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CONSENSUS STATEMENT

Appropriate management of growth hormone deficiency during the age of transition: an Italian Delphi consensus statement

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Introduction

Growth hormone deficiency (GHD) describes the impairment of growth hormone (GH) secretion by the pituitary somatotroph cells [1]. GHD may be congenital, with causes, including genetic alterations and structural brain malformations, or acquired, including midline tumours, cranial irradiation, traumatic brain injury, central nervous system infections and inflammatory conditions [2, 3]. GHD in children is characterised by short stature, delayed bone maturation and abnormalities in substrate metabolism, body composition, physical and psychosocial functioning, all of which improve with recombinant human GH (rhGH) therapy [4]. The diagnosis of GHD is based on clinical signs and symptoms, biochemistry and imaging. Although GH stimulation tests are considered the mainstay of diagnostic investigations, the results must be interpreted with caution owing to the variability in cut-off values and reproducibility [3].

Transition refers to the physical and psychosocial changes in adolescent patients during the mid-teens to late teens (usually 15–18 years of age) until about 6–7 years after achievement of adult height [3, 5]. During the transition age, only a small residual capacity of longitudinal growth is left, but body maturity is not yet complete [6]. Discontinuation of rhGH treatment at the end of longitudinal growth in adolescents with permanent GHD is associated with decreased muscle strength and mass, increased body fat (mainly in the abdomen), the arrest or reversal of muscle mass and bone mass density (BMD) gain and lipid profile deterioration [3, 6]. For these reasons, patients whose GHD persists during the transition age need to continue rhGH treatment to obtain full somatic maturation and normalisation of body composition, BMD, quality of life (QoL) and lipid metabolism [3]. There is some evidence that rhGH treatment during transition may result in improved growth and bone health, as well as a better prognosis for metabolic and cardiovascular risks in the long term [3, 7, 8]. Since these patients need to continue treatment to complete their body development [3, 6], a multidisciplinary approach is required to ensure continuity of care during the transfer from paediatric to adult endocrinology services [7].

Guidelines for the diagnosis and treatment of young adults with GHD have been published by the American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), Endocrine Society, European Society of Paediatric Endocrinology (ESPE), Lawson

A full list of collaborators (members of the expert panel) can be found in Appendix 1.

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Wilkins Society, European Society of Endocrinology, Japan Endocrine Society and Endocrine Society of Australia [3, 8–11]. However, clinical practice lacks uniformity in terms of diagnosis and treatment of transition-age patients, the impact of GH replacement during transition has not been adequately assessed in randomised clinical trials (RCTs), validated questionnaires to assess QoL in patients on rhGH treatment in the transition period are not available and there is still uncertainty about the multidisciplinary approach during transition [8]. Hence, a structured transition protocol is essential to establish the best practice for transitioning adolescents with GHD to adult care [7].

A study in Italy in 2015 identified a low level of awareness of these issues in clinical practice and real-world gaps in the management of GHD patients during transition [8]. To address these gaps and assist endocrinologists (adult and paediatric) in the diagnosis and treatment of GHD in transition-age patients, a Delphi consensus process was undertaken to develop clinically relevant recommendations. The current consensus statements address the diagnosis of GHD, benefits of treatment, monitoring and management of transition-age patients with GHD, along with treatment adherence and safety concerns.

Methods

A Delphi consensus study was conducted between July 2020 and July 2021, involving Italian endocrinologists. Members of the scientific board (the authors of this article) identified four topics of interest and formulated statements around those topics based on available evidence. The topics were as follows: (1) Definition of transition age, diagnosis of GHD in transition-age patients and the role of insulin-like growth factor-1 (IGF-1) and other pituitary deficiencies; (2) Benefits of rhGH treatment during the transition (including improvements in lipid, glucose, bone and body composition); (3) Clinical monitoring of transition-age patients to check for development of pituitary deficiencies and adherence, joint management by paediatric endocrinologists and transition-phase endocrinologists, and psychological aspects of care for patients during the transition age; and (4) Continuum of care during the transition, safety issues and new developments.

An expert panel was convened consisting of 45 Italian endocrinologists, selected from among 130 endocrinologists authorised to prescribe GH, who met the following criteria: (1) practised at paediatric endocrinology centres and were involved in the management of children with childhood-onset GHD who are followed up until reaching adult height, and who were experienced in the re-evaluation of pituitary function at the time of transition; or (2) practised at adult endocrinology centres and were involved in the management of adolescents with GHD and in following young adult patients with permanent GHD confirmed after re-evaluation of GH secretion. In a two-round voting system, members of the expert panel voted and provided their opinion on the statements using a web-based survey, after which the results were statistically analysed to arrive at a consensus. Consensus was defined as $\geq 66.6\%$ agreement (i.e. the percentage of votes with scores of 4 or 5 on a 5-point Likert scale [1 = strongly disagree, 2 = disagree, 3 = partially agree, 4 = agree, 5 = strongly agree]).

Detailed methodology is provided in the supplementary material, and details about the participating endocrinologists are provided in Appendix 1.

Results and discussion

The Delphi process yielded 37 recommendations in the first round and 36 in the second round over the four topics (Tables 1, 2, 3 and 4). In round 1, 41 out of 45 endocrinologists completed the questionnaire (91% response rate), with consensus achieved on 14 out of 37 items. In round 2, 35/45 clinicians completed the questionnaire (78%) and consensus was reached on 23 out of 36 items. Below, the statements from each topic will be discussed along with the most relevant results from the preliminary survey and the supporting scientific evidence when available. The statements which failed to gain consensus are discussed in supplementary materials.

Topic 1: Definition and diagnosis (Table 1)

GHD diagnosis depends on clinical features, such as short stature and reduced growth velocity, delayed bone age and insufficient GH response to ≥ 2 stimulation tests [12]. According to guidelines [10, 13], the decision when to reassess depends largely on attainment of adult height, as defined by height velocity < 2 cm/year [7, 14]. Consensus guidelines from various Italian (Italian Society for Pediatric Endocrinology and Diabetes, Association of Medical Endocrinologists, Italian Society of Endocrinology and Italian Society of Adolescent Medicine) and international associations (Endocrine Society, ESPE, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society and Endocrine Society of Australia) for the diagnosis and treatment of GHD in adults recommend retesting for individuals with idiopathic GHD during their transition age unless there is a proven genetic/structural lesion persisting from childhood [8, 10, 11].

Multiple pituitary hormone deficiencies (MPHDs) or isolated GHD can be caused by genetic defects affecting transcriptional factors involved in hypothalamic–pituitary development or genes coding GH, growth hormone-releasing hormone (GHRH) or proteins regulating GH synthesis [5,

Table 1 Statements for definition of transition age, diagnosis of GHD in transition-age patients and role of IGF-1 and other pituitary deficiencies

ID	Item	Level of consensus, % Cut-off ≥ 66.6%		Status
		First round	Second round	
1	**According to the 2006 consensus [48], patients with genetic isolated GHD or MPHD do not need to be retested**	**83**	**91**	**Keeps agreement**
2	**All patients with isolated GH deficiency (with the exception of genetic forms) must be retested upon reaching adult stature**	**88**	**94**	**Keeps agreement**
3	**The gold standard for the diagnosis of GH deficiency in transition-age patients is the ITT [GH peak < 5.0 µg/L (AACE 2019 [3] and Endocrine Society 2011 [11]) or < 6.0 µg/L (in Italy)]**	**49**	**77**	**Gains agreement**
4	During the transition age, the GHRH + arginine test is no longer recommended by AACE 2019 [3] although it is still used as a test during transition in Italy	22	41	Keeps disagreement
5	**All transition-age patients with ≤ 2 PHD and with IGF-1 < –2.0 SDS must be retested to confirm the diagnosis (AACE 2019 [3])**	**59**	**70**	**Gains agreement**
6	Retesting is required in transition-age patients with < 3 PHDs and in patients with structural hypothalamic–pituitary abnormalities (AACE 2019 [3])	29	18	Keeps disagreement
7	In patients with isolated GHD or with the presence of organic hypothalamic–pituitary disease, if clinical suspicion is high, only one test is sufficient, while if clinical suspicion is low, a second test is required (AACE 2019 [3])	46	63	Keeps disagreement
8	The glucagon test can be performed when appropriate using a GH cut-off of ≤ 3.0 µg/L for BMI < 25 kg/m^2 or BMI 25–30 kg/m^2 in patients with a high pretest probability (AACE 2019 [3])	47	53	Keeps disagreement
9	The glucagon test can be performed using a GH cut-off of ≤ 1.0 µg/L for BMI of 25–30 kg/m^2 in patients with a low pretest probability and in obese patients (BMI > 30 kg/m^2) (AACE 2019 [3])	43	44	Keeps disagreement
10	During transition, the macimorelin test can be considered as an alternative test for diagnosis using a GH cut-off ≤ 2.8 mg/L (AACE 2019 [3])	53	50	Keeps disagreement
11	Retesting during transition age is not required in patients with isolated GHD or ≤ 2 pituitary deficits and a history of cranial irradiation or intrathecal chemotherapy if clinical suspicion is high	40	48	Keeps disagreement
12	**In childhood-onset GHD patients, retesting should be considered at completion of linear growth documented by growth velocity < 1.5–2.0 cm/year, or epiphyseal growth plate closure**	**51**	**97**	**Gains agreement**

AACE American Association of Clinical Endocrinologists, *BMI* body mass index, *GH* growth hormone, *GHD* growth hormone deficiency, *IGF-1* insulin-like growth factor-1, *ITT* insulin tolerance test, *MPHD* multiple pituitary hormone deficiencies, *PHD* pituitary hormone deficiency, *SDS* standard deviation score

Statements in bold are those with consensus achieved or maintained at the second round

10, 11]. In these patients, GHD is permanent and it is therefore sufficient to measure serum IGF-1 in the absence of rhGH treatment. However, a stimulation test will be required if the IGF-1 level is not abnormally low in the absence of rhGH treatment [5].

Retesting is also not required in patients with organic hypothalamic–pituitary disease (e.g. suprasellar mass with previous surgery and cranial irradiation, craniopharyngioma, pituitary hypoplasia or ectopic posterior pituitary [EPP]) or with hypothalamic–pituitary structural brain defects or biochemical evidence of ≥ 3 PHDs, together with low-serum IGF-1 levels (< – 2.0 standard deviation score [SDS]) [3, 7, 8, 14], but retesting may be required by local policies and medical insurance companies [5]. Caution should be exercised in patients with EPP as they have less severe clinical and hormonal phenotypes, and some may have normal response to retesting after attaining adult height [15]. However, patients with a low probability of persistent GHD, such as patients with ≤ 2 PHDs and low-serum IGF-1 levels (< – 2.0 SDS), should undergo re-evaluation of the GH axis before resuming rhGH replacement therapy [3, 7].

Surgery and/or irradiation of tumours of the pituitary and hypothalamic area may cause hypopituitarism. The risk of developing GHD after irradiation is positively correlated with the dose and duration of therapy; therefore, retesting in the transition period is required in patients who initially test as GH-sufficient since GHD can develop at a later age [3, 5].

Most individuals (> 60%) receiving rhGH treatment have childhood-onset idiopathic GHD and normal GH responses when retested at the attainment of adult height. The possible reasons could be transient GHD, partial GHD, lack of maturation of the GH/IGF-1 axis or inaccuracy of the

Table 2 Statements for benefits of GH treatment (lipid, glucose, bone, heart, body composition) during the transition age

ID	Item	Level of consensus, % Cut-off ≥ 66.6%		Status
		First round	Second round	
13	**With regard to patients undergoing retesting during transition age, it is necessary to discontinue rhGH therapy for ≥ 1 month to allow a better evaluation of the patient's endocrine, metabolic, and subjective well-being (e.g. QoL)**	**93**	**91**	**Keeps agreement**
14	**Prolonged rhGH withdrawal before retesting in severe GHD patients may have detrimental metabolic effects (especially with regard to lipid profile, body composition and bone mineral density)**	**27**	**71**	**Gains agreement**
15	**With regard to rhGH therapy prescription in patients during transition age, clinicians should follow the cut-offs of their National Drug Agencies (e.g. AIFA Note 39: peak GH < 6.0 µg/L after ITT and < 19.0 µg/L after GHRH + arginine)**	**63**	**85**	**Gains agreement**
16	**With regard to the GH stimulation test in patients during transition age, cut-offs should be adapted to specific clinical scenarios (e.g. obesity) or the pretest probability with particular attention to confirming previous test findings (e.g. clonidine, arginine, etc.)**	**77**	**85**	**Keeps agreement**
17	**The discontinuation of rhGH therapy in transition age is associated with a worsening lipid profile in severe GHD, especially in individuals with a long withdrawal period, whereas the restart of rhGH therapy is associated with an improvement in lipid profile**	**73**	**83**	**Keeps agreement**
18	**Glucose and HbA1c evaluation are useful for monitoring metabolic risk, despite glucose metabolism abnormalities being infrequent during the transition phase**	**23**	**80**	**Gains agreement**
19	**rhGH therapy improves bone density after final height achievement and peak bone mass maintenance during adulthood**	**85**	**94**	**Keeps agreement**
20	**There are insufficient data to consider reduction of muscle strength as a criterion to restart rhGH therapy during the transition phase**	[a]	**71**	**Gains agreement**

AIFA Italian Medicine Agency, *GH* growth hormone, *GHD* growth hormone deficiency, *GHRH* growth hormone–releasing hormone, *HbA1c* glycated haemoglobin, *ITT* insulin tolerance test, *QoL* quality of life, *rhGH* recombinant human growth hormone

[a]The question was not included in round 1 of the Delphi process

Statements in bold are those with consensus achieved or maintained at the second round

diagnostic procedures [5, 10]. According to AACE guidelines, GH stimulation tests should be performed in individuals with a history of GHD if the intention is to initiate rhGH therapy upon confirmation of diagnosis, and should only be performed after other PHDs are optimally corrected with stable hormone replacement doses [3].

Although the panel disagreed on the number of retests based on degree of clinical suspicion, AACE guidelines and the 2007 GH Deficiency Consensus suggest that the number of GH stimulation tests should be guided by the degree of clinical suspicion for GHD. If clinical suspicion is high, one GH stimulation test is sufficient, but if clinical suspicion is low, then a second GH stimulation test should be performed [1, 3, 10].

The insulin tolerance test (ITT; based on insulin-induced hypoglycaemia) is the gold standard test to establish the diagnosis of adult GHD. Although guidelines differ on suggested cut-offs for GHD diagnosis during transition, based on present evidence, the suggested peak GH cut-off is < 5.0 µg/L [3] or < 6.0 µg/L [8, 10]. An ITT cut-off for peak GH of 5.6 µg/L for young adults in the transition period has also been reported [5, 11]. However, this test carries a potential risk of severe hypoglycaemia and is contraindicated in patients with epilepsy or heart disease [3, 7].

We assessed whether there was any difference in responses from adult and paediatric endocrinologists for items where there was disagreement. Some differences were noted. For item #4, adult endocrinologists were more likely to disagree with the statement regarding the GHRH + arginine test (i.e. consider that the test is appropriate). This test is widely used in Italy, with largely positive results in adults, despite concerns about the risks and costs compared with alternative tests, such as the ITT. Regarding item #6, a higher percentage of adult than paediatric endocrinologists were in agreement with retesting, even when pituitary function appears to be extensively compromised. This may indicate these adult endocrinologists are more cognisant of the need to comply with the Italian Medicine Agency (AIFA) Note #39 (which outlines diagnoses for which rhGH can be reimbursed by the Italian National Health Service). In contrast to a general disagreement among paediatric endocrinologists with item #7, this item just reached consensus among adult endocrinologists. For item #11, there was a higher degree of disagreement among adult, compared with

Table 3 Statements for clinical monitoring of patients in the transition age and treatment adherence

ID	Item	Level of consensus, % Cut-off ≥ 66.6%		Status
		First round	Second round	
21	Monitoring of BMI and W/H ratio are sufficient for routine evaluation of body composition during transition age, and other investigations (e.g. BIA or DXA) are unnecessary	44	34	Keeps disagreement
22	**Cardiometabolic parameters should be monitored at least once a year during transition age (e.g. total cholesterol and triglyceride profile, blood pressure monitoring)**	**59**	**89**	**Gains agreement**
23	Only patients with reduced BMD should have a repeat DXA scan after ≥ 2 years. TBS could be useful for evaluation of vertebral fracture risk	80	60	Loses agreement
24	**QoL should be monitored once a year (e.g. with QoL-AGHDA questionnaire)**	**80**	**77**	**Keeps agreement**
25	**In patients with GHD due to hypothalamic–pituitary tumours, brain MRI should be periodically performed, irrespective of tumour remnant size**	**83**	**91**	**Keeps agreement**
26	**IGF-1 serum levels should be assessed every 6–12 months, and should always be measured in the same laboratory**	**98**	**97**	**Keeps agreement**
27	**The transition of the GHD patient from paediatric to adult care should be conducted by a multidisciplinary team involving both paediatric and adult endocrinologists together with mental health professionals, within a single hospital setting, addressing patients' needs in order to improve therapeutic adherence**	**90**	**94**	**Keeps agreement**
28	**The role of the injection schedule for rhGH therapy, frequent monitoring of response and patient support are all important for maintaining adherence**	**98**	**94**	**Keeps agreement**

BIA bioelectrical impedance analysis, *BMD* bone mineral density, *BMI* body mass index, *DXA* dual-energy X-ray absorptiometry, *GHD* growth hormone deficiency, *IGF-1* insulin-like growth factor-1, *MRI* magnetic resonance imaging, *QoL* quality of life, *QoL-AGHDA* Quality of Life Assessment of Growth Hormone Deficiency in Adults, *rhGH* recombinant human growth hormone, *TBS* trabecular bone score, *W/H* waist-to-hip ratio

Statements in bold are those with consensus achieved or maintained at the second round

Table 4 Statements for continuum of care during the transition, safety and new developments

ID	Item	Level of consensus, % Cut-off ≥ 66.6%		Status
		First round	**Second round**	
29	Therapy should continue at the same paediatric dose range (rhGH 0.025–0.035 mg/kg/day) and, towards the end of transition age, down-titrated to an adult dose	21	12	Keeps disagreement
30	**Therapy should continue at a dosage intermediate between paediatric and adult dose ranges (0.012–0.025 mg/kg/day), and progressively reduced every 6–12 months, to attain IGF-1 levels between 0 and + 1.0 SDS of the age-specific reference range**	**58**	**68**	**Gains agreement**
31	Therapy should continue with the adult dosages (0.1–0.3 mg/day)	26	15	Keeps disagreement
32	If > 12 months have elapsed between discontinuation of therapy and retesting, rhGH should be restarted at adult dosages (0.1–0.3 mg/day), with progressive increases to attain IGF-1 levels of between 0 and + 1.0 SDS of the age-specific reference range	30	48	Keeps disagreement
33	**It is recommended that serum IGF-1 is the biomarker used for guiding rhGH dose adjustments, and IGF-1 SDS should be maintained between 0 and + 1.0**	**85**	**83**	**Keeps agreement**
34	**Adverse events of rhGH therapy during the transition age are uncommon, especially in the absence of a long interval between retesting and restarting therapy**	**78**	**85**	**Keeps agreement**
35	**The occurrence of adverse events during rhGH therapy in transition age is rare, and these are mainly musculoskeletal symptoms, which may require dose adjustment (or even treatment discontinuation)**	**63**	**71**	**Gains agreement**
36	A previous malignancy history represents an absolute contraindication to rhGH therapy during transition for the increased risk of relapse or the increased risk of a second malignancy	17	9	Keeps disagreement

IGF-1 insulin-like growth factor-1, *rhGH* recombinant human growth hormone, *SDS* standard deviation score

Statements in bold are those with consensus achieved or maintained at the second round

paediatric, endocrinologists, again related to AIFA Note #39.

Topic 2: Benefits of rhGH during transition (Table 2)

An algorithm proposed in a consensus statement from the ESPE suggested that a GH stimulation test should be performed when growth velocity decreases to < 1.5 or 2.0 cm/year, but after discontinuing rhGH therapy for 1–3 months [16]. rhGH therapy raises IGF-1 levels, and together, they suppress endogenous GH secretion through negative feedback; therefore, any retesting is advised at least 1 month after cessation of rhGH therapy [5].

Discontinuation of rhGH treatment in patients with GHD during transition induces significant and potentially unfavourable changes in IGF-1 and body composition, both of which are reversed after resuming rhGH treatment [5, 17]. According to the AACE guidelines, retesting for GHD with GH stimulation tests is required after longitudinal growth is completed in transition patients with idiopathic isolated GHD, and those with low-normal (between 0 and – 2.0 SDS) or low-serum (< – 2.0 SDS) IGF-1 levels ≥ 1 month after discontinuation of rhGH therapy [3].

GHD is a known cardiovascular risk factor as it alters the lipid profile (increases low density lipoprotein [LDL] and decreases high density lipoprotein [HDL] cholesterol), induces hypercoagulability, atherosclerosis and endothelial dysfunction and contributes to increased morbidity and mortality of adults with GHD and hypopituitarism without rhGH therapy [18]. Reportedly, a longer gap in rhGH re-initiation results in greater derangements in lipid profile parameters [7, 19]. While 2-year rhGH discontinuation was associated with a significant increase in waist circumference ($P < 0.0001$), serum total cholesterol ($P < 0.0001$) and serum fibrinogen ($P = 0.0004$) [20], a mean 4.4-year discontinuation significantly increased total cholesterol, LDL cholesterol and triglycerides ($P < 0.0001$) in half of the cohort [19]. Re-initiation of rhGH therapy has been shown to improve cholesterol levels, endothelial function and QoL [7, 19]; however, only long periods of rhGH therapy (in the range of 5–10 years) were associated with improved lipid profiles in adult GHD patients [7].

There is no clear evidence that changes in glucose homeostasis can be attributed to GHD or body composition/adiposity or both, or that such changes increase the risk of developing diabetes [7]. Adolescents with childhood-onset GHD have been reported to show greater insulin sensitivity at the time of initial diagnosis and after rhGH is withdrawn when they reach final height, whereas adults with GHD have been found to have an increased likelihood of insulin resistance [7].

Studies showed that, in patients with persistent GHD who discontinued rhGH therapy in the transition period, lean mass decreased by 8% and fat mass increased by 10–17% compared with either GH-sufficient individuals or those who continued rhGH after 2 years of observation [17, 21–23]. Early changes occurred in body composition after a median of 6 months' cessation of rhGH therapy in patients who attained final height, with significantly lower muscle cross-sectional area (CSA) and a two-fold increase in fat CSA compared with patients who were no longer GH-deficient at final height [18]. Re-initiation of rhGH therapy resulted in a notable improvement in body composition, with a 14% increase in lean mass and 7% reduction in fat mass over 2 years of GH replacement [7, 18]. Reduced muscle strength in GHD patients has been attributed to reduced muscle mass and not to reduced contractile function [7]. Thus, short-term body composition changes during rhGH therapy withdrawal are good clinical markers of severe GHD [24].

Childhood-onset GHD can result in developmental bone mass deficits both at the time of diagnosis and at retesting after reaching final height [7]. A study by Tritos et al. showed that an interval of 6–12 months' cessation of rhGH therapy was associated with reduced femoral neck BMD [25]. Results from studies with reinstitution of rhGH therapy after the attainment of final height have been inconsistent; some have reported a positive effect on BMD, with a 3–6% increase up to 2 years [26–30], while others did not find any change in BMD up to 2 years after either discontinuation of rhGH or after reinstituting rhGH therapy [21, 31]. GH replacement therapy seems to produce a mild but continuous beneficial effect on bone balance if given over a prolonged period and might be crucial during the transition age for the achievement of peak bone mass [32].

An assessment of the consistency of views between paediatric and adult endocrinologists for items with disagreement suggested that there was only a difference in item #14, where a lower level of agreement with the item statement was seen among adult endocrinologists. This appeared to be based on the paucity of data supporting the contention (i.e. that prolonged rhGH withdrawal before retesting in patients with severe GHD may have detrimental metabolic effects).

Topic 3: Clinical monitoring during transition (Table 3)

Long-term monitoring of pituitary function is recommended, irrespective of the aetiology of GHD, because development of additional PHDs may be delayed and can develop up to 21 years after GHD diagnosis [20, 33, 34]. MPHD is more likely to develop in patients with severe organic isolated GHD, especially those with history of intracranial tumour, congenital abnormalities of pituitary development (e.g. ectopic posterior pituitary and pituitary stalk anomalies; pituitary stalk interruption syndrome) or genetic mutations affecting hypothalamic–pituitary axis development and/or function [15, 33].

Other factors associated with a higher incidence of MPHD are older age, female gender and longer follow-up duration [33]. A study by Otto and colleagues showed a 45% increase in the occurrence of MPHD, where half the patients with isolated GHD developed the second hormone deficiency 5 years after diagnosis [34]. Common PHDs include luteinising hormone/follicle-stimulating hormone deficiencies, followed by thyroid-stimulating hormone, adrenocorticotropic hormone and antidiuretic hormone deficiencies [34].

All guidelines recommend that height, weight, body mass index (BMI), waist and hip circumference, lipid profile, IGF-1 levels, serum glucose and HbA1c should be monitored every 6 months, and BMD, intima media thickness and specific QoL questionnaires should be evaluated every year [3, 5, 8, 10]. Since adults with GHD have an increased risk of cardiovascular morbidity and mortality, cardiovascular parameters, including fasting lipids, systolic and diastolic blood pressure and heart rate, should be monitored at 6- to 12-month intervals, while more detailed examinations, such as electrocardiogram, echocardiogram and carotid echo-Doppler examinations, may be performed if clinically indicated according to local best practice [3]. Body composition can be measured annually by simple anthropometry using internationally accepted recommendations, including those issued by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) or International Diabetes Federation, and ethnicity-specific guidelines where available [10]. Measurement of bone mineral content and BMD is suggested in GH-deficient patients before starting rhGH therapy, as adults with GHD have an increased risk of developing osteopenia and osteoporosis [3, 32]. In case of abnormal BMD, dual-energy X-ray absorptiometry (DXA) scans should be repeated at 2- to 3-year intervals to assess the requirement for additional bone-directed treatment modalities [3, 10, 35]. DXA scans can also be used for the accurate measurement of lean mass and fat mass [10, 35]. Monitoring of, and potentially supplementation with, vitamin D in children with GHD has been suggested, with the aim of optimising the effects of rhGH [36], an approach that may also be useful in transition-age individuals.

Although rhGH therapy is not associated with an increased incidence of either type 1 or type 2 diabetes mellitus, it may increase insulin resistance and at times lead to worsening of glucose tolerance. Thus, careful monitoring is required in individuals who are at risk of developing type 2 diabetes, such as those with a positive family history, or who are obese. If type 2 diabetes develops, rhGH therapy can be continued along with diabetes management [10].

Untreated transition-age GHD patients frequently report impaired QoL; therefore, baseline QoL should be assessed using specific Quality of Life in Adult Growth Hormone Deficiency Assessment (QoL-AGHDA) questionnaires before rhGH treatment is commenced, and at 12-month intervals to monitor the impact of rhGH therapy on QoL [3]. Many GHD patients lack self-confidence (due to short height), abstain from socialising and may have psychological difficulties [18, 37, 38]. While Stouthart and colleagues reported an improvement in QoL within 6 months of rhGH therapy re-initiation [39], no significant changes were observed in many RCTs, indicating that the data on QoL remain inconclusive [17, 29, 30].

IGF-1 responses are a marker of GH replacement outcomes in young adults, are associated with increases in lean body mass and HbA1c during rhGH therapy and are dependent on age, gender, BMI and baseline IGF-1 levels [10, 40]. Indicators of severe GHD, such as low GH peak levels, young age at diagnosis and severe short stature, are associated with low-serum IGF-1 levels [7]. Currently, there are no alternative markers of GH action that are superior to IGF-1 [10].

There was consensus that periodic brain magnetic resonance imaging (MRI) should be conducted in patients with GHD due to hypothalamic–pituitary tumours. Guidelines also suggest that clinicians should perform baseline MRI in patients with any post-surgical tumour remnant in the hypothalamic–pituitary region before initiating rhGH, and conduct periodic MRIs during rhGH therapy [3].

Transition is a critical period when adolescents may drop out of follow-up medical care, which leads to increased morbidity and mortality. Persistence with rhGH therapy was reported in 75.3% and 67% of children and adolescent patients, respectively [41, 42]. Therefore, it is imperative that paediatricians provide early counselling to patients and caregivers about the potential of future transition to the adult endocrinologist and collaborate closely to facilitate a seamless transition for improved long-term outcomes and patient experience [3, 41]. Factors responsible for low adherence include lower socioeconomic status, failure to take the injection or refill the prescription, being away from home, apathy with long-term injection therapy, concern about long-term complications, drug shortage and limited access to the pharmacy [43]. Patient adherence can be improved by involving the patient in the choice of rhGH injection, which consequently improves the therapeutic effects of rhGH therapy [44], and the use of rhGH delivery systems that are easy for patients to use and that automatically provide information on adherence directly to healthcare professionals [45].

An assessment of the consistency of views between paediatric and adult endocrinologists for items with disagreement did not identify any differences.

Topic 4: Continuum of care, safety and new developments (Table 4)

It is recommended that serum IGF-1 levels are used as a biomarker for guiding rhGH dose adjustments [3, 10]. Dose selection among transition-age patients should focus on raising serum IGF-1 levels into the normal range

while avoiding adverse effects [3, 30]. Doses ranging from 0.0125 to 0.025 mg/kg/day have been used in the transition phase in several studies, and GHD patients receiving doses of 0.025 mg/kg/day performed better than those receiving 0.0125 mg/ kg/day, but this dose-dependent effect was not consistent between studies [35].

Guidelines recommend restarting rhGH therapy in transition patients at a dose that is 50% of the dose used in childhood (0.01–0.03 mg/kg/day). Serum IGF-1 levels should be monitored every 1–2 months to avoid exceeding the age-specific upper limit of the normal range (IGF-1 > 2.0 SDS) [3, 8, 10]. Once maintenance doses are achieved, follow-up can be implemented at approximately 6- to 12-month intervals [3, 7, 8]. Modification of doses based on the clinical response, serum IGF-1 levels, adverse effects and individual patient considerations have shown improved treatment efficacy in patients who adhere to treatment [3].

Treatment with rhGH is generally regarded as being safe [1, 5, 10]. Adverse effects are usually mild and dose dependent, are more common in elderly and overweight/obese patients and less frequent in adults who adhere to treatment [1]. Common adverse effects include swelling due to fluid retention, nausea, pain in the joints and muscles, muscle stiffness and paraesthesia. Occasionally reported adverse effects include headaches with tinnitus, gynaecomastia (in older men), carpal tunnel syndrome, benign intracranial hypertension, papilloedema, arterial hypertension, glucose intolerance, hyperinsulinaemia and diabetes [1].

Long-acting GH (LAGH) formulations that can be administered weekly (in contrast to the daily rhGH injections) are being developed to facilitate treatment adherence [3]. RCTs of some LAGH preparations have reported noninferiority compared with daily rhGH injections for improved growth velocity and body composition, with no unexpected LAGH-related adverse events being reported during short-term therapy [46]. However, long-term studies of LAGH preparations in patients with GHD are needed to address questions about methods of dose adjustment, timing of IGF-1 monitoring, safety, efficacy and cost effectiveness [46]. The first LAGH Skytrofa (lonapegsomatropin-tcgd; Ascendis Pharma) received FDA approval in August 2021 for the treatment of GHD patients aged ≥ 1 year [47].

For items #29–31, the adult endocrinologists broadly agreed with all statements, while the paediatric endocrinologists broadly disagreed. Regarding item #35, the proportion of paediatric endocrinologists who considered adverse events to be rare was lower than that of adult endocrinologists. This discrepancy may be associated with therapeutic inertia, whereby paediatrician endocrinologists sometimes delay reducing the rhGH dose and, as a result, are more likely to encounter adverse events.

Conclusion

Although the existing guidelines have described how to re-evaluate GHD during transition, there is no clear plan about the delivery of transitional care from paediatric to adult services. Using the Delphi method, we have provided recommendations in several areas of diagnosis and management of GHD in transition-age patients. It is hoped that these statements will help increase adherence to guideline recommendations and improve the diagnosis and management of long-term outcomes of patients with permanent GHD after the attainment of adult height.

Appendix 1

Panel of participating experts ($n = 41$).

Delphi panel members (paediatric and adult endocrinologists)	Affiliations
Gianluca Aimaretti	Università del Piemonte Orientale, Novara
Maria Rosaria Ambrosio	University of Ferrara, Section of Endocrinology, Geriatrics & Internal Medicine, Department of Medical Sciences, Ferrara
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Manuela Caruso	UOC Clinica Pediatrica Università di Catania, Centro di Endocrinologia Pediatrica, Dipartimento di Medicina Clinica e Sperimentale, Catania
Roberto Castello	A.O.U.I. Verona, Medicina Generale A, Verona
Filippo Ceccato	Università di Padova, Dipartimento di Medicina, Unità di Malattie Endocrine, Padova
Tania Cerbone	AORN—S. G. Moscati Avellino, UOS di Genetica Medica e Centro Regionale Diagnosi e Terapia Bassa statura, Avellino
Valentino Cherubini	Ospedali Riuniti di Ancona "G. Salesi", Azienda Ospedaliero-Universitaria, Head, Pediatric Endocrinology and Diabetology Unit, Department of Women's and Children's Health, Ancona
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Delphi panel members (paediatric and adult endocrinologists)	Affiliations
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Silvia della Casa	Università Cattolica Fondazione Policlinico Gemelli, Endocrinologia, Roma
Carolina Di Somma	A.O.U Federico II Napoli, UOC Endocrinologia, Napoli
Maria Felicia Faienza	Università degli Studi di Bari "A. Moro", Dipartimento di Scienze Biomediche e Oncologia umana, Unità di Pediatria, Bari
Valentina Gasco	Città della Salute e della Scienza di Torino, Università di Torino, SCDU Endocrinologia, Diabetologia e Metabolismo, Torino
Rossella Gaudino	University of Verona, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Division, Verona
Claudio Giacomozzi	Carlo Poma Hospital, ASST-Mantova, U.O.C. of Pediatrics, Department of Maternal and Child Health, Mantova
Claudia Giavoli	IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Endocrinology Unit, Department of Clinical Sciences and Community Health, Milan
Laura Guazzarotti	Azienda Ospedaliera Universitaria di Padova, Dipartimento Salute Donna e Bambino, UOSD Endocrinologia Pediatrica, Padova
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Gabriela Malgorzata Wasniewska	Dipartimento "G. Barresi" Università di Messina, Dipartimento di Patologia Umana dell'adulto e dell'età evolutiva, Messina
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Author contributions SC, MM and MS designed the project. All authors were members of the scientific board, and thus prepared and revised the survey statements, and analysed and interpreted the results. All the authors critically reviewed and approved the final manuscript for submission.

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Declarations

Conflict of interest S. Cannavò has received payment from Sandoz for participating in this project and received lecture fees from Pfizer, HRA and Recordati. S. Loche has received consultancy and lecture fees and research support from Merck Serono, consultancy and lecture fees from Sandoz, and lecture fees from Ipsen and Pfizer. D. Ferone has received consultancy fees from Novartis-AAA, Recordati, Sandoz and Camurus. M. Cappa has received consultancy and lecture fees from Sandoz, Novo Nordisk, Pfizer and Merck Serono. A. Isidori has received consultancies and lecture fees from Sandoz, Merck Serono, Takeda and Novo Nordisk Foundation. M. Salerno has received consultancy fees from Sandoz, Merck, Novo Nordisk and Pfizer, and research support from Merck. M. Maghnie has received consultancy fees from Pfizer, Sandoz, Merck, Novo Nordisk, Ascendis and Biomarin, research support from Pfizer and Merck, and honoraria from Pfizer, Sandoz, Merck, Novo Nordisk, Ascendis and Biomarin.

Ethical approval This article does not contain any studies with human or animal participants performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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