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PSYCHOLOGICAL EFFECTS OF WITHDRAWAL OF GROWTH HORMONE THERAPY FROM ADULTS WITH GROWTH HORMONE DEFICIENCY

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Abstract

Objective: Growth hormone (GH) is known to be required for physical well-being. Whilst it is also widely believed to be important for quality of life (QoL) and psychological health, there is less supportive evidence. The objective of this study was to investigate the psychological effects of discontinuation of GH replacement from adults with severe GH deficiency (GHD).

Design: A double-blind, placebo-controlled trial in which GH replacement therapy was discontinued for 3 months from 12 of 21 GH-deficient adults, where 9 continued with GH replacement.

Patients: GH-treated adults (10 men, 11 women), all with severe GHD (peak GH < 7.7 mU/L on provocative testing), mean age 44.9 years (range 25–68 years).

Measurements: Semi-structured interviews were given at baseline and end-point plus questionnaires that included a new hormone-deficiency specific, individualised, QoL questionnaire (HDQoL), the General Well-being Index (GWBI), the Well-being Questionnaire (W-BQ12), Short-Form 36 health status questionnaire (SF-36), the Nottingham Health Profile (NHP) and the General Health Questionnaire (GHQ).

Results: Three months after baseline the serum total IGF-I of placebo-treated patients fell from normal, age-related levels (mean 26.6 ± 13.2 nmol/ L) to levels indicative of severe GHD (11.6 ± 6.6 nmol/ L) (P <0.001). Psychological symptoms of GH withdrawal, reported in interviews at end-point by placebo-treated patients, included decreased energy, and increased tiredness, pain, irritability and depression. Patients who believed they knew which treatment they had received, correctly identified the treatment (GH or placebo) at end-point (χ^2 = 11.25, P <0.01). Significant between-treatment-group differences in change scores were found for SF-36 General Health (P <0.05), W-BQ12 Energy (P <0.01) and HDQoL *do physically* (P <0.05), indicating reduced general health, reduced energy and greater perceived impact of hormone deficiency on physical capabilities in the placebo-treated group at end-point relative to GH-treated patients.

Conclusion: Withdrawal of GH-treatment from adults with severe GHD has detrimental psychological effects.

Introduction

The physiological effects of GHD in adults and the beneficial effects of GH replacement are well documented (Carroll *et al.,* 1998). Psychological aspects of adult GHD are also important (Powrie *et al.,* 1995; Bengtsson *et al.,* 2000), but consistently demonstrating psychological benefits of GH treatment in placebo-controlled studies has proved elusive, perhaps because the measures have been insufficiently sensitive. Psychological effects (as measured by the frequently-used Nottingham Health Profile (NHP) (Hunt & McKenna, 1989) and/or the Psychological General Well-being Index (PGWB) (Dupuy, 1984), in placebo-controlled trials of 6 months' GH treatment include increased energy (McGauley *et al.,* 1990; Mardh *et al.,* 1994; Carroll *et al.,* 1997; Wallymahmed *et al.,* 1997); better emotional functioning (Carroll *et al.,* 1997); increased physical mobility and social functioning (Attanasio *et al.,* 1997; Carroll *et al.,* 1997); reduced depression (McGauley *et al.,* 1990); increased general health, positive well-being and vitality (Carroll *et al.,* 1997). Other studies have not found significant effects using the NHP (Whitehead *et al.,* 1992) or PGWB (Whitehead *et al.,* 1992; Burman *et al.,* 1995; Baum *et al.,* 1998). Spouses or partners have noted significant positive changes in patients 21 months after starting GH treatment (Burman *et al.,* 1995).

Many adults have been receiving GH for many years (Gibney *et al.,* 1999). Long-term treatment is expensive and the treatment regimen of daily injections inconvenient for patients. It is important to determine whether discontinuation of long-term treatment has deleterious effects. The few studies investigating the effects of discontinuation of GH replacement have shown that GH withdrawal has detrimental effects on some physiological variables. Body fat increases and lean mass decreases (Sönksen *et al.,* 1991; Biller *et al.,* 2000), abdominal obesity and other cardiovascular risk factors increase in young people (aged 16 to 21 years) (Johannsson *et al.,* 1999), although bone mineral density does not, however, return to pre-GH-treatment levels (Biller *et al.,* 2000). Deterioration in psychological well-being was noted in some small studies of discontinuation, but was either not significant or reports were anecdotal. In one study, one of the 13 patients, whose GH therapy was discontinued, withdrew prematurely from the study owing to increased depression (Biller *et al.,* 2000). All 4 patients in another study (Bengtsson *et al.,* 1993) tended to have worse scores on the Comprehensive Psychopathological Rating Scale (Asberg *et al.,* 1978) 26 weeks after GH-withdrawal, 2 patients had worse scores on the Symptom Check-List-90 (Derogatis *et al.,* 1983), with one patient evaluated for mild depression. In another study, 3/10 patients 'felt totally unable to continue' with GH withdrawal after 3 months and were restarted on GH treatment, and after 6 months, 6 of the remaining 7 patients asked to restart treatment (Sönksen *et al.,* 1991). A prospective investigation of the effects of discontinuation in a sample of 16 to 21 year olds with childhood onset of GHD (Wiren *et al.,* 2001), noted increased anxiety in those patients later determined to be GH-deficient in adulthood (N = 21) compared to those who were GH-sufficient as adults (N = 19), decreased sociability and changes in responsiveness and memory. Furthermore 3 patients in the GH-deficient group withdrew from the study owing to severe psychological symptoms and were restarted on GH therapy.

The psychological objectives of the present randomised, placebo-controlled study were to investigate the effect of 3 months' GH withdrawal on quality of life (QoL), and related patient reported outcomes of perceived health and psychological well-being in adults with GHD. It was hypothesised that after 3 months' GH withdrawal placebo-

treated patients would exhibit, relative to baseline, increased negative well-being (depression and anxiety); but decreased energy/ vitality, perceived health, physical mobility/ functioning, social functioning, and positive well-being; and that patients' present QoL would deteriorate; but that the GH-treated group would show little change.

Patients and Methods

Design

Patients were allocated to placebo or continued treatment with GH in a randomised, double-blind, placebo-controlled, parallel-groups study, in which patients self-administered either GH (0.125 to 0.25 IU/ kg body weight/ week) or placebo for a period of 3 months. Lilly Industries Ltd supplied the vials of GH (Humatrope) which were indistinguishable from placebo. IGF-I was measured at baseline, 1 month later and at end-point, by double-antibody radioimmunoassay after acid/ ethanol extraction, using a commercially available reagent pack (Amersham, Arlington Hts., Ill., within-assay coefficient of variation < 5%).

Patients

Inclusion criteria: All participating patients had received GH-replacement therapy for at least six months immediately prior to the study; were aged between 22 to 70 years; were severely GH deficient as determined by an Insulin Tolerance or Pituitary Function Test in which a dose of insulin reduced the blood glucose to $\leq$2.0 mmol/ L with peak GH concentration of 7.7 mU/L; had received appropriate adrenal, thyroid and gonadal hormone replacement therapy, as required by their hormonal condition, for at least 12 months prior to the study; were taking adequate contraception (women of childbearing age and potential). Exclusion criteria: these included diabetes mellitus and active malignancy and are fully described in McMillan et al., 2003.

Of the 144 GH-treated adults with GHD at the study centre only 66 fulfilled the stringent inclusion criteria and were approached. However, 62% declined to participate, the majority because they were satisfied with their current treatment – not wishing to risk the 50:50 chance of withdrawal. Twenty-two patients were finally recruited, but one patient withdrew from psychological aspects of the study just prior to baseline. Another patient, (Placebo group), withdrew suddenly and prematurely, 2 weeks before end-point, owing to adverse symptoms, but she was interviewed and completed some questionnaires. The study sample was representative of the patient pool in terms of age and sex.

Sex ratio, age, and duration of previous GH treatment were very similar in the two treatment groups, (Table 1), and the proportion of childhood onset (COGHD) and adult onset (AOGHD) patients was not significantly different. At baseline, the Placebo group had significantly higher Body Mass Index (BMI) (31.3 kg/ m^2) compared with the GH-treatment group (24.7) [$t(14.35) = 2.57$, $P < 0.05$].

All patients were attending the Endocrine Clinic of St Thomas' Hospital, London and gave informed consent to their participation. The Guy's and St Thomas' Hospital Trust Ethics Committee approved the study.

(Table 1 here)

Measures

Questionnaires, semi-structured interviews were given at baseline and end-point, 3 months later.

(1) The questionnaires

A battery of several questionnaires measuring QoL and aspects of health status and psychological well-being were administered. Two measures of health status: the NHP and Short-form 36 (SF-36) (Ware & Sherbourne, 1992); 2 measures of psychological well-being: the General Well-being Index, (GWBI) (Hunt & McKenna, 1992) – British version of the PGWB, and the 12-item Well-being Questionnaire (W-BQ12) (Bradley, 1994; Bradley, 2000); a measure of condition-specific QoL: the Hormone Deficiency-Dependent Quality of Life questionnaire (HDQoL) (Bradley, 1999; McMillan & Bradley, 2000; McMillan, 2001). The reliability and validity in adult GHD of these measures have been reported previously, (McMillan & Bradley, 2000) and (McMillan, 2001) (PhD thesis). Two other measures were used: the General Health Questionnaire (GHQ-30) (Goldberg & Williams, 1988) and an English version of a Swedish questionnaire (Burman *et al.,* 1995) for completion by spouses or partners, to measure their view of changes in patients during the study.

Description and scoring of measures

SF-36: Eight subscales to measure Bodily Pain, General Health, Mental Health, Physical Functioning, Role-Emotional, Role-Physical, Social Functioning and Vitality. Score range 0 to 100 (poor to good health status).

NHP: Six subscales to measure Emotional Reactions, Energy, Pain, Physical Mobility, Sleep and Social Isolation. Score range 0 to 100 (good to poor health status).

W-BQ12: Three subscales to measure Negative Well-being, Positive Well-being and Energy. Score range 0 to 12 (higher scores indicating increased mood of the subscale label) and a General Well-being total (range 0 to 36 with higher score indicating better well-being).

GWBI: A Total score, range 0 to 100, (higher score indicating reduced well-being).

HDQoL: A recently developed individualised questionnaire to measure individuals' perceptions of the impact of their hormonal condition and its treatment on their QoL in 13 domains of life. The domains include family life, sex life, physical appearance, physical capabilities (*do physically*), motivation and confidence. For example, in the domain *do physically*, patients are asked about the impact of hormone deficiency on the things they can physically do. A "not applicable" option is provided for domains that may not be applicable to any individual. Otherwise, respondents rate the impact of the hormonal condition on each domain and the importance of that domain. These two scores are multiplied to provide a weighted impact score ranging from -9 to +9 (maximum negative to maximum positive impact of hormone deficiency on that domain). Weighted domain scores are summed and divided by the number of applicable domains to give the HDQoL Average Weighted Impact score (HDQoL AWI), (range from -9 to +9), the maximum negative to maximum positive weighted impact of hormone deficiency on overall QoL. Domains can be analysed separately.

Spouse/ partner Questionnaire (SPQ): The 12-item questionnaire was designed for spouses or partners to assess any changes in mood and behaviour of adults with GHD. The original Swedish version was translated into English using a native English speaker fluent in Swedish, and this English translation was compared with an English version produced by the author (Dr Burman). A native Swedish expert was also consulted, and 4 items (concerning self-confidence, memory, concentration, and stress tolerance) were added to the English translation by native English language

speakers experienced in questionnaire design. The patient may nominate a spouse, partner, relative or friend to complete the questionnaire, and that person chooses between a *negative change* (scoring –1) in the patient over the study period, a *positive change* and *no change* (both scoring 1). Domains are analysed separately. The SPQ was not validated psychometrically before use.
GHQ-30: The 30-item self-completion measure detects non-psychotic psychiatric disturbance and/or affective disorders, with items on depression, anxiety and social function. The total score ranges from 0 to 90, (low to high psychological distress).

(2) Interviews
Semi-structured interviews were held at baseline and end-point. The number of serious negative life events and difficulties occurring in the 12 months prior to end-point was assessed in the end-point interviews, using a short checklist [*Life events and difficulties screening checklist* (unpublished, available from Dr Bernice Andrews, at Psychology Department, Royal Holloway, University of London, Egham, Surrey, TW20 0EX)] modified from a screening checklist for stressful life events and chronic difficulties (Costello & Devins, 1998). Negative life events and difficulties that occurred not only during the 3-month study period, but also in the months before the study, might precipitate depression during the study.

Statistical analyses

Between-treatment-group differences in questionnaire change scores over the withdrawal period were tested using *t*-tests or Mann-Whitney tests. Several questionnaires have multiple end-points (e.g. the SF-36, with 8 subscales). In order to minimise the number of false positive conclusions that may be derived from the many tests to be carried out within such questionnaires but, at the same time, minimising what might be considered overly severe adjustments for multiplicity of end-points entailed by the Bonferroni correction for familywise error, adjustments were carried out in the following way. Previous clinical experience strongly suggested that certain variables were most likely to be affected by GH withdrawal, but for other variables previous experience did not allow specific directional hypotheses to be formulated. The variables within any questionnaire that had subscales or multiple end-points were therefore divided into 2 'families': a confirmatory family (of variables within the questionnaire for which predictions were made), and an exploratory family (of questionnaire variables for which no predictions were made). The Bonferroni correction for familywise error was then based on the number of variables in the family to which that variable belonged. That is, alpha was set initially to 0.05/*n* where *n* was the number of variables within the family. Thus, in questionnaires where there were several variables, the numbers of exploratory variables did not prevent the confirmatory variables from reaching significance and vice-versa. In addition to these procedures, the Holm's sequential Bonferroni procedure (Holm, 1979) was employed within each family, whereby the family size reduces with each significant result. One-sided tests were performed in the confirmatory family and two-sided tests in the exploratory family. (See Table 2). Frequencies of positive and negative change in the treatment groups found by spouse/ partners (SPQ) were compared using Chi-Square tests.

(Table 2 here)

Results

Biochemical changes

Three months after baseline the serum total IGF-I of placebo-treated patients fell from normal, age-related levels (mean 26.62 ± 13.24 nmol/ L) to levels indicative of severe GHD (11.6 ± 6.65 nmol/ L) (P <0.001). Only a small, non-significant decrease was noted in GH-treated patients. One patient in the GH-treatment group reported several adverse symptoms. A large drop (-20.2 nmol/L or 39.3%) in his IGF-I levels were noted over the study, well outside the mean change of -1.74 ± 10.68 for the GH-treatment group and more than the mean change of -15.02 ± 12.38 in IGF-I levels for the Placebo group. However, his IGF-I level at end-point (31.2) was in the normal range. After study codes had eventually been broken, the patient was asked if there were any reasons for this result. He suggested that the injection pen may have malfunctioned. It was also possible that he did not fully adhere to the injection regimen as he had a history of non-adherence. Analyses were therefore undertaken excluding this anomalous patient's data. The mean drop in IGF-I levels within the Placebo group for men (20.4 ± 13.8) was over twice that of women (9.63 ± 8.81) but not significantly greater on a *t*-test (P = 0.138).

Interviews

There were interesting sex differences in reporting of symptoms of GH-withdrawal at end-point with placebo-treated women tending to describe more symptoms of withdrawal and greater severity of symptoms than men (Table 3). Placebo-treated women: all reported loss of energy/ stamina as being the prime symptom during the withdrawal; some showed changes in sleep patterns with overwhelming feelings of daytime drowsiness. Five reported unprovoked crying episodes and 3 reported depressed mood. There was increased irritability and intolerance of others. Physical symptoms noticed were: changes in hair condition, and in growth of hair and nails, increased skin dryness, increased bruising, increased joint pain and muscle aches particularly associated with exercise. Placebo-treated men: The 3 youngest men noticed reduced energy levels after GH withdrawal. There were reports of weight gain, muscle aches and joint pain. The three oldest men (aged 53 to 66 years) reported very few effects of withdrawal: two reported increased weight, and one no symptoms at all. Three placebo-treated patients reported negative life events/ difficulties. GH-treated patients: Five patients reported no changes in QoL, health or well-being over the study, but two women reported some changes in such areas as depression and tiredness owing to family problems and another woman had noticed some minor symptoms for which she had no explanation. The GH-treated male whose IGF-I levels fell by 39% over the study, and who may not have fully adhered to the injection regimen, experienced some typical symptoms of GHD. He reported depression; reduced energy, fitness and immune function; increased drowsiness, irritability and abdominal adiposity; changes in sleep pattern and skin.

Patients were asked at end-point whether they thought they had been receiving GH or placebo over the withdrawal period. Whilst all 6 placebo-treated women suspected that they had been receiving placebo, only 3 of the 6 men suspected, the others were not sure. Five of 9 GH-treated patients believed they had received their usual GH during the study, 1 believed the injections were placebo, and 3 were not sure. A Fisher's exact test, performed on those volunteering an opinion on their treatment-group allocation, found a significant difference between expected and actual frequencies in cells (χ^2 = 11.25, P <0.01). Thus, when patients believed they knew which treatment they had been receiving, they correctly identified the treatment group

to which they had been assigned. Whilst the drop in IGF-I values for placebo-treated men was over twice that for women, women reported more symptoms than men and these symptoms tended to be more extreme. All 6 women had strong suspicions that they had received placebo, compared to only half the men. This poses the question whether women might be more sensitive psychologically than men to smaller changes in IGF-I levels resulting from GH withdrawal.

(Table 3 here)

Questionnaire data

Analyses were conducted excluding the above-mentioned anomalous case, the male patient in the GH-treatment group whose drop in IGF-I levels was so extreme and who may not have fully adhered to the injection regimen. The placebo-treated female patient who withdrew from the study 2 weeks before end-point, owing to adverse symptoms, only completed the W-BQ12 and GHQ questionnaires at this stage, and these data were included in the questionnaire analysis. The only significant between-treatment-group difference in baseline scores, once Bonferroni corrections had been applied, was for the HDQoL domain *holiday* ($P = 0.001$). Significant 1-tailed between-group differences in change scores were found for SF-36 General Health [$t(17) = 2.76$, $P = 0.007$ (required P after Bonferroni correction: 0.01)], W-BQ12 Energy [$t(18) = 3.25$, $P = 0.002$ (required P: 0.017)], and HDQoL domain *do physically* [$t(16) = 2.47$, $P = 0.013$ (required P: 0.017)] where patients are asked about the impact of hormone deficiency on the things they can do physically. SF-36 Mental Health was close to required 1-tailed significance of 0.013 [$t(17) = 2.41$, $P = 0.014$]. (See Table 4). Thus, on GH discontinuation Placebo-group patients showed significantly greater change and in the direction of decreased general health (SF-36), decreased energy (W-BQ12) and greater perceived impact of hormone deficiency on physical capabilities (HDQoL) than GH-treated patients (whose scores tended to improve over the study). Analysis of the single SF-36 health transition item showed that, by end-point, 4 Placebo-treated patients considered their health worse than one year before, but no GH-treated patients, (not significant on a Chi-Square test, $P = 0.103$). There were no significant findings for the NHP and GWBI questionnaires.

There were no significant differences between the treatment groups in change in GHQ-30 Total (Table 4). The GHQ-30 score of the placebo-treated female who withdrew from the study prematurely, increased from 28.0 at baseline to 69.6 two weeks before end-point, indicative of significant psychological distress. Two patients preferred not to nominate anyone to complete the Spouse/ partner Questionnaire. Excluding the data of the anomalous case in the GH-treatment group, negative change was reported by spouse/ partners of patients in both treatment groups and there were no significant differences in reports of negative change.

Although interviews showed sex differences in reporting of symptoms at end-point, this was not reflected in significant sex differences in change in questionnaire scores. There were no significant between-group differences in numbers of life events and difficulties on a Mann-Whitney test ($P = 0.62$) that might account for between-group differences in psychological variables.

(Table 4 here)

Discussion

This randomised double-blind, placebo-controlled study has demonstrated for the first time that when GH replacement is discontinued for 3 months from adults with severe GHD there are detrimental psychological effects. In particular these patients experienced significantly decreased general health (SF-36), significantly decreased energy (W-BQ12) and significantly greater perceived impact of hormone deficiency on physical capabilities (HDQoL) in comparison with patients whose GH therapy continued throughout the study. Trends (albeit non-significant) were in the expected direction of worsening QoL, well-being, and health status for the great majority of variables in patients whose GH was discontinued. Women tended to report more symptoms of withdrawal and greater severity of symptoms than men in interviews, though there were only non-significant trends in this direction in questionnaire data. In general the findings support those of other studies that reported increased depression following GH discontinuation (Bengtsson *et al.,* 1993; Biller *et al.,* 2000). The scores of GH-treated patients tended to improve over the study, but not significantly so. All questionnaires except the GHQ-30 and SPQ had the advantage of having been previously validated psychometrically for use with adults with GHD (McMillan & Bradley, 2000). This study confirmed the sensitivity to change of the SF-36 in adult GHD found in a recent study (Bernabeu *et al*., 2002). Although the HDQoL, and W-BQ12 had not previously been used in trials of GH replacement, this study showed them to be sensitive to change, but the frequently used NHP and the British version of the PGWB (the GWBI) were not sufficiently sensitive.

Interesting and rich qualitative data emerged from the interviews. The key psychological symptoms of GH discontinuation reported by placebo-treated patients were reduced energy, increased daytime drowsiness, crying episodes, depression and irritability. Reported physical symptoms included increased pain in joints and muscle aches, weight gain and changes to skin, hair and nails. The interview data were highly compatible with results obtained from questionnaire analysis, both significant and trends, and particularly with respect to energy where 9/12 patients reported reduced energy by end-point, giving rise to a significant result for W-BQ12 Energy. Reduced energy and reported physical symptoms are likely to explain the significant effects of GH discontinuation on perceived general health (SF-36) and physical capabilities (HDQoL). Interview reports of increased depression, crying episodes and increased irritability support the trend towards reduced mental health (SF-36) that approached significance.

It is interesting that 75% of Placebo-group patients (and *all* the women in that group) strongly and correctly suspected that they were in the Placebo group. This was prompted by the return of symptoms they had experienced before receiving GH treatment in the first place, and in some cases more extreme or new symptoms. Others have noted, in double-blind, placebo-controlled studies of GH treatment provision to adults with GHD, that suspicions of patients as to treatment group were correct (Degerblad *et al.,* 1990), or that clinicians' suspicions proved correct when a study's randomisation codes were broken (Sönksen *et al.,* 1991). Clinicians may see large changes in IGF-I levels, body composition or metabolic factors over the course of a study - changes that can only be explained by the effects of GH treatment or its withdrawal. Neither patients nor clinicians are likely to be all truly 'blind' in these studies of GH treatment.

The SPQ yielded no significant differences in reports of negative change over the withdrawal period by spouse/ partners. It is possible that the 3-month period was too short for changes to become very noticeable to spouse/ partners, even if the patients

themselves had noted changes. In a previous study (Burman *et al.,* 1995) significant positive change was reported by spouse/ partners 21 months after introduction of GH treatment, and with a larger sample than the present study. The SPQ (now adapted for use in the UK) could be useful in larger studies (but will require psychometric validation), and it may be more sensitive to change when patients are first given GH therapy, when predominantly positive changes might be expected. One general problem with such a questionnaire is that many patients have neither spouse nor partner, particularly if they have COGHD (Rikken *et al.,* 1995). Friends, though willing to complete the questionnaire, may not be in a good position to notice subtle changes in a patient's mood or various aspects of life.

There were recruitment difficulties for this study, as the majority of patients declined to participate because they did not want to risk withdrawal from GH-treatment. This study has shown that they were right in anticipating detrimental effects of discontinuation, even for a short period of 3 months. However, it should be noted that some patients (the older men) tolerated withdrawal from GH well, with no perceived symptoms other than weight gain (for 2 men) over the 3-month period. Unfortunately the small pool of patients willing and suitable for inclusion resulted in a small sample of 21 patients, albeit representative of a much larger pool of patients at this single centre. The possible non-adherence to the study protocol of one patient in the GH-treatment group also reduced the data available for analysis. Furthermore, one patient in the placebo group withdrew from the study just prior to end-point owing to adverse symptoms, but the interview conducted at this point showed her to be experiencing considerable psychological distress, confirmed by a high GHQ-30 score.

Note that the method of analysis reported here and the results for the SF-36 differ slightly from those already published in this journal (McMillan et al., 2003) owing to the need to accommodate the opinions of different reviewers on the controversial issue of the best method of correcting for multiplicity of end-points, without applying too severe criteria which could result in Type II errors.

Conclusion

Three months' withdrawal of GH treatment from GH-treated adults with severe GHD had detrimental psychological effects, particularly in terms of energy, general health and physical capabilities.

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Table 1: Characteristics of study participants

	Placebo-treated (N = 12)	**GH-treated (N = 9)**	***P***
Men	6	4	
Women	6	5	
Mean age at baseline (years) [range]	45.8 [25 – 68]	43.8 [25 - 66]	
Mean duration of GH treatment (months) [range]	61 [12 - 132]	60 [18 - 132]	
COGHD : AOGHD ratio	2 : 10	4 : 5	
BMI at baseline (kg/ m^2)	31.3 ± 8.3	24.7 ± 2.9	< 0.05
Isolated GHD	0	2	
Gonadal hormone deficiency	8	6	
Thyroid hormone deficiency	9	5	
Corticosteroid deficiency	10	5	
Antidiuretic hormone deficiency	1	1	
Acromegaly	0	1	
Cushing's disease	4	1	
Craniopharyngioma	1	1	
Chromophobe adenoma	4	1	
Macroprolactinoma	1	1	
Prolactinoma	1	1	
Traumatic hypopituitarism	1	0	

Table 2: The Holm's sequential Bonferroni corrections employed in questionnaires with multiple end-points.

Questionnaire	***n* {Variables for which predictions were made} [Confirmatory alpha levels*]**	***n* {Variables for which no predictions were made} [Exploratory alpha levels*]**
HDQoL	3 {QA: *present QoL.* Domains: *Do physically*, *Social life*} [0.017, 0.025. 0.05]	12 {QB: *impact on QoL*. All 11 remaining HDQoL domains} [0.004, 0.0045, 0.005 etc.]
NHP	4 {Emotional Reactions, Energy, Physical Mobility, Social Isolation} [0.013, 0.017, 0.025 etc.]	2 {Pain, Sleep} [0.025, 0.05]
SF-36	5 {General Health, Mental Health, Physical Functioning, Social Functioning, Vitality} [0.01, 0.013, 0.017 etc.]	3 {Bodily Pain, Role-Emotional, Role-Physical} [0.017, 0.025, 0.05]
W-BQ12	3 {Negative Well-being, Energy, Positive Well-being} [0.017, 0.025, 0.05]	-

n: the number of variables within each family (of either exploratory or confirmatory variables).
*Required alpha levels increasing for each significant result using Holm's sequential Bonferroni procedure.

Table 3: Key symptoms reported by Placebo-treated patients at end-point

	Women	**Men**
Loss of energy	6	3
Increased drowsiness	4	1
Change in sleep pattern	4	1
Depression	3	1
Crying episodes	5	-
Increased irritability/ intolerance	3	1
Change in memory and concentration	3	-
Decreased sociability	2	1
Increased aches and pains	3	1
Changes in hair/ skin/ nails	3	1
Weight gain	1	3
Believed randomised to Placebo group	6	3

Women: N = 6, mean age 45.5 years
Men: N = 6, mean age 46 years

Table 4: Treatment-group means for questionnaires

	Placebo-treated (mean ± SD)		GH-treated (mean ± SD)		*P*
	Baseline	**End-point**	**Baseline**	**End-point**	
GHQ-30 Total	23.42 ± 9.06	32.79 ± 17.54	18.40 ± 4.58	20.00 ± 4.04	
GWBI Total	47.58 ± 16.40	51.27 ± 19.34	43.25 ± 12.61	41.25 ± 6.32	
HDQoL AWI	0.18 ± 2.29	-1.36 ± 1.14	-2.12 ± 1.20	-1.92 ± 1.44	
HDQoL *do physically*	-0.25 ± 3.02	-1.80 ± 1.81	-3.50 ± 2.51	-2.38 ± 1.19	0.013*
NHP Emotional Reactions	13.86 ± 24.46	14.42 ± 24.91	3.78 ± 7.43	0.0 ± 0.0	
NHP Energy	24.95 ± 35.06	26.33 ± 37.89	7.90 ± 15.18	7.90 ± 15.18	
NHP Pain	4.12 ± 10.85	5.17 ± 17.14	4.77 ± 9.44	5.29 ± 12.77	
NHP Physical Mobility	5.42 ± 15.74	7.15 ± 23.73	2.75 ± 7.77	5.42 ± 11.60	
NHP Sleep	17.43 ± 25.98	21.67 ± 29.84	5.16 ± 7.20	0.0 ± 0.0	
NHP Social Isolation	13.13 ± 24.11	13.09 ± 26.10	9.68 ± 14.08	0.0 ± 0.0	
SF-36 Bodily Pain	72.08 ± 20.57	71.55 ± 28.00	70.0 ± 14.05	81.50 ± 27.52	
SF-36 General Health	63.50 ± 19.58	57.00 ± 23.19	62.75 ± 23.89	66.12 ± 25.16	0.007*
SF-36 Mental Health	75.00 ± 15.92	69.45 ± 21.04	77.5 ± 20.05	84.50 ± 7.23	
SF-36 Physical Functioning	78.52 ± 26.43	72.27 ± 30.20	83.13 ± 14.13	85.63 ± 15.45	
SF-36 Role-Emotional	77.78 ± 35.77	63.33 ± 48.30	87.50 ± 35.36	91.67 ± 23.57	
SF-36 Role-Physical	70.83 ± 39.65	72.73 ± 41.01	84.38 ± 18.60	90.63 ± 12.94	
SF-36 Social Functioning	82.95 ± 25.78	77.27 ± 28.95	93.75 ± 9.45	90.63 ± 12.94	
SF-36 Vitality	60.00 ± 22.76	51.82 ± 28.40	59.38 ± 15.22	60.00 ± 13.63	
W-BQ12 General Well-being total	23.83 ± 9.08	21.83 ± 9.87	25.56 ± 6.21	27.31 ± 3.06	
W-BQ12 Negative Well-being	2.42 ± 2.57	3.00 ± 3.52	1.88 ± 2.8	1.50 ± 1.41	
W-BQ12 Energy	6.83 ± 3.64	5.90 ± 4.12	7.06 ± 2.08	8.13 ± 1.25	0.002*
W-BQ12 Positive Well-being	7.42 ± 3.32	6.92 ± 2.94	8.38 ± 2.13	8.69 ± 1.75	
Minimum N	12 (W-BQ12, GWBI) 11 (GHQ, NHP) 10 (SF-36, HDQoL)		8 (SF-36, W-BQ12, GWBI) 6 (HDQoL, GHQ, NHP)		

*Significance of between group differences in change scores (1-tailed).

** Results of significant HDQoL domains only. A more negative score indicates greater negative impact of hormone deficiency on the domain.

Score ranges: GHQ-30: 0 - 90 (from low to high psychological distress). HDQoL: -9 to +9 (maximum negative to maximum positive impact of hormone deficiency. GWBI and NHP: 0 – 100 (good to poor well-being/ health status). SF-36: 0 to 100 (poor to good health status). W-BQ12: subscale range 0 – 12 (higher scores indicating increased mood of the subscale label); General Well-being total range 0 – 36 (higher score indicating better well-being).

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