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Review Article

Management of childhood-onset growth hormone deficiency in patients transitioning from pediatric to adult care: A review of the literature and consensus report from a panel of experts in Saudi Arabia

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Abstract

Despite increased recognition of the importance of optimizing care for patients with childhood-onset growth hormone deficiency (CO-GHD) during the transition period from pediatric to adult services, its implementation in clinical practice in Saudi Arabia remains challenging. By an initiative from the Saudi Society of Endocrinology and Metabolism, a panel comprising 11 experts, including both pediatric and adult endocrinologists with practical experience in the clinical management of patients with CO-GHD, was convened to discuss issues relating to transition care in this patient population. The primary objective of this consensus document was to develop the first clinician-led consensus statement that establishes best practices when transitioning adolescents with persistent CO-GHD to adult care in Saudi Arabia. A modified Delphi method was applied to develop consensus statements. A literature review was performed, and 20 statements were subsequently formulated. After two rounds of Delphi, consensus was achieved for 18 of the 20 statements.

Keywords: Adult endocrinologist, Consensus, Childhood-onset growth hormone deficiency, Growth hormone replacement, Pediatric endocrinologist, Saudi Arabia, Transition of care

Introduction

Childhood-onset growth hormone deficiency (CO-GHD) is an endocrine condition associated with several health issues that require specific attention during the transition period from adolescence to young adulthood.[1] Since the timing of this transition period coincides with the transfer of care from a pediatric to an adult endocrinologist, a care gap is created as a consequence of losing patients to follow-up. A suboptimal transition from pediatric to adult services can lead to measurable adverse outcomes, higher costs to both the health system and the family, as well as low levels of patient and family satisfaction.[2,3] Despite the availability of international clinical practice guidelines providing the framework for transitioning young adults with CO-GHD, notable variation exists between healthcare providers in daily practice in clinical assessment, coordination of care, and management among pediatric and adult services.[4–8]

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A panel comprising 11 experts, including both pediatric and adult endocrinologists with practical experience in the clinical management of patients with CO-GHD, was convened to discuss and debate on issues related to transition care in this patient population. The primary objective of the meeting was to use the Delphi technique to develop a consensus statement that establishes best practices when transitioning adolescents with persistent CO-GHD to adult care and provides practical guidance to pediatric and adult endocrinologists in the clinical setting to ensure optimal patient outcomes.

The topics reviewed in this document include the definition of the transition period and CO-GHD, diagnostic criteria, eligibility criteria for retesting, and the management of patients with CO-GHD during the transition period. These recommendations are intended to support rather than replace physicians' clinical judgment.

Materials and Methods

A consensus-based approach, utilizing a modified Delphi technique, was employed.[9–12]

Preparatory Phase

In preparation for the in-person meeting, the appointed chairperson identified seven main topics of interest that would serve as the sections for review. A panel of 11 experts from various healthcare sectors in Saudi Arabia across different geographical regions, specializing in both pediatric and adult endocrinology with extensive experience in treating transition patients with CO-GHD, was invited to take part in the consensus process. Members of the selected expert panel were assigned to one of the seven workstreams depending on their interests and expertise, and they developed content within their respective sections to be presented during the in-person meeting. A literature search was conducted in April 2022 using PubMed by each panelist to identify relevant publications.

The first step in the Delphi process involved the generation of an initial list of topics for the voting consensus process. The appointed chairperson formulated an initial list of practical statements to guide the discussions around aspects related to the management of patients with CO-GHD during the transition period. A steering committee consisting of six experts was formed, and a virtual meeting was held in May 2022, where they reviewed and confirmed the list of statements for inclusion in the Delphi consensus process. The steering committee also reached an agreement on the process, such as defining the criteria for consensus and the number of rounds.

Round 1 Delphi Survey

Prior to round 1, data on the experts' backgrounds and relative experience with the topic were collected via an online questionnaire. For the first round of voting, a total of 20 statements were circulated by e-mail to all 11 panel members. Experts were asked to independently rate their level of agreement with each statement using a 5-point Likert scale. A free-text response was also available, providing the opportunity to elaborate or explain responses. Statements rated ≥4 by 75% or more of the participants were accepted as achieving consensus.[13]

Round 2 Delphi Meeting

An expert consensus development meeting was held in person for round two to facilitative interactive discussion. The Saudi Society of Endocrinology and Metabolism oversaw and supported the process. The presentations prepared by the panel members were presented, followed by the results of the round one of the Delphi process. Statements that did not meet the criteria for agreement or were ambiguous were reviewed, discussed, refined, and reformulated as needed. A second round of votes was conducted using the same voting method as described for round 1.

Definition of the Transition Period

Blum *et al*. defined transition care as: *"The purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care systems."* The term *"transition"* refers to a complex set of attitudes, skills, and processes that facilitate this movement, while *"transfer"* refers to the change in service delivery from pediatric to adult services.[14] Adolescence is a transitional period from childhood to adulthood. It starts with the onset of physiologically normal puberty and ends when an adult's identity and behaviors are accepted. The age range for adolescence is not fixed and agreed on; however, according to the World Health Organization, it corresponds to the period between 10 and 19 years old. Given the sensitivity of this period, flexibility from healthcare providers is required during this phase since a young person with a chronic condition can experience late development or prolonged dependency.[15] The aims of management in the transition period include assessment of etiology and recombinant human growth hormone (rhGH) replacement therapy regimen; achievement of full adult somatic development; completion of pubertal, sexual, and reproductive maturation; reduction of metabolic and cardiovascular risks; attainment of adult psychosocial development; and ongoing patient education.

Challenges in Transitional Care

With the increasing number of CO-GHD cases, and despite the increased recognition of the importance of optimizing transitional care, its implementation in clinical practice remains challenging. The challenges include the lack of dedicated service, no implementation of joint transition visits, shortage of nurse educators, lack of knowledge and skill by both pediatric and adult healthcare providers, as well as cost issues due to a lack of integrated and comprehensive services. *"The National Audit (UK & ROI) of Adolescent*

Health Care and Transition in Endocrinology—2016 Report" has shown that for the transition to be effective, the aspects of health care supporting growth need to be "young person friendly," as defined by the *"You're Welcome Quality Criteria"* which consists of 10 criteria that include accessibility, publicity, confidentiality and consent, sexual and reproductive health services.[16] Pediatric and adult endocrinologists say that there is no "one size fits all" transition model. Care needs to be tailored during adolescence to prevent complications since it is difficult for young people to detach emotionally from their pediatric endocrinologist and transition from parental responsibility to autonomy.[17] Some of the challenges reported by young people were mainly related to the environment and process rather than the provider, except for the one about "staff who they could talk to about sensitive issues." Parents added the following: "opportunities to meet parents" and "for them to have time alone."[16]

In Saudi Arabia, there are some examples of transition processes; however, they are mostly confined to individual clinics, with little evidence of nationwide planning.[18,19] The use of globally standardized solutions to transition care is unlikely to be practical because of substantial differences in

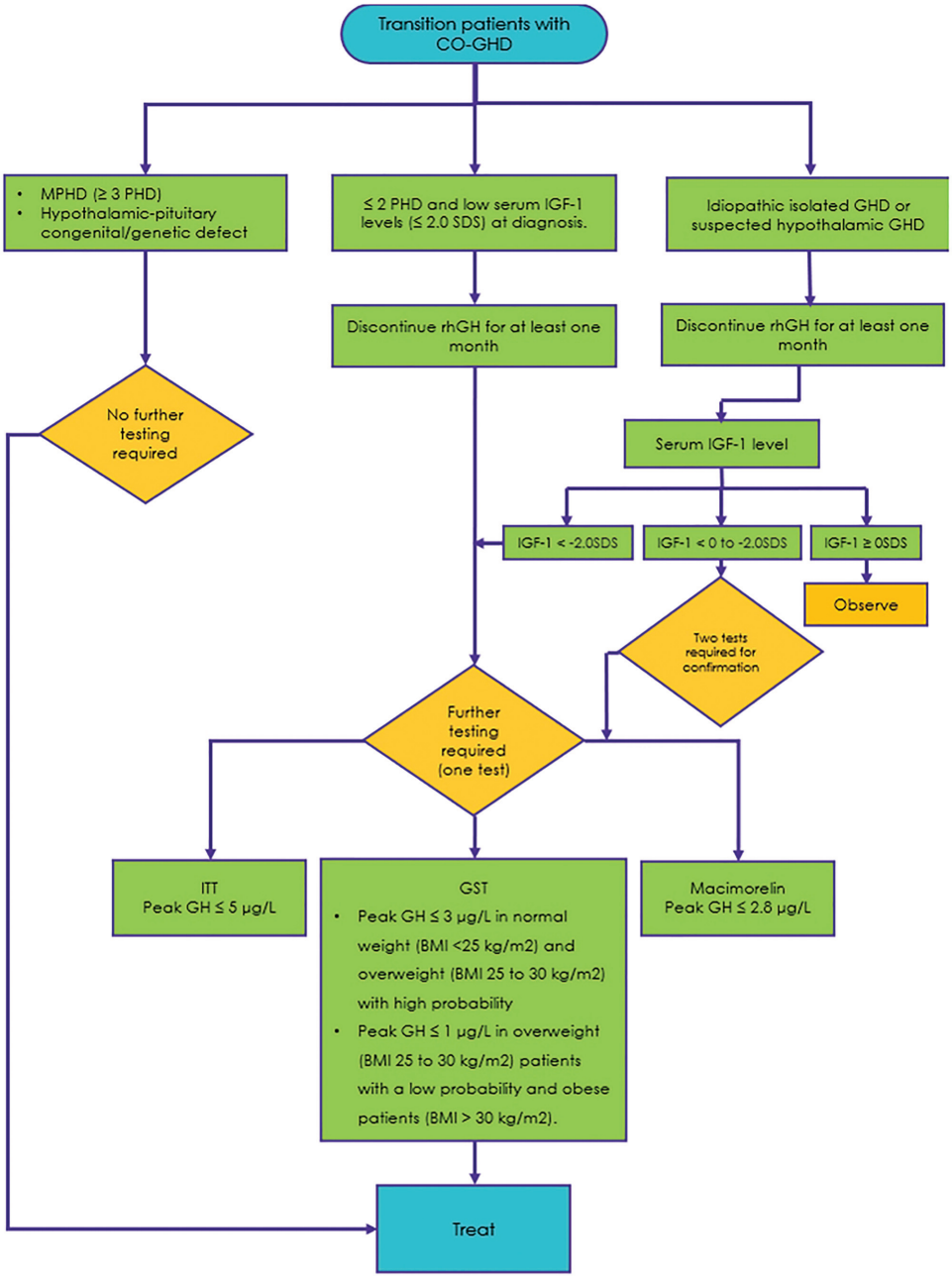

Figure 1: Algorithm for testing transition patients with childhood-onset isolated growth hormone deficiency. BMI = body mass index, GH = growth hormone, GHD = growth hormone deficiency, GST = glucagon-stimulation test, IGF = insulin-like growth factor-1, ITT = insulin tolerance test, MPHD = multiple pituitary hormone deficiency, PHD = pituitary hormone deficiency.

cultural practices and barriers such as resource limitations, variations in the age of transfer, and the separation of medical care between pediatric and adult endocrinology services. Endocrine specialists view the transition period differently. Pediatric endocrinologists mainly deal with congenital diseases, in which auxology is important, and are more likely to be involved with the patient and their family. On the contrary, adult endocrinologists are more concerned with body composition and metabolic factors.

Testing Transition Patients with Childhood-onset Growth Hormone Deficiency

Criteria for Childhood-onset Growth Hormone Deficiency Retesting

Despite recent evidence suggesting the importance of ongoing rhGH replacement therapy during the transition period, there remains a challenge and inconsistency in its implementation in clinical practice.[20,21] The rationale behind retesting is to confirm persistent growth hormone deficiency (GHD) during the transition period,[22] allowing the continuation of rhGH replacement therapy.[23]

Figure 1 summarizes the recommended algorithm for testing transition patients with CO-GHD.[5,24–34]

Retesting is required for transition patients with idiopathic GHD (IGHD) and serum insulin-like growth factor-1 (IGF-1) <0 standard deviation score (SDS) at the time of diagnosis. It is also required for patients with IGHD due to organic hypothalamic–pituitary diseases, such as previous surgery, pituitary hypoplasia, ectopic posterior pituitary, or previous cranial irradiation, except for patients with genetic disorders. Retesting patients who initially tested GH sufficient is required in cases where the risk of developing persistent GHD after previous radiation therapy is high.

Transition patients with two or fewer pituitary hormone deficiencies (PHDs) and low-serum IGF-1 levels (≤2.0 SDS) at the time of diagnosis should also be retested. However, retesting is not required for transition patients with IGHD or suspected hypothalamic GHD and serum IGF-1 > 0 SDS, as the majority show normal GH responses when retested after the final height is achieved.[5,24–34] For patients with multiple PHDs (≥3 PHD) and patients with hypothalamic–pituitary congenital/genetic defects, retesting is not required, and rhGH therapy should be continued. Factors that increase the likelihood of developing adult GHD after cranial irradiation include higher radiation doses, younger age, and longer intervals after the completion of radiotherapy.

Time for Retesting and Tests to be Performed

The interval between the re-evaluation and the discontinuation of rhGH should not be less than 1 month to allow for the reassessment of GH status.[4] The gold-standard test to establish the diagnosis of adult GHD is the insulin tolerance test (ITT) using a peak GH cut-point of 5 μg/L. However, it is important to consider associated safety concerns, including the potential to cause severe hypoglycemia, its contraindication in older patients, patients with seizure disorders, and patients with cardio/cerebrovascular disease.[35–37]

Glucagon-stimulation test (GST) is an alternative test to ITT.[38] It is commonly used because of its availability, reproducibility, safety, lack of influence by sex, and hypothalamic causes of GHD and its few contraindications.[39,40] Peak GH levels decrease with increasing body mass index (BMI), and the following cut-off points are used: 3 μg/L for normal weight (BMI <25 kg/m^2) and overweight individuals (BMI 25–30 kg/m^2) with a high probability and 1 μg/L for overweight individuals (BMI 25–30 kg/m^2) with a low probability and obese patients (BMI >30 kg/m^2).[41,42] However, the diagnostic accuracy of the GST remains unclear for patients with glucose intolerance.[43]

The third test used is the Macimorelin-stimulation test, which is the Food and Drug Administration–approved diagnostic test for adult GHD since December 2017. Its GH cut-point of 2.8 μg/L.[44,45] The Macimorelin-stimulation test offers several advantages, including oral administration with good tolerability, reproducibility, safety, absence of hypoglycemia, high sensitivity and specificity compared to the ITT, and a duration of only 90 minutes with only four sample collections. However, it is costly and can cause mild dysgeusia and drug interaction.[44,45] Arginine and levodopa testing are no longer recommended due to a lack of systematic evaluation, validation, and low sensitivity and specificity in adults and transitioning patients with CO-GHD.[46]

The number of required GH stimulation tests should be determined by the clinical suspicion of the treating endocrinologist at the time of diagnosis. If the clinical suspicion is high, such as in patients with GHD with two or fewer PHDs and low-serum IGF-1 levels (≤2.0 SDS) or in cases with IGHD with previous surgery, pituitary hypoplasia, ectopic posterior pituitary, or previous cranial irradiation (IGF-1 levels <0 SDS), one GH stimulation test is recommended. However, in genetically confirmed cases, retesting is not required. If clinical suspicion is low, as in patients with IGHD or suspected hypothalamic GHD, two GH stimulation tests are required to confirm persistent GHD.[43]

Management of Childhood-onset Growth Hormone Deficiency during Transition

Treatment during Transition and Dose Adjustment

The benefits of resuming rhGH replacement therapy during the transition period include long-term improvement in body composition, muscle strength, and cardiovascular risk markers, including improvements in dyslipidemia, with a lesser impact on bone mineral density, insulin sensitivity, and quality of life.[5,20,21,47–63] Patients with confirmed GHD upon retesting should restart rhGH replacement therapy. The recommended dose of rhGH replacement therapy in the transition phase is 0.4 to 0.5 mg/day. The dose used prior

to the interruption of rhGH replacement therapy can be used as a guide for the restart dose. It is recommended to resume rhGH replacement therapy at 50% of the dose used in childhood. The treatment goal is to achieve IGF-1 levels between 0 and +2 standard deviation with adjustments made at 1- to 2-month intervals initially, increasing the rhGH dosage by 0.1 to 0.2 mg per day depending on the clinical response, IGF-1 levels, and side effects. Once maintenance dosage is reached, follow-up may be scheduled every 6 to 12 months thereafter until the patient is in their mid-twenties.

Follow-up and monitoring of rhGH replacement therapy

Monitoring should include clinical evaluation (blood pressure, pulse rate, BMI, waist circumference), assessment of adverse events, serum IGF-1 level, fasting glucose level, hemoglobin A1c, lipid profile, thyroid function, cortisol level, and quality of life measurements (annually if feasible).[5,6,64,65]

Since GH affects body composition and the regional distribution of body fat, a dual-energy X-ray absorptiometry (DXA) scan for body composition and bone mineral density should be obtained at the onset of therapy. If the initial bone DXA scan is abnormal, it is recommended to repeat the evaluation at 2- to 3-year intervals to objectively define the response to therapy.[5,6,64,65] Individuals with GHD during childhood caused by radiation therapy should be followed with serial stimulation tests during adulthood, even if the test during the transition period suggested no residual GHD. This is because the damage to the hypothalamus and pituitary function caused by radiation may continue to progress over 5 to 10 years after the end of radiation therapy. If a pituitary lesion is present, baseline and periodic MRIs should be performed according to local best clinical practice. Patients who are on concurrent levothyroxine and glucocorticoid hormone replacement may need dose increments after starting rhGH replacement therapy. On the contrary, patients who are not already on levothyroxine or glucocorticoid replacement should be monitored for the possibility of deficiencies, and replacement therapy should be given if needed.[5,6,64,65] If no benefits are seen after 1 year of treatment, discontinuation of rhGH replacement therapy should be considered.

Strategies to Improve Delivery of Transition Care

(1) A clear process for transferring patients with CO-GHD to adult care is needed to assure good continuity of care and outcome.
(2) The transitional care discussion and patient/family preparation should be initiated in early adolescence (11–12 years of age) with a gradual transition process

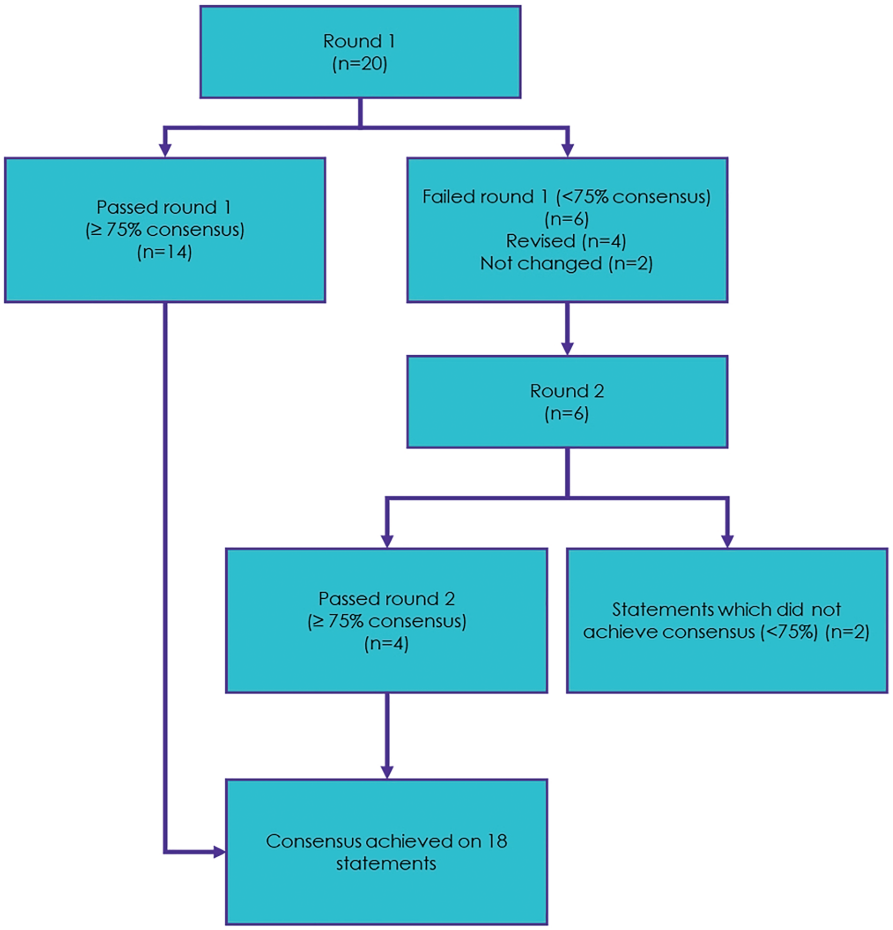

Figure 2: Flow chart showing the number of statements and outcomes of each Delphi round.

(3–4 years). Patients and their parents should be well informed, and expectations for transfer should be set.

(3) Education regarding disease management and treatment options should be provided from an early age and continue throughout the transition period. Both pediatric and adult endocrine specialists need to be involved, as well as the patient, their family, and other members of the healthcare team. This interaction with the healthcare team will improve adherence to rhGH replacement therapy, resulting in better efficacy outcomes.

(4) A structured transition clinic is ideal in a center where both pediatric and adult endocrinologist clinics are available.

(5) An adolescent who is followed at a children's hospital should be examined first in a transitional clinic at the hospital for assessment of readiness and preparation of a medical report ensuring transfer to the appropriate service. The adolescent should be seen in the pediatric clinic for one to two visits (involving overlapping visits) to ensure the completion of transitional care and continuity of care. Additionally, involving a transitional clinical coordinator is highly recommended to ensure a proper transition. Furthermore, the utilization of telemedicine care should be encouraged for patients commuting from long distances for their visits and for communication in the transitional care clinic and the transfer of patients if both services are away.

Results of the Delphi Rounds

Expert Panel Member Participation

Of the 11 panel members invited to the meeting, 73% ($n = 8$) were pediatric endocrinologists, 27% ($n = 3$) were adult endocrinologists, and 36% were females. Panel members had an average of 10 to 20 years of relevant clinical experience and had been previously involved in medical research. The same number of voting panel members was maintained across both rounds of the modified Delphi technique.

Statement Consensus

The number of statements at each voting stage is summarized in Figure 2. In round 1, consensus was achieved for 70% ($n = 14$) of the 20 statements. Prior to round two voting, the six statements that did not meet 75% agreement in round 1 were reviewed and modified/rephrased by the expert panel members. Only four statements were reworded. In round 2, consensus was achieved for 67% ($n = 4$) of the six statements. After two rounds, consensus was finally achieved for 90%

Figure 3: Consensus statements relating to strategies to improve delivery of transition care. CO-GHD = childhood-onset growth hormone deficiency, FAH = final adult height.

	Statement	Results	Level of Consensus
3	rhGH replacement therapy during transition is needed to help individuals with CO-GHD attain appropriate final adult height, body composition, peak bone mass, and psychosocial development while lowering metabolic and cardiovascular risks	Passed 2nd Round	82%
11	It is recommended that patients with confirmed persistent CO-GHD resume/continue rhGH replacement therapy throughout the transition phase after reaching their final height.	Passed 1st Round	100%
12	Since adherence to rhGH replacement therapy is associated with clinical benefit and better outcomes, adherence tracking is critical, especially in the transition phase with adolescents who require psychological support and patient education	Passed 1st Round	100%
13	The rhGH replacement therapy dose during the transition care period should be adjusted, as the dose varies between pediatric and adult GHD patients.	Passed 1st Round	100%

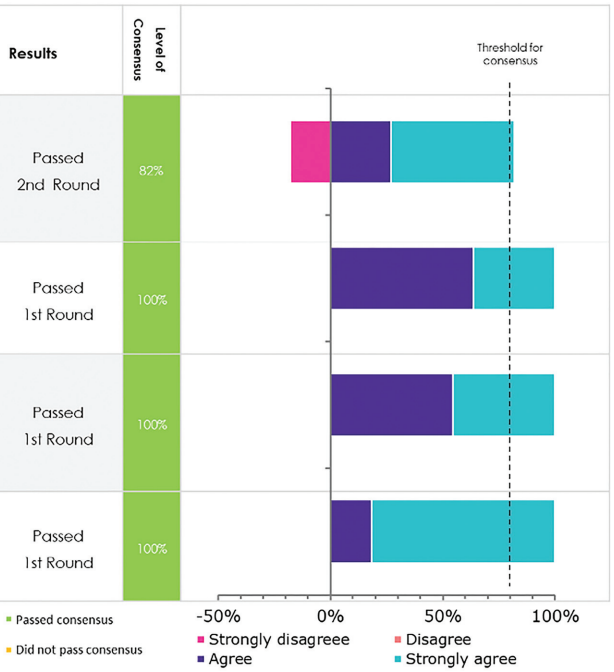

Figure 4: Consensus statements relating to treatment with rhGH replacement therapy during transition. CO-GHD = childhood-onset growth hormone deficiency, rhGH = recombinant human growth hormone.

	Statement	Results	Level of Consensus
5	Following completion of statural growth or after a patient reaches their final adult height (typically before the age of 20 years) in patients with CO-GHD, the necessity for continued rhGH replacement therapy should be assessed.	Passed 1st Round	91%
6	rhGH replacement therapy should be discontinued for at least 1 month prior to GH stimulation retesting	Passed 1st Round	82%
7	Patients with CO-GHD genetically confirmed or due to combined pituitary hormone deficiency with structural pituitary-hypothalamus anomaly/lesions or due to brain tumors can be exempted from retesting as the persistent of GHD is very likely.	Passed 1st Round	100%
8	Retesting is recommended using serum IGF-I as screening test with/without proceeding to insulin induced hypoglycemia.	2nd Round	73%
9	Normal serum IGF-I level makes persistent GHD very unlikely.	2nd Round	73%
10	Insulin-induced hypoglycemia is recommended as a growth hormone provocative test for transition period.	Passed 2nd Round	82%

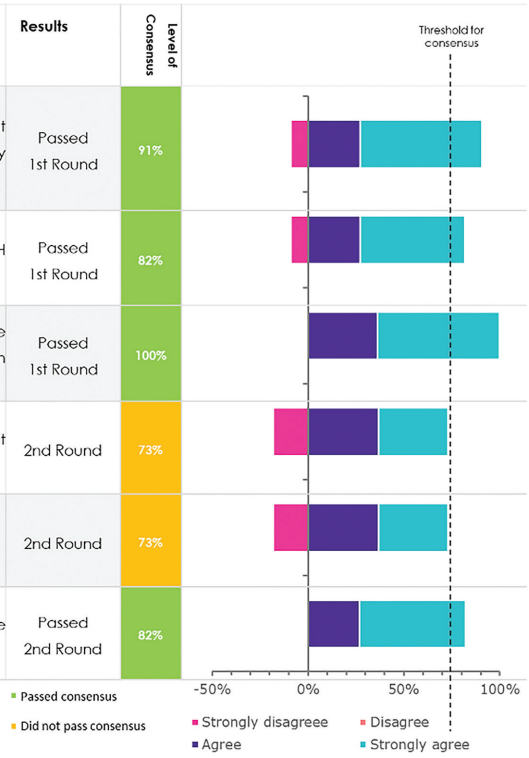

Figure 5: Consensus statements relating to CO-GHD testing. CO-GHD = childhood-onset growth hormone deficiency, GHD = growth hormone deficiency, IGF-1 = insulin-like growth factor-1, rhGH = recombinant human growth hormone.

($n = 18$) of the 20 statements. Figures 3–6 illustrate the statements for which consensus was obtained (in their final wording), presented according to the following key domains: strategies to improve the delivery of transition care (8/8 statements), treatment with rhGH replacement therapy during transition (4/4 statements), CO-GHD testing (4/6 statements), and diagnosis and monitoring (2/2 statements).

The panel members acknowledged that transition care for patients with CO-GHD requires a multidisciplinary approach

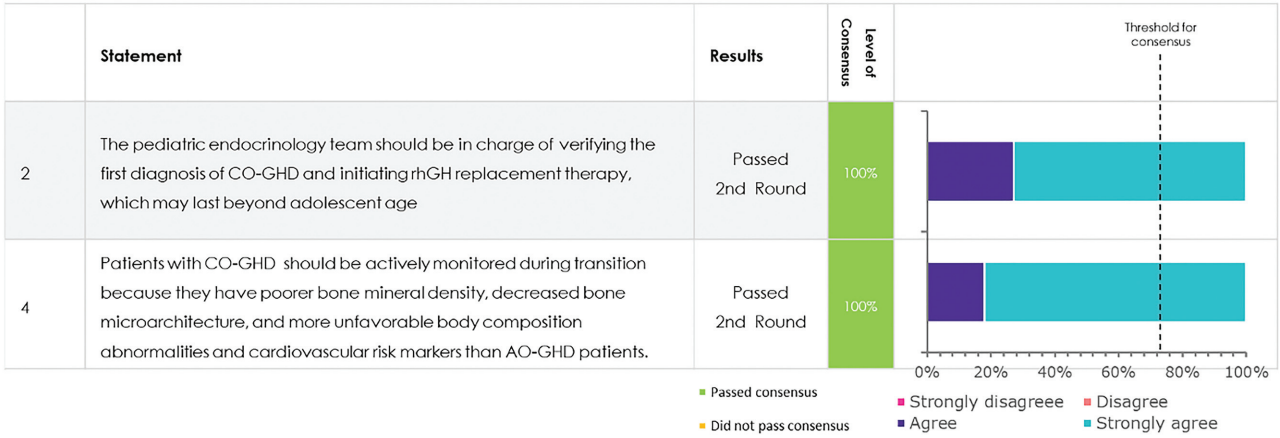

Figure 6: Consensus statements relating to diagnosis and monitoring. AO-GHD = adult-onset growth hormone deficiency, CO-GHD = childhood-onset growth hormone deficiency, rhGH = recombinant human growth hormone.

that ensures continuity of healthcare while adolescents are transferred from pediatric to adult care. It was recommended to ensure that transition patients are retested and offered rhGH replacement therapy without delay. Monitoring adherence to rhGH replacement therapy through a tracking system is crucial to ensure better treatment and health outcomes. Consensus also supported the utilization of telemedicine to improve communication between patients and physicians, ensuring proper access to care. Moreover, serum IGF-1 can be measured to screen adolescents with IGHD since mild cases usually have a low likelihood of persistent GHD, and laboratory testing of IGF-1 is often unavailable.

Conclusion

A successful transition from pediatric to adult services for adolescents and young adults with CO-GHD is fundamental in the treatment and management of their condition. It is essential for optimizing patient acceptance and compliance and minimizing interruption of care, thereby ensuring effective continuity of care for optimal patient outcomes. As the beneficial effects of structured transition care protocols are recognized in Saudi Arabia, there is a growing need to introduce new and more effective transition practices.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) guardian(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest

References

1. Ahmid M, Ahmed SF, Shaikh MG. Childhood-onset growth hormone deficiency and the transition to adulthood: current perspective. Ther Clin Risk Manag 2018;14:2283–91.
2. Kerr H, Widger K, Cullen-Dean G, Price J, O'Halloran P. Transition from children's to adult services for adolescents/young adults with life-limiting conditions: developing realist programme theory through an international comparison. BMC Palliat Care 2020;19:115.
3. Hepburn CM, Cohen E, Bhawra J, Weiser N, Hayeems RZ, Guttmann A. Health system strategies supporting transition to adult care. Arch Dis Child 2015;100:559–64.
4. Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. Eur J Endocrinol 2005;152:165–70.
5. Yuen KCJ, Biller BMK, Radovick S, *et al.* American association of clinical endocrinologists and American College of Endocrinology guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. Endocr Pract 2019;25:1191–232.
6. Ho KK. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. Eur J Endocrinol 2007;157:695–700.
7. Radovick S, DiVall S. Approach to the growth hormone-deficient child during transition to adulthood. J Clin Endocrinol Metab 2007;92:1195–200.
8. Cook DM, Rose SR. A review of guidelines for use of growth hormone in pediatric and transition patients. Pituitary 2012;15:301–10.
9. Barrett D, Heale R. What are Delphi studies? Evid Based Nurs 2020;23:68–9.

10. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000;32:1008–15.
11. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ 1995;311:376–80.
12. Niederberger M, Spranger J. Delphi technique in health sciences: a map. Front Public Health 2020;8:457.
13. Diamond IR, Grant RC, Feldman BM, *et al.* Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 2014;67:401–9.
14. Blum RW, Garell D, Hodgman CH, *et al.* Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine. J Adolesc Health 1993;14:570–6.
15. Sacks D, Canadian Paediatric Society, Adolescent Health Committee. Age limits and adolescents. Paediatr Child Health 2003;8:577–8.
16. Gleeson H. National audit (UK & ROI) of adolescent health care and transition in endocrinology report. Available from https://www.endocrinology.org/media/ 3628 /national-audit-of-adolescent-health-care-and-transition-in-endocrinology-report.pdf; 2016 [Accessed June 10, 2023]
17. Hokken-Koelega A, van der Lely AJ, Hauffa B, *et al.* Bridging the gap: metabolic and endocrine care of patients during transition. Endocr Connect 2016;5:R44–54.
18. Al-Jahdali E, Mosli M, Saadah O. A cross-sectional survey of Saudi gastroenterologists: transition strategies for adolescents with inflammatory bowel disease. Saudi J Gastroenterol 2017;23:233–7.
19. Saudi Diabetes Clinical Practice Guidelines (SDCPG): Saudi National Diabetes Center (SNDC)— 2021. Available from https://www.moh.gov.sa/Ministry/MediaCenter/Publications/Documents/Saudi-Diabetes-Clinical-Practice-Guidelines.pdf; 2021 [Accessed June 10, 2023].
20. Clayton P, Gleeson H, Monson J, Popovic V, Shalet SM, Christiansen JS. Growth hormone replacement throughout life: insights into age-related responses to treatment. Growth Horm IGF Res 2007;17:369–82.
21. Carroll PV, Christ ER, Bengtsson BA, *et al.* Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. J Clin Endocrinol Metab 1998;83:382–95.
22. Prestidge C, Romann A, Djurdjev O, Matsuda-Abedini M. Utility and cost of a renal transplant transition clinic. Pediatr Nephrol 2012;27:295–302.
23. Harden PN, Walsh G, Bandler N, *et al.* Bridging the gap: an integrated paediatric to adult clinical service for young adults with kidney failure. BMJ 2012;344:e3718.
24. Shalet SM, Toogood A, Rahim A, Brennan BM. The diagnosis of growth hormone deficiency in children and adults. Endocr Rev 1998;19:203–23.
25. Meazza C, Gertosio C, Pagani S, *et al.* Is retesting in growth hormone deficient children really useful? Minerva Endocrinol 2017;42:325–30.
26. Secco A, di Iorgi N, Napoli F, *et al.* Reassessment of the growth hormone status in young adults with childhood-onset growth hormone deficiency: reappraisal of insulin tolerance testing. J Clin Endocrinol Metab 2009;94:4195–204.
27. Bonfig W, Bechtold S, Bachmann S, *et al.* Reassessment of the optimal growth hormone cut-off level in insulin tolerance testing for growth hormone secretion in patients with childhood-onset growth hormone deficiency during transition to adulthood. J Pediatr Endocrinol Metab 2008;21:1049–56.
28. Longobardi S, Merola B, Pivonello R, *et al.* Reevaluation of growth hormone (GH) secretion in 69 adults diagnosed as GH-deficient patients during childhood. J Clin Endocrinol Metab 1996;81:1244–7.
29. Penta L, Cofini M, Lucchetti L, *et al.* Growth hormone (GH) Therapy during the transition period: should we think about early retesting in patients with idiopathic and isolated GH deficiency? Int J Environ Res Public Health 2019;16:307.
30. Aimaretti G, Attanasio R, Cannavò S, *et al.* Growth hormone treatment of adolescents with growth hormone deficiency (GHD) during the transition period: results of a survey among adult and paediatric endocrinologists from Italy. Endorsed by SIEDP/ISPED, AME, SIE, SIMA. J Endocrinol Invest 2015;38:377–82.
31. Sklar CA, Antal Z, Chemaitilly W, *et al.* Hypothalamic-pituitary and growth disorders in survivors of childhood cancer: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2018;103:2761–84.
32. Gleeson HK, Gattamaneni HR, Smethurst L, Brennan BM, Shalet SM. Reassessment of growth hormone status is required at final height in children treated with growth hormone replacement after radiation therapy. J Clin Endocrinol Metab 2004;89:662–6.
33. Mulder RL, Kremer LC, van Santen HM, *et al.* Prevalence and risk factors of radiation-induced growth hormone deficiency in childhood cancer survivors: a systematic review. Cancer Treat Rev 2009;35: 616–32.
34. Nicolson A, Toogood AA, Rahim A, Shalet SM. The prevalence of severe growth hormone deficiency in adults who received growth hormone replacement in childhood [see comment]. Clin Endocrinol (Oxf) 1996;44:311–6.
35. Jones SL, Trainer PJ, Perry L, Wass JA, Bessser GM, Grossman A. An audit of the insulin tolerance test in adult subjects in an acute investigation unit over one year. Clin Endocrinol (Oxf) 1994;41:123–8.
36. Lange M, Svendsen OL, Skakkebaek NE, *et al.* An audit of the insulin-tolerance test in 255 patients with pituitary disease. Eur J Endocrinol 2002;147:41–7.
37. Sfeir JG, Kittah NEN, Tamhane SU, *et al.* Diagnosis of GH deficiency as a late effect of radiotherapy in survivors of childhood cancers. J Clin Endocrinol Metab 2018;103:2785–93.
38. Gordon MB, Levy RA, Gut R, Germak J. Trends in growth hormone stimulation testing and growth hormone dosing in adult growth hormone deficiency patients: results from the answer program. Endocr Pract 2016;22:396–405.
39. Yuen KC, Biller BM, Molitch ME, Cook DM. Clinical review: is lack of recombinant growth hormone (GH)-releasing hormone in the United States a setback or time to consider glucagon testing for adult GH deficiency? J Clin Endocrinol Metab 2009;94:2702–7.
40. Yuen KC, Biller BM, Katznelson L, *et al.* Clinical characteristics, timing of peak responses and safety aspects of two dosing regimens of the glucagon stimulation test in evaluating growth hormone and cortisol secretion in adults. Pituitary 2013;16:220–30.
41. Pijl H, Langendonk JG, Burggraaf J, *et al.* Altered neuroregulation of GH secretion in viscerally obese premenopausal women. J Clin Endocrinol Metab 2001;86:5509–15.
42. Utz AL, Yamamoto A, Sluss P, Breu J, Miller KK. Androgens may mediate a relative preservation of IGF-I levels in overweight and obese women despite reduced growth hormone secretion. J Clin Endocrinol Metab 2008;93:4033–40.
43. Yuen KC, Tritos NA, Samson SL, Hoffman AR, Katznelson L. American Association of Clinical Endocrinologists and American College of Endocrinology disease state clinical review: update on growth hormone stimulation testing and proposed revised cut-point for the glucagon stimulation test in the diagnosis of adult growth hormone deficiency. Endocr Pract 2016;22:1235–44.
44. Garcia JM, Biller BMK, Korbonits M, *et al.* Macimorelin as a diagnostic test for adult GH deficiency. J Clin Endocrinol Metab 2018;103:3083–93.
45. Garcia JM, Swerdloff R, Wang C, *et al.* Macimorelin (AEZS-130)-stimulated growth hormone (GH) test: validation of a novel oral stimulation test for the diagnosis of adult GH deficiency. J Clin Endocrinol Metab 2013;98:2422–9.
46. Biller BM, Samuels MH, Zagar A, *et al.* Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency. J Clin Endocrinol Metab 2002;87:2067–79.
47. Feldt-Rasmussen U, Klose M. Adult growth hormone deficiency clinical management. In: Feingold KR, Anawalt B, Boyce A, *et al.*, eds. Endotext. South Dartmouth, MA: MDText. com, Inc 2000.
48. Reed ML, Merriam GR, Kargi AY. Adult growth hormone deficiency—benefits, side effects, and risks of growth hormone replacement. Front Endocrinol (Lausanne) 2013;4:64.

49. Ahmid M, Perry CG, Ahmed SF, Shaikh MG. Growth hormone deficiency during young adulthood and the benefits of growth hormone replacement. Endocr Connect 2016;5:R1–11.
50. Díez JJ, Sangiao-Alvarellos S, Cordido F. Treatment with growth hormone for adults with growth hormone deficiency syndrome: benefits and risks. Int J Mol Sci 2018;19:893.
51. Modesto Mde J, Amer NM, Erichsen O, *et al.* Muscle strength and body composition during the transition phase in patients treated with recombinant GH to final height. J Pediatr Endocrinol Metab 2014; 27:813–20.
52. Baroncelli GI, Bertelloni S, Sodini F, Saggese G. Longitudinal changes of lumbar bone mineral density (BMD) in patients with GH deficiency after discontinuation of treatment at final height; timing and peak values for lumbar BMD. Clin Endocrinol (Oxf) 2004;60:175–84.
53. Shalet SM, Shavrikova E, Cromer M, *et al.* Effect of growth hormone (GH) treatment on bone in postpubertal GH-deficient patients: a 2-year randomized, controlled, dose-ranging study. J Clin Endocrinol Metab 2003;88:4124–9.
54. Underwood LE, Attie KM, Baptista J. Growth hormone (GH) dose-response in young adults with childhood-onset GH deficiency: a two-year, multicenter, multiple-dose, placebo-controlled study. J Clin Endocrinol Metab 2003;88:5273–80.
55. Mauras N, Pescovitz OH, Allada V, Messig M, Wajnrajch MP, Lippe B. Limited efficacy of growth hormone (GH) during transition of GH-deficient patients from adolescence to adulthood: a phase III multicenter, double-blind, randomized two-year trial. J Clin Endocrinol Metab 2005;90:3946–55.
56. Boot AM, van der Sluis IM, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density and body composition in adolescents with childhood-onset growth hormone deficiency. Horm Res 2009;71: 364–71.
57. Hyldstrup L, Conway GS, Racz K, *et al.* Growth hormone effects on cortical bone dimensions in young adults with childhood-onset growth hormone deficiency. Osteoporos Int 2012;23:2219–26.
58. Colao A, Di Somma C, Salerno M, Spinelli L, Orio F, Lombardi G. The cardiovascular risk of GH-deficient adolescents. J Clin Endocrinol Metab 2002;87:3650–5.
59. Colao A, Di Somma C, Rota F, *et al.* Common carotid intima-media thickness in growth hormone (GH)-deficient adolescents: a prospective study after GH withdrawal and restarting GH replacement. J Clin Endocrinol Metab 2005;90:2659–65.
60. Attanasio AF, Shavrikova EP, Blum WF, Shalet SM. Quality of life in childhood onset growth hormone-deficient patients in the transition phase from childhood to adulthood. J Clin Endocrinol Metab 2005; 90:4525–9.
61. Johannsson G, Albertsson-Wikland K, Bengtsson BA. Discontinuation of growth hormone (GH) treatment: metabolic effects in GH-deficient and GH-sufficient adolescent patients compared with control subjects. Swedish Study Group for Growth Hormone Treatment in Children. J Clin Endocrinol Metab 1999;84:4516–24.
62. Vahl N, Juul A, Jørgensen JO, Orskov H, Skakkebaek NE, Christiansen JS. Continuation of growth hormone (GH) replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. J Clin Endocrinol Metab 2000;85:1874–81.
63. Carroll PV, Drake WM, Maher KT, *et al.* Comparison of continuation or cessation of growth hormone (GH) therapy on body composition and metabolic status in adolescents with severe GH deficiency at completion of linear growth. J Clin Endocrinol Metab 2004;89: 3890–5.
64. Grimberg A, DiVall SA, Polychronakos C, *et al.* Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr 2016;86:361–97.
65. Tavares ABW, Collett-Solberg PF. Growth hormone deficiency and the transition from pediatric to adult care. J Pediatr (Rio J) 2021;97: 595–602.

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