REVIEW

THERAPY IN ENDOCRINE DISEASE

Body composition and quality of life in adults treated with GH therapy: a systematic review and meta-analysis

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Abstract

Objective: To summarise the evidence about the efficacy and safety of using GH in adults with GH deficiency focusing on quality of life and body composition.

Data sources: We searched MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science and Scopus through April 2011. We also reviewed reference lists and contacted experts to identify candidate studies.

Study selection: Reviewers, working independently and in duplicate, selected randomised controlled trials (RCTs) that compared GH to placebo.

Data synthesis: We pooled the relative risk (RR) and weighted mean difference (WMD) by the random effects model and assessed heterogeneity using the I^2 statistic.

Results: Fifty-four RCTs were included enrolling over 3400 patients. The quality of the included trials was fair. GH use was associated with statistically significant reduction in weight (WMD, 95% confidence interval (95% CI): -2.31 kg, -2.66 and -1.96) and body fat content (WMD, 95% CI: -2.56 kg, -2.97 and -2.16); increase in lean body mass (WMD, 95% CI: 1.38 , 1.10 and 1.65), the risk of oedema (RR, 95% CI: 6.07 , 4.34 and 8.48) and joint stiffness (RR, 95% CI: 4.17 , 1.4 and 12.38); without significant changes in body mass index, bone mineral density or other adverse effects. Quality of life measures improved in 11 of the 16 trials although meta-analysis was not feasible.

Results: GH therapy in adults with confirmed GH deficiency reduces weight and body fat, increases lean body mass and increases oedema and joint stiffness. Most trials demonstrated improvement in quality of life measures.

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Introduction

GH and its effector insulin-like growth factor 1 (IGF1) serve mainly in regulating growth during childhood, while in adults it is thought to contribute to the regulation of weight, fat mass and muscle mass (1). Adult GH deficiency has been increasingly described as a syndrome, causing weight gain, decreased muscle mass and bone mineral density (BMD) and increased fat mass, impaired physical activity and poor quality of life and life expectancy.

Currently, the FDA-approved indications for GH replacement include short stature associated with Turner syndrome, renal failure, small size for gestational age, Prader–Willi syndrome, idiopathic short stature and for substitution in hypothalamic–pituitary disease (1). Availability of recombinant human GH

provides a potential benefit to patients with GH deficiency but also carries disadvantages as there are safety and cost concerns related to long-term therapy. Previously published recommendations of GH use in adult GH deficiency were based on GH effects on physical function and quality of life (1, 2).

The evaluation of the efficacy of this intervention would not be complete without consideration of the potential adverse effects. Of those, the most commonly described are hyperglycaemia, hypertension, dyslipidaemia, oedema and joint complaints. Recently, concerns have been raised about the effect of GH use and the emergence or recurrence of cancer, and concerns about pituitary and craniopharyngioma tumour growth or recurrence (3).

In 1989, Jorgensen *et al.* (4) published the first randomised controlled trial (RCT) investigating the efficacy

of using GH replacement therapy in deficient adults. The trial found that GH had several potential benefits in the patient population, including decrease in adipose volume, increase in muscle volume, increase in strength and exercise capacity of the quadriceps muscle and recovery of glomerular filtration rate and renal plasma flow. The trial concluded by encouraging future long-follow up trials to further investigate the effects of GH (5).

Since then, there have been several trials with varying durations of follow-up assessing the effects of GH on body composition, exercise capacity, strength and quality of life. Therefore, this systematic review aims to summarise the available randomised trial evidence in adults with GH deficiency treated with GH focusing on body composition (weight, body fat, lean body mass, BMD and body mass index (BMI)), functional outcomes and quality of life and adverse effects including oedema, joint stiffness and carpal tunnel syndrome. In this review, included trials were restricted – by *a priori* protocol – to trials that enrolled patients with confirmed diagnosis of GH deficiency. We excluded trials that used GH on patients with other conditions that are reportedly associated with GH deficiency including but not limited to obesity and the healthy elderly patients.

Methods

The report of this protocol-based review is consistent with the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (6).

Eligibility criteria

Eligible studies were randomised parallel placebo-controlled clinical trials of GH use in adult (age > 18) patients with presumed GH deficiency (as defined in each study). Brief trials (< 3 months) of GH use were excluded from our study.

Study selection and data extraction

An expert reference librarian (P J E) designed and conducted an electronic search strategy with input from study investigators with experience in systematic reviews (V M M and M H M). We searched electronic databases to identify relevant studies. These include: Ovid Medline, OVID EMBASE, OVID Cochrane Library, Web of Science, Scopus, PsycInfo and CINAHL through April 2011. We also sought input from content experts to suggest potentially eligible published and unpublished trials.

Two reviewers working independently and blindly considered the potential eligibility of each of the abstracts and titles that resulted from executing the search strategy; then evaluated the full text versions of all potentially eligible studies and extracted data from vetted references. Data extracted included description of study characteristics and participants' description,

study quality indicators and outcomes. We used the GRADE approach to rate the quality of the evidence (7). Disagreements were resolved by consensus or if not possible, by arbitration.

Statistical analysis

The efficacy outcomes of interest were: i) health-related quality of life, ii) changes in body composition (anthropometric measurement or dual X-ray absorptiometry), iii) BMI and iv) skeletal mass. The safety outcomes were i) clinically significant hyperglycaemia, ii) hypertension, iii) dyslipidaemia, iv) clinically significant oedema, v) joint stiffness, vi) carpal tunnel syndrome, vii) cardiovascular events and viii) tumour occurrence or recurrence.

For dichotomous outcomes, we determined the relative risk (RR) and for continuous outcomes, we determined the weighted mean difference (WMD). Data were pooled by the DerSimonian and Laird random effects models (8). The I^2 statistic was used to measure inconsistency in results across studies. The I^2 statistic quantifies differences in results between studies that are not attributable to chance, therefore reflecting true inconsistency between different trials. An I^2 of more than 50% means that the inconsistency is large. Our analyses were performed by Comprehensive Meta-Analysis (CMA) version 2.2 (Biostat, Inc., Englewood, NJ, USA).

To seek explanations for inconsistency in results across trials, we planned several subgroup analyses. The *a priori* hypotheses included i) the proportion of participants lost to follow-up (over 10% versus under 10%), ii) the quality of allocation concealment and iii) the age of onset of the GH deficiency (childhood versus adulthood). For each of these analyses, we pooled results with random effects meta-analyses within each subgroup and then compared the results across pooled subgroups with a test of interaction (9). Furthermore, we performed *post hoc* meta-regression analysis for three continuous moderators: GH dose, baseline IGF1 and duration of GH treatment. We completed our analyses with assessment of publication bias using funnel plots that use the correlation of big sample size trials and positivity of their results as a basis to project an estimate of trials with negative results that are unpublished (10).

Results

Search results

From our primary search, we identified 2085 articles of which, 402 were selected for full text screening. Those were fully retrieved and screened for eligibility yielding 129 articles that met our inclusion criteria. Ultimately, following exclusion of articles with incomplete data and accounting for single trial dual and triple publications, there were 54 original parallel randomised placebo-controlled trials with sufficient data for analysis

included in our review. Included trials enrolled over 3400 adult patients.

Author contact

We contacted authors of nine studies for clarification of published study details.

Characteristic and quality of included trials

Supplementary Table 1, (see section on supplementary data given at the end of this article) describes the characteristics of included studies. Included studies had a fair methodological quality with the majority (70%) of included studies following up patients for 6 months (range: 3–24 months). Loss to follow-up was reported in 80% of included studies and averaged a mean (s.d.) of 7.44% (7.31). Eighty-nine percent of included studies reported the blinding of at least patients and caregivers while 7% were unblinded. Methods of randomisation and allocation concealment were reported in 11 and 5% of included studies in that order. Furthermore, 23 and 44% of included studies reported implementing measures for assessment of adherence and efficacy of intervention. Source of funding was reported in 56% of the studies and was found to have a for-profit component in ~90% of those.

GH efficacy

Quality of life We found 16 trials that assessed quality of life outcomes in adult patients with GH deficiency. Pooling of the findings of those trials was not possible due to the heterogeneity in outcome reporting and the lack of quantitative data reported in trial reports (particularly, lack of reporting of measures of precision needed for meta-analysis).

All but five trials reported a statistically significant improvement in at least one subsection of used quality of life assessment tool, in patients who received active treatment. These findings are summarised in Supplementary Table 2, see section on supplementary data given at the end of this article.

Body composition GH use significantly and consistently reduced weight and body fat content while increasing lean body mass. WMD for weight was -2.31 kg with a 95% confidence interval (CI) of -2.66 to -1.96 , and I^2 of 0%. WMD (95% CI) for body fat content was -2.56 kg (-2.97 and -1.3) and I^2 of 73.7% (Fig. 1). WMD (95% CI) for lean body mass was 1.38 kg (1.10 and 1.65). GH did not significantly affect BMI or BMD.

Figure 1 Meta-analysis of fat content change, measured in kg. $I^2 = 73.7\%$. P, placebo; M, males; F, females; 95% CI, 95% confidence interval.

Adverse effects The data about adverse effects was in general of short-term relevance and the incidence of these events was too low, and very imprecise. GH use seems to reliably increase the risk of clinically significant oedema: RR 6.07 (95% CI 4.34 and 8.84), $I^2=0\%$ and joint stiffness: RR (95% CI) 4.17 (1.40 and 12.38). We also found a trend that did not reach statistical significance for increasing the risk of carpal tunnel syndrome ($P=0.09$).

There were no significant effects on risks of dyslipidaemia, hypertension, myocardial infarction, stroke, treatment requiring hyperglycaemia and tumour occurrence or recurrence.

Subgroup analyses, meta-regression and publication bias Subgroup analyses indicated that trials with a relatively high loss to follow-up rate ($>10\%$) reported significantly better lean body mass results ($P=0.02$). Furthermore, we found a significant difference in the risk of carpal tunnel syndrome in trials that reported allocation concealment ($P=0.02$). Sensitivity analysis was done with the exclusion of the one trial that did not report allocation concealment demonstrating a now-significant risk of carpal tunnel syndrome: RR (95% CI) 5.83 (1.30 and 26.06).

Meta-regression demonstrated significant positive correlations between decrease in fat content and duration of follow-up ($P=0.01$), baseline IGF1 ($P<0.01$) and GH dose ($P<0.01$). We found a similar correlation between increase in lean body mass and baseline IGF1 ($P<0.01$) and GH dose ($P=0.003$).

Assessment for publication bias using funnel plots indicated significant publication biases for the outcomes of weight ($P=0.008$), lean body mass ($P=0.0007$), BMI (0.045) and carpal tunnel syndrome ($P=0.04$).

Discussion

Summary of our findings

This systematic review and meta-analysis demonstrated that GH replacement in adults with presumed GH deficiency is effective in decreasing patients' weight and body fat content while increasing their lean body mass. Changes to BMI and BMD were not statistically significant likely due to imprecision (small sample size). GH improves certain components of the quality of life indices; however, this inference is limited due to the heterogeneity in these indices. Safety data remains quite imprecise and inconclusive.

Limitations and strengths of our review

This study has several strengths including the comprehensive literature review, the appraisal of the risk of bias and the parsimonious set of planned analyses. However, several limitations exist. Most studies did not report the outcomes, we set out to summarise, increasing the risk

of outcome reporting bias (11). Publication bias has affected several of the reported outcomes. Quality of life data was heterogeneous and meta-analysis was not feasible. Overall, the quality of evidence regarding the reduction in weight and body fat content is high; however, for all other outcomes remains low.

Comparison with previous reviews

The effects of GH replacement were assessed by a number of meta-analyses. Two recently published reviews described the efficacy of GH on physical activity and physiologic function. Widdowson & Gibney (12) pooled the studies that measured the isometric and isokinetic quadriceps strength, while Rubeck *et al.* (13), looked at aerobic exercise capacity, $\text{VO}_{2\text{max}}$, maximal oxygen uptake, muscle strength and volume. This is in contrast to our review that focused primarily on the effects of GH on body composition, quality of life and safety.

The role of GH in improving quality of life was the focus of a systematic review conducted by Deijen *et al.* (14) in 2004. The review was not exclusive to randomised trials and included observational studies. As for the effects of GH on body composition, these were investigated by Maison *et al.* (15) in 2003. Our review brings the evidence base up to date and increases the precision of treatment estimates.

Implications for practice and research

While GH deficiency in adults has been reported to be associated with abnormalities in body composition, BMD, lipid and carbohydrate metabolism and quality of life, high quality evidence only supports the effects on the reductions in weight and body fat content. The clinical implication of these changes in body composition in GH deficient adults are unknown; as no studies to date have shown evidence that these changes are maintained on a long-term basis or that hard endpoints such as cardiovascular or cerebrovascular disease or mortality are improved. On the contrary, as of December 2010, the FDA is investigating the safety of recombinant human GH after a European observational study (Safety and Appropriateness of GH treatments in Europe: SAGhE) reported a 30% increase in mortality risk with long-term use. The investigation is still underway, and the FDA recommends that any patient currently receiving rhGH to continue taking their medication (16).

Increase in fat mass is characteristic to GHD patients and is thought to be predominantly due to an increase in visceral compartment fat mass and a decrease in fat-free mass and total body water (17, 18). Various investigators demonstrated that fat mass was higher by around 7% in GHD patients compared with age, sex and height adjusted predicted values (5, 19, 20). Reduction in fat mass after GH replacement therapy has been described mostly in the visceral fat mass using anthropometric

measurements and imaging (17, 19, 21). A recent study on the effect of GH replacement on different fat compartments by whole-body magnetic resonance imaging suggests GH replacement effect on both subcutaneous and visceral fat mass compartments (22).

GH implications in bone health and fracture reduction had been a matter of debate in endocrinology. Reduced BMD at various skeletal sites in GH deficiency subjects had been described. However, the results of GH replacement on bone mass had been conflicting. BMD gain had been noted to depend on variables as the level of BMD before commencement of GH therapy, replacement period of longer than 12–24 months, childhood versus adult onset GHD (23) and sex (24). Data on fracture incidence risk in untreated GHD is limited but seems to be increased (25, 26) and replacement with GH could decrease it especially in adult onset GHD men (27). In this review, GH was not found to be effective in increasing BMD.

Multiple studies demonstrate reduced quality of life in untreated patients with GH deficiency (28–30). Demonstration of a positive influence of GH replacement on the quality of life had been sought by several investigators with conflicting results (31–34). Recent observational data (35) showed long-term beneficial effects of GH replacement on quality of life as measured by adult GH deficiency assessment (AGHDA) score (36). In this review, this outcome was not commonly reported in published randomised trials included. Sixteen trials measured quality of life utilising various methods for quality of life assessment, most commonly including the aforementioned AGHDA score, along with the psychological general well-being index and the general health questionnaire. Frequently, the data was presented in a manner that rendered meta-analysis not possible, often omitting either pre- or post-intervention data and sometimes opting to verbally indicate whether there was any significant improvement. It is also worth noting that all available and utilised methods of quality of life assessment are self-reported and are susceptible to what is known as the response shift phenomenon (37, 38). With that in mind, we found that all but five of the 16 trials reported a statistically significant improvement in at least one subsection (e.g. energy, mental health and somatic health in the Nottingham Health Profile, the SF-36 and the symptom questionnaire) of the utilised quality of life assessment tool.

Interpretation of studies of the effectiveness of GH replacement in adults with GH deficiency is hampered by a number of confounding factors including identification of treatment goals. A major challenge to clinicians is how best to monitor and hence optimise GH replacement in their patients. At present, clinical guidelines on adult GH replacement recommend that treatment goals for each patient be individualised and guided by patient tolerability, appropriate clinical response and achievement of an IGF1 level in the age- and sex-appropriate reference range (1, 2, 39).

However, to where exactly within the reference range an individual's IGF1 should be titrated remains unknown (40). In the general population, higher circulating IGF1 levels are associated with increased incidence of prostate, colorectal and premenopausal breast cancer (41). To date, however, there have been no published long-term studies in adults with GH deficiency treated with GH with respect to the development of non-pituitary malignancies. Another confounding factor when interpreting studies related to the efficacy of GH replacement in GH deficient adults is that most of these patients also have other pituitary hormone deficiencies that require replacement with glucocorticoid, thyroid hormone or sex steroids. The lack of biochemical tests to guide optimal replacement of these hormones, however, renders it possible that some symptoms and signs attributed to GH deficiency may in fact have been related to under- or over-replacement of other pituitary hormones. In addition, initiation of GH therapy in patients with hypopituitarism may alter dynamics of cortisol and thyroid hormone metabolism leading to unmasking of secondary hypothyroidism and hypoadrenalism that may subsequently go unrecognised by the physician (42, 43). To the extent that experts today understand and are able to use GH despite these uncertainties, important differences in outcomes between arms in randomised trials should arise, as we have seen with body composition outcomes, but not conclusively with other outcomes.

The development of recombinant GH replacement therapy in 1985 stimulated interest in the role of GH in adult life and the subsequent consequences of adult GH deficiency and its treatment. Despite the many studies published in this area, important questions still remain unanswered. Future research in the field should include conducting RCTs with long-term follow-up that enroll homogenous groups of GH deficient patients with similar causes and onset of disease and evaluate patient-important outcomes such as mortality and cardiovascular events, fractures and quality of life. These trials may compare varying doses of GH or include comparisons to other active interventions since comparison with placebo for a long time may be considered unethical. Funding of such trials may be challenging considering that GH already has an approved indication.

Conclusion

GH therapy in adults with GH deficiency reduces weight and body fat, increases lean body mass; but increases oedema and joint stiffness. Most trials demonstrated improvement in quality of life measures.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-11-0558>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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