An audit of growth hormone replacement for growth hormone deficient adults in Scotland

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Title: An Audit of Growth Hormone replacement for GH-deficient adults in Scotland.

Short title: Scottish growth hormone audit

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Summary

Objective: Guidelines on the clinical use of growth hormone therapy in adults were issued by the UK National Institute for Clinical Excellence (NICE) in August 2003. We conducted a retrospective clinical audit on the use of growth hormone (GH) in Scotland to evaluate the use of these guidelines and their impact on clinical practice. The audit had 2 phases. In Phase I, the impact of NICE criteria on specialist endocrine practice in starting and continuing GH replacement was assessed. In Phase II, the reasons why some adults in Scotland with growth hormone deficiency were not on replacement therapy were evaluated.

Methods: A retrospective cross-sectional case note review was carried out of all adult patients being followed up for growth hormone deficiency during the study period (1st March 2005 to 31st March 2008). Phase I of the audit included 208 patients and Phase II 108 patients.

Results: Sellar tumours were the main cause of GH deficiency in both phases of the audit. In Phase I, fifty-three patients (77%) had an AGHDA-QoL score >11 documented before commencing GH post-NICE guidance, compared with 35 (25%) pre-NICE guidance. Overall, only 39 patients (18%) met the full NICE criteria for starting and continuing GH (pre-NICE, 11%; post-NICE, 35%). Phase II indicated that the main reasons for not starting GH included perceived satisfactory quality of life (n=47, 43%), patient reluctance (16,15%) or a medical contraindication (16,15%).
Conclusions: Although the use of quality of life assessments has increased following publication of the NICE guidelines, most adults on GH in Scotland did not fulfill the complete set of NICE criteria. The main reason for not starting GH therapy in adult GH-deficient patients was perceived satisfactory quality of life.
Introduction

Since recombinant growth hormone (GH) became available in 1985, there has been considerable debate regarding its use and cost-effectiveness in adults with growth hormone deficiency (AGHD). In 2001, the United Kingdom National Institute for Clinical Effectiveness (NICE) appraised the clinical effectiveness and cost-effectiveness of GH and Bryant et al carried out a Health Technology Assessment for NICE. However, economic modeling was limited by the lack of availability of a suitable cost-effectiveness measure. Sensitivity analyses showed the overall cost of GH therapy in adults was sensitive to GH dose, GH pricing and length of treatment. GH replacement in adults using an average maintenance dose was estimated to cost £3420 annually. The initial conclusion of the appraisal committee was that effectiveness was unproven but, following challenge by patient groups and clinicians, NICE subsequently published guidelines for the use of growth hormone in AGHD (Appendix 1).

There are five major areas of recommendation in the NICE guidance: (1) biochemical for diagnosing severe growth hormone deficiency, quality of life inclusion criterion for starting therapy (2) biochemical and quality of life criteria for response to growth hormone therapy, (3) criteria for continuing replacement in children on replacement who have completed linear growth, (4) recommendations on who should initiate GH therapy, and (5) the need for a shared care protocol if maintenance therapy is monitored in primary care. The criteria place particular emphasis on the use of the condition-specific quality of life tool, Assessment of Growth Hormone Deficiency in Adults, Quality of Life (AGHDA-QoL).
In order to evaluate the impact of these guidelines on routine clinical practice, an audit group was set up under the auspices of the Society for Endocrinology with the primary objective of assessing the impact of the NICE criteria on the prescribing of GH in AGHD by endocrinologists in Scotland.

The purpose of the audit was to ascertain how many of the patients currently on GH therapy in Scotland satisfy the NICE criteria and whether the publication of the NICE guidance has had impact on clinical practice. The aim of Phase II was to ascertain the reasons why some patients with AGHD were not started on GH replacement. Though the NICE guidance stated that all NHS patients who were on therapy at the time of publication should have the option to continue treatment until they and their consultant consider it is appropriate to stop, we felt it would be useful to use them as a comparator group to assess change in practice.

**Methods**

The audit was coordinated by a Steering Group which comprised consultant endocrinologists from the main Scottish endocrine units. All endocrinologists in Scotland were surveyed at the outset, in order to identify centres using GH therapy in AGHD.

**Phase I**

Patients commenced on GH before March 2008 and under specialist review were identified by centre and their case notes were retrieved. The case notes
were reviewed by endocrine specialist teams based at five main centres and data were collected from the case-notes of their own and neighbouring smaller centres. A research nurse (MC) coordinated data collection in the various centres. Anonymised details of each patient were entered into a research database. Members of the Steering Group provided local assistance in the interpretation of data where required. Data were collected on GHD aetiology, demographic information, other pituitary hormone deficiencies, hormone replacement therapies, vascular risk factors and measures of treatment efficacy.

Two hundred and thirty patients were identified for potential inclusion in the audit. However, only 208 patients had adequate information regarding initial assessment and the indications for starting GH therapy (figure 1). Patients on GH replacement were divided into two groups. Group A (Pre-NICE, 139 patients) comprised patients who were started on GH before August 2003 and Group B (Post NICE, 69 patients) comprised patients started after the NICE guidelines were published in August 2003.

**Phase II**

Patients with growth hormone deficiency not currently on GH replacement were identified. 117 patients were identified for potential inclusion in the audit. However, on detailed evaluation, only 108 patients were confirmed to have GH deficiency and included in the study (figure 1).

**Audit Standards**
I. Patients should meet the biochemical criteria for severe GH deficiency.

II. Patients should meet AGHDA-QoL criteria for severe GH deficiency.

III. All patients should have first been assessed for other hormone deficiencies and optimally replaced.

IV. All patients on long term GH replacement should meet the AGHDA-QoL improvement criteria after starting GH therapy and have achieved optimal dose titration.

Results

Phase 1
Of 208 patients included, 106 were female (51%). The mean age at diagnosis of the primary cause of GH deficiency was 32 years (SD 16). Mean age at the start of GH therapy was 41 years (SD 14, Range 10-76). The majority of patients were Caucasian (193, 93%); ethnicity information was not available in 10 patients.

Sixty-nine patients (41%) were started on GH after the NICE criteria were published (Group B). Occupational details were available in 167 patients (80%); professional (n=58, 28%), manual skilled (36, 17%), non-manual skilled (16, 8%), partly skilled (12, 6%), managerial (4, 2%), unemployed (14, 7%), unskilled (27,12%).

The causes of GH deficiency are shown in Table 1: sella tumours were the commonest cause (137, 66%). Vascular risk factors and co-morbidities in the study population were hypertension (45, 21.6%), hyperlipidaemia (30, 14.4%),
diabetes mellitus (14, 6.2%), stroke (10, 4.8%), ischaemic heart disease (8, 3.8%) and peripheral vascular disease (1, 0.5%).

**Audit Standard 1. Biochemical diagnosis of Growth Hormone deficiency**

187 patients had a dynamic GH stimulation test. Of these 183 patients (89%) the dynamic GH stimulation test performed confirmed severe GH deficiency (< 9 mu/l on Insulin Tolerance Test, < 27 mu/l on GHRH + Arginine testing, < 17 mu/l on Arginine testing). The most commonly used test was insulin-induced hypoglycaemia. 122 patients (89%) in Group A met this criterion, compared to 61 patients (88.4%) in Group B. Four patients had a partial GH deficiency (peak GH levels between 9 and 15 mu/l). Twenty one patients did not have any dynamic tests performed and were diagnosed on the basis of low age-related IGF-1 levels and more than 2 baseline pituitary hormone deficiencies. 8 patients had isolated GH deficiency. Only one patient with isolated GH deficiency had 2 different dynamic tests for GH secretion.

**Audit Standard 2. Assessment of AGHDA-QoL**

The median AGHDA-QoL for patients in phase 1 was 17 (IQR 9). There was a significant increase in the proportion of patients who had a formal QoL assessment, from 51 patients (37%) in group A to 60 patients (87%) in group B (P<0.001, Fig. 2). Nevertheless, 12 patients in Group A and 6 patients in Group B who had AGHDA-QoL scores below 11 were started on GH therapy (10.8% of all patients). In the six patients in Group B, three had previously been on GH therapy and had noticed a significant deterioration in quality of life. The
remaining three had AGHDA-QOL scores close to 11 (range 8-10) and the consultant felt that a trial of GH therapy would be justified. In group A 7 patients were perceived to have a poor quality of life, 5 patient had a low bone mineral density.

Audit Standard 3. Assessment of other pituitary hormone deficiencies

All patients (100%) had appropriate baseline pituitary function testing. Most patients were taking other pituitary hormone replacements; thyroxine 83%, hydrocortisone 79%, testosterone 70% of men, oestrogens 46% of women and desmopressin 25%. Baseline AGHDA was obtained after optimal replacement of other pituitary deficiencies.

Audit Standard 4. Improvement in AGHDA-QoL.

The median fall in AGHDA-QOL was 6 points( IQR 10, Range 0-25). Forty-five patients (32%) in Group A and 52 patients (75.4%) in Group B had a recorded AGHDA-QoL before and after starting GH (Fig. 3). In group A, 17 patients (12%) satisfied the AGHDA improvement criteria while, for 28 patients (41%) in Group B, the AGHDA score improved by 7 points or more.

In group B, 24 patients had a less than 7 point change in AGHDA-QOL and were continued on growth hormone therapy despite the desired lack of improvement in AGHDA-QoL. Of these five had an initial AGHDA of greater than 20 and one had an AGDHA of 25. Sixteen of the 24 patients in group B, who did not meet audit standard 4, showed a lesser improvement in AGHDA-
QOL and a clinical comment in the notes stating an improvement in quality of life since starting growth hormone therapy.

The median time between baseline and repeat estimation of AGHDA was 10 months (interquartile range 6 months). The median dose of growth hormone used was 0.5 mgs (interquartile range 0.2mgs)

Twenty six patients (38%) met all the NICE standards (38%) in Group B. Only 15 (11%) in Group A would have met the current criteria. There was a variation in the use of AGHDA-QoL among the centres and one of the major centres did not use AGHDA-QoL at all. If data from this centre are excluded, the overall proportion of patients meeting the AGHDA-QoL criteria increased from 12% to 44% (Fig. 4).

There is a significant variation in the pattern of Growth hormone prescribing within Scotland. Only 2 of the 5 centres prescribed Growth hormone therapy in significant numbers following the NICE guidance and both centres showed an improvement in adherence to the NICE criteria. There was significant fall in numbers started on Growth hormone in Centre B as it was involved in trial of Growth hormone therapy prior to 2003 and hence most of the candidates suitable for growth hormone therapy were already considered for the same.

**Phase II**

There were 108 patients with a diagnosis of GHD who were not taking GH; 54 (50%) were female. Details regarding occupation were available in 83 patients (Managerial 3, 3%; Professional 15, 14%; Manual Skilled 18, 17%; Non-manual
Skilled 9, 8%; Partly skilled 8, 7%; Unemployed 10, 9%; Unskilled 20, 19%; Not recorded 25, 23%.

The mean age at diagnosis of the primary cause of GH deficiency was 46.2 years (SD 21.8). The mean age at the time of the study was 57.9 years (SD 17.4). The co-existing vascular risk factors in the study population were hypertension (39, 36.1%), hyperlipidaemia (32, 29.6%), diabetes mellitus (8, 7.3%), stroke (11, 10.0%), ischaemic heart disease (17, 15.4%) and peripheral vascular disease (2, 1.8%).

Most patients were on other pituitary hormone replacement therapies; hydrocortisone 79 (73.1%), thyroxine 81 (75%), testosterone 49 (91% of men) oestrogen 39 (72% of women) and desmopressin 21 (19.4%). Fifty-four patients had a low IGF-1 but no dynamic tests to confirm GH deficiency. Forty-eight of 54 patients who had a dynamic test had a GH peak lower than 9.0 mU/l (mean peak GH level 5.6 mU/L, SD 11.8). Table 2 lists the reasons why patients were not on GH therapy. Table 3 compares the characteristic of the patients in the two phases of the audit.

**Discussion**

The Society for Endocrinology estimates the prevalence of adult-onset GH deficiency is approximately 1 in 10,000 of the UK adult population and if adults with childhood-onset GH deficiency are also considered, the prevalence may be as high as 3 in 10,000. Based on the 2001 census, this would imply there should be around 1200 patients with GH deficiency in Scotland. We identified
208 patients on GH therapy and another 108 untreated with GHD in Scotland, which represents approximately 25% of the individuals who might be expected to have GHD. Although it is likely a small number of patients on GH therapy will have been missed in the survey and others will have declined the offer of GH, it seems probable that many patients who may benefit from GH replacement are not being considered. This may reflect concerns about costs of treatment and the clinical practice of specialists involved in patient care.

While it is possible we missed patients who were not being followed in specialist centres, all patients included in this audit were managed by a consultant endocrinologist with an interest in pituitary disease. Few patients in Scotland with pituitary disease are cared for by non-endocrinologists. Patients on Growth hormone therapy were diagnosed with their primary condition at a younger age and there was also greater proportion of managerial and professional individuals in this group (table 3).

The present data suggest that adherence to guidelines for the use of GH in adult patients has improved following NICE guidance in two of the Scottish centres (A and D), but remains suboptimal in the other centres. In centre B all relevant patients had been actively recruited as part of a clinical trial before 2003 and therefore there was a relative fall in the number of patients started on growth hormone between 2003 and 2006. The overall compliance rate with all NICE criteria increased from 11% to 38% with greater use of AGHDA-QoL after the NICE criteria were published; this was the case in all centres. Indeed, although most patients now meet the criteria for initiation of therapy, the commonest reason for not meeting the NICE criteria is a failure to achieve the
required improvement in AGHDA-QoL. This suggests clinicians and patients are keen to continue therapy despite the AGHDA score not improving by at least 7 points. Our impression is that many patients request continuation of therapy as they feel subjectively better on GH, even though this has not been corroborated by an improved AGHDA-QoL score. This suggests a 7-point improvement in AGHDA-QoL may be an inappropriate criterion and worthy of review. Indeed, the use of AGHDA-QoL to assess quality in life has been controversial, with one study showing that it could not discriminate between extremes of GH output and thus having limited ability to detect improvement in quality of life during GH replacement. Normative data for AGHDA-QoL are available in a UK cohort; in all age groups there were statistically higher scores AGHDA-QoL scores in GHD patients. However patients with adult-onset GHD on GH replacement had mean AGHDA-QOL scores of 12.6 in men (SD 6.6) and 15.1 in women (SD 6.3) demonstrating that the range of AGHDA scores for the patients on treatment in this cohort would fall outside NICE Guidelines. Finally, in a study of the KIMS database there was a decrease in mean AGHDA score of 2.2 points at 6 months and 2.8 points at 12 months in men; in women a mean decrease of 2.8 and 4.8 points at 6 and 12 months was seen. Again, these changes would not meet the pre-specified NICE criteria, but may suggest that patients started on GH may still achieve clinical improvement that is not reflected in this rather arbitrary end point and the thresholds for baseline values and incremental change expected may need to reconsidered based on observed change in prospective cohorts.
Of the centres surveyed, three had a formal shared care protocol, and one had developed an informal approach which had been in successful use for over 12 years. However, we believe that a formal protocol can offer a robust mechanism that ensure support for prescribing in primary care and should be seen as the most appropriate way of managing GH replacement.

The main reason for not starting GH therapy in our cohort of patients was a perceived normal quality of life (43.5%). However only half these patients were formally assessed using a formal AGHDA-QoL. However, it is possible that some of these patients may not have been assessed with an AGHDA questionnaire or with dynamic tests because they had indicated that they had made a clear decision not to have a trial of GH therapy. More data are required about the potential benefits of GH replacement beyond those of improved quality of life before such patients should be given greater encouragement to initiate GH. Thus, while it is possible that many patients may miss possible long term benefits, such as improved bone density and cardiovascular health, lack of firm end-point data makes this speculative at present.

The Scottish Medicines consortium states that ‘patients must have growth hormone deficiency as a result of hypothalamic or pituitary disease and at least one other hormone deficiency diagnosed (except for prolactin) and adequate replacement therapy instituted, before replacement therapy using growth hormone may begin’. Healthcare Improvement Scotland issue alerts to notify NHS Scotland of the publication of NICE Guidance and advises on its applicability to Scotland. However this mechanism was only started in April
2011. Therefore part of the reason for the reduced adherence to the NICE guidance may be that the AGHDA-QoI criteria is not considered important for funding treatment by the Scottish health boards.

In summary, this study has shown that, even in centres with a specialist endocrinology interest, the implementation of NICE Guidelines on GH replacement in adults remains incomplete. This may reflect individual specialist interpretation of the Guidelines, and pragmatic decision-making in consultation with patients. In particular, the AGHDA-QoL score criteria were not fully implemented, calling their actual validity into question. Finally, it is clear that a substantial proportion of patients who might qualify for GH replacement do not receive this, reflecting a mixture of patient choice, clinical reasoning and, possibly, failure by clinicians to offer therapy. We have presented the results of the audit at regional and national endocrine professional conferences. We plan to develop a simple paper based audit tool based on the NICE criteria to act as a prompt and to re-audit the use of growth hormone in the 4 major centres in 2015.

The limitations of the study were its retrospective nature and the incomplete retrieval of information for some patients who had part of their management outside their current centre of follow up. The strengths are that this was a
national survey, in a relatively static population, of actual management in daily clinical practice.
References


### Table 1: Causes of GH deficiency

<table>
<thead>
<tr>
<th>Cause of GH deficiency</th>
<th>Phase I</th>
<th></th>
<th>Phase II</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>%</td>
<td>No of patients</td>
<td>%</td>
</tr>
<tr>
<td>Sellar tumour</td>
<td>137</td>
<td>65.9</td>
<td>71</td>
<td>65.8</td>
</tr>
<tr>
<td>Post-radiotherapy for haematological malignancies</td>
<td>12</td>
<td>5.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-radiotherapy for non-sellar brain tumours</td>
<td>12</td>
<td>5.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sheehan’s syndrome</td>
<td>7</td>
<td>3.4</td>
<td>4</td>
<td>3.7</td>
</tr>
<tr>
<td>Head trauma</td>
<td>3</td>
<td>1.4</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>2</td>
<td>1.0</td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td>Non-sellar brain tumour</td>
<td>2</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>33</td>
<td>15.9</td>
<td>28</td>
<td>25.9</td>
</tr>
</tbody>
</table>
Table 2: Reasons for patients not being on GH replacement therapy

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGHDA-QOL score &lt;11</td>
<td>22 (20.4%)</td>
</tr>
<tr>
<td>Normal QOL (clinical judgement)</td>
<td>25 (23.1%)</td>
</tr>
<tr>
<td>GH replacement not considered</td>
<td>12 (11.1%)</td>
</tr>
<tr>
<td>Other medical reason (e.g malignancy, respiratory failure, stroke*)</td>
<td>16 (14.8%)</td>
</tr>
<tr>
<td>Patient unwilling</td>
<td>16 (14.8%)</td>
</tr>
<tr>
<td>Planning pregnancy</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Previously tried and stopped GH - no QOL change</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Previously tried and stopped GH - side effects</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Optimising other pituitary hormone replacements before considering GH</td>
<td>6 (4.6%)</td>
</tr>
<tr>
<td>Age (range 78-86 yrs)</td>
<td>6 (5.6%)</td>
</tr>
</tbody>
</table>

(*e.g occipitoparietal meningioma, Sigmoid adenocarcinoma, Cerebellar Stroke, Severe Chronic Obstructive airway disease, Metastatic prostate cancer, severe osteoarthritis)
Table 3: Comparison of characteristics of patients GH-treated (phase 1) and non GH-treated groups (phase 2)

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Phase 1 GH-treated n=208</th>
<th>Phase 2 Non GH-treated n=108</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>106 (50.9%)</td>
<td>54 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age</td>
<td>32 years (SD 16)</td>
<td>46.2 (SD 21.8)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>(at diagnosis of the primary cause of GH deficiency)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (Managerial, Professional)</td>
<td>58 (27.9%)</td>
<td>15 (13.9%)</td>
<td>P=0.02</td>
</tr>
<tr>
<td>Group 2 (Manual Skilled, non manual Skilled, partly skilled)</td>
<td>50 (24.0%)</td>
<td>26 (24.1%)</td>
<td></td>
</tr>
<tr>
<td>Group 3 (Unemployed, Unskilled)</td>
<td>40 (19.2%)</td>
<td>30 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>60 (28.8%)</td>
<td>37 (34.3%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>193 (92.8%)</td>
<td>106 (98.1%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS : not significant
Figure 1: Outline of patients included in the 2 phases of the Growth Hormone audit

**Phase 1**
- 230 Patients on GH therapy
- 21 patients excluded incomplete information
- 208 patients included

**Group A**
- Pre NICE
  - 139 patients

**Group B**
- Post NICE
  - 69 patients

**Phase 2**
- 117 Patients identified not on GH therapy
- 9 patients excluded incomplete information
- 108 Patients included in the analysis

Figure 2: Assessment of AGHDA QOL

**Pre NICE**
- AGHDA not done 88.63%
- AGHDA >=11 39.28%
- AGHDA <11 12.9%

**Post NICE**
- AGHDA >=11 54.78%
- AGHDA <11 6.9%
- AGHDA not done 9.13%
Figure 3. Improvement in AGHDA-QOL
Figure 4: Patients satisfying all NICE criteria in the 5 main centres.