REVIEW

EXTENSIVE EXPERTISE IN ENDOCRINOLOGY

UK stance on adult GH replacement: the economist vs the endocrinologist

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Abstract

In the UK, through the use of a forced economic model, endocrinologists are in the curious position of offering GH replacement to some patients with severe GH deficiency (GHD) but withholding it from other patients with even more severe GHD. This approach is counter-intuitive to endocrine practice in treating endocrine deficiency states. For all other endocrine deficiencies, one would opt for treating those with the most severe biochemical evidence of deficiency first. If this endocrine approach was applied to adult GH replacement in an era of rationing, one would start with the GHD patients with a pathologically low IGF1 level. Given that the prevalence of subnormal IGF1 levels in a GHD population is age-dependent, this would result in GH replacement being offered to more young adult onset (AO) GHD and childhood onset GHD adults, and less often to middle-aged and elderly AO GHD adults. This in itself has the added advantage that the skeletal benefits appear more real in the former cohort of patients.

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Introduction

In adults beneficial effects of growth hormone (GH) replacement on a variety of biological endpoints were first convincingly shown in 1989 (1, 2). These two pioneer studies assessed the effects of GH replacement in adults with documented hypothalamic–pituitary disease and GH deficiency (GHD); the studies (1, 2) were double-blind, placebo-controlled, and of 4–6 months' duration. Positive effects, potentially beneficial and attributable to GH, were seen in body composition, consisting of increased lean body mass (LBM) and reduced fat mass (FM), exercise capacity, glomerular filtration rate and renal plasma flow, cholesterol and insulin-like growth factor 1 (IGF1) status. A further endpoint, studied but published separately (3), was quality of life (QoL), which was measured using

generic estimates (Nottingham Health Profile, Psychological General Well-being) and was significantly impaired at baseline in GHD adults compared with the background normal population. However, after 6 months of GH therapy QoL had improved significantly compared with baseline values and the placebo-treated group.

The scene was set for therapeutic advance. No longer could it be stated that GH had no function in adult life. Subsequently a series of predominantly epidemiologically based studies explored the key disadvantages to be expected in populations of adult GHD patients if left untreated for many years. Thus epidemiological and radiological studies (4, 5, 6) concluded that hypopituitary adults, on full endocrine replacement with the exception of GH, had an approximately threefold increase in fracture rate.

Author profile

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Professor Shalet has extensive research interests in the late endocrine effects following treatment of cancer, pituitary disorders and in particular abnormalities of growth hormone (GH) secretion. He is the author/co-author of over 500 articles and more than 200 of these are related to clinical disorders of the GH-IGF-1 axis and/or therapeutic use of GH therapy.

Unsurprisingly there was an early focus on mortality in cohorts of patients with hypopituitarism on full endocrine replacement except for GH. Six large early epidemiological studies (7, 8, 9, 10, 11, 12) had certain features in common; they excluded patients treated for acromegaly or Cushing's disease, the median patient age ranged from 46 to 52 years, the duration of follow-up, i.e. minimum length of time a patient was GH deficient, ranged between 10 and 13 years, and there was a slight preponderance of males (51–62%) in the studied cohorts. Overall, these studies, despite not being in complete agreement, concluded that the standardised mortality ratio (SMR) was increased twofold in these hypopituitary adults, and the main contributor to the increased SMR was vascular disease. The increased vascular mortality was more predominant in females than in males but whether or not the increased vascular mortality reflected cardiovascular rather than cerebrovascular disease remained unsettled.

Definition of GHD

GHD, like all endocrine deficiency states, exists as a continuum from severe to mild (13) merging seamlessly into normality. The key biochemical study defining the GH status threshold below which GH therapy might be offered to a patient was published in 1994 by Hoffman *et al.* (14). These authors (14) compared four methods of assessing GH status in middle-aged adults with hypopituitarism and age-matched controls. The four estimates consisted of the peak GH response to an insulin tolerance test (ITT), 24-h GH profile, basal IGF1 and IGFBP3; the greatest discrimination was achieved with the peak GH response to an ITT, whereby no patient achieved a peak GH response > 3 ng/ml and no control a response < 5 ng/ml. Throughout the article Hoffman *et al.* (14) referred only to GHD; it was only later that their biochemical threshold of a peak GH response of 3 ng/ml was adopted by formal guidelines (15), and quite casually used to define severe GHD as opposed to the broader term GHD which encompasses all degrees of GHD. Pursuing that point further, it is important to appreciate that the vast majority of hypopituitary patients, studied by Hoffman *et al.* (14), had multiple pituitary hormone deficiencies (MPHD). This observation leads to the understanding that the 'gold standard' for diagnosing severe GHD is not a particular provocation test threshold response but rather the presence of MPHD. Confirmatory data published in the same year (1994) by Toogood *et al.* (16), with a much larger cohort of patients, supported the belief that, even if arbitrarily defined, a peak GH threshold of 3 ng/ml to an ITT was a reasonable starting point for deciding which patients qualified for the advancing use of GH replacement in adults.

Benefits of GH replacement

Gradually over time and with an expanding literature, certain key benefits, potential and/or real, were attributed to GH replacement in adults with severe GHD. These consisted of an improvement in body composition, improvement in QoL, reduction in the increased SMR and fracture rate reported in hypopituitary adults or improvement in the surrogate markers for these unwanted adverse outcomes.

Body composition

In almost any new 6-month or 1-year trial of a new method of administering GH, i.e. depot formulations, body composition change is usually the primary endpoint chosen, reflecting, at least in part, the consistency of the responses.

The advantage of the increased LBM and reduced FM appeal because of the associated increase in exercise capacity, potential reduction in insulin resistance, and possible decrease in the elevated SMR reported in the untreated state. Long-term follow-up studies (17) show that the gain in LBM is maintained for at least 10 years of GH replacement both in men and women, although the time course of change differs between the genders. In men, most of the FM lost in the first year of GH replacement does not recur over the next 9 years; whereas in women, the FM that is lost within the first year is regained during the subsequent 2 years of GH replacement, after which FM status is unchanged up until 10 years of GH replacement therapy.

Quality of life

Approximately 35–40% of patients with severe GHD perceive their QoL to be severely impaired (18). Significant benefit in QoL is seen within the first few months of GH replacement in those in whom QoL is impaired at baseline (19). The data supporting these observations are gathered from patient interviews, and the use of generic and disease-generated questionnaires. The benefit in QoL is maintained for at least 6–10 years and the evidence is derived from audit of practice single centre studies (20, 21) and pharmaceutical database registries (22).

As well as the typically early QoL response to GH replacement, the greatest gain in QoL is seen in those patients with the worst QoL at baseline; both attributes are attractive to the clinician and the patient. Curiously and unexplained, severe impairment of QoL is more frequently seen in adult patients with adult onset (AO) GHD compared with patients with childhood onset (CO) GHD (23).

There are additional, even more critical, gaps in our understanding of the impact of GH on QoL. There has been no conclusive demonstration of any correlation

between QoL at baseline or QoL response to GH replacement and baseline peak GH response to a stimulation test or IGF1 status. However, the first glimmer of a relationship was hinted at recently when Varewijck *et al.* (24) observed a weak correlation ($r=0.28$) between QoL status and IGF1 bioactivity after 12 months' GH replacement.

The mechanism underlying the improvement in QoL also remains speculative. Various possibilities have been put forward: a direct CNS effect or an indirect effect via changes in cardiac function, body composition or hydration status. Unfortunately there is no study correlating a change in any of the speculative mechanisms with a change in QoL. Finally, no randomised, placebo-controlled study has ever been carried out in the subset of patients with severe impairment of QoL.

Vascular mortality

In the epidemiological studies which revealed an increased SMR in patients with hypopituitarism on full endocrine replacement with the exception of GH, it was tempting to speculate that the increased mortality was a direct consequence of untreated GHD. The plausibility of the latter suggestion was compromised by the heterogeneity of the cohorts of patients studied (7, 8, 9, 10, 11, 12); there were: i) differences in the primary pituitary pathology, i.e. craniopharyngioma vs pituitary adenoma; ii) variation in the number of patients that received pituitary radiotherapy, known itself to be associated with cerebrovascular disease; and iii) undoubtedly differences in the degree of hypopituitarism and manner of endocrine replacement amongst the cohorts of patients studied.

Furthermore, the epidemiological study cohorts had been GH deficient for at least 10 years (7, 8, 9, 10, 11, 12) and clearly a 10-year randomised, placebo-controlled trial would never take place. Thus an alternative strategy has been employed in which the mortality data available in GH deficient patients on GH replacement have been compared with that of the background population of the country from which the patients were studied. Van Bunderen *et al.* (25) reviewed mortality in 2229 GHD adults treated with GH for a median time of 5.7 years; GH deficient men receiving GH had a mortality not different from the background population, whereas in women, after exclusion of high-risk patients, mortality was not different from the background population except for cardiovascular disease.

Svensson *et al.* (26) used a similar comparative approach with 229 Swedish GH deficient patients who had received GH replacement for a mean time of 5 years and found no difference in overall mortality from that of the background population. More recently, Burman *et al.* (27) investigated all-cause and cause-specific mortality in 1286 Swedish patients with hypopituitarism

prospectively monitored in the KIMS registry database (1995–2009) and compared the data with that of the general population in the Swedish National Cause of Death Registry. In contrast to earlier studies, cardiovascular or cerebrovascular mortality did not significantly exceed that of the reference population. However, an excess mortality in the patient cohort was observed due to two important causes: hypocortisolism in response to acute stress and intercurrent illness; and secondly, increased risk of a *de novo* malignant brain tumour in patients who previously received radiotherapy.

However, in view of the multiple changes taking place in the overall management of patients with pituitary tumours and hypopituitarism since the early epidemiological studies, it cannot be assumed that the normalisation of cardiovascular and cerebrovascular mortality in this cohort of patients is necessarily attributable to GH replacement.

In the absence of unequivocal mortality evidence that GH replacement is beneficial, there is heavy reliance on changes in surrogate markers of vascular disease. Abnormalities in numerous vascular risk factors have been reported in untreated GH deficient adults; these include increased waist-to-hip ratio, dyslipidaemia, endothelial dysfunction, increased intima media thickness, increased fibrinogen, increased PAI-I, increased CRP, insulin resistance and hypertension.

The short-term effects of GH replacement on cardiovascular risk factors are known. A meta-analysis of placebo-controlled studies in GH deficient adults showed favourable effects of short-term (up to 1.5 years) GH replacement therapy on total cholesterol and HDL-cholesterol levels, diastolic blood pressure (BP) and body composition but unfavourable effects on glucose and insulin levels (28). Claessen *et al.* (29) recently reported the effects of long-term GH therapy beyond 5 years on metabolic parameters. Total cholesterol and LDL-cholesterol levels were lower, and HDL-cholesterol levels were significantly higher during long-term GH replacement compared with baseline. Both waist circumference and BMI were significantly higher after 10 years, as were fasting glucose levels. No significant changes were observed in triglycerides, waist-to-hip ratio and BP during follow-up (29).

In a subset of patients who had received 15 years of GH therapy, similar metabolic effects were found. The prevalence of metabolic syndrome was increased after 10 years both in comparison with baseline but also compared with normative age-matched Dutch data (29). Thus the exact net beneficial effect of GH replacement on overall cardiovascular risk remains unknown.

Fractures

In a single centre open-label study, Elbornsson *et al.* (30) studied the effects of 15 years of GH replacement on bone mineral content (BMC) and bone mineral density

(BMD) measured by dual X-ray absorptiometry in 126 hypopituitary adults with a mean age of 49.4 years. There was a sustained increase in total body and lumbar spine BMC and BMD. In femur neck, BMC and BMD peaked at 7 years and then decreased towards baseline values. The authors suggest quite reasonably that this increase in bone mass and density is likely to reduce the fracture risk in GHD patients.

There are, however, a large number of confounding variables which may explain the early epidemiological reports of a two- to threefold increase in fracture rate in hypopituitary adults on full endocrine replacement other than GH; these include adequacy and dosage of glucocorticoid replacement, sex steroid replacement and thyroxine replacement, visual impairment and increased falls and, of course, GHD.

Low bone mass is reported to be, and widely accepted as a characteristic of the adult GH deficient state. However, accumulating data suggest that BMD may not be reduced in the majority of individuals with GHD. Our own experience in GH deficient adults revealed BMD to be dependent on age, with low BMD being observed in the young patients but with patients over the age of 60 years demonstrating a mean BMD Z-score above that of the reference population (31); few patients over 30 years had a Z-score < -2 (31). Further volumetric bone studies revealed no morphometric abnormalities in AO GH deficient patients, whereas CO GH deficient patients have marginally reduced cortical density but significantly reduced cortical bone as a result of reduced cortical thickness and bone size (32).

The bone abnormalities described in the adults with CO GHD are consistent with the studies of GH deficient post-pubertal patients (mean age 19 years) in whom the acquisition of peak bone mass is sub-optimal if they remain off GH replacement following treatment in childhood (33). It should be emphasised however that the most persuasive evidence that GH replacement significantly increases total BMC in this situation was obtained in severely GH deficient subjects defined by an IGF1 level below the first centile (33).

There have been attempts to determine whether the fracture incidence falls in GH deficient adults on GH replacement (34). In reality, however, the goal of determining the contribution of GH replacement, rather than the other confounding variables, in a patient cohort followed long enough over several decades is simply impossible to achieve.

The UK attitude to adult GH replacement

Economist

In 2003 the National Institute of Clinical Excellence (NICE) completed and published its evaluation of the appropriateness of GH replacement in GHD adults in the

UK. To be eligible for GH replacement, it needs to be demonstrated that patients have severe impairment of QoL, reflected by a reported score of at least 11 in the 'QoL Assessment of GHD in Adults' (QoL-AGHDA) questionnaire; this has a score range of 0–25 with a higher score denoting poorer QoL. The guidance further stipulated that patients commenced on GH replacement should be re-assessed 9 months after the initiation of therapy (allowing for a dose titration period of 3 months followed by a 6-month therapeutic trial period) and that GH therapy should be discontinued in those patients demonstrating a QoL improvement of less than seven points on the QoL-AGHDA score.

The initial assessment report commissioned by NICE confined itself to double-blind, placebo-controlled clinical studies; however, in clinical practice there has been a significant reduction in GH replacement dosage subsequent to the early controlled trials as current titration uses IGF1 generation rather than body weight. In addition, it was not possible to determine utility gain and cost per quality-adjusted life years (QALYs) from this initial assessment report and therefore a subsequent health economic cost-effectiveness analysis was undertaken by the Sheffield School of Health and Related Research (SCHARR). This analysis concluded that the long-term beneficial effects of GH on risk factors for fractures and cardiovascular disease had a minor impact on cost-effectiveness; the subsequent analysis was based solely on QoL improvement with GH therapy. To determine the latter, SCHARR used data from KIMS that included ~80% of adult GH replaced patients in the UK at that time.

The Appraisal Committee concluded that a minimum improvement of at least seven points in the QoL-AGHDA score would be needed to achieve an acceptable level of cost-effectiveness. The guidance also indicated that a baseline QoL-AGHDA score of 11 or worse must be present in order for an individual patient to qualify for commencement of GH replacement. The latter ruling was based on data from KIMS indicating that an average improvement of seven points in QoL-AGHDA was only achieved in patients with a baseline QoL-AGHDA score of 11 or worse.

The UK endocrine community argued strongly against the NICE economic argument, pointing out that it was inappropriate to take mean data for cost-effectiveness and to then derive stringent cut-offs for individual patients based on these mean data. It was further argued that the application of an entry hurdle of 11 points on QoL-AGHDA was incorrect when considering individual patient data, as such a baseline score is not a prerequisite for demonstrating an improvement of seven points. In the event, these points of appeal were rejected and the final guidance was published. In reaching this decision, NICE had moved from the usual situation of requiring a demonstration of cost-effectiveness in a treatment population to one in which each patient treated must demonstrate cost-effectiveness against the

mean cost-effectiveness criterion – thereby presumably reducing the cost per QALY to below the level that had been considered cost-effective in the first place!

Endocrine perspective

The approach to GH replacement in adults in the UK clearly represented a form of health care rationing. By forcing the benefit gained in one symptom complex, QoL, into a health economic model, the guidelines for adult GH replacement could be inserted into therapeutic guidance for all treatments across all specialties of medicine with the appearance of a level playing field for all such decision making.

In the meantime, in many European countries and the USA, the overall impact on body composition, cardiovascular risk factors, predictors of skeletal health and QoL was considered sufficiently persuasive for GH replacement to be offered to severely GHD adults on holistic grounds.

It should not be thought however that the 'holistic' approach to adult GH replacement avoided rationing decisions. In the last 10 years published data have shown that adults with partial GHD (GH insufficiency) have abnormalities of body composition and cardiovascular risk factors but to a lesser degree than seen in adults with severe GHD (13). Notwithstanding the fact that the diagnosis of partial GHD in an individual patient may prove extremely difficult, there has been no clinical trial of GH replacement in such a patient cohort and no attempt based on holistic grounds to recommend GH replacement for partially GHD adults. Thus even when the therapeutic decision is based on holistic grounds, rationing insists that GH replacement be reserved for those adults with severe GHD despite the fact that the severity of the GHD is defined in a completely arbitrary manner.

The UK model of adult GH replacement based solely on QoL impairment throws up another conundrum. The conundrum is caused by the lack of any clear relationship between QoL and any biochemical marker of GH status. Thus in individuals with panhypopituitarism and failed GH responses to provocative testing, only those with sufficiently impaired QoL will be offered GH replacement. However, only 50% of middle-aged adults with panhypopituitarism have a subnormal IGF1 level; therefore, this means that endocrinologists are restricted to offering GH replacement to severely GH deficient adults with severely impaired QoL irrespective of IGF1 status, but withholding GH replacement from adults with severe GHD, a subnormal IGF1 level but a reported reasonable QoL.

In 2007, however, Brabant *et al.* (35) clearly showed that in adults with severe GHD, defined by their GH responses to provocative tests, there is a relationship between the peak GH response and IGF1 status; in other words, not surprisingly, those with subnormal IGF1

levels are more severely GH deficient than those with normal IGF1 levels.

Thus in the UK through the use of a forced economic model, endocrinologists are in the curious position of offering GH replacement to some patients with severe GHD but withholding it from other patients with even more severe GHD.

This approach is counter-intuitive to endocrine practice in treating endocrine deficiency states. For all other endocrine deficiencies, one would opt for treating those with the most severe biochemical evidence of deficiency first.

If this endocrine approach was applied to adult GH replacement in an era of rationing, one would start with the GHD patients with a pathologically low IGF1 level. Given that the prevalence of subnormal IGF1 levels in a GHD population is age-dependent, this would result in GH replacement being offered to more young AOGHD and COGHD adults, and less often to middle-aged and elderly AOGHD adults. This in itself has the added advantage that the skeletal benefits appear more real in the former cohort of patients.

A counter-argument to such an approach might be that the QoL indication is predictive of greater patient compliance with GH replacement than the holistic approach. Although there is no evidence to support this counter-argument, it is likely to be true.

However, with the advent of depot GH, which only requires an injection once weekly for replacement purposes, rather than the daily injection, the force of the counter-argument is weakened considerably.

Declaration of interest

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