The effect of growth hormone (GH) replacement on muscle strength in patients with GH-deficiency: a meta-analysis

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Summary

Context/objectives GH replacement increases muscle mass and reduces body fat in growth hormone deficiency (GHD) adults. A recent meta-analysis has demonstrated that this improvement in body composition is associated with improved exercise performance. The current meta-analysis was carried out to determine whether high-quality evidence exists to support a beneficial effect of GH replacement on strength.

Design/methods An extensive Medline search/literature review identified eight studies with utilizable, robust data, involving 231 patients in nine cohorts. Previously unpublished data were sought from authors and obtained in two cases. All studies included were randomized, double-blind, placebo-controlled, of parallel or crossover design and of an average 6.7 months duration. Information was retrieved in uniform format, with data pertaining to patient numbers, study-design, GH-dose, mean age, IGF-I levels and muscle strength measurements (isometric or isokinetic quadriceps strength) recorded. Data were analysed using a fixed-effects model, utilizing continuous data measured on different scales. A summary effect measure (d) was derived for individual strength variables, whereas an overall summary effect was derived from the sum of all studies incorporating different variables; 95% CIs were calculated from the weighted variances of individual study effects.

Results Analysis revealed no significant improvement, neither when all studies were combined (d = +0.01 ± 0.26) nor when measured individually (isometric quadriceps strength, d = +0.02 ± 0.32 and isokinetic quadriceps strength, d = 0.00 ± 0.45).

Conclusions Evidence from short-term controlled studies fails to support a benefit on muscle strength of GH replacement in GHD patients, which is likely to occur over a longer time-course, as seen in open-label studies.

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Introduction

Growth hormone deficiency (GHD) in adults is associated with reduced lean body and skeletal muscle mass compared with age- and gender-matched normal subjects. Reduced muscle mass in GHD subjects is associated with reduced isometric muscle strength, whereas some but not all studies have also demonstrated reduced isokinetic strength. Reduced strength appears to be largely accounted for by the reduction in muscle mass but there may also be intrinsic muscle weakness associated with GHD.

Whether GH replacement increases muscle strength in GHD adults is not known. Short-term studies have produced conflicting results with some but not all suggestive of a beneficial effect. In one of the first reported studies of GH replacement, Cuneo et al. carried out an extensive series of strength tests at the beginning and end of 6 months of GH replacement. Strength increased in most of the nine muscle groups that were studied although only reached statistical significance in one of the groups, and the mean z score for the range of muscle groups also failed to reach significance. It is possible that this and other studies in which the effect of GH replacement on strength was addressed were not adequately powered to demonstrate a statistically significant effect.

Using meta-analysis techniques, we have recently provided persuasive evidence that GH replacement results in improvement in exercise capacity in GHD patients. The current meta-analysis was carried out to determine whether high-quality evidence exists that GH-replacement also improves muscle strength. This is important because while GH replacement has clearly been shown to improve certain variables including body composition, cardiovascular risk factors and surrogate cardiovascular end-points, and bone mineral density, there is relatively little evidence regarding functional end-points, which are more relevant to GHD patients’ quality of life.

Materials and methods

Data sources

Original studies were identified using an online Medline database comprising the years from 1950 to January 2009 inclusive. The search strategy used the terms GH, human GH, hypopituitarism and muscle, muscle strength, skeletal muscle, muscle contraction. Abstracts and titles were then screened for relevance to the topic,
and appropriate full-text articles obtained. Further studies were identified from the reference lists of these retrieved articles and several appropriate related review publications. Authors were contacted for additional data if there was insufficient available in the published study. The retrieved studies utilized different muscle groups for measurement of strength, predominantly the lower limb quadriceps or upper forearm. Various biomechanical variables were also used, including isokinetic and isometric muscle strength, hand-grip strength and jump tests. For inclusion, quadriceps strength, either isometric or isokinetic, were utilized because of the use of well-validated, reproducible recording methods. Full details of the retrieval protocol and studies retrieved are shown in Fig. 1.

Study selection/data extraction

A sole investigator using a uniform information database extracted data. Studies were assessed in terms of design quality and appropriateness for inclusion in the meta-analysis. Appropriate studies for inclusion needed to be of a randomized, placebo-controlled design, either in cross-over or parallel format. The lack of control or comparator groups in those studies employing an open or uncontrolled design meant that the data was not able to be included in the statistical analysis and therefore were not appropriate for inclusion. Authors were contacted to clarify data or obtain missing data as required. Data quality was also rated based on that which was presented in the paper, either in text, table or figure format. In general, data could be included if mean change over the duration of the study along with appropriate SEM or SD were presented in any of those three formats, for both placebo and treatment groups.

Statistical analysis

Data were included utilized strength variables of isometric and isokinetic muscle strength. These variables were analysed separately, and also, to increase patient numbers and improve statistical power, combined using a single variable from each study.

Data analysis was carried out using a fixed-effects model. The analysis used statistical formulae for the derivation of an effect size in each study, where studies measured exercise capacity on different scales (isometric and isokinetic quadriceps strength), as described by Hedges,10 and published in Petitti.11 Analysis required documentation of values for the mean change in both placebo and experimental groups, as well as a pooled SD of the effect measure from the study population as a whole. A summary estimate of effect size was then calculated measured in a common metric \(d\): this involved the computation of an individual study effect size \(d_i\), the weight of each study \(w_i\), and subsequent computation of the overall summary estimate of effect for the group of studies. Confidence intervals could then be estimated at the 95% significance level for \(d\) using the variance, as described by Hedges. A test of homogeneity was carried out by deriving a Q statistic from the values of \(d_i\), \(w_i\) and \(d\). This could then be referred to a \(\chi^2\) distribution with degrees of freedom equal to the number of studies included –1.

Results

The database and subsequent search of references returned 527 abstracts, of which 26 were retrieved in full-text form for further analysis. Of these, eight studies met criteria for inclusion in the meta-analysis, incorporating nine separate patient cohorts. One study reported male and female subjects individually, with separate statistical analysis for the two groups.12 These were thus incorporated in the meta-analysis as separate cohorts. Of the 18 studies excluded from analysis, five did not present data in a format or completeness that allowed inclusion in the meta-analysis,13–17 used a study design that did not meet inclusion criteria (nonrandomized, open or uncontrolled),4,5,18–27 and one incorporated insufficient numbers to be included in the statistical analysis.7 Table 1 summarizes the patient characteristics and study design of the included studies, as well as those excluded and the reasons for their exclusion.

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DB, double blind; PC, placebo controlled; R, randomized; X, cross-over; M, isometric quadriceps strength; K, isokinetic quadriceps strength; AO, adult onset; I, insulin tolerance test; G, glucagon stimulation tests; GHRH, gonadotrophin releasing hormone stimulation test; ?, data not presented; ~, not evaluated.
Within the studies included, which had a mean duration of 6.8 months, isometric quadriceps strength was measured in six patient cohorts, and isokinetic quadriceps strength was utilized in the remaining three studies. The total number of patients pooled from the nine cohorts was 231:154 from the studies measuring isometric quadriceps strength and 77 from those measuring isokinetic quadriceps strength. The majority of studies measured isometric and isokinetic strength in Newton metres (N⋅m) of torque or Newtons (N) of work produced during muscle action, while one study converted such data to z scores for both treatment and placebo groups.

Improvements in muscle strength compared with placebo ranging from 1% to 15% were demonstrated in six studies, while three cohorts demonstrated a reduction in strength compared to placebo of 3–5%, as shown in Fig. 2. Analysis of the data using the methods described above failed to show any significant improvement from baseline when compared with placebo in any of the measured variable groups. The summary effect measure (d) for the combined variable was 0.01 (95% CI: −0.25 to 0.27), for isometric quadriceps strength alone was 0.02 (−0.30 to 0.33), and for isokinetic muscle strength alone was 0.00 (−0.45 to 0.45). Tests for heterogeneity revealed significant levels of variation between the studies, illustrated by Q statistics and P values in Table 2. Removal of the three cohorts with negative raw effects made no significant difference to the effect size or CIs involved (combined variable; d = 0.09, 95% CI: −0.22 to 0.41).

No correlation was detected between mean age at study entry, GH dose or presenting IGF-1 level and the effect size of combined or single strength measures (data not shown).

**Discussion**

This meta-analysis, combining the results of nine patient cohorts with a total of 231 patients, demonstrates no significant effect of GH replacement over a mean duration of 6.7 months on either isometric or isokinetic muscle strength in GHD patients. These findings contrast with the findings of a recent similar meta-analysis which demonstrated a significant benefit of GH replacement for a similar duration on exercise capacity. They also contrast with the findings of longer term studies which have demonstrated a positive effect of GH replacement on strength but which have lacked a placebo arm.

An obvious limitation of this finding is the relative lack of randomized, controlled studies in the literature, and the small size of those studies that do exist. This meta-analysis highlights the lack of high-quality (randomized, placebo-controlled) studies investigating this aspect of GH deficiency, and the lack of a positive finding should be interpreted in light of this. Coupled with the small sample sizes and short duration of study (mean 6.7 months), the fact that the majority of the included studies did not analyse muscle strength as a primary end-point, but more as part of a spectrum of end-points, meant that the studies were not likely to be powered to determine any positive effect.

The most persuasive evidence that GH replacement over a longer duration results in increased muscle strength comes from a large ongoing Swedish study of open-label, prospective, non-randomized design. Over 10 years of continuous follow-up, GH replacement in adult-onset GHD patients resulted in a transient increase (up to 5 years) in absolute values for most measures of isometric and isokinetic muscle strength and a sustained increase in absolute values for isometric knee flexor strength. By the end of 10 years of follow-up, all measures of muscle strength were comparable with an age-related reference population. While
these are clearly important findings, interpretation must take into account the lack of a placebo-group and also the possibility that some of the improvement in the GH-replaced subjects reflected long-term recovery from the original disease process that resulted in GH deficiency or associated treatment modalities including surgery, radiotherapy and nonphysiologic replacement of other pituitary hormones.

A further limitation of the current study is the possibility of inclusion bias resulting from a lack of data presented in some of the studies retrieved. An attempt was made to obtain raw data directly from the authors of the relevant papers and previously unpublished data from two studies was included in the analysis.32,33 The remaining studies whose data were not available largely reported no significant improvement in muscle strength with GH replacement. It is likely that the lack of benefit seen could at least in part be due to a lack of statistical power in the individual studies because of small patient numbers, as mentioned above, and that with inclusion in a comprehensive meta-analysis such as this, any positive effects may have been more likely to be exposed. A suggestion that this might be the case is the fact that examination of the mean effect in the studies included reveals a positive effect in six of the nine cohorts examined, with improvements ranging from 1% to 15%. These effects were not statistically significant due to the large degree of variability within the studies, contributed to by small study numbers. It is possible that with a greater number of included studies and patient numbers, an overall positive effect may have been seen.

The differing effects of short-term GH replacement on exercise and strength are potentially explained by the observation that determinants of exercise capacity are more extensive and complicated than determinants of strength. In addition to possible effects on strength, GH could improve exercise performance through increased delivery of substrate and oxygen to exercising muscle, increased fat oxidation with glycogen sparing, changes in body composition or more efficient thermoregulation. Some of these effects are observed within days to weeks of commencement of GH replacement and are likely to have a more immediate impact on exercise performance compared to changes in muscle strength which could conceivably occur more slowly.

Evaluation of the raw results suggests a greater improvement in strength in earlier studies which utilized a more supraphysiological GH dosage regimen,4,28,31 than those from the later period with lower dose,12,30,32,33 (Fig. 2). The difference in GH dosage could explain some of the difference in the effects seen, although closer evaluation failed to show any significant effect of dosage, age or treatment time on the magnitude of strength effect elicited.

In summary, although long-term open-label studies provide compelling evidence that GH replacement in GHD improves muscle strength over a period of 1–10 years, the current meta-analysis of placebo-controlled trials fails to confirm this. This is almost certainly because of the short-term nature of such studies, and provides proof that unless carried out for a duration exceeding 12 months, an unlikely situation given the ethical implications involved, the ‘gold standard’ randomized controlled trial is unlikely to provide appropriate answers to the question of an improvement in muscle strength with GH replacement in GHD.

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Competing interests/financial disclosure

The authors have nothing to declare.

References


