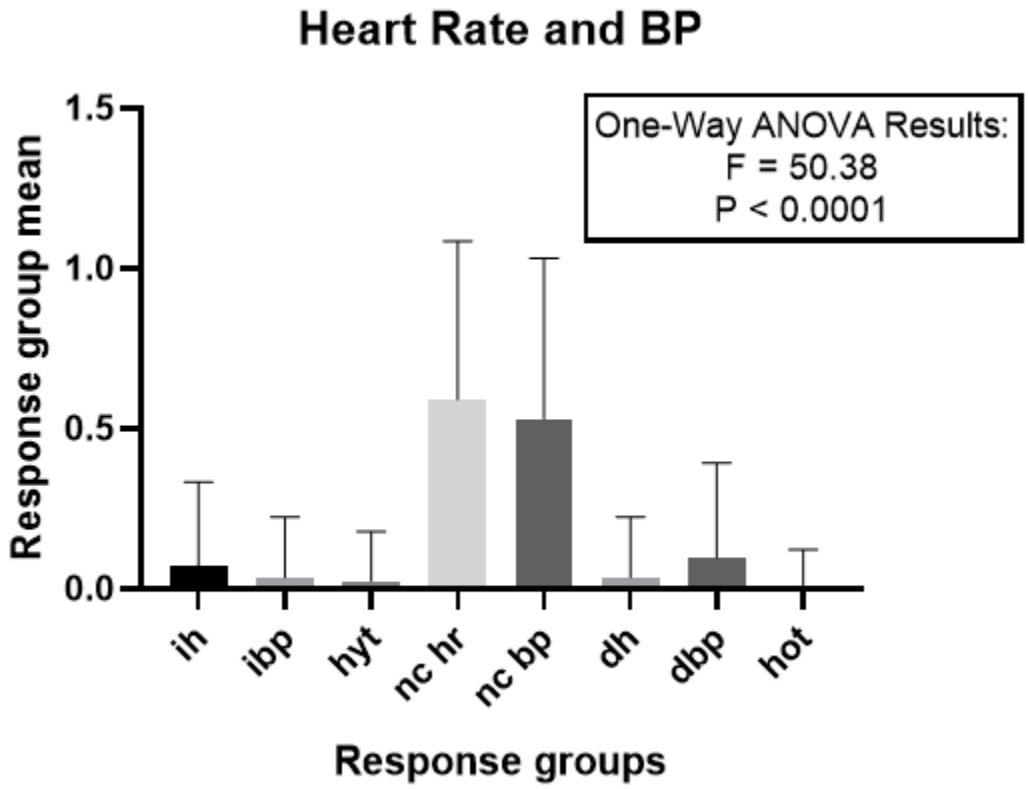

Figure 13. ANOVA results, response choice mean, and standard deviation for each response group from survey question 14 data. IH: increased heart rate; IBP: increased blood pressure; HYT: hypertension; NC HR: no change in heart rate; NC BP: no change in blood pressure; DH: decreased heart rate; DBP: decreased blood pressure; HOT; hypotension.

More than 50% of those surveyed said that GH treatment did not affect their blood pressure or heart rate. No other response choices were chosen by more than 10% of the subjects. These results do not oppose or support if GH effects cardiovascular vital signs.

Skin:

Recent findings suggest that GH also regulates integumentary system functions. A 2016 article in the *Journal of Reviews in Endocrine and Metabolic Disorders* that focused on this on topic will be discussed. The researchers examined how both hyper secretion (acromegaly) and hypo secretion (GHD) of GH affected skin health. Acromegaly patients are observed to have hyperhidrosis (i.e. excess sweat secretion), thick skin, skin roughness, the appearance of skin growths known as acrochordons, and excessive oil secretions by sebaceous glands (Gantenbein et al. 261). GHD patients often have hypohidrosis (i.e. diminished or a complete absence of sweat secretions) and skin that is thin and dry (Gantenbein et al. 264). The scientists responsible for this review mention that this near ubiquitous appearance of these symptoms in patients with altered GH secretion could be used in the future to diagnose both conditions (Gantenbein et al. 265). This apparent high prevalence of symptoms suggests GH regulates the integumentary system in some way. Furthered corroboration of this notion is the fact that nearly all integumentary cells possess GH receptors (Gantenbein et al. 259).

The survey conducted for this thesis also includes questions relating to the integumentary system. The first asked “Have you noticed any changes in your skin since you began GH therapy?” The available answer choices were: yes, I have

noticed a thinning of my skin since I began GH therapy; yes, I have noticed an increase in the dryness of my skin since I began GH therapy; yes, I have noticed an increase in the elasticity of my skin since I began GH therapy; no, I have noticed no changes in my skin; yes, I have noticed a thickening of my skin since I began GH therapy; yes, I have noticed a decrease in the dryness of my skin since I began GH therapy; and yes, I have noticed a decrease in the elasticity of my skin since I began GH therapy The prevalence of responses chosen for this question can be found in Figure 34 (Appendix C). ANOVA analysis (Figure 14) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

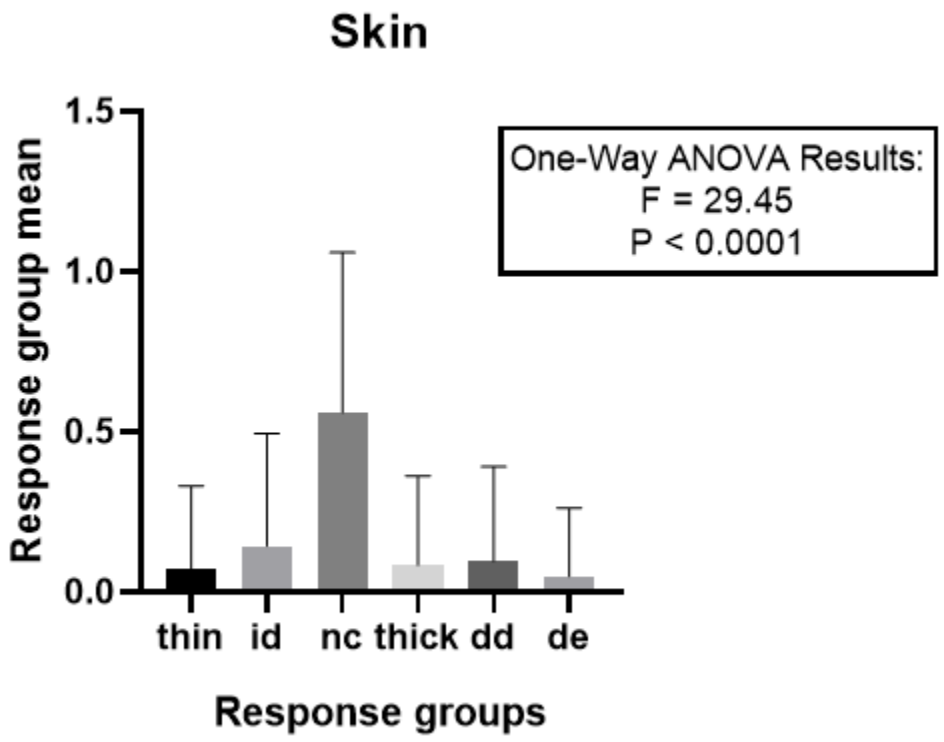

Figure 14. ANOVA results, response choice mean, and standard deviation for each response group from survey question 15 data. Thin: thin skin apparent; ID: increased dryness apparent; NC: no change; Thick: thick skin apparent; DD: decreased dryness; DE: decreased elasticity.

Fifty six percent of patients reported no noticeable change in their skin since they began GH therapy. Reports of increased skin thickness and dryness were roughly equal to reports decreased thickness and dryness. This data may indicate that current GH treatment may be ineffective at reducing symptoms of thin and dry skin. More research is needed to determine if this is true.

The second question focuses on sweat. “Has your ability to sweat been affected by your growth hormone treatment?” The available answer choices were: yes, I sweat a lot more now that I administer GH injections; yes, I sweat a lot less now that I administer GH injections; no, I have noticed no change in my perspiration rates since I began Growth Hormone treatment; and I am unsure because I have not thought about my rate of perspiration until now. The prevalence of responses chosen for this question can be found in Figure 35 (Appendix C). ANOVA analysis (Figure 15) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

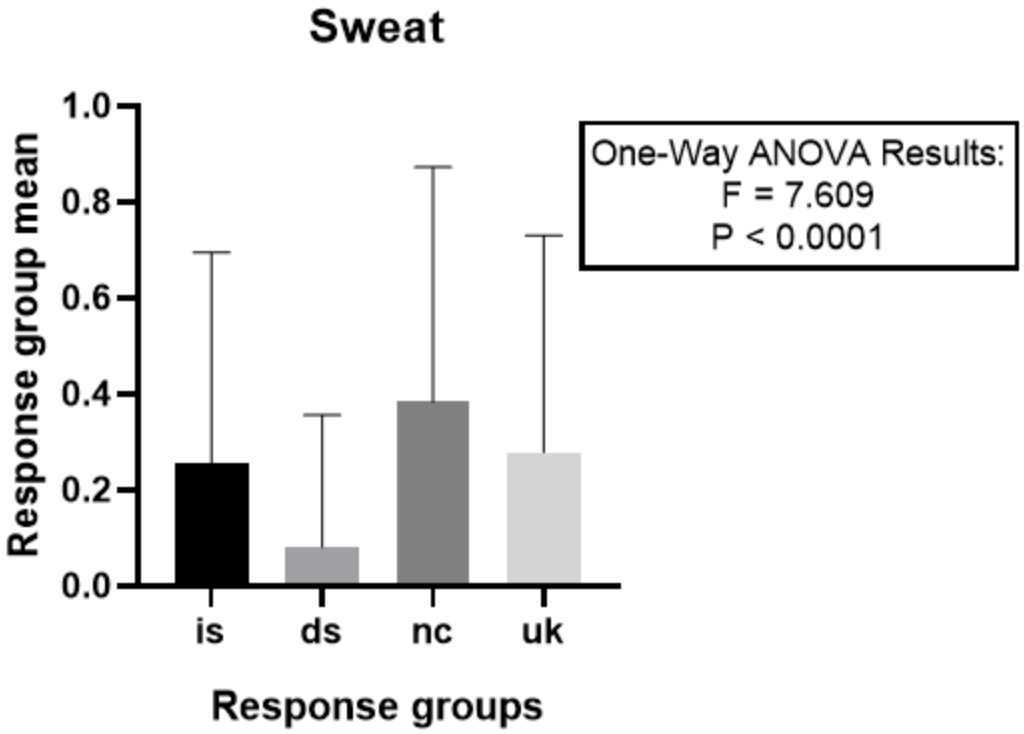

Figure 15. ANOVA results, response choice mean, and standard deviation for each response group from survey question 16 data. IS: increased sweating; DS: decreased sweating; NC: no change; UK: unknown.

Twenty five percent of subjects said that GH therapy has caused them to sweat much more than they used to. This result supports that GH therapy might increase sweating ability in some GHD patients.

The importance of skin health may not be as well-known as that of cognitive and heart health. It should be mentioned that the integumentary system is the first line of defense against harmful agents (e.g. chemical toxins and pathogens) and a regulator of body temperature. Aspects of the skin such as thickness and oil lubrication are integral to the prevention of harmful agents entering the body. Sweat secretion benefits temperature regulation. Merocrine glands are the exocrine glands that secrete sweat which is 99% water and 1% electrolytes. To properly illustrate

sweat's importance, its role in attenuating temperature increase during exercise will be described. Muscles release excess heat during exercise because they are working harder and using more energy. Excess heat causes blood temperature to increase. Peripheral blood vessels will dilate to transfer heat to the skin surface. Heat does not easily escape through the skin to the atmosphere without another participating molecule. This molecule is the water from the sweat. Merocrine glands will begin to secrete sweat when body temperature increases. The heat is then transferred from the skin to the sweat. This causes a lot of the sweat to evaporate. Evaporation of sweat allows heat to be more easily removed from the body. Thus, sweat is integral to proper thermoregulation in humans. The role of GH in regulating the skin is important to the overall health of an individual

Thermoregulation:

The fact that GH deficiency causes hypohidrosis may indicate that GHD patients are at an increased risk of hyperthermia. In 1995, Researchers from the University of Copenhagen performed a controlled study on sweating and body temperature regulation during exercise in the heat. Sixteen GH-treated GHD patients and 10 healthy subjects were studied. Each subject exercised on a bicycle ergometer for 60 minutes at a workload corresponding to 45% of their individual maximal oxygen consumption (VO_2 max), in a room maintained at 35C°. GH serum concentrations increased significantly after approximately 10 min of exercise in the normal subjects ($P < 0.001$) but remained low in the GHD patients. Skin temperature increased significantly during exercise in the GHD patients but remained unaltered in the healthy subjects (Hjortskov et al. 3337-8).

These results support that GH-deficient patients may be at risk for developing hyperthermia during physical activity in hot environments. It also indicates that the traditional GH treatment of one injection every evening may not truly attenuate all of the symptoms of GH deficiency.

A more recent study concerning the same topic was published in 2014. In it, researchers recorded the variance of water loss, blood plasma volume, and blood serum HGH in 8 highly trained triathlon athletes between resting and high impact exercise states. All subjects had normal functioning pituitary glands. The athletes were subjected to 2 exercise tests consisting of 20 minutes of running and 20 minutes of cycling separated by a break period of 30 seconds. The exercise environment was such that each participant was performing at a level where their bodies were consuming oxygen at rate that was 75% of its maximal value. Subjects were divided randomly to either do cycling then running or running then cycling. These individuals then returned after two weeks to perform the test in reverse order of what they had done previously. Water loss was estimated by weighing the subjects before and after each trial. Plasma volume and GH serum level were recorded at rest and after each phase of a trial. The importance of cycling and running was to test the researchers own hypothesis. They hypothesized that GH secretion might be inhibited during exercise by baroreceptors and a known baroreceptor reflex involved the quick transition from the angle the body is at while cycling and the angle the body is at when running (Galy et al. 1). Plasma volume and water loss were recorded to observe how the alteration of GH secretion might affect sweat regulation. Measurement of water loss indicated the degree of sweat

produced throughout a trial. Measurement of plasma volume is used in addition to water loss detection because sweating causes merocrine glands to increase plasma filtration which decreases plasma volume. Therefore, increased sweating was detected via decreased plasma volume and decreased sweating was detected via increased plasma volume. Average water loss was significantly lower in the cycling1st-running2nd (C1R2) trial than the water loss amount after the running1st-cycling2nd (R1C2) trial. A significant negative correlation was also observed between plasma volume and serum HGH levels. As HGH increased in the blood, plasma volume decreased further and further from the resting baseline. Perhaps the most notable observation was that the C1-R2 trial (i.e. which was designed to elicit the baroreceptor reflex) had a significantly lower serum HGH concentration at the end of R2 than the HGH concentrations recorded for C2. R2 plasma volume was also above resting baseline. C1, C2, and R1 plasma volumes were all lower than the resting baseline (Galy et al. 4-5). This indicates that the reflex significantly inhibited sweat secretion. In tandem, the results of the experiment support the researchers' initial hypothesis that baroreceptors inhibit GH secretion during exercise. The results also further support that GH increases sweating during exercise.

The results of these studies support that GH regulates thermoregulation through its effects on the integumentary system. Baroreceptors seem to inhibit this response, but the full mechanism for how GH elicits these effects is not yet known. What is known is that the hypothalamus regulates body temperature and secretes GHRH to stimulate the secretion of GH. Merocrine glands also have GH receptors (10 of triathlon study). These correlations could allude to a possible pathway for how

GH regulates sweating. The hypothalamus might receive signals that indicate that body temperature is increasing and react to those signals by increasing GH secretion via GHRH in order to stimulate merocrine glands to secrete more sweat. More research is needed to determine if this possible pathway is true.

The survey conducted for this thesis also has a question relating to thermoregulation. “Has your sensitivity to heat exposure been altered by GH therapy?” The available answer choices were: yes, I feel that I am more susceptible to heat stroke after beginning GH treatment; yes, I feel that I am less likely to succumb to heat stroke after beginning GH treatment; no, I notice no change in my heat sensitivity; and no, I am not heat sensitive and I have never had a sensitivity to the heat. The prevalence of responses chosen for this question can be found in Figure 36 (Appendix C). ANOVA analysis (Figure 16) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

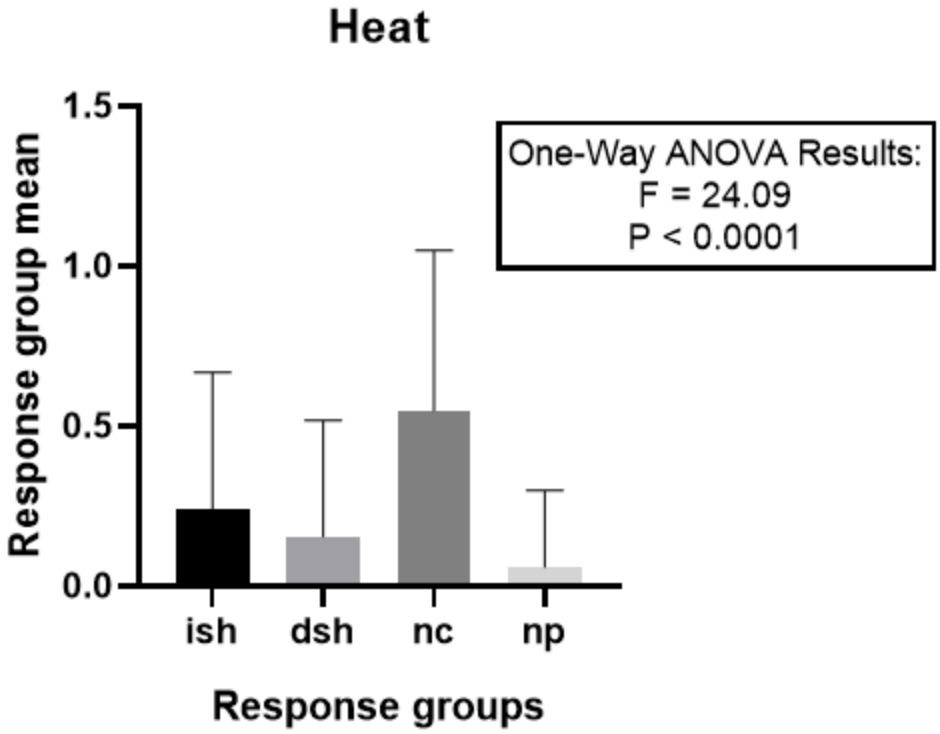

Figure 16. ANOVA results, response choice mean, and standard deviation for each response group from survey question 17 data. ISH: increased sensitivity to heat; DSH: decreased sensitivity to heat; NC: no change; NP: Never experienced a problem with heat sensitivity.

Six percent of those surveyed reported that they never were heat sensitive. This indicates that 94% of those surveyed are heat sensitive. This result supports that GHD patients may be at an increased risk of hyperthermia. Nearly 55% of those surveyed said that GH therapy did not affect their heat tolerance. Twenty five percent of those surveyed reported having decreased heat tolerance since they started GH therapy. These results support that current GH treatment measures may not attenuate heat sensitivity in all GHD patients.

Regenerative Effects:

GH may also elicit additional proliferative and recovery effects during injury or sickness. The first of these studies on wound recovery involves the role of GH as a neurotropic factor. One treatment that may allow deaf patients to hear is known as a cochlear implant. These implantations are only successful if deaf patients have normally functioning spiral ganglion neurons. Recent studies indicate that neurotropic factors may be able to repair degenerative damage to spiral ganglion neurons in patients with hearing loss. GH stimulates neurite growth and neuronal branching in other neuron types, so it might also exhibit these effects on spiral ganglion neurons. A research group in Frankfurt, Germany attempted to evaluate whether GH is a possible treatment to reverse spiral ganglion degeneration. They examined the effects of GH on the inner ear spiral ganglia from mice. This experiment was conducted in vitro. They observed significant neurite growth in the petri dish ganglia which supports that GH could be a possible neuro regenerative treatment to enable the use of cochlear implants (Gabrielpillai et al. 638-642).

Peripheral nerves are able to spontaneously recover without treatment, but when regenerated in this manner, they lose a good proportion of their functional capabilities. This dilemma has caused scientists to search for treatments that improve nerve regeneration. A research group from the University of Santiago de Compostela attempted to evaluate if GH treatment could be the solution physicians have been searching for. A transection was performed on the left sciatic nerve of studied adult rats. Transected rats were then either treated with GH or saline for a period of 8 weeks. GH treated rats were observed to have more responsive axons

and more Schwann cells than the saline treated rats. GH treated rats also performed better in treadmill tests than did the saline rats (Devesa et al. 385-91). These results support that GH could be a possible treatment to induce peripheral nerve regeneration.

Growth hormone may also be able to accelerate and improve wound healing in other types of tissue. Some believe that this effect may be caused by GH stimulating the wound area to produce more IGF-1. One study published in the journal *Wounds* discussed the effects of GH on wounded pigs. Pigs were given either GH (2.5 IU/L applied to topically to the wound) or saline every other day. Eleven applications (i.e. for each pig) of the saline or GH were given overall. Weekly biopsies were used to evaluate the rate of wound healing in the pigs. Wounds were observed to consistently heal faster in the GH-treated group than the control group ($p < 0.05$). GH-treated pigs also had more collagen 1 and IGF-1 produced than saline pigs (Kim et al. 159-161). These results support that GH may expedite wound healing. Further research is necessary to determine if GH has similar effects in humans though.

GH does regulate bone elongation. Could these effects and the above wound healing data indicate that GH treatment might accelerate bone repair as well? A study done in 2007 investigated this very subject. Researchers measured how GH treatment affected the duration of time required to repair different types of tibia fractures. Four hundred and six human patients (93 females and 313 males with ages ranging between 18 and 34) were examined in this double-blind study. Subjects had either an open or closed tibial fracture. Each patient was randomly

assigned to either receive saline or growth hormone (15, 30, or 60 mg/kg daily depending on the subgroup). Treatment ceased after full recovery was observed or after 16 weeks of continuous treatment. Patients were observed every 4 weeks until 24 weeks had passed. Post assessment was also conducted 9 months and 12 months after the treatment began. There was no significant difference in open fracture healing time between the control and the GH treated patients. GH treatment for closed fracture patients yielded drastically different results. The subgroup treated with 60 mg/kg of GH daily had an average 26% decrease in recovery time over the control group (Raschke et al. 343-349). Why there is such a stark contrast for effectiveness of GH between both fracture types is still unknown. Regardless, the data does support that GH treatment could reduce healing time for closed fractures.

The survey conducted for this thesis also asked GHD patients to describe their wound healing rate. “What is the average duration of time that you have spent out of work or school due to an injury?” The available answer choices for this question were: I typically stay out of work/school for more than one month; I typically stay out of work/school for about one month; I typically stay out of work/school for about 3 weeks; I typically stay out of work/school for about 2 weeks; I typically stay out of work/school for about 10-13 days; I typically stay out of work/school for about 7-9 days; I typically stay out of work/school for about 4-6 days; and I typically stay out of work/school for about 1-3 days. The prevalence of responses chosen for this question can be found in Figure 37 (Appendix C). ANOVA analysis (Figure 17) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

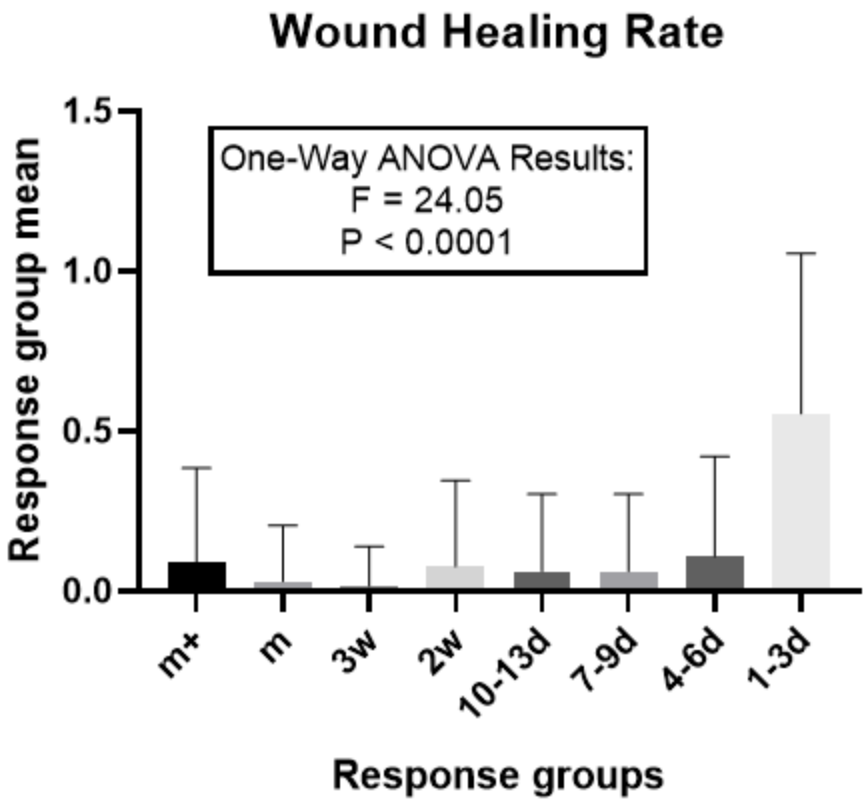

Figure 17. ANOVA results, response choice mean, and standard deviation for each response group from survey question 18 data. M+: stayed out for more than a month, M: stayed out for a month; 3W: stayed out for 3 weeks; 2W: stayed out for 2 weeks; 10-13D: stayed out for 10-13 days; 7-9D: stayed out for 7-9 days; 4-6D: stayed out for 4-6 days; 1-3D: stayed out for 1-3 days.

Fifty five percent of those surveyed said that they stayed out for 1 to 3 days. This result could support that GH boosts wound regeneration rates, but more research is needed to truly determine a cause and effect. This data might have more validity if it were to be compared with that of a control group which was asked the same question.

Immune System:

GH's effects on the immune system will now be discussed. A 2009 study reviewed how GH and Ghrelin affect the immune system. These hormones have

been observed to interact with T lymphocytes, B lymphocytes, monocytes and neutrophils. Each of these cells also contain GHRs and Growth Hormone Secretagogue Receptors (GHS-Rs). Ghrelin appears to cause a signal cascade when it interacts with GHS-R. This may indicate that Ghrelin plays an important role in the regulation of the hypothalamic-pituitary axis. The conservative nature of cells signifies that all molecules produced by a cell are also used by the cell in some way. Thus, the sheer fact that these immune cells possess GHRs and GHS-Rs corroborates the claim that Ghrelin and GH have a role in regulating the immune system. This study reports that GH is responsible for “enhancing thymopoiesis and T cell development, modulating cytokine production, enhancing B cell development and antibody production, priming neutrophils and monocytes for superoxide anion secretion, enhancing neutrophil adhesion and monocyte migration and anti-apoptotic action” (Hattori 347). Ghrelin plays a role in the reduction of inflammation, the regulation of thymopoiesis, the reduction of sepsis, and the regulation of phagocytosis. It remains to be known whether the effects of Ghrelin are elicited by GH or if the GH effects are elicited by IGF-1.

Results from other studies further support that GH affects the innate immune system. A 2019 cancer cachexia study in the Journal *PloS One* observed that GH activates and stimulates the proliferation of NK cells in cancer induced rats (Wei et al. 6-7). Another study done in 2013 found that in vivo GH treatment of peritoneal macrophages had caused these cells to be more phagocytic than the control (Reis et al. 1). A 2004 review in the *Journal of Pediatric Endocrine Reviews* compiled a list of other innate immune system effects. It mentions that GH was observed to

stimulate the proliferation and differentiation of myeloid progenitor cells, that GH stimulated monocyte chemotaxis and migration, and also caused monocytes; macrophages; and neutrophils to increase production of phagocytic chemicals (i.e. superoxide anions and hydrogen peroxide for monocytes) (Meazza et al. 5-6).

These studies support that GH could affect leukocyte regulation. They also suggest that HGH could be used to boost immune function. There were also questions in the survey conducted for this thesis that asked GHD patients to describe how GH therapy effected their immune system. “Has your rate of contracting an illness changed since you began GH therapy?” The available answer choices were: yes, I have noticed that I have contracted 4 or more illnesses on average than I did before I began GH treatment; yes, I have noticed that I have contracted 2 to 3 more illnesses on average than I did before I began GH treatment; no, I have noticed no change in my rate of contracting illnesses; yes, I have noticed that I catch 2 to 3 fewer illnesses on average that I did before I began GH treatment; and yes, I have noticed a major change in my health to such a degree that I now typically only contract 1 to 2 illnesses a year. This question is designed to measure the strength of the innate immune system within the subjects. Contracting fewer illnesses would indicate that the physical barriers and innate immune system leukocytes are strong enough to prevent more pathogens from multiplying to the degree which would cause the subject to develop symptoms. GH seems to boost the protective function of the skin and stimulate innate immune cells such as nk cells, so it is possible that GH could enhance the innate immune system and reduce the overall number of contracted illnesses. The prevalence of responses chosen for this

question can be found in Figure 38 (Appendix C). ANOVA analysis (Figure 18) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

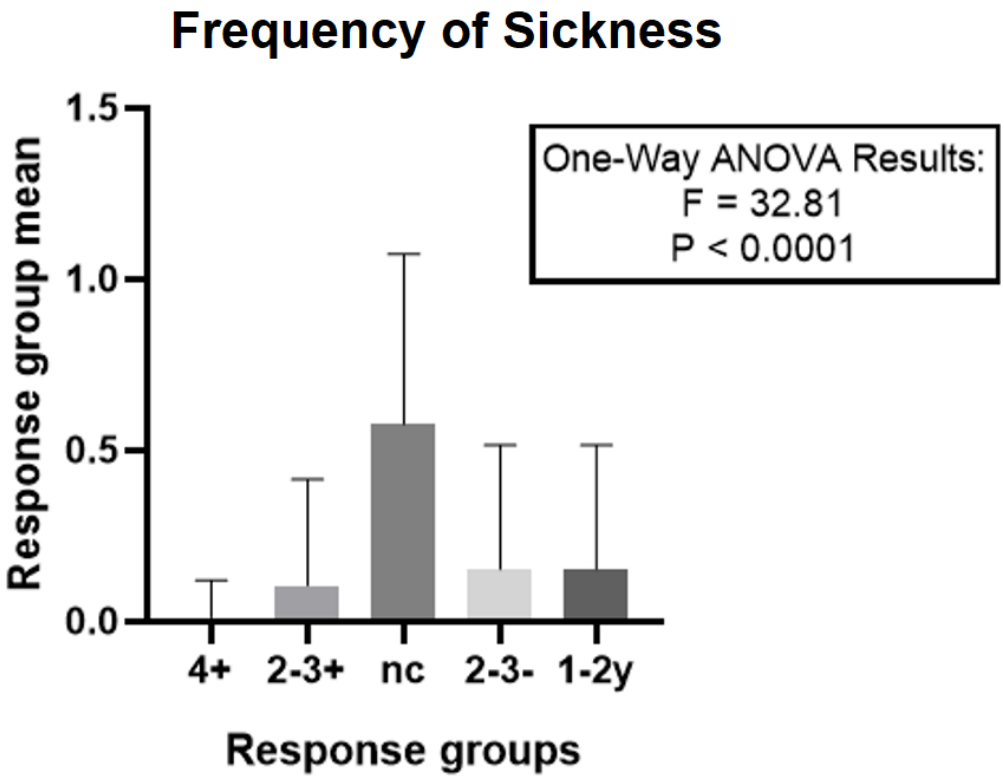

Figure 18. ANOVA results, response choice mean, and standard deviation for each response group from survey question 19 data. 4+: additional 4 or more contracted illnesses per year; 2-3+: additional 2 to 3 more contracted illnesses per year; NC: no change; 2-3-: decrease of 2 to 3 contracted illnesses per year; 1-2Y: 1 to 2 contracted illnesses per year.

Fifty seven percent of those surveyed report that they noticed no change. Fifteen percent noticed they had contracted 2-3 fewer illnesses. Another 15% reported that GH therapy vastly improved their innate immune function to a degree where they now only get sick once or twice a year. The high prevalence of no noticeable change may be because individuals do not often think of how many

illnesses they contract in a year, but this is only a hypothesis. These results support that GH could improve inmate immune system function in some GHD patients.

"Has the duration of an illness changed since you began GH therapy?" The answer choices for this question were: yes, I noticed that a sickness duration is on average a week or more longer than it would have been before I began GH treatment; yes, I noticed that a sickness duration is on average 4-6 days longer than it would have been before I began GH treatment; yes, I noticed that a sickness duration is on average 1-3 days longer than it would have been before I began GH treatment; I have noticed no change in the average length of sickness following the contraction of a pathogen; yes, I noticed that a sickness duration is on average 1-3 days shorter than it would have been before I began GH treatment; yes, I noticed that a sickness duration is on average 4-6 days shorter than it would have been before I began GH treatment and yes, I noticed that a sickness duration is on average 7-10 days shorter than it would have been before I began GH treatment. This question is meant to assess whether GH treatment may cause the adaptive immune response (i.e. activation and proliferation of B and T lymphocytes) to occur at an earlier point than when the response occurred while these patients did not receive GH treatment. Said alteration of response time would shorten the duration of sickness in the patients. Thus, the overall duration is gauged to assess adaptive immune response time. The prevalence of responses chosen for this question can be found in Figure 39 (Appendix C). ANOVA analysis (Figure 19) revealed that variance between selected answers was statistically significant ($p < 0.0001$).

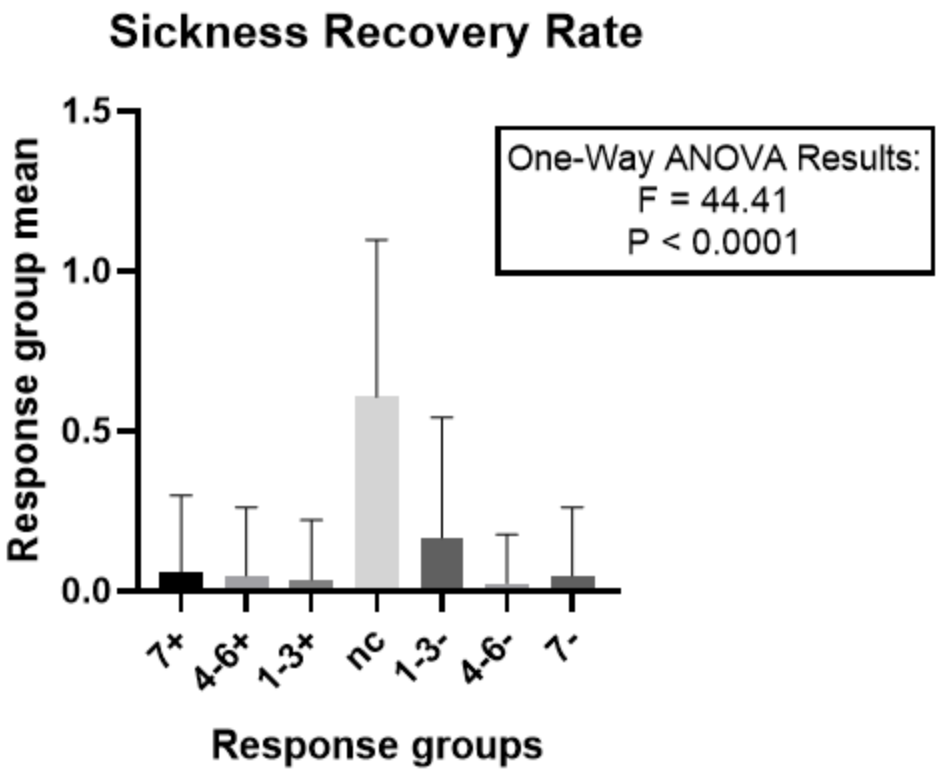

Figure 19. ANOVA results, response choice mean, and standard deviation for each response group from survey question 20 data. 7+: 7 or more day increase in sickness duration; 4-6+: 4 to 6 day increase in sickness duration; 1-3+: 1 to 3 day increase in sickness duration; NC: no change; 1-3-: 1 to 3 day decrease in sickness duration; 4-6-: 4 to 6 day decrease in sickness duration; 7-: 7 or more day decrease in sickness duration.

Sixty two percent of those surveyed report no noticeable change. Nearly 17% of those surveyed said that their average sickness duration has decreased by 1 to 3 days. These results support that GH therapy could accelerate adaptive immune response in some GHD patients.

Further Interpretation of Miscellaneous Findings:

There is evidence to support that GH may regulate cardiac, integumentary, thermoregulation, healing, and immune system functions. Survey results on cardiac function do not support that GH effects cardiac function, but more objective studies

estimate that GHD patients are at a higher risk of having a heart attack. Survey results also support that GH treatment could improve wound healing and immune function in GHD patients. Results of literary analyses support that GH might be a possible treatment to improve wound healing and boost immune system function in normal patients. GHD patients could also have integumentary ailments, but findings oppose that GH therapy can attenuate these side effects. Survey results also support that GH therapy does not improve thermoregulation. GH has been shown to increase while normal individuals are exercising. GHD patients only receive GH once in the evening. These results suggest that GH therapy may need to be altered. It is hypothesized that a GH pump similar to insulin pumps could attenuate these currently unaltered integumentary and thermoregulation impairments because it would mimic the natural pulsatile and physical state dependent secretions of GH in normal patients. More research is needed to support this hypothesis. Regardless, results from the survey and literary analysis of recent findings support that GH could be necessary to maintain healthy cardiac, integumentary, recovery, and immune system functions.

Chapter 4: Conclusion

There is evidence to support that GH regulates many more functions than bone elongation. This thesis has discussed both the analysis of its survey and recent study results that evaluate these additional roles. Previously mentioned data supports that GH could regulate energy, metabolism, physical capacity, mental health, sleep, cognition, cardiovascular health, the integumentary system, thermoregulation, wound regeneration, and immune system function. Findings suggest that GH is much more important to the body than was once thought.

Recent findings and analysis of the survey conducted for this thesis support that GH treatment could be necessary for GHD patients to live a long and healthy life. Without GH these patients could have mental health conditions, low energy levels, obesity, impaired immune system function, impaired cardiovascular system function, impaired exercise ability, cognitive impairment, dysfunctional sleep, and heat sensitivity. Each of these factors would greatly diminish the quality of the patient's life and could shorten the length of their life. There is strong evidence to support that GH therapy is a necessity for GHD patients of any age. These findings also suggest that clinicians may need to rethink how they treat GHD patients. One dose a day may not be enough to attenuate all of the aforementioned side effects. In the future, patients might take small dosages of GH when they go to bed, when they are fasting, and when they intend to exercise for a long period. GH is not only secreted to increase bone elongation, so the cessation of bone elongation does not support that GH treatment should cease in adult GHD patients.

The discovery of the effects of GH might also improve the lives of normal individuals. GH has been observed to improve immune system function in rats with cancer, to improve wound healing in pigs, to improve some types of bone repair in humans, to improve cognitive function in a patient with a severe traumatic brain injury, and to minimize stroke damage in mice. These results support that GH could be a possible treatment to boost immune system function, accelerate healing, and repair damage that current medicines cannot treat. GH may be used as a treatment for these impairments in the coming decade. Though clinical trials of larger samples will truly determine if GH is a safe treatment for the aforementioned conditions.

It should now be apparent that growth hormone affects much more than growth. What should be researched next is how GH treatment can improve the lives of individuals without GHD.

Limitations:

There are limitations of the survey conducted for this thesis. The survey had a low number (86) of respondents, so results should not be used as proof of the effects of GH on all individuals with GHD. The sample of subjects includes mostly Caucasian women. Results thus do not properly represent all GHD patients. Patients were asked to report how they felt about their symptoms. These feelings may not translate into objective results if tested further. Patients could have lied. It is also possible that the cost of GH may have incentivized the patients to feel that GH has had a positive effect on their symptoms.

Appendix A:

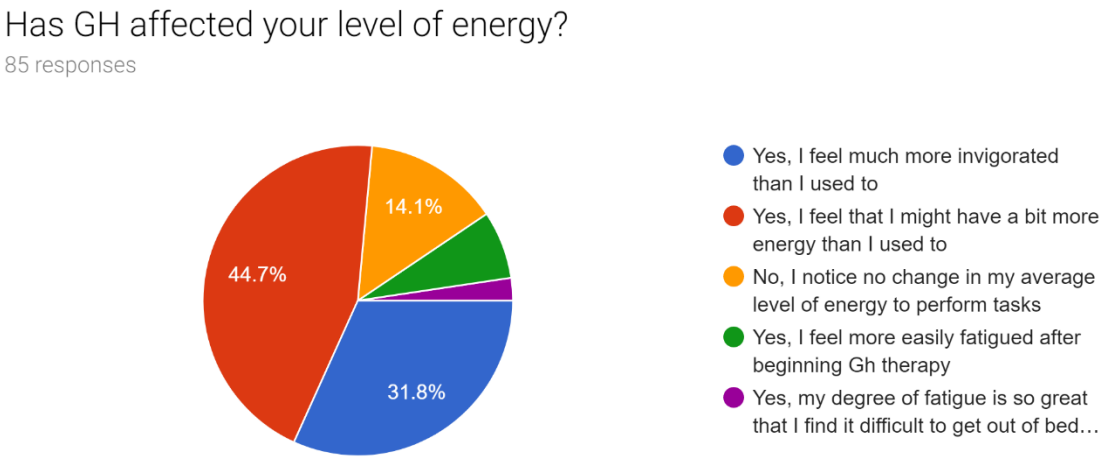

Figure 20. Prevalence of responses chosen for survey question 1.

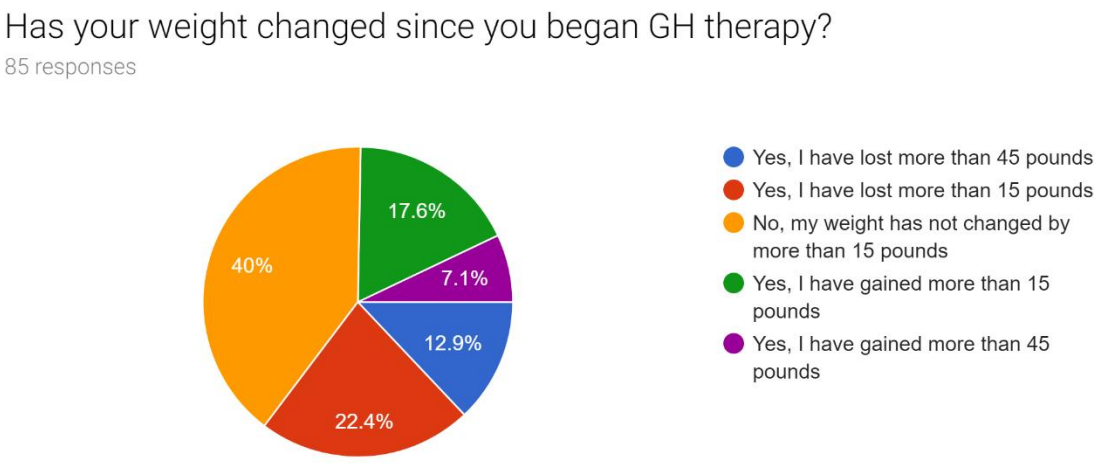

Figure 21. Prevalence of responses chosen for survey question 2.

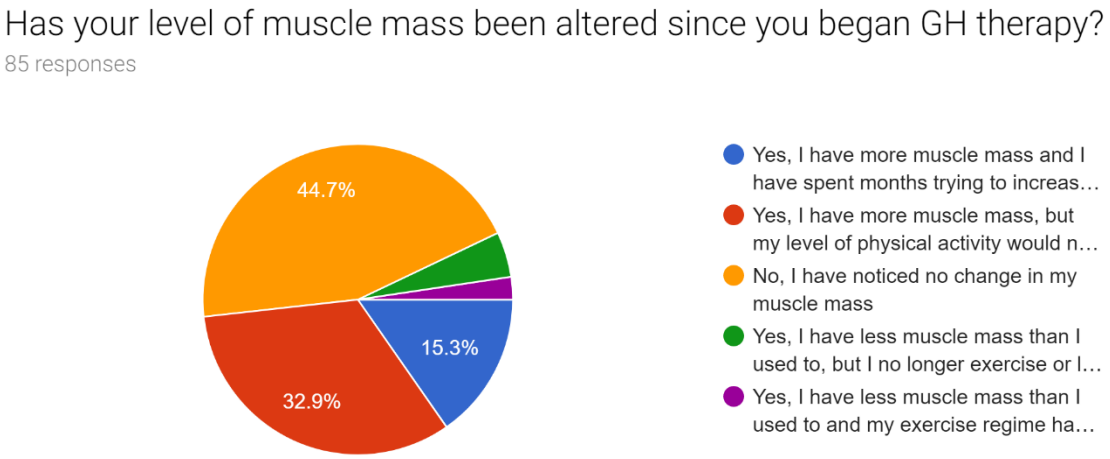

Figure 22. Prevalence of responses chosen for survey question 3.

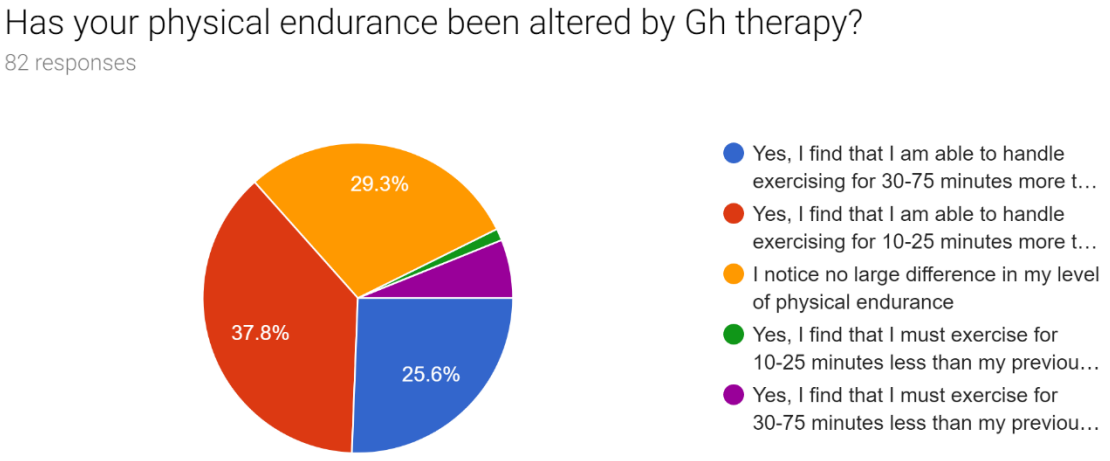

Figure 23. Prevalence of responses chosen for survey question 4.

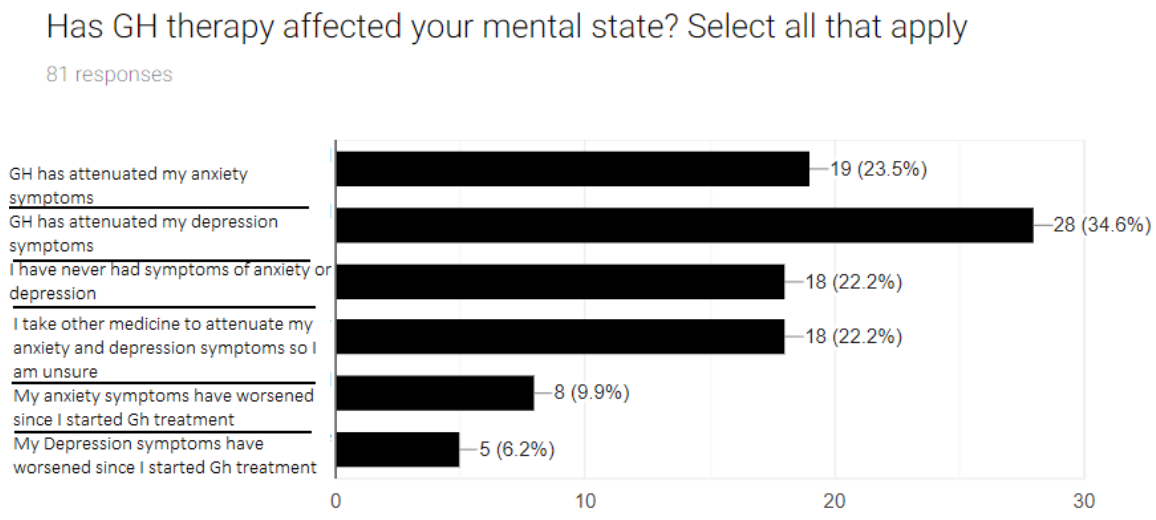

Figure 24. Prevalence of responses chosen for survey question 5.

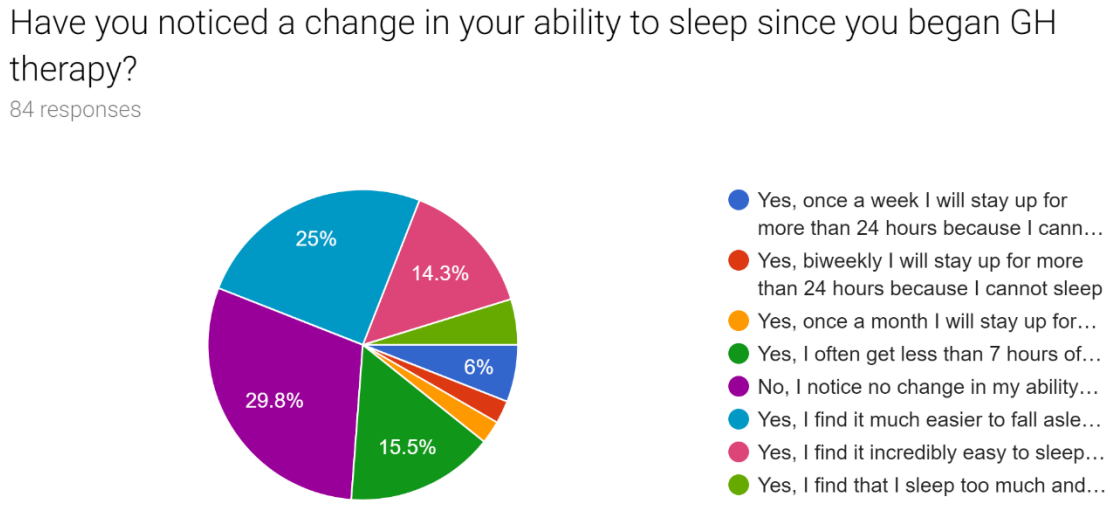

Figure 25. Prevalence of responses chosen for survey question 6.

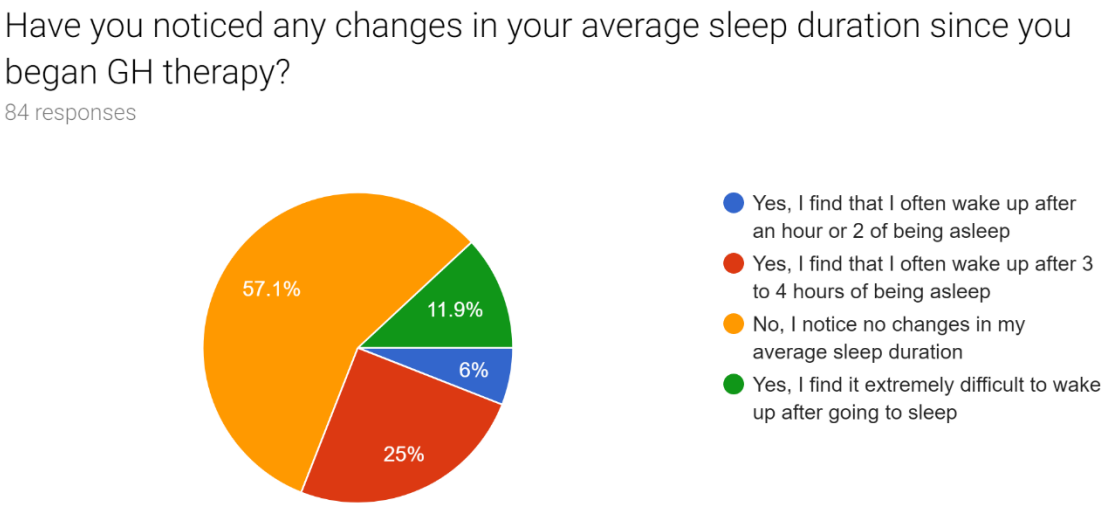

Figure 26. Prevalence of responses chosen for survey question 7.

Appendix B:

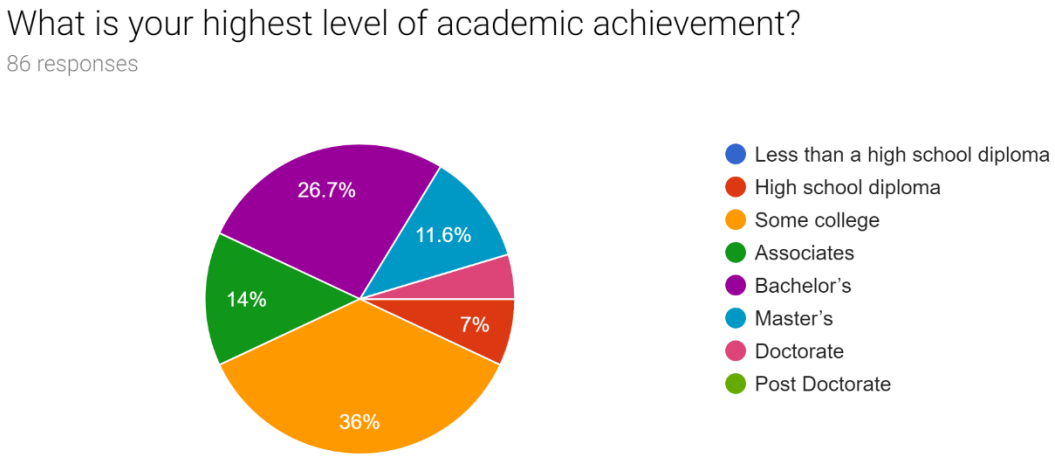

Figure 27. Prevalence of responses chosen for survey question 8.

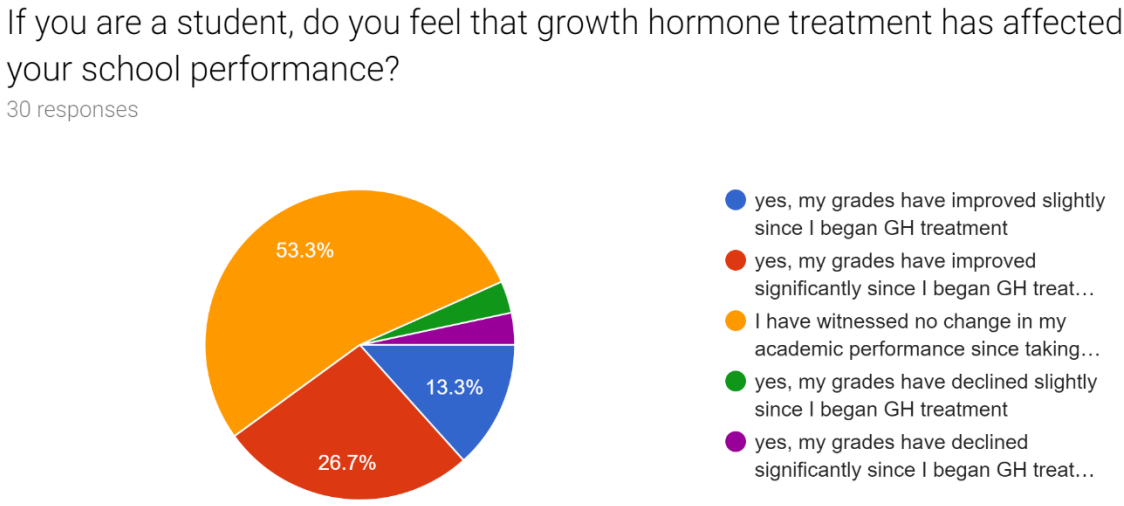

Figure 28. Prevalence of responses chosen for survey question 9.

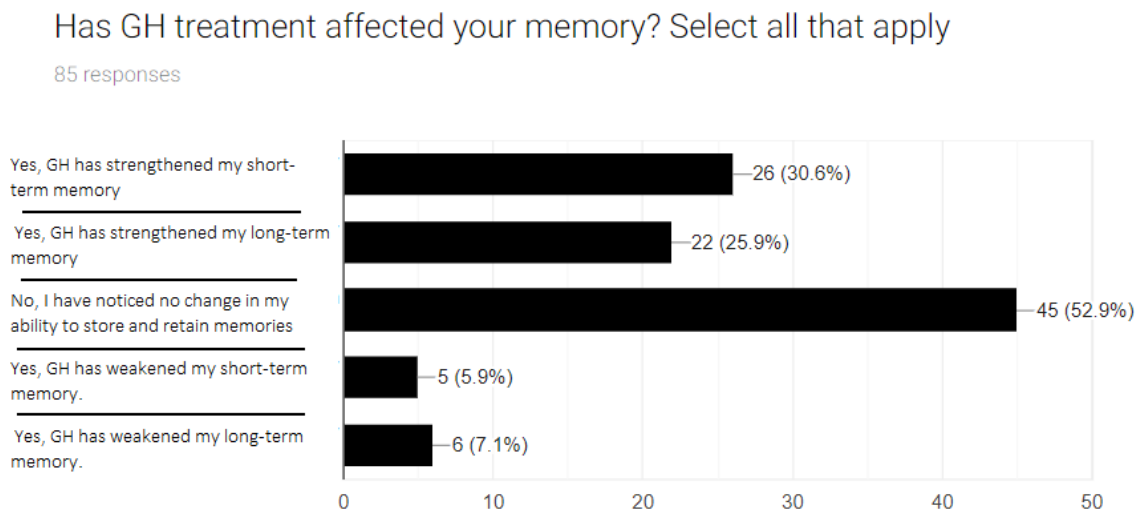

Figure 29. Prevalence of responses chosen for survey question 10.

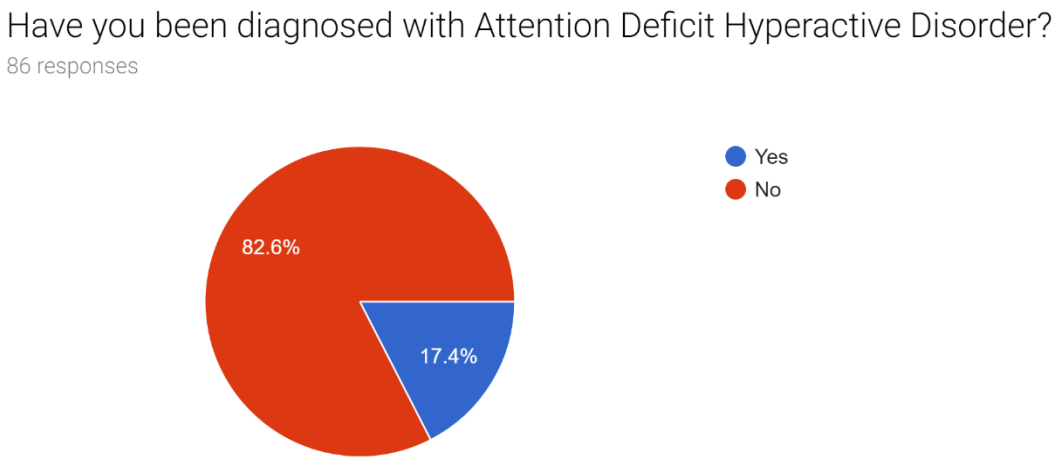

Figure 30. Prevalence of responses chosen for survey question 11.

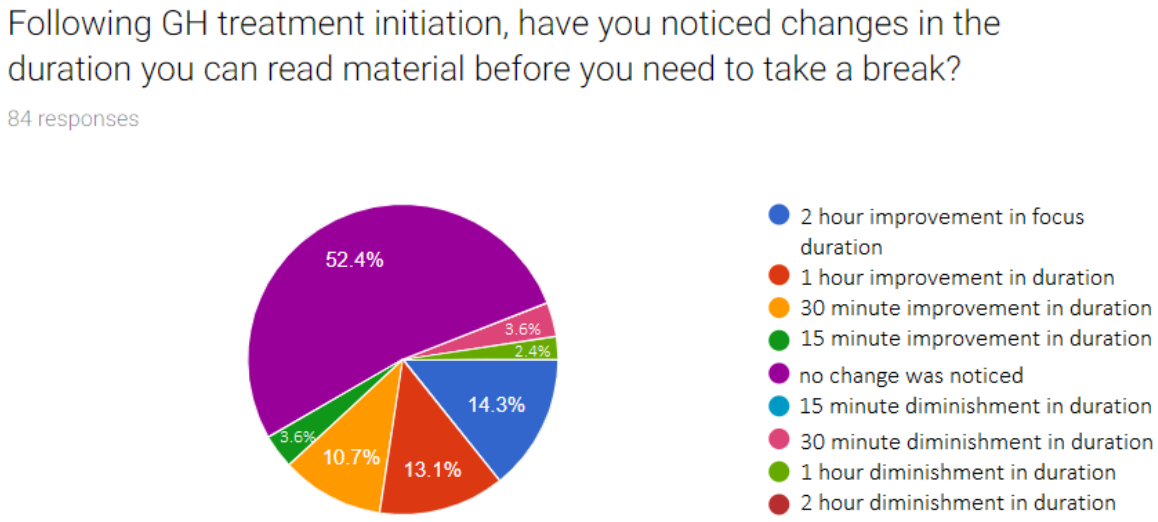

Figure 31. Prevalence of responses chosen for survey question 12.

Appendix C:

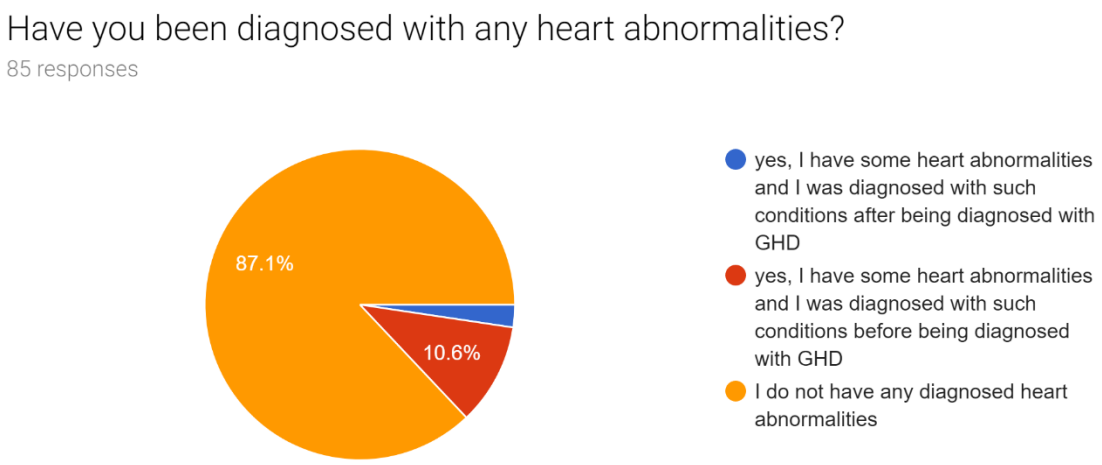

Figure 32. Prevalence of responses chosen for survey question 13.

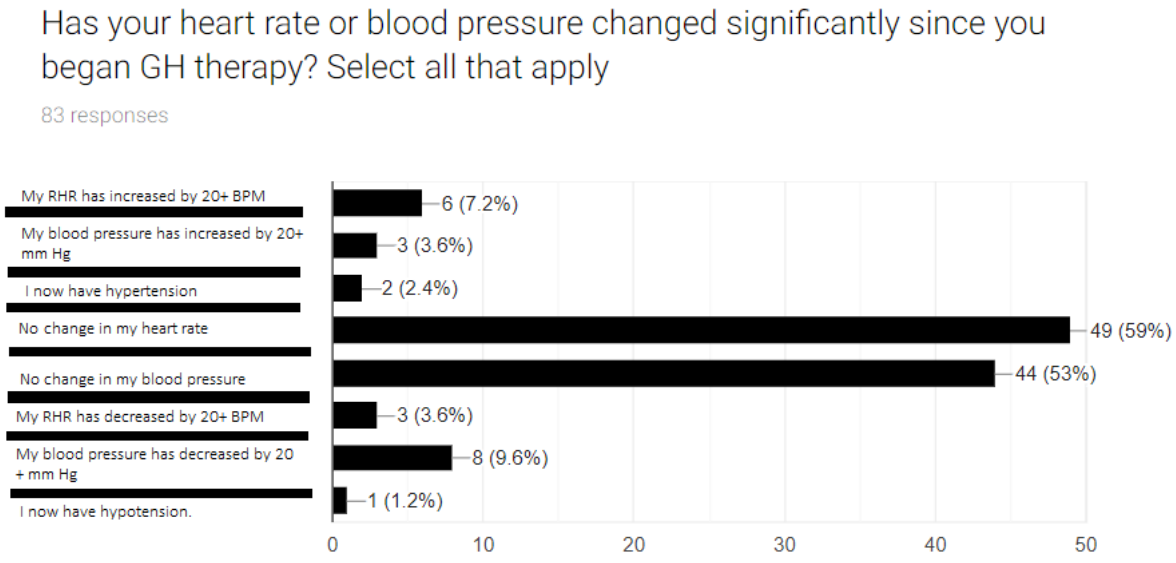

Figure 33. Prevalence of responses chosen for survey question 14.

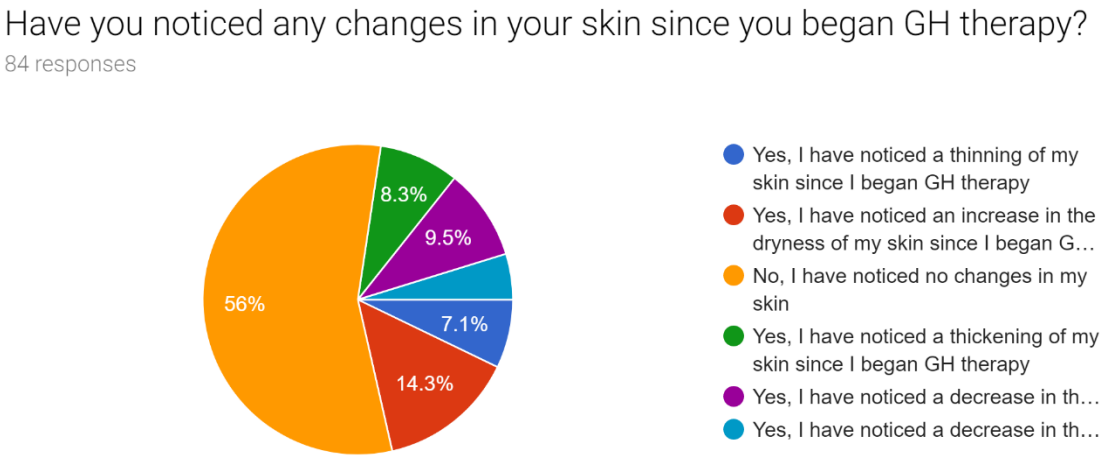

Figure 34. Prevalence of responses chosen for survey question 15.

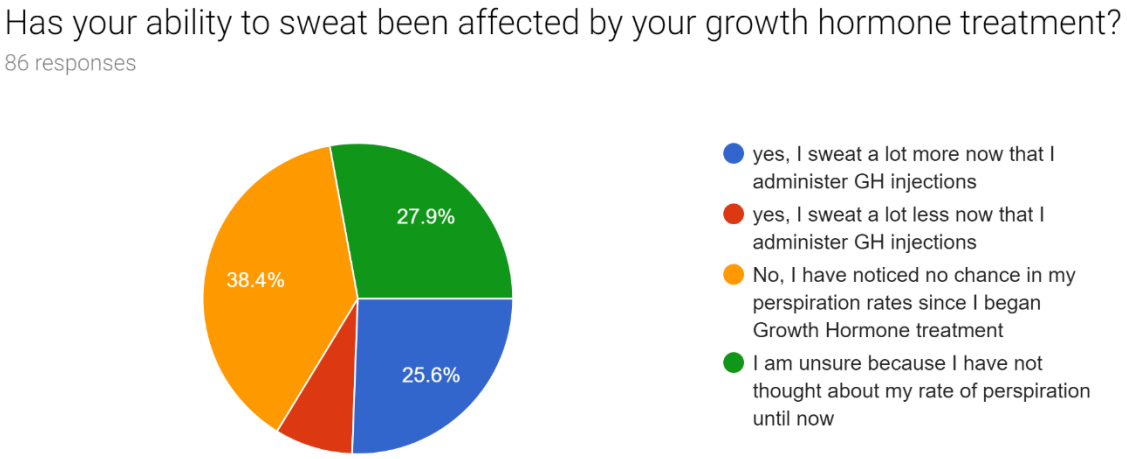

Figure 35. Prevalence of responses chosen for survey question 16.

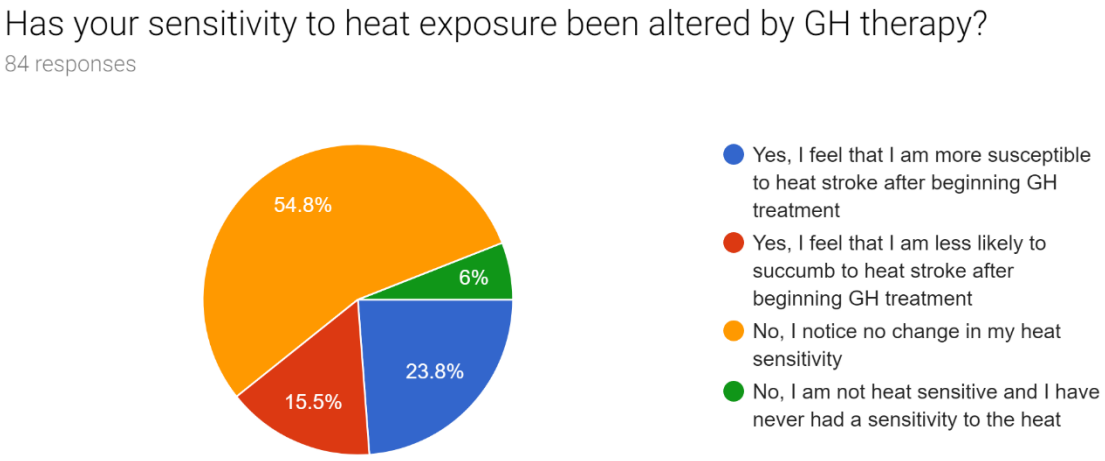

Figure 36. Prevalence of responses chosen for survey question 17.

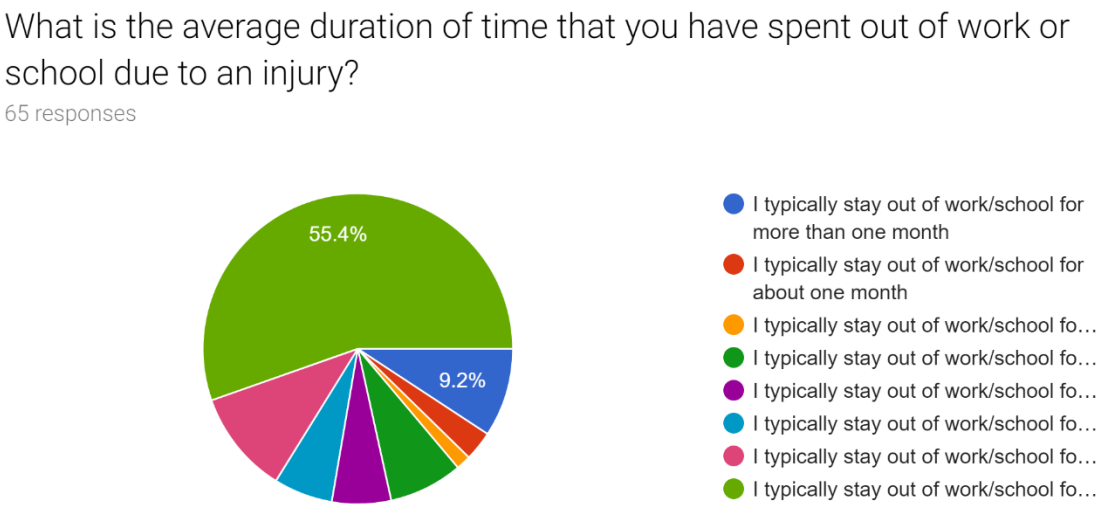

Figure 37. Prevalence of responses chosen for survey question 18.

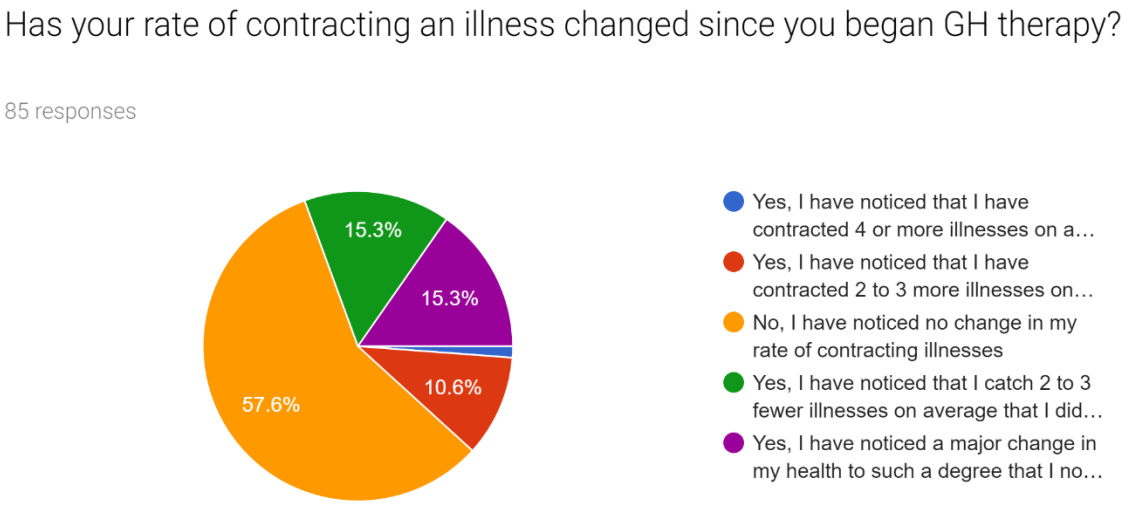

Figure 38. Prevalence of responses chosen for survey question 19.

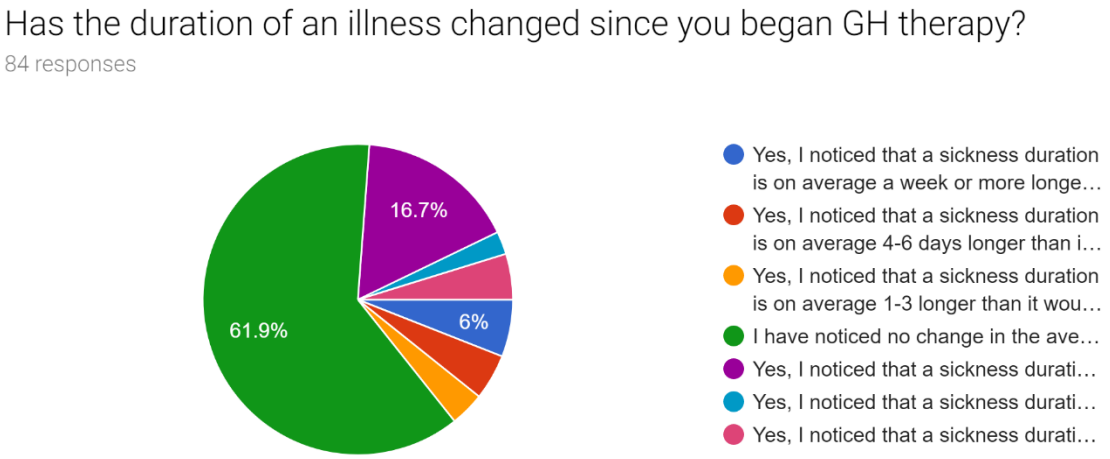

Figure 39. Prevalence of responses chosen for survey question 20.

References

Akaltun, İ., Çayır, A., Kara, T., & Ayaydın, H. (2018). Is growth hormone deficiency associated with anxiety disorder and depressive symptoms in children and adolescents?: A case-control study. Growth Hormone & IGF Research, 41, 23-27. doi:10.1016/j.ghir.2018.06.001

Alonzo, Frances. “Highest Educational Levels Reached by Adults in the U.S. Since 1940.” The United States Census Bureau, The United States Census Bureau, 19 Jan. 2018, www.census.gov/newsroom/press-releases/2017/cb17-51.html.

Anderson, L. J., Tamayose, J. M., & Garcia, J. M. (2018). Use of growth hormone, IGF-I, and insulin for anabolic purpose: Pharmacological basis, methods of detection, and adverse effects. Molecular and Cellular Endocrinology, 464, 65-74. doi:10.1016/j.mce.2017.06.010

Arcopinto, Michele et al. “Growth Hormone Deficiency Is Associated with Worse Cardiac Function, Physical Performance, and Outcome in Chronic Heart Failure: Insights from the T.O.S.CA. GHD Study” PloS one vol. 12,1 e0170058. 17 Jan. 2017, doi:10.1371/journal.pone.0170058

Arwert, L. I., Deijen, J. B., Müller, M., & Drent, M. L. (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, 47(3), 343-349. doi:10.1016/j.yhbeh.2004.11.015

Attanasio, F. A., Peter C. Bates, Ken K. Y. Ho, Susan M. Webb, Richard J. Ross, Christian J. Strasburger, Roger Bouillon, Brenda Crowe, Keith Selander, Domenico Valle, Steven W. J. Lamberts; Human Growth Hormone Replacement in Adult Hypopituitary Patients: Long-Term Effects on Body Composition and Lipid Status—3-Year Results from the HypoCCS Database, The Journal of Clinical Endocrinology & Metabolism, Volume 87, Issue 4, 1 April 2002, Pages 1600–1606, https://doi.org/10.1210/jcem.87.4.8429

Baquedano, E., Chowen, J., Argente, J., & Frago, L. (2013). Differential effects of GH and GH-releasing peptide-6 on astrocytes, Journal of Endocrinology, 218(3), 263-274. Retrieved Dec 4, 2018, from https://joe.bioscientifica.com/view/journals/joe/218/3/263.xml

Barro, Robert J. & Lee, Jong Wha, 2013. "A new data set of educational attainment in the world, 1950-2010," Journal of Development Economics, Elsevier, vol. 104(C), pages 184-198.

Basu, A., McFarlane, H. G., & Kopchick, J. J. (2017). Spatial learning and memory in male mice with altered growth hormone action. Hormones and Behavior, 93, 18-30. doi:10.1016/j.yhbeh.2017.04.001

Berberoğlu, M., Sıklar, Z., Darendeliler, F., Poyrazoğlu, S., Darcan, S., Işgüven, P., Bideci, A., Ocal, G., Bundak, R., Yüksel, B., … Arslanoğlu, I. (2008). Evaluation of permanent growth hormone deficiency (GHD) in young adults with childhood

onset GHD: a multicenter study. Journal of clinical research in pediatric endocrinology, 1(1), 30-7.

Bergan-Roller, H. E., & Sheridan, M. A. (2017). The growth hormone signaling system: Insights into coordinating the anabolic and catabolic actions of growth hormone. General And Comparative Endocrinology, doi:10.1016/j.ygcen.2017.07.028

Birzniece, V., Nelson, A. E., & Ho, K. K. Y. (2011). Growth hormone and physical performance. Trends in Endocrinology & Metabolism, 22(5), 171-178. doi:10.1016/j.tem.2011.02.005

Birzniece, Vita, Anne E. Nelson, and Ken K. Y. Ho. "Growth Hormone and Physical Performance." Trends in Endocrinology & Metabolism, vol. 22, no. 5, 2011, pp. 171-178

Brod, M., Pohlman, B., Højbjerre, L., Adalsteinsson, J. E., & Rasmussen, M. H. (2014). Impact of adult growth hormone deficiency on daily functioning and well-being. BMC research notes, 7, 813. doi:10.1186/1756-0500-7-813

C. Diamond, Marian & B. Scheibel, Arnold & Murphy, G.M. & Harvey, Thomas. (1985). On the brain of a scientist: Albert Einstein. Experimental neurology. 88. 198-204. 10.1016/0014-4886(85)90123-2.

Caicedo, D., Díaz, O., Devesa, P., & Devesa, J. (2018). Growth hormone (GH) and cardiovascular system. International Journal of Molecular Sciences, 19(1), 290. doi:10.3390/ijms19010290

Camilla M. Hoyos, Roo Killick, Daniel M. Keenan, Robert C. Baxter, Johannes D. Veldhuis, Peter Y. Liu; Continuous Positive Airway Pressure Increases Pulsatile Growth Hormone Secretion and Circulating Insulin-like Growth Factor-1 in a Time-Dependent Manner in Men With Obstructive Sleep Apnea: A Randomized Sham-Controlled Study, Sleep, Volume 37, Issue 4, 1 April 2014, Pages 733–741, https://doi.org/10.5665/sleep.3580

Chaplin, J. E., Kriström, B., Jonsson, B., Tuvemo, T., Albertsson-Wikland, K., Medicinska fakulteten, . . . Umeå universitet. (2015). Growth hormone treatment improves cognitive function in short children with growth hormone deficiency. Hormone Research in Paediatrics, 83(6), 390-399. doi:10.1159/000375529

Copinschi, Georges et al. “Sleep disturbances, daytime sleepiness, and quality of life in adults with growth hormone deficiency” Journal of clinical endocrinology and metabolism vol. 95,5 (2010): 2195-202.

Darendeliler F, Karagiannis G, Wilton P: Headache, Idiopathic Intracranial Hypertension and Slipped Capital Femoral Epiphysis during Growth Hormone Treatment: A Safety Update from the KIGS Database. Horm Res 2007;68(suppl 5):41-47. doi: 10.1159/000110474

Deijen, J. B., Arwert, L. I., & nt, M. L. (2011). The GH/IGF-I axis and cognitive changes across a 4-year period in healthy adults. ISRN Endocrinology, 2011, 249421-6. doi:10.5402/2011/249421

Devesa, J., Díaz-Getino, G., Rey, P., García-Cancela, J., Loures, I., Nogueiras, S., . . . Devesa, P. (2015). Brain recovery after a plane crash: Treatment with growth hormone (GH) and neurorehabilitation: A case report. International Journal of Molecular Sciences, 16(12), 30470-30482. doi:10.3390/ijms161226244

Devesa, J., Lema, H., Zas, E., Munín, B., Taboada, P., & Devesa, P. (2016). Learning and Memory Recoveries in a Young Girl Treated with Growth Hormone and Neurorehabilitation. Journal of clinical medicine, 5(2), 14. doi:10.3390/jcm5020014

Devesa, P., Gelabert, M., Gonźlez-Mosquera, T., Gallego, R., Luis Relova, J., Devesa, J., & Arce, V. M. (2012). Growth hormone treatment enhances the functional recovery of sciatic nerves after transection and repair. Muscle & Nerve, 45(3), 385-392. doi:10.1002/mus.22303

Díez, J. J., Sangiao-Alvarellos, S., & Cordido, F. (2018). Treatment with growth hormone for adults with growth hormone deficiency syndrome: Benefits and risks. International Journal of Molecular Sciences, 19(3), 893. doi:10.3390/ijms19030893

Elbornsson, M., Horvath, A., Götherström, G., Bengtsson, B., Johannsson, G., & Svensson, J. (2017). Seven years of growth hormone (GH) replacement improves quality of life in hypopituitary patients with adult-onset GH deficiency, European Journal of Endocrinology, 176(2), 99-109.

Falleti, Marina G., et al. "The Effects of Growth Hormone (GH) Deficiency and GH Replacement on Cognitive Performance in Adults: A Meta-Analysis of the Current Literature."Psychoneuroendocrinology, vol. 31, no. 6, 2006, pp. 681-691.

Gabrielpillai, Jennis & Geißler, Christin & Stock, Belinda & Stöver, Timo & Diensthuber, Marc. (2018). Growth hormone promotes neurite growth of spiral ganglion neurons. NeuroReport. 29. 1. 10.1097/WNR.0000000000001011.

Galy, Olivier, et al. "Sequential Exercise in Triathletes: Variations in GH and Water Loss."PloS One, vol. 9, no. 4, 2014, pp. e96145.

Gonzalez, Susana, et al. "Effects of Growth Hormone Replacement on Peripheral Muscle and Exercise Capacity in Severe Growth Hormone Deficiency." Frontiers in Endocrinology, vol. 9, 2018, pp. 56.

Grönbladh, A., Johansson, J., Nöstl, A., Nyberg, F., & Hallberg, M. (2013). GH improves spatial memory and reverses certain anabolic androgenic steroid-induced effects in intact rats, Journal of Endocrinology, 216(1), 31-41. Retrieved Dec 5, 2018, from https://joe.bioscientifica.com/view/journals/joe/216/1/31.xml

Halperin, J. M., Newcorn, J. H., McKay, K. E., Siever, L. J., & Sharma, V. (2003). Growth hormone response to guanfacine in boys with attention deficit hyperactivity disorder: A preliminary study. Journal of Child and Adolescent Psychopharmacology, 13(3), 283-294. doi:10.1089/104454603322572615

Hattori, N. (2008;2009;). Expression, regulation and biological actions of growth hormone (GH) and ghrelin in the immune system. Growth Hormone and IGF Research, 19(3), 187-197. doi:10.1016/j.ghir.2008.12.001

Hua, K., Forbes, M. E., Lichtenwalner, R. J., Sonntag, W. E., & Riddle, D. R. (2009). Adult-onset deficiency in growth hormone and insulin-like growth factor-I alters oligodendrocyte turnover in the corpus callosum. Glia, 57(10), 1062-1071. doi:10.1002/glia.20829

Hwa Kim, Suk & Eun, Ju & Heo, Bs & Sang, Woo & , Lee. (2015). The Effect of Topically Applied Recombinant Human Growth Hormone on Wound Healing in Pigs. Wounds : a compendium of clinical research and practice. 21.

"Intelligence." Merriam-Webster.com. Merriam-Webster, 2019.

Isgaard, J., Arcopinto, M., Karason, K. et al. Endocrine (2015) 48: 25. https://doi.org/10.1007/s12020-014-0327-6

Juul A, Hjortskov N, Jepsen LT, Nielsen B, Halkjaer-Kristensen J, Vahl N, Jørgensen JO, Christiansen JS, Skakkebaek NE. Growth hormone deficiency and hyperthermia during exercise: a controlled study of sixteen GH-deficient patients. JCEM. 1995 Nov;80(11):3335-40. https://doi.org/10.1210/jcem.80.11.7593447

Kaltschmidt, Barbara, and Christian Kaltschmidt. "NF-KappaB in Long-Term Memory and Structural Plasticity in the Adult Mammalian Brain." Frontiers in Molecular Neuroscience, vol. 8, 2015, pp. 69.

Gantenbein, C., Kogia, C., Abdel-Naser, M.B. et al. Rev Endocr Metab Disord (2016) 17: 259. https://doi.org/10.1007/s11154-016-9378-8

Kumar, P.A., Chitra, P.S., Lu, C. et al. Growth hormone (GH) differentially regulates NF-kB activity in preadipocytes and macrophages: implications for GH's role in adipose tissue homeostasis in obesity, J Physiol Biochem (2014) 70: 433. https://doi.org/10.1007/s13105-014-0321-8

Liu H, Bravata DM, Olkin I, Friedlander A, Liu V, Roberts B, et al. Systematic Review: The Effects of Growth Hormone on Athletic Performance. Ann Intern Med. ;148:747–758. doi: 10.7326/0003-4819-148-10-200805200-00215

Liu, X., Green, K. J., Ford, Z. K., Queme, L. F., Lu, P., Ross, J. L., Lee, F. B., Shank, A. T., Hudgins, R. C., … Jankowski, M. P. (2017). Growth hormone regulates the sensitization of developing peripheral nociceptors during cutaneous inflammation. Pain, 158(2), 333-346.

Liu, Zhihai, et al. "Growth Hormone Increases Lung NF-kappaB Activation and Lung Microvascular Injury Induced by Lipopolysaccharide in Rats." Annals of Clinical and Laboratory Science, vol. 32, no. 2, 2002, pp. 164.

Lourenço, J., & Bacci, A. (2017). Human-specific cortical synaptic connections and their plasticity: Is that what makes us human? PLoS Biology, 15(1), e2001378. doi:10.1371/journal.pbio.2001378

Malenka RC, Nestler EJ, Hyman SE (2009). "Chapter 8: Atypical Neurotransmitters". In Sydor A, Brown RY. Molecular Neuropharmacology: A Foundation for Clinical Neuroscience (2nd ed.). New York: McGraw-Hill Medical. pp. 199, 211–221. ISBN 9780071481274

Malenka RC, Nestler EJ, Hyman SE (2009). "Chapter 8: Atypical Neurotransmitters". In Sydor A, Brown RY. Molecular Neuropharmacology: A Foundation for Clinical Neuroscience (2nd ed.). New York: McGraw-Hill Medical. pp. 199, 211–221. ISBN 9780071481274

Maria, Dos S. R., et al. "Modulation of Macrophage Function by Growth Hormone." Frontiers in Immunology, vol. 4, 2013.

Meazza C, Pagani S, Travaglino P, Bozzola M. Effect of growth hormone (GH) on the immune system. Pediatr Endocrinol Rev 2004 Aug;1(Suppl 3):490-5.

"Memory." Merriam-Webster.com. Merriam-Webster, 2019.

Merlo, E., Freudenthal, R., Maldonado, H., & Romano, A. (2005). Activation of the transcription factor NF-κB by retrieval is required for long-term memory reconsolidation.Learning & Memory, 12(1), 23-29. doi:10.1101/lm.82705

Merlo, Emiliano et al. “Activation of the transcription factor NF-kappaB by retrieval is required for long-term memory reconsolidation” Learning & memory (Cold Spring Harbor, N.Y.) vol. 12,1 (2005): 23-9.

Molina, D. P., Ariwodola, O. J., Linville, C., Sonntag, W. E., Weiner, J. L., Brunso-Bechtold, J. K., & Adams, M. M. (2012). Growth hormone modulates hippocampal excitatory synaptic transmission and plasticity in old rats. Neurobiology of Aging, 33(9), 1938-1949. doi:10.1016/j.neurobiolaging.2011.09.014

Morselli, Lisa L, Arlet Nedeltcheva, Rachel Leproult, Karine Spiegel, Enio Martino, Jean-Jacques Legros, Roy E Weiss, Jean Mockel, Eve Van Cauter, and Georges Copinschi. "Impact of GH replacement therapy on sleep in adult patients with GH deficiency of pituitary origin". European Journal of Endocrinology 168.5 (2013): 763-770. < https://doi.org/10.1530/EJE-12-1037>. Web. 19 Mar. 2019.

N Dubick, Marc & H Ravin, Thomas & Michel, Yvonne & Morrisette, David. (2015). Use of localized human growth hormone and testosterone injections in addition to manual therapy and exercise for lower back pain: A case series with 12-month follow-up. Journal of pain research. 8. 295-302. 10.2147/JPR.S81078.

Niels Møller, Jens Otto Lunde Jørgensen; Effects of Growth Hormone on Glucose, Lipid, and Protein Metabolism in Human Subjects, Endocrine Reviews, Volume 30, Issue 2, 1 April 2009, Pages 152–177, https://doi.org/10.1210/er.2008-0027

Nyberg, F., Hallberg, M., Medicinska och farmaceutiska vetenskapsområdet, Institutionen för farmaceutisk biovetenskap, Uppsala universitet, & Farmaceutiska fakulteten. (2013). Growth hormone and cognitive function. Nature Reviews. Endocrinology, 9(6), 357-365. doi:10.1038/nrendo.2013.78

Ong LK, Chow WZ, TeBay C, Kluge M, Pietrogrande G, Zalewska K, Crock P, Åberg ND, Bivard A, Johnson SJ, et al. Growth Hormone Improves Cognitive Function After Experimental Stroke. Stroke. 2018 May;49(5):1257-1266. doi: 10.1161/STROKEAHA.117.020557. Epub 2018 Apr 10. PubMed PMID: 29636425.opiod

Peker, Y. , Svensson, J. , Hedner, J. , Grote, L. and Johannsson, G. (2006), Sleep apnoea and quality of life in growth hormone (GH)-deficient adults before and after 6 months of GH replacement therapy. Clinical Endocrinology, 65: 98-105. doi:10.1111/j.1365-2265.2006.02555.x

Peterfi, Zoltan et al. “Growth hormone-releasing hormone activates sleep regulatory neurons of the rat preoptic hypothalamus” American journal of physiology. Regulatory, integrative and comparative physiology vol. 298,1 (2009): R147-56.

Quik, E. H., Conemans, E. B., Valk, G. D., Kenemans, J. L., Koppeschaar, H. P. F., & van Dam, P. S. (2012). Cognitive performance in older males is associated with growth hormone secretion. Neurobiology of Aging, 33(3), 582-587. doi:10.1016/j.neurobiolaging.2010.03.022

Raschke, Michael, Michael Højby Rasmussen, Shunmugam Govender, David Segal, Mette Suntum, and Jens Sandahl Christiansen. "Effects of growth hormone in patients with tibial fracture: a randomised, double-blind, placebo-controlled clinical trial". European Journal of Endocrinology eur j endocrinol 156.3: 341-351. < https://doi.org/10.1530/EJE-06-0598>. Web. 20 Mar. 2019.

Renehan, Andrew G., PhD, FRCS, & Brennan, Bernadette M., MD, FRCPCH. (2008). Acromegaly, growth hormone and cancer risk. Best Practice & Research: Clinical Endocrinology & Metabolism, 22(4), 639-657. doi:10.1016/j.beem.2008.08.011

Rhodin, A et al. “Recombinant human growth hormone improves cognitive capacity in a pain patient exposed to chronic opioids” Acta anaesthesiologica Scandinavica vol. 58,6 (2014): 759-65.

Romijn JA. Pituitary diseases and sleep disorders. Current Opinion in Endocrinology, Diabetes, and Obesity. 2016 Aug;23(4):345-51. doi: 10.1097/MED.0000000000000265. Review. DOI: 10.1097/MED.0000000000000265

Sébastien Jeay, Gail E. Sonenshein, Marie-Catherine Postel-Vinay, Elena Baixeras; Growth Hormone Prevents Apoptosis through Activation of Nuclear Factor-κB in Interleukin-3-Dependent Ba/F3 Cell Line, Molecular Endocrinology, Volume 14, Issue 5, 1 May 2000, Pages 650–661, https://doi.org/10.1210/mend.14.5.0462

Smyczyńska J, Stawerska R, Lewiński A, Hilczer M. Incidence and predictors of persistent growth hormone deficiency (GHD) in patients with isolated, childhood-onset GHD. Endokrynologia Polska. 2014;65(5):334-41. doi: 10.5603/EP.2014.0046. DOI: 10.5603/EP.2014.0046

Spina, L. D. C., Soares, D. V., Brasil, R. R. L. O., da Silva, E. M. C., Lobo, P. M., Conceição, F. L., & Vaisman, M. (2004). Glucose metabolism and visceral fat in

GH deficient adults: 1 year of GH replacement. Growth Hormone & IGF Research, 14(1), 45-51. doi:10.1016/j.ghir.2003.08.002

Tauchmanova, L & Di Somma, Carolina & Rusciano, A & Lombardi, Giuliano & Colao, Annamaria. (2007). The role for growth hormone in linking arthritis, osteoporosis, and body composition. Journal of endocrinological investigation. 30. 35-41.

Turchi, Janita, and Martin Sarter. "Antisense Oligodeoxynucleotide-Induced Suppression of Basal Forebrain NMDA-NR1 Subunits Selectively Impairs Visual Attentional Performance in Rats: Basal Forebrain NMDA-R1 and Attention." European Journal of Neuroscience, vol. 14, no. 1, 2001, pp. 103-117.

W. Matthew Widdowson, James Gibney; The Effect of Growth Hormone Replacement on Exercise Capacity in Patients with GH Deficiency: A Metaanalysis, The Journal of Clinical Endocrinology & Metabolism, Volume 93, Issue 11, 1 November 2008, Pages 4413–4417, https://doi.org/10.1210/jc.2008-1239

Wei, Lianping, et al. "Recombinant Human Growth Hormone (rhGH) Treatment of MKN-45 Xenograft Mice Improves Nutrition Status and Strengthens Immune Function without Promoting Tumor Growth." PloS One, vol. 14, no. 1, 2019, pp. e0210613.

Yi C, Cao Y, Wang SR, Xu YZ, Huang H, Cui YX, Huang Y. Beneficial effect of recombinant human growth hormone on the intestinal mucosa barrier of septic rats. Brazilian Journal of Medical and Biological Research. 2007 Jan;40(1):41-8. http://dx.doi.org/10.1590/S0100-879X2007000100006

Zhou, M., Yang, W., Aziz, M., Ma, G., & Wang, P. (2017). Therapeutic effect of human ghrelin and growth hormone: Attenuation of immunosuppression in septic aged rats. BBA - Molecular Basis of Disease, 1863(10), 2584-2593. doi:10.1016/j.bbadis.2017.01.014