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RESEARCH

Discontinuation of long-term growth hormone treatment in adults with growth hormone deficiency: a survey of UK practice

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Abstract

Objective: We conducted a survey of UK endocrine clinicians between June 2022 and August 2022 to understand current practices regarding GH treatment discontinuation in adults with growth hormone deficiency.

Design and methods: Using Survey Monkey®, a web-based multiple-choice questionnaire was disseminated to the UK Society for Endocrinology membership. It consisted of 15 questions on demographics, number of patients receiving GH and current practice on GH treatment discontinuation.

Results: In total, 102 endocrine clinicians completed the survey. Of these, 65 respondents (33 endocrinologists and 32 specialist nurses) indicated active involvement in managing patients with growth hormone deficiency. In total, 27.7% of clinicians were routinely offering a trial of GH discontinuation to adults receiving long-term GH therapy. Only 6% had a clinical guideline to direct such practice. In total, 29.2% stated that GH discontinuation should be routinely offered as an option to patients on long-term treatment, whilst 60% were not clearly in favour or against this approach but stated that it should probably be considered, and 9.2% were against. During the GH withdrawal period, most clinicians monitor signs and symptoms (75.4%), measure IGF-1 (84.6%), and complete a quality-of-life assessment (89.2%).

Conclusion: The practice of offering a trial of GH discontinuation in growth hormone deficiency adults on long-term GH therapy is highly variable, reflecting the lack of high-quality evidence. Around a quarter of clinicians offer GH withdrawal for a number of reasons, but only a few have a local clinical guidance. A further 60% of clinicians stated they would probably consider such an approach. Methodologically sound studies underpinning the development of safe and cost-effective guidance are needed.

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Significance statement

In this UK survey of endocrine clinicians managing adults with growth hormone deficiency on long-term GH therapy, we explored for the first-time current practice and views on offering GH treatment discontinuation. In total, 27.7% of clinicians were routinely offering this option for a variety of reasons. Only 6% have local clinical guideline available to direct their practice on this. The majority of clinicians (60%), were not clearly in favour or against this approach but indicated it should probably be considered. In the absence of robust evidence on consequences of GH withdrawal, clinicians proposed monitoring of various clinical, biochemical and quality-of-life parameters during the period of discontinuation. Methodologically sound studies that will underpin the development of a safe, cost-effective guidance are needed.

Keywords: adult growth hormone deficiency; growth hormone; discontinuation

Introduction

Growth hormone deficiency (GHD) is a clinical condition that can present in childhood or adult life. Adult-onset GHD is usually caused by a pituitary tumour and/or its treatments (surgery, radiotherapy) (1). Although the true prevalence and incidence of adult-onset GHD have not been fully established, it is estimated that it affects approximately one per 100,000 people annually; this number doubles when childhood-onset GHD patients are also taken into account (2). GHD in adults (AGHD) is associated with a wide range of clinical features, including abnormal body composition, reduced bone mineral density, decreased muscle strength and exercise capacity, adverse metabolic and cardiovascular risk profiles and impaired general well-being and quality of life (QoL) (3, 4).

In adults, treatment with recombinant human growth hormone (GH) improves many of the clinical features associated with GHD (5). In young adults with severe GHD, GH treatment, following completion of linear growth, continues to provide benefits in lean body mass accrual, bone mineralisation, cardiac function, exercise tolerance and quality of life (6, 7, 8, 9). In the UK, the National Institute for Health and Care Excellence (NICE) recommends treating patients with childhood-onset GHD until achievement of peak bone mass (estimated to be at around the age of 25 years) (10). For adults with GHD aged above 25 years, GH replacement can continue indefinitely, provided that at least a 7-point improvement on the 25-point QoL assessment scale (QoL-AGHDA) is demonstrated during the first 9 months of treatment. It remains uncertain, however, if the beneficial effects of GH administration are sustained throughout adult life. In fact, the few published longitudinal studies in adults over the age of 25 have shown that long-term treatment with GH does not normalise the metabolic profile and it even increases body mass index (BMI) (3, 11, 12).

Currently, GH treatment in adults involves daily subcutaneous injections. Whilst most patients are willing to continue treatment long-term, adherence has been shown to decrease significantly after the first year of therapy, particularly in young adults and in those with childhood-onset GHD (13). Furthermore, a small but significant number of patients choose to stop their GH injections due to a perceived lack of benefit from this treatment, side effects, concerns about long-term safety or due to the burden of the daily subcutaneous administration (3, 13, 14, 15). Additionally, treatment of adults with GHD is associated with considerable healthcare costs. In the UK, the average annual cost is around £3,350 per adult patient, with a lifelong treatment cost of between £42,000 and £45,400 (10).

National and international guidelines provide criteria for treatment initiation and monitoring; however, they do not offer any recommendation on the optimal duration of therapy (10, 16, 17). Consequently, many adults are receiving GH indefinitely, as the evidence on the impact of discontinuing long-term treatment is very limited. A small study with 64 patients by Appelman-Dijkstra *et al.* in 2016 showed no negative effects of GH discontinuation on the overall metabolic profile in patients aged above 60 (14). In adolescents transitioning to adulthood, studies on the effects of GH discontinuation have yielded various results (8, 9, 18, 19, 20, 21, 22, 23, 24). Shalet *et al.* found that adolescents, who discontinue GH treatment after achieving final growth, had lower bone mass accrual compared with those who continue GH therapy (8). Carroll *et al.*, in a group of adolescents with severe GHD at completion of linear growth, showed that lean body mass increased during GH continuation and remained unchanged in those stopping GH treatment; no significant changes in fat mass were demonstrated in either group (9). Given the significant healthcare costs associated with GH treatment, establishing the clinical and cost-effectiveness of long-term therapy is of major importance.

At present, the responsibility for initiating and prescribing GH is confined to clinicians in secondary care with expertise in managing patients with GHD. In the UK, it is unclear how many endocrine centres offer GH to adults with GHD, as no relevant central

registry is available. Furthermore, an audit of GH prescribing in adults has not yet been conducted. To understand the current practice of managing GHD in adults and particularly the aspect of offering treatment discontinuation after long-term GH therapy, a survey of endocrine clinicians (doctors and specialist nurses) was conducted in the UK between June and August 2022. This survey was the first of its kind and aimed to provide baseline information and to establish a foundation for discussion about best practice when offering GH discontinuation in adults on long-term therapy.

Materials and methods

A web-based multiple-choice questionnaire was developed, drawing on current guidance, clinicians' opinions and practice, gaps in the evidence on GH treatment in adults and patients' perspectives. The questions were reviewed for content validity by patients with GHD and by expert clinicians managing patients with AGHD at the authors' institution, which is a tertiary UK endocrine referral centre. The survey was administered by an online platform Survey Monkey® and was distributed to the UK Society for Endocrinology membership. It was also sent to individual clinician contacts and through the Society for Endocrinology social media platform (Facebook®). It remained open from 6 June 2022 until 29 August 2022.

The online survey consisted of demographics inquiries and 12 questions on the number of adults treated with GH in the respondents' centre, the number of adults on GH for more than 5 years and the current practice/criteria used by clinicians when offering a period of GH discontinuation in adults (shown in Supplementary Table 1, see section on supplementary materials given at the end of this article).

Since the survey did not include collecting patient or clinical data and only sought the opinion of healthcare professionals, ethical approval was not required. The research complied with the Declaration of Helsinki.

Statistical analyses

Categorical variables are presented as numbers and percentages. The chi-square test was used to compare differences between categorical variables. A P value of <0.05 was considered significant.

Results

A total of 102 endocrine clinicians (doctors and specialist nurses) completed the survey, the largest proportion of whom were from England (n = 91, 89%). The responses to all questions are summarised in Supplementary Table 2. The general demographics of the respondents are shown in Table 1.

Out of the total respondents, 65 (33 consultant endocrinologists and 32 endocrine specialist nurses) indicated that they were actively involved in managing adults with GHD, and analysis of the replies to the succeeding survey questions relied on this group.

Reported number of patients with AGHD

There were wide variations in the estimated number of patients treated with GH as reported by clinicians in each centre, ranging from 4 to over 1,000 (Figs. 1 and 2). Most respondents (69.2%, n = 45) reported they were treating between 1 and 100 adults (aged above 18 years), with only two clinicians managing over 1,000 patients. About 75.4% (n = 49) of respondents were managing up to 100 patients aged above 25 who have been on GH treatment for longer than 5 years (Fig. 3).

Table 1 Characteristics of endocrine clinicians who participated in the online survey (n = 102).

	Consultant endocrinologists (n)	**Specialist nurses** (n)	**Other*** (n)	**Total number** (%)
Endocrine clinicians who completed the survey				
Consultant endocrinologist	48			48 (47.1%)
Specialist nurse		51		51 (50.0%)
Other*			3	3 (2.9%)
Place of work				
England	39	49	3	91 (89.2%)
Scotland	3	2		5 (4.9%)
Wales	5	0		5 (4.9%)
Northern Ireland	1	0		1 (1.0%)
Clinicians actively involved in managing patients with AGHD				
Consultant endocrinologist	33			33 (32.4%)
Specialist nurse		32		32 (31.4%)
Other*			0	0 (0%)

*Specialist registrar/fellow.
AGHD, adults with growth hormone deficiency.

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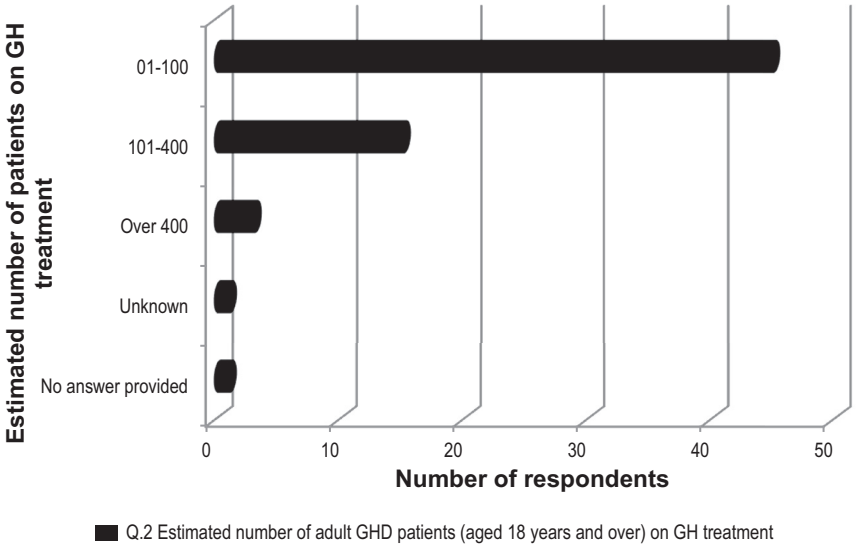

Figure 1

Number of adult patients (aged 18 years and over) with growth hormone deficiency (GHD) on growth hormone (GH) treatment (responses to question 2: 'In total, how many adult patients (over the age of 18 years) with GHD do you currently treat with growth hormone in your practice?').

Practice on offering GH treatment discontinuation

Amongst the 65 respondents managing patients with AGHD, 27.7% (n = 18) were routinely offering a trial period of GH discontinuation to those who had been on treatment for at least 5 years (Table 2). Only 6.2% (n = 4) indicated that they had a guideline/protocol to guide discontinuation of long-term GH treatment in adults, whereas for the majority (90.8% (n = 59)), such guideline/protocol did not exist.

In total, 29.2% of respondents (n = 19) stated that GH discontinuation should be routinely offered to adults with GHD on long-term treatment, whilst 60% (n = 39) reported that this approach should perhaps be considered. The remaining 9.2% (n = 6) would not offer this option (Table 2).

The criteria used by clinicians when considering GH discontinuation in adults on long-term therapy are shown in Fig. 2. Both consultant endocrinologists and specialist nurses proposed patient's choice and clinical judgment as the most important factors dictating this decision (Supplementary Table 2). Specifically, perceived lack of benefits and side effects from GH injections were the most common reasons for stopping the treatment (Supplementary Table 2).

Practice on monitoring after GH treatment discontinuation

When offering (or considering to offer) GH discontinuation, 89.2% (n = 58) of clinicians indicated that patient review should occur within 3–6 months of stopping treatment, and 9% (n = 6) would carry out patient review within 12 months. On this review, the majority (n = 33–54) would complete anthropometric, biochemical, QoL and signs/symptoms monitoring. None of the respondents specified the signs and symptoms

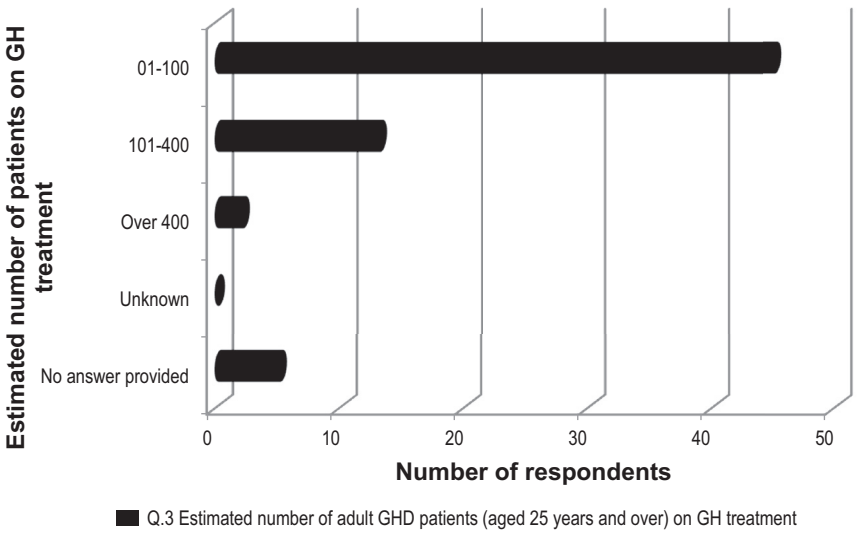

Figure 2

Number of adult patients (aged 25 years and over) with growth hormone deficiency (GHD) on growth hormone (GH) treatment (responses to question 3: 'How many of your adult patients on growth hormone treatment are over the age of 25 years?').

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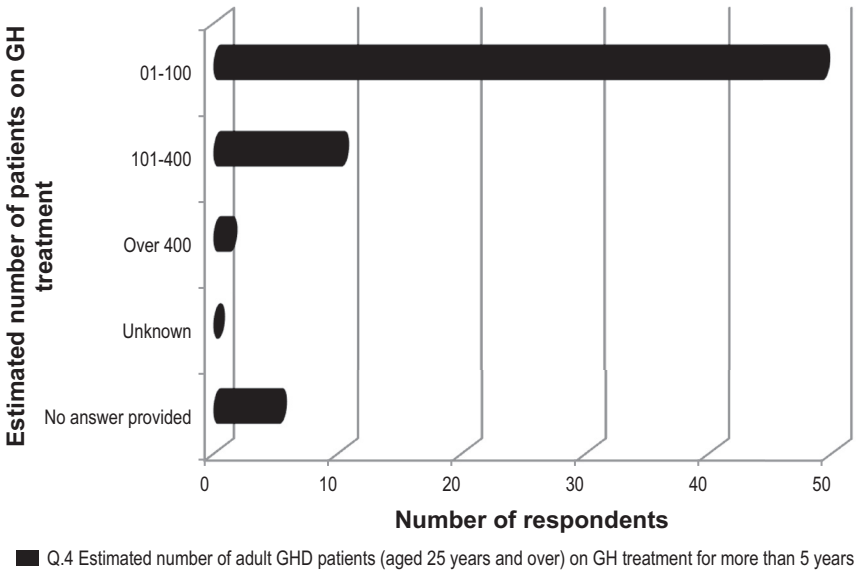

Figure 3

Number of adult patients (aged 25 years and over) with growth hormone deficiency (GHD) on growth hormone (GH) treatment for more than 5 years (responses to question 4: 'How many of your adult patients, over the age of 25 years who are currently on growth hormone treatment, have been on this therapy for more than 5 years?').

they would monitor. A small proportion (n = 8–11, 12–16%) would complete radiological assessments (i.e. bone mineral density and/or body composition measurements) (Fig. 4).

Comparison of responses between consultants and specialist nurses

When comparing responses between endocrine consultants and specialist nurses, a higher number of consultants proposed duration of treatment of more than 15 years or factors like side effects from GH treatment, poor concordance, patient finding the routine injection cumbersome, needle phobia and patient no longer experiencing positive effects as the criteria that should be used for considering a trial of GH discontinuation ($P < 0.05$).

Discussion

This national UK survey highlighted areas of variability and consensus in managing adults with GHD treated with GH. Specifically, in the area of GH discontinuation, 27.7% of endocrine clinicians were already routinely offering a trial period of treatment discontinuation to those who have been on long-term GH therapy, whilst a further 60% were not clearly in favour or against this approach but stated that it should probably be considered. Only 6.2% of the respondents confirmed that a clinical guideline/protocol was available to guide their practice. Additionally, there was general agreement on the criteria that should be used for offering GH discontinuation (mainly patient choice and clinical judgment). In particular, patients having side effects and those who no longer benefit from the treatment were deemed suitable

Table 2 Current practice of offering growth hormone treatment discontinuation in adults with growth hormone deficiency.

	Consultant endocrinologists (n)	Specialist nurses (n)	Total number (%)
Q5. Do you routinely offer a trial period of discontinuation of growth hormone treatment to adult patients who have been on treatment for a long time?			
Yes	13	5	18 (27.7%)
No	20	27	47 (72.3%)
Q7. Do you have a clinical guideline/protocol for discontinuing long-term growth hormone treatment in adults in your department?			
Yes	1	3	4 (6.1%)
No	31	28	59 (90.8%)
Did not answer the question	1	1	2 (3.1%)
Q8. Should adult patients who have been taking growth hormone treatment for a long time be offered routinely a trial period of discontinuation of treatment?			
Yes	10	9	19 (29.2%)
Maybe	18	21	39 (60.0%)
No	5	1	6 (9.2%)
Did not answer the question	0	1	1 (1.5%)

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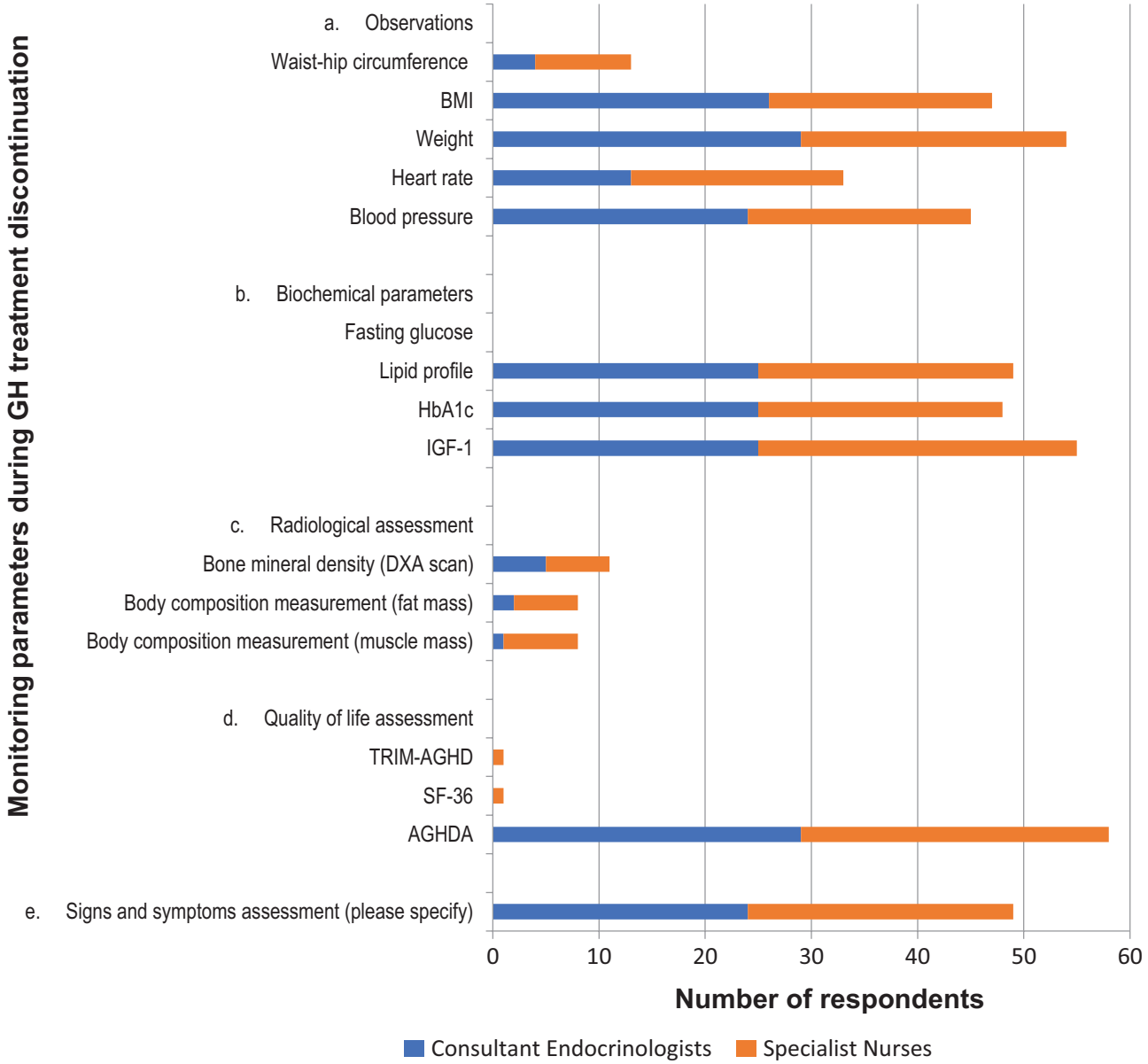

Figure 4

Responses to Q11 of the survey: 'If you are currently offering (or if you were to offer) a trial of growth hormone treatment discontinuation in adult patients, what monitoring do you complete during follow-up clinic visit?'

for a period of GH discontinuation. The optimal timing of the first follow-up has not been established; most clinicians would re-evaluate the patients within the first 6 months of stopping GH.

It is well known that in healthy individuals, GH and IGF-1 secretions decrease with advancing age (25). To date, the optimal duration of GH treatment in adults with GHD has not been established, as it remains unclear if its beneficial effects are sustained in the long term. Our survey showed that most endocrine clinicians (72.3%) do not routinely offer GH discontinuation to adult patients. Furthermore, specifically amongst those who do, only 22.2% confirmed using a locally devised guideline/protocol. These findings are not surprising, given that the existing guidelines do not provide recommendations on the optimal duration of GH treatment in adults or when withdrawal should be considered (16, 17).

Our survey explored further the clinicians' views on GH discontinuation, irrespective of the approach they adopt in their daily practice. Interestingly, the majority (60%) did not have a robust view as to whether GH discontinuation should be offered routinely to adults on long-term therapy (question 8, response 'maybe'), highlighting the lack of sufficient evidence on the

potential sequelae of this approach. Appelman-Dijstra *et al.* suggested that GH could be discontinued in patients aged above 60, provided that dyslipidaemia and hypertension are managed as per cardiovascular guidelines (14). However, this study was not designed to investigate the optimal duration of GH treatment or when discontinuation should be considered. On the other hand, Colao *et al.* found an increase in the total/HDL-cholesterol ratio and the C-reactive protein after 6 months of GH discontinuation in adults with severe GHD; in this report, patients were treated only for 6 months and those above the age of 50 were not included (26).

Amongst the respondents, 60% considered age as a factor influencing the decision on stopping GH. However, there was no consensus on the age limit for this, with the most commonly proposed cut-off being 80 years. The effects of GH discontinuation amongst elderly patients have not been systematically evaluated. To date, only three relevant studies have included patients older than 60 (14, 27, 28), and comparison of their findings is challenging due to differences in methodology and endpoints.

We found that clinicians regard clinical judgement and patient choice as the main drivers for considering a period of GH discontinuation. In particular, patients' perceived lack of therapeutic benefit was highlighted as the main reason (80%). Experience of side effects and poor concordance with the daily injections were the second and third most indicated reasons. These findings are in accord with previous literature reporting that the perception of minimal therapeutic benefit, the fear of side effects and concerns on long-term safety, alongside the dislike of daily injections are the most frequent reasons for which adults with GHD stop their treatment (3, 13, 15). Patients' fear of needles was also noted, although not as prominent as other factors. In comparison with consultant endocrinologists, fewer nurses indicated patients' fear of side effects or of needles as the main reasons. The limited qualitative studies investigating adherence with GH specifically in adults report that patient education incorporating information about potential positive therapeutic effects increases concordance with treatment and promotes self-empowerment (15, 29). Patient education is typically the remit of nurses who usually recognise this specific role as having a positive impact on adherence with treatment. Consequently, nurses tend to not consider needle-phobia or side effects as a barrier to treatment adherence to the same degree as consultant endocrinologists.

An evidence-based protocol for monitoring patients after GH discontinuation is lacking, highlighting a gap in clinical practice. Based on our survey, there seems to be agreement amongst clinicians (66.7%) that review should occur within 3–6 months of stopping GH. The suggested monitoring included mostly clinical (blood pressure, heart rate, weight and BMI) and biochemical parameters (IGF-1, HbA1c and lipid profile), as well as QoL assessment using the AGHDA questionnaire. These findings are consistent with some literature, although scarce, which suggests that GH discontinuation has a negative impact on cardiovascular risk factors and recommending ongoing assessment of lipid abnormalities and hypertension (14, 26, 28, 30). Radiological monitoring (e.g. measurement of bone mineral density, fat mass and muscle mass) was suggested by only 12–16% of the respondents. Limited studies have not shown significant deterioration in bone mineral density after GH discontinuation (14, 28, 31, 32), a finding potentially explaining the responses in our survey.

To date, the impact of GH treatment on patient-reported outcomes remains an open question, as none of the original studies, systematic reviews or meta-analyses have been able to provide clear answers (33, 34, 35, 36, 37, 38). QoL is compromised in treatment-naive patients, and improvements have been noted during the first 12 months of GH administration, particularly amongst those with the most severely affected pre-treatment QoL scores (39, 40, 41). In the UK, NICE recommends that patients over the age of 25 should complete a QoL assessment using the AGHDA questionnaire before commencing on GH and 9 months later (10). In two studies utilising this questionnaire, patients scored worse on emotional reactions and well-being, and also had increased levels of tiredness after a 3–4 months period of GH discontinuation, illustrating the importance of evaluating QoL (27, 28). However, these negative effects were observed only in younger males and were almost absent in older patients. In our survey, the AGHDA questionnaire remained the main monitoring tool during the period of GH discontinuation, with only one clinician opting for the use of treatment-related impact measure – adult growth hormone deficiency (TRIM-AGHD) (42).

The main strength of our study is that, for the first time, it provides real-world information from clinicians specifically involved in the care of patients with GHD on an important topic which is deprived from high-quality evidence. Our survey presents a snapshot of the landscape and gaps in current practice on GH discontinuation. Its endorsement by the Society for Endocrinology facilitated national distribution and engagement by its membership. It is of note that in the UK, GH prescribing is limited within large tertiary endocrine centres, and it is likely that the number of respondents provides a reasonable representation of the group of clinicians actively managing adults with GHD in the UK healthcare system. A limitation is the anonymous design of the survey, which did not allow identification of the geographical distribution of the participating endocrine centres. As a result, we were not able to ascertain if the responses were representative of all UK GH prescribing centres' practice. Further drawback is a possible selection bias, inherent to all surveys. Although we used the Society for Endocrinology membership as our main target audience (due to the lack of other reliable means of disseminating the survey to the appropriate respondents), we also used other recruitment strategies including online dissemination,

social media and targeted e-mails to clinicians to enhance optimal participation. Similar surveys in other countries could clarify the generalisability of our findings.

In conclusion, the practice of offering a trial of GH discontinuation in GHD adults is surrounded by dilemmas and variations, reflecting the lack of high-quality evidence. Around a quarter of clinicians offer this for a number of reported reasons, but only a few have local clinical guidance available. Moreover, a further 60% would probably consider it as an approach. Methodologically sound studies underpinning the development of safe and cost-effective guidance in this field are needed and eagerly awaited.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-23-0533.

Declaration of interest

SC had previously received funding for education grants and lecture fees from Novo Nordisk, Pfizer and Sandoz. HG has received speaker fees from Novo Nordisk, Pfizer and Sandoz. AAT has received speaker fees from Novo Nordisk and Pfizer. NG and AT have no conflicts of interest to declare. NK has served as speaker, investigator and on the advisory board for Pfizer.

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