Quality of Life Assessment in Adults with Somatotropin (Growth Hormone) Deficiency: Response to Treatment with Symbiotropin® an Effervescent Glycoamino Analogue.

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Introduction

*Adults with growth hormone (**GH**) deficiency (**GHD**) often have a plethora of physical and psychological complaints, collectively referred to as low quality of life (**QoL**). The somatotroph cells of the anterior pituitary gland produce **GH**, commonly referred to as **Somatotropin** in the scientific literature. In recent years, substantial clinical trials have demonstrated that **GHD** is an intervening salient causative factor in **QoL**, and significantly improved **QoL** scores have been reported during **GH** replacement therapy [1,2,42].*

*The first controlled clinical trials of **GH** replacement in adult-onset GH deficiency (**AGHD**) were reported in 1989 [3,4]. Further analysis of more recent clinical data, have led to the identification of a characteristic cluster syndrome of **AGHD**:* decreased mood, reduced energy levels and well-being; and significant adverse alterations in body composition and substrate metabolism [5]*. In terms of other **QoL** parameters, adults with **Somatotropin** deficiency report lower* openness, less assertiveness, less energy, greater emotional liability, more difficulty with sexual relationships and a greater sense of social isolation [6, 7, 8]*. Evidence suggests that the severity of these psychological distresses correlate* positively*, with the duration of **AGHD** [8]. Potentially, the greatest immediate indication for **Somatotropin** therapy, is in patients who are assessed as having an impaired **QoL** [9,10]. Consistently, **QoL** studies have shown that adults with **GHD** are both* psychologically and physically less healthy*--than are their age-matched peers, and that **GH** therapy results in both substantial and sustained benefits [11, 13, 14, 15, 27]. The possibility that **Somatotropin** is involved in cognitive deficits has been recognized for several years [9, 38, 40, 41]. Findings from a recent 6-year follow-up of nearly 500 patients, found that impaired cognitive function is a risk factor for all-cause mortality in middle-aged adults, much as it is in elderly adults [43]. More recent epidemiological data suggests that adults with **GHD**,* have signs of reduced life expectancy *[12, 27].*

*Elevated serum levels of the pro-inflammatory biomarkers High Sensitive--C-Reactive Protein (**CRP**), Interleukin (**IL**) IL-1, IL- 6,*

*LDL-C, etc. have been reported in both men and women with **AGHD** [18, 19, 20]. The critical need for routine patient screening for **CRP** is vital, as this diagnostic tool relates to insidious on-going low-grade inflammatory processes: that relate to the risks of obesity, cancer pathogenesis, exacerbated cardiovascular risk factors and even skin aging, etc. [16, 17, 21, 22, 23, 24]. The role of **Somatotropin** in alleviating the potential adverse effects of these inflammatory biomarkers, will become of increasing clinical usefulness in future studies.*

*Bülow et al., recently reported that female patients with **AGHD** who were being administered controlled therapeutic doses of thyroid, estrogen and progesterone, but without **Somatotropin** replacement--had a more than **2-fold** increase in cardiovascular mortality, compared to the general population. These women, also demonstrated a d*ecreased sense of psychological well-being, a lower degree of physical exercise during their spare time, a higher waist/hip ratio, lower high density lipoprotein cholesterol and higher low density/high density lipoprotein ratio's [18]*. McGauley was the first to demonstrate in a double-blind, placebo-controlled study that **GH** therapy was associated with, an improvement in mood and energy levels in adults with **AGHD** [25]. Murray and colleagues recently used the disease specific **GHD** instrument **AGHDA** (adult growth hormone deficiency assessment) in assessing 65 patients with **AGHD**. Significant improvements were seen in the **AGHDA** scores and, most importantly--those with the highest baseline morbidity, demonstrated the* greatest improvement *in **QoL** [26].*

*In recent years, there has been a growing interest in the assessment of **QoL**, particularly in chronic disabling conditions [9,27, 28]. For example, in rheumatoid arthritis and other chronic disabling diseases, the use of measures of **QoL** to assess the efficacy of treatment modalities is now routine [46]. This increased emphasis on chronic illness and prevention, has required the development of new measures of patient outcome to supplement existing indicators [9]. Increased longevity per se, is no longer a sufficient justification for treatment.*

Pathophysiology of AGHD

Somatotropin at the age of 20–30 is released in circadian bursts, predominantly at night during the third and fourth stages of deep sleep. With aging, the amplitude and the frequency of these bursts are diminished in both men and women. The hypothalamus, is the "central control center," regulating the secretion of Somatotropin from the pituitary. Both the production and secretion of Somatotropin from anterior pituitary somatotrophs, are stimulated by hypothalamic GH-releasing hormone (GHRH) and by the endogenous GH secretagogue (GHS) Ghrelin [30, 31, 32]. Somatostatin (SRIH) is a hormone that inhibits the secretion, but not the synthesis of Somatotropin and more effectively, that stimulated by GHRH than that by Ghrelin. With aging there is a relative hyperfunctioning of the SRIH-ergic system [39]. Ghrelin was only recently discovered in 1999 by Kojima et al., [44] indicating that the true critical physiological importance of the GHS's, is now just being discovered [33, 34].

Somatotropin secretion declines abruptly, beginning in the age range of 25–30 years [3,11, 36], and declines at an average rate of 14% per decade.

Somatotropin (GH) Decline with Chronological Age

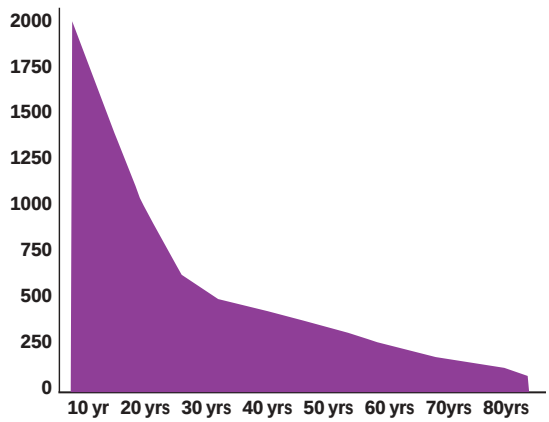

Figure 1. Daily release of Somatotropin is approximately 500 mcg at age 20, then declining to 200 mcg at age 40 and 25 mcg at age 80 [16].

Table 1. Summary of Beneficial Effects of Somatotropin Therapy in AGHD

A. Body Composition and Exercise Performance

- Increased muscle mass and strength
- Improved exercise capacity
- Improved pulmonary function
- Increased bone mineral density (BMD)

B. Metabolism

- Increased resting energy expenditure (basal metabolic rate)
- Decreased body fat
- Increased protein synthesis, which increases lean muscle mass
- Decreases LDL cholesterol
- Diminution of elevated pro-inflammatory biomarkers CRP and cytokines, e.g. IL-1, IL-6

C. Immunomodulation

- Improved B and T cell proliferation
- Enhanced Natural Killer Cell activity
- Enhanced Macrophage activity

D. Psychological Well-Being and Quality of Life (QoL)

- Improved mood and energy levels
- Improved perception of well-being and QoL
- Improved cognitive function, more openness and decreased social isolation
- Improved sexual function

Safety of Long-Term GH Replacement

A recent study evaluated the clinical safety data, of the long-term effects of GH therapy in hypopituitary adults. Their conclusions, based on clinical research evaluations over the last 10 years were that, "there is no compelling clinical evidence that there is an increase in malignancy or primary tumor propagation in adult patients, treated with long-term GH replacement therapy."[49]

Study Design

This was a prospective, open treatment design clinical trial to investigate the relationship between the administration of Symbiotropin®, an effervescent growth hormone secretagogue (GHS), also known as a glycoamino analogue, against two standardized clinical assessment measures of QoL. The analysis of statistically significant mean differences was performed using, paired student's t-test's. The subsequent statistical assumptions were met for all of the analyses: the data were normally distributed; homogeneity of variance, or constant variance among groups, was established; and the presence of outliers, or bad observations, were not found. There was no missing data. Effect Sizes (ES's) were reported as measures of standardized mean differences between the two groups of study. The ES calculated for this study was Cohen's d, used for unpaired t-tests. Values of d that represent small, medium and large ES's are 0.20, 0.50, and 0.80, respectively.

Patients

The subject population consisted of a sample of twenty-five

patients who participated in this study, of which sixteen were female (64%) and nine (36%) were male. The mean age of all the patients was 59 years, with a range from 41 to 78. All patients had baseline scores on the QoL~AGHDA , that were indicative of severely reduced QoL, due to Somatotropin deficiency. The subjects were not instructed with any new information about changing their nutritional habitus or exercise routines.

Measurements

THE GENERAL TERM QoL encompasses individual patient perceptions of mental and physical health, subjective feelings of energy and vitality, psychological reactions (depressions, anxiety, etc.), as well as cognitive function and memory capabilities [24]. There were two methods of QoL assessment evaluated in our clinical trial. The first instrument was the disease-specific, Assessment of Growth Hormone Deficiency in Adults Questionnaire (QoL~AGHDA) which was used to quantify the degree of patient QoL impairment at baseline, and then after three-months of therapy with Symbiotropin®. The QoL~AGHDA questionnaire has been translated and validated in several languages (Swedish, German, Italian and Spanish), and each language version has been shown to have good reliability, internal consistency and construct validity (Doward, 1995; McKenna & Doward, 1999) [7, 48] and has also proved to be a sensitive measure of improvement in QoL during long-term follow-up of Somatotropin treated adults (Drake, et al, 1998; Abs, et al. 1999) [37, 45].

The second method used in the analysis of QoL, was a modified version of the instrument, The General Growth Hormone Patient Self-Assessment Questionnaire (GGPSAQ (modified)) [29]. This instrument was used to assess the change in patients perceived improvement or no improvement in QoL, from baseline. The GGPSAQ (modified) consisted of 21 questions measured on a 1 (none) to 4 (excellent) Likert-Type scale of QoL. The reliability for the GGHPSAQ (modified) scores in this study, were in the high level, which meant that this testing instrument had very good internal consistency, and the questions contained within this clinical assessment instrument shared a suitable percentage of the variance.

Results

There were no patient adverse events, during the 3-month study period.

In analyzing the patient QoL~AGHDA scores from our study, there were statistically significant mean differences within the whole group, between the baseline scores and the three-month reassessment scores, where (P = .001). That is, within this group of 25 patients, regardless of gender or age, results for both sexes and both age groups were statistically significant in demonstrating an overall improvement in QoL. Interestingly, the baseline QoL~ AGHDA scores were higher in women compared to men, indicating women had a greater degree of QoL impairment in their baseline assessment. However, the women's total gain in mean score improvement, during this three-month analysis, was greater than men (i.e., male mean decrease = 5.00 and female mean decrease = 6.81). Thus, the degree of improvement in the women's overall QoL, was greater than men in our study.

In analyzing the patient variables using the GGHPSAQ (modified), improved well-being was statistically significant (P = .002). Improved well-being also demonstrated practical importance, which was indicated via its very large ES of 1.48. Increased energy was another variable that was statistically significant (P = .011). When looking at the mean differences by age, the variable increase in exercise endurance was statistically significant (P = .034), as was also, improved flexibility (P = .045). Of note were three additional variables, improved mental focus, increased strength and improved sleeping patterns, which were not statistically significant (P = .052; P = .076; P = .072; respectively), but had ES's of (.86; .77; .79; respectively) that were highly substantial, that will summon further clinical investigations.

IN CONCLUSION, during this prospective clinical trial, in as early as three months, the administration of the effervescent GHS, a glycoamino analogue, Symbiotropin®, resulted in a statistically significant improvement in overall QoL, in both men and women, irrespective of their chronological age or gender. The degree of improvement in overall QoL was greater in women during the administration of this GHS. This is an interesting finding. All of the women in this study at baseline, had QoL~AGHDA scores that were indicative of severely reduced QoL, due to Somatotropin deficiency. Additionally, women had a greater degree of impairment of QoL at baseline, but their degree of improvement in QoL improved more than men during Symbiotropin® administration. During this time trial, men and women received the same dose of Symbiotropin®. However, several recent clinical trials, have compared the dosing requirements of recombinant HGH (r-hGH) via subcutaneous injections for men and women based on differences in gender. These studies have demonstrated that female patients with adult-onset hypopituitarism, have a decreased overall sensitivity to GH and

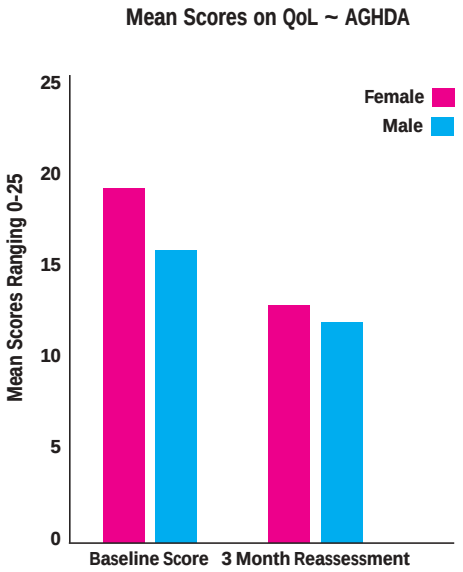

Figure 2: Improvement in male and female scores on the QoL~AGHDA at baseline, and after 3 months of Symbiotropin® therapy. Note: A decrease in total score, represents an improvement in overall in QoL. P=.001

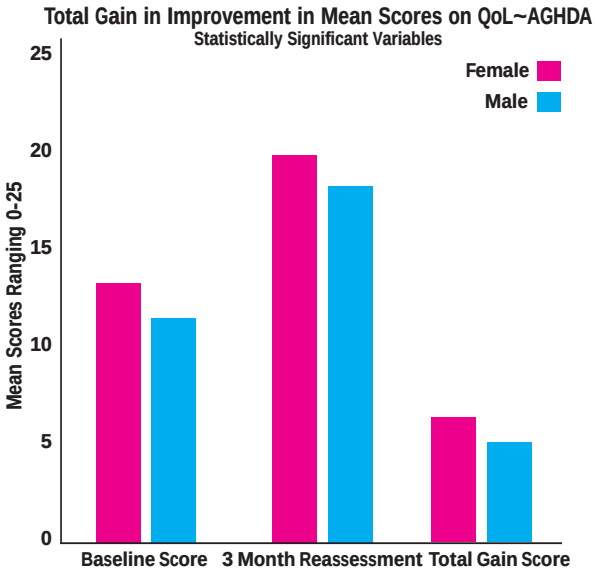

Figure 3: Total gain in improvement in male and female mean scores on the QoL~AGHDA at baseline, and after 3 months of Symbiotropin® therapy. Note: A decrease in mean score, represents an improvement in overall QoL. P=.001

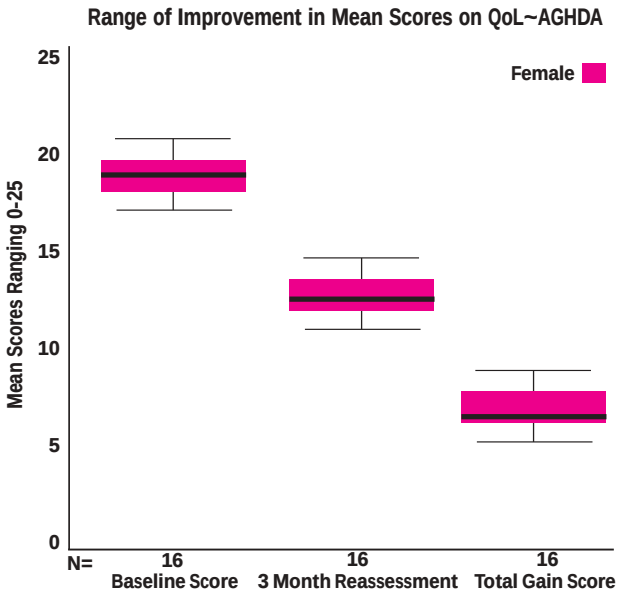

Figure 4: Range of improvement in female overall QoL, reflected by mean scores at baseline, and 3 months after Symbiotropin® therapy. P=.001

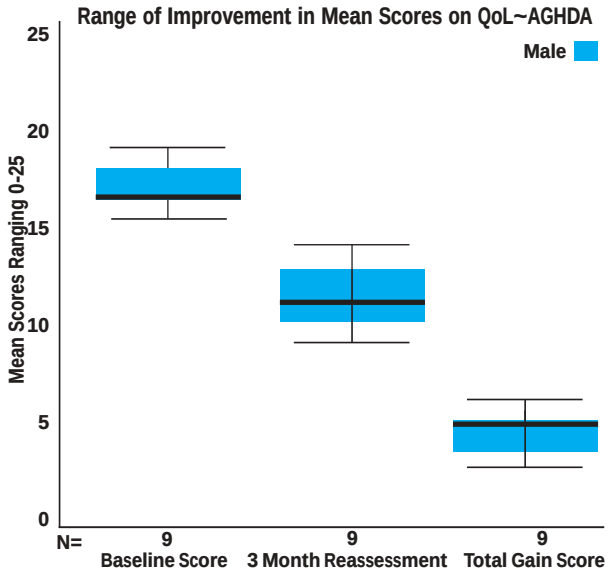

Figure 5: Range of improvement in male overall QoL, reflected by mean scores at baseline, and 3 months after Symbiotropin® therapy. P=.001

require higher doses of r-HGH (up to 2x more) to achieve similar clinical effects as males [21, 36, 47]. Distinct GHS receptor sites have been cloned in the hypothalamus, gastroenteropancreatic circulation and many other tissues. It is plausible from a review of the literature of the physiological functions of GHS's, that they intercede at divergent and unique levels of mechanisms of action and therapeutic intervention, in comparison to r-hGH [31, 32, 35, 39]. Thus, this may explain these interesting and profound clinical findings after Symbiotropin® administration in women, during our study.

Other demonstrated statistically significant changes in QoL

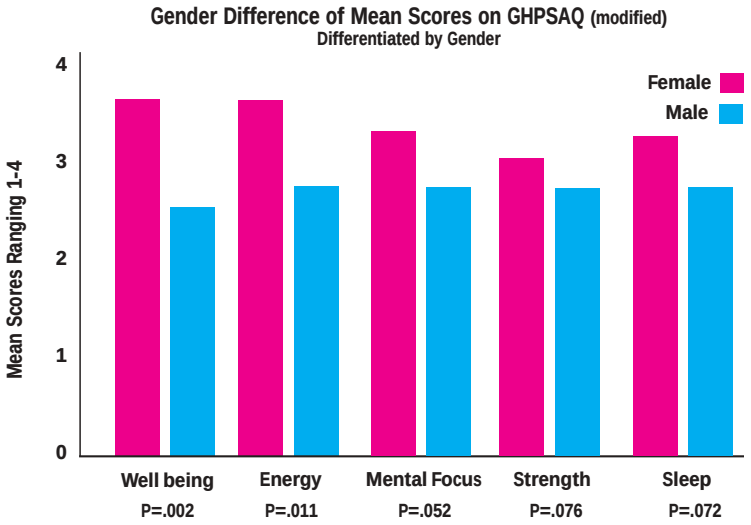

Figure 6: Statistically significant and practically significant variables in mean scores, related to improved well-being, increased energy, improved mental focus, increased strength and improved sleeping patterns, after 3 months of Symbiotropin® therapy.

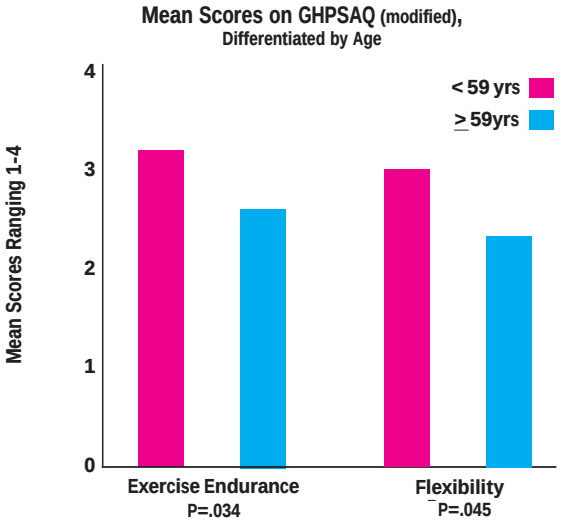

Figure 7: Statistically significant variables in mean scores, related to increased exercise endurance and improved flexibility, after 3 months of Symbiotropin® therapy.

were found regarding: improved well-being, increased energy, increase in exercise endurance and improved flexibility. Three additional variables, improved mental focus, increased strength and improved sleeping patterns, were not statistically significant (P = .052; P = .076; P = .072; respectively), but had substantial ES's of (.86; .77; .79; respectively). More importantly, these beneficial changes occurred, in the absence of any patient side-effects.

Impaired cognitive function is a risk factor for all-cause mortality in middle-aged adults, much as it is in elderly adults [43], and epidemiological data suggests that adults with GHD, have signs of reduced life expectancy [11,12,13,14,15]. McGauley demonstrated that those with the highest baseline morbidity based on QoL~AGHDA scores, demonstrated the greatest improvement in QoL following GH therapy [26].

This was an open treatment designed study. It could be argued that the improvement in QoL we found during this clinical trial, was related to a placebo effect and regression toward the mean. However, all previously known controlled placebo studies in AGHD patients have failed to demonstrate any statistically significant improvement in QoL, in the placebo group, in comparison to patients treated with GH therapy (e.g. McGauley, 1989, Berman et al., 1995)[8, 25]. Furthermore, the large and very substantial, ES's demonstrated by these two independent means of assessment, by both the GGHPSAQ (modified) and the QoL~AGHDA were: 1.48; 1.16; 0.94; 0.862 and 4.27; 3.82; 3.00; 2.43, respectively for these statistically significant variables. Values of ES's that represent small, medium and large ES's are 0.20, 0.50, and 0.80. Additionally, in this study's data collection, there were no outliers, deviant scores or missing data that might cause a regression to the mean. Regression to the mean on a 1 to 4 scale (GGHPSAQ (modified)) is very unlikely statistically. Also the GGHPSAQ (modified) was used only once in terms of assessment, thus it would be very difficult to regress to the mean, if there isn't a second measure to regress to. In regards to the QoL~AGHDA, each patient had a composite score, and in the final analysis every pair was matched with no missing data found. Thus, it is therefore unlikely that a placebo effect is responsible for the statistically significant, marked improvements in overall QoL, improved well-being, increased energy, increase in exercise endurance and improved flexibility that we observed in our study, following Symbiotropin® therapy.

Based on the results of this preliminary analysis of the GHS, Symbiotropin®--when taken together with adequate physical activity and healthy lifestyle interventions--might provide a personal blue-print in delaying the usual aging process, helping to prevent recurrent disability and assisting in contributing to maintain and improve--our now constantly shifting upwards aging population, into future well-integrated members of society and thus, enabling them to enjoy the very highest quality of life (QoL) thought possible. It is likely that hGH and its GHs's--glycoamino analogues, along with other synergistic complementary therapies will become of increasing clinical usefulness in future decades.

References

1. McKenna, SP et al. The QoL-AGHDA: an instrument for the assessment of quality of life in adults with growth hormone deficiency. *Qual. Life Res.* 8 (1999), pp. 373-383.
2. Holmes SJ, Shalet SM. 1995. Development of a questionnaire to assess the quality of life in adults with growth hormone deficiency. Endocrinol Metab 2:63-69.
3. Jorgensen JOL, Pedersen SA, Thuesen L, et al. 1989. Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet. 1:1221-1225.
4. Salomon F, Cuneo RD, Hesp R, Sönksen PH. 1989. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med. 321:1797-1803.
5. Binnerts A, Swart GR, et al. 1992. The effect of growth hormone administration in growth hormone deficient adults on bone, protein, carbohydrate and lipid homeostasis, as well as on body composition. Clin Endocrinol (Oxf). 37:79-87.
6. Holmes SJ, Shalet SM. 1995. Development of a questionnaire to assess the quality of life in adults with growth hormone deficiency. Endocrinol Metab 2:63-69.
7. McKenna SP, Doward LC. 1999. What is the impact of GH deficiency and GH replacement on quality of life in childhood-onset and adult-onset GH deficiency. In: Monson JP, ed. Challenges in growth hormone therapy. Oxford: Blackwell Science; 160-176.
8. Burman P, Broman JE, et al. Quality of life in adults with growth hormone (GH) deficiency: response to treatment with recombinant human GH in a placebo-controlled 21-month trial. J Clin Endocrinol Metab. 1995; 80:3585-90.
9. Bengtsson B-Å, et al. 1999. The effects of treatment and the individual responsiveness to growth hormone (GH) replacement therapy in 665 GH-deficient adults. KIMS Study Group and the KIMS International Board. J Clin Endocrinol Metab 84:3929-3935.
10. McKenna SP, Koppeschaar HP, et al. The impact of replacement GH on the quality of life of patients: Results of a clinical trial in the Netherlands. Endocrinology and Metabolism 1997; 4 (Suppl B): 167.
11. Rosen T, Bengtsson B-Å. 1990. Premature mortality due to cardiovascular disease in hypopituitarism. Lancet. 336:285-288.
12. Bates AS, et al. 1996. The effect of hyopituitarism on life expectancy. J Clin Endocrinol Metab. 81:1169-1172.
13. Shahi M, Beshyah SA, Hackett D, Sharp PS, Johnston DG, Foale RA. 1992. Myocardial dysfunction in treated adult hypopituitarism: a possible explanation for increased cardiovascular mortality. Br Heart J 67:92-96.
14. Markussis V, Beshyah SA, Fischer C, Sharp P, Nicolaides AN, Johnson DG. Detection of premature atherosclerosis by high resolution ultrasonography in symptom-free hypopituitary adults. Lancet. 1992, 340, 1188-92.
15. Capaldo B, Patti L, Oliverio U, Longobardi S, Pardo F, et al. Increased arterial intimi-media thickness in childhood onset growth hormone deficiency. *J. Clin. Endocrinol. Metab*. 1997, 82, 1378-81.
16. Monson JP, Abs R, Bengtsson B-A, et al. 2000. Growth hormone deficiency and replacement in elderly hypopituitary adults. Clin Endocrinol (Oxf). 53:281-286.
17. Weaver JU, et al.1995.The effect of low dose recombinant growth hormone replacement on regional fat distribution, insulin sensitivity, and cardiovascular risk factors in hypopituitary adults. J Clin Endocrinol Metab 80:153-159.
18. Bülow Birgitta, et al. Hypopituitary Females Have a High Incidence of Cardiovascular Morbidity and an Increased Prevalence of Cardiovascular Risk Factors. J of Clin Endocrinol & Metab. Vol. 85, No. 2 574-584.
19. Hak, A Elizabeth, et al. Markers of Inflammation and Cellular Adhesion Molecules in Relation to Insulin Resistance in Nondiabetic Elderly: The Rotterdam Study. J of Clin Endocrinol & Metab Vol. 86, No. 9 4398-4405.
20. Sesmilo G, Miller K, Hayde D, Klibanski A. Inflammatory Cardiovascular Risk Factors in Women with Hypopituitarism. J of Endocrinol & Metab. 86 (12) 5774-81.
21. Johannsson G, et al. The individual responsiveness to growth hormone (GH) treatment in GH-deficient adults is dependent on the level of GH-binding protein, body mass index, age, and gender. J Clin Endocrinol Metab 81:1575-1581.
22. Binnerts A, et al. 1992. The effect of growth hormone administration in growth hormone deficient adults on bone, protein, carbohydrate and lipid homeostasis, as well as on body composition. Clin Endocrinol (Oxf). 37:79-87.
23. Bengtsson B-Å, Eden S, Lonn L, et al. 1993. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. J Clin Endocrinol Metab. 76:309-317.
24. Mårdh G, et al. Growth hormone replacement therapy in adult hypopituitary patients with growth hormone deficiency: Combined data from 12 European placebo-controlled clinical trials. *Endocrinol. Metab.* 1994, (Suppl A), 43-9.
25. McGauley, GA. 1989. Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. Acta Paediatr Scand Suppl. 356:70-72; discussion 73-74.
26. Murray, RD, et al. Dose titration and patient selection increases the efficacy of GH replacement in severely GH deficient adults. *Clin. Endocrinol.* 50 (1999), pp. 749-757.
27. Jonsson B, Nilsson B. 2000.The impact of pituitary adenoma on morbidity. Increased sick leave and disability retirement in a cross-sectional analysis of Swedish national data. Pharmacoeconomics 18:73-81.
28. Davies JS, Obuobie D, Smith J. 2000. A therapeutic trial of growth hormone in hypopituitary adults and its influence upon continued prescription by general practitioners. Clin Endocrinol (Oxf). 52:395-303.

29. Chein E, Vogt D, Terry C. Clinical experiences using a low-dose, high-frequency human growth hormone treatment regimen. J of Adv in Med. Volume 12, Number 3, Fall,1999.

30. Rosicka M, et al. Ghrelin - a new endogenous growth hormone secretagogue. Physiol Res 2002;51(5):435-41.

31. Wren AM, et al. The hypothalamic mechanisms of the hypophysiotropic action of ghrelin. Neuroendocrinology 2002 Nov;76(5):316-24.

32. Muller EE, et al. GH-related and extra-endocrine actions of GH secretagogues in aging. Neurobiol Aging 2002 Sep-Oct;23(5):907-19.

33. Shuto Y, Shibasaki T, et al. Hypothalamic growth hormone secretagogue receptor regulates growth hormone secretion, feeding, and adiposity. J Clin Invest 2002 Jun;109.

34. Cunha SR, Mayo KE. Ghrelin and growth hormone (GH) secretagogues potentiate GH-releasing hormone (GHRH)-induced cyclic adenosine 3',5'-monophosphate production in cells expressing transfected GHRH and GH secretagogue receptors. Endocrinology 2002 Dec;143(12):4570-82.

35. Bluet-Pajot MT, et al. Growth hormone secretagogues and hypothalamic networks. Endocrine 2001 Feb;14(1):1-8.

36. Span JP, et al. 2000. Gender difference in insulin-like growth factor in response to growth hormone (GH) treatment in GH-deficient adults: role of sex hormone replacement. J Clin Endocrinol Metab 85: 1121-25.

37. Drake WM, et al. Optimizing growth hormone replacement therapy by dose titration in hypopituitary adults. J Clin Endocrinol Metab. 1998 Nov;83(11):3913-9.

38. Stabler, B et al. Reactivity to stress and psychological adjustment in adults with pituitary insufficiency. Clin. Endocrinol. 6 (1992), pp. 467-473.

39. Root AW, Root MJ. Clinical pharmacology of human growth hormone and its secretagogues. Curr Drug Targets Immune Endocr Metabol Disord 2002 Apr;2(1):27-52.

40. Johansson JO, Larson G, et al.1995. Treatment of growth hormone-deficient adults with recombinant human growth hormone increases the concentration of growth hormone in the cerebrospinal fluid and affects neurotransmitters. Neuroendocrinology 61:57-66.

41. Burman, P et al. Growth hormone affects brain neurotransmitters and thyroxine. *Clin. Endocrinol*. 44 (1996), pp. 319-324.

42. Chrisolidiou A, Kousta E, Beshyah SA, Robinson S, Johnston DG. 1998. How much, and by what mechanism, does GH replacement improve the quality of life in GH-deficient adults? Clin Endocrinol Metab. 12:261-279.

43. Pavlik V, et al. Cognitive Function in Middle Age Linked to Mortality Risk. Am J Epidemiol 2003;157:327-334.

44. Kojima M, et al. 1999. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999. Dec 9;402(6762):656-60.

45. Abs R, Bengtsson B-Å, et al. 1999. GH replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. Clin Endocrinol (Oxf) 50:703-713.

46. Falcao DM, Ciconelli RM, Ferraz MB. Translation and cultural adaptation of quality of life questionnaires: an evaluation of methodology. J Rheumatol 2003 Feb;30(2):379-85.

47. Johansson A, et al. Gender Differences in the Effects of Long Term Growth Hormone (GH) Treatment on Bone in Adults with GH Deficiency. J of Clinical Endocrinology & Metabolism Vol. 84, No. 6 2002-2007.

48. Doward LC. 1995. The development of the AGHDA: a measure to assess quality of life in childhood-onset and adult-onset GH deficiency. Qual Life Res 4:420-421.

49. Verhelst Johan, Abs, Roger. Long-Term Growth Hormone Replacement in Hypopituitary Adults.Drugs 2002. 62 (16): 2399-2412.