REVIEW PAPERS

Quality of Life in Adults with Growth Hormone Deficiency: A Comprehensive Review of Clinical Evidence and Psychological Impacts

Jakość życia u dorosłych z niedoborem hormonu wzrostu: kompleksowy przegląd danych klinicznych i aspektów psychologicznych

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KEYWORDS:

- adult growth hormone deficiency
- quality of life
- growth hormone replacement therapy
- treatment outcomes
- psychological factors

ABSTRACT

Adult growth hormone deficiency (AGHD) negatively affects quality of life (QoL) through physical, metabolic, and psychological impairments. Growth hormone (GH) replacement therapy may improve QoL, but individual responses vary. This review summarizes current evidence on QoL in untreated and treated AGHD, explores factors influencing outcomes, and highlights gaps in research and clinical practice. Growth hormone therapy improves QoL in most patients, especially those with low baseline well-being. Women and younger patients report greater benefits. Psychological and behavioral factors, including coping strategies and beliefs about treatment, significantly influence outcomes. Improvement in QoL should be a central outcome in AGHD management. Future research must address long-term outcomes, adherence, and patient-centered metrics, especially in underrepresented subgroups such as traumatic brain injury (TBI) survivors and transitioning adolescents.

SŁOWA KLUCZOWE:

- niedobór hormonu wzrostu u dorosłych
- jakość życia
- terapia hormonem wzrostu
- ocena skuteczności leczenia
- czynniki psychologiczne

STRESZCZENIE

Niedobór hormonu wzrostu u dorosłych (AGHD) negatywnie wpływa na jakość życia (QoL), powodując zaburzenia fizyczne, metaboliczne i psychiczne. Terapia zastępcza GH może poprawiać QoL, jednak odpowiedź na leczenie jest zróżnicowana. Celem niniejszego przeglądu jest podsumowanie aktualnych danych dotyczących QoL u pacjentów z AGHD, zarówno nieleczonych, jak i leczonych substytucyjnie, oraz identyfikacja czynników wpływających na wyniki i obszarów badawczych wymagających analizy. Terapia GH poprawia QoL u większości pacjentów, szczególnie u tych z niskim wyjściowym dobrostanem. Kobiety i osoby młodsze zgłaszają większe korzyści. Czynniki psychologiczne i behawioralne, takie jak strategie radzenia sobie i przekonania na temat leczenia, znacząco wpływają na efekty. Poprawa QoL powinna być kluczowym celem leczenia AGHD. Potrzebne są dalsze badania nad długoterminowymi wynikami, przestrzeganiem terapii oraz ocena w poszczególnych grupach pacjentów.

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Introduction

Growth hormone deficiency (GHD) in adults is a well-recognized clinical syndrome characterized by a constellation of physical, metabolic, and psychological abnormalities. Unlike in children, where GHD primarily manifests as growth failure, adult GHD (AGHD) presents with more subtle and often non-specific symptoms, such as increased visceral adiposity, reduced muscle mass, impaired lipid and glucose metabolism, reduced bone mineral density, fatigue, and diminished psychological well-being (1, 2). The syndrome frequently develops in the context of hypopituitarism due to pituitary adenomas, other tumors in the hypothalamic-pituitary region, in traumatic brain injury (TBI), post cranial radiotherapy, or as a sequela of childhood-onset GHD (CO-GHD) (3, 4).

Since the introduction of recombinant human growth hormone (rhGH) therapy in the late 1980s, numerous studies have investigated its benefits in AGHD. While objective improvements in body composition and cardiovascular risk profiles have been well-documented (5, 6), the impact of GH therapy on more subjective outcomes such as quality of life (QoL) remains an area of ongoing debate and research (7, 8). Assessment of QoL has gained increasing importance in chronic disease management, serving not only as a patient-centered endpoint but also as a critical factor in evaluating the cost-effectiveness and necessity of long-term therapy (9).

Impaired QoL in AGHD spans various domains including emotional stability, energy levels, sexual functioning, sleep quality, cognitive clarity, and social integration (10-12). It is influenced by a range of variables such as age, sex, etiology, disease duration, comorbidities, and adherence to GH therapy (13, 14). Importantly, improvements in QoL following GH replacement have not been uniformly observed across all studies, partly due to methodological heterogeneity, variations in measurement tools, and differing baseline characteristics of study populations (15, 16).

This review aims to provide a comprehensive and critical synthesis of the current literature on quality of life in adults with GH deficiency. We summarize baseline impairments, the effectiveness of rhGH replacement therapy, the role of psychological and demographic factors, and the limitations in existing evidence.

Epidemiology and Etiology of AGHD

Adult Growth Hormone Deficiency (AGHD) is a rare but increasingly recognized endocrine disorder. Its exact prevalence is difficult to determine due to diagnostic variability and underrecognition of symptoms, particularly in older adults and those with non-classical presentations. Nevertheless, epidemiological studies estimate the prevalence of AGHD at approximately 2-3 per 10,000 individuals (1), though this figure may be higher when accounting for underdiagnosed cases following TBI or cranial irradiation (4, 11).

AGHD can be broadly classified into two categories based on the age of onset: childhood-onset GHD (CO-GHD) and adult-onset GHD (AO-GHD). CO-GHD might persists into adulthood in a subset of individuals who previously required GH therapy for growth promotion. In contrast, AO-GHD develops in adulthood, typically due to acquired hypothalamic-pituitary disease. The most common causes include pituitary adenomas, craniopharyngiomas, pituitary surgery or radiotherapy, TBI, subarachnoid hemorrhage, and hypophysitis (6, 17). Notably, hypopituitarism develops in up to 20-30% of individuals with moderate-to-severe TBI, and GH is the most commonly deficient pituitary hormone in this population (4, 11).

In many cases, AGHD is not an isolated condition but part of multiple pituitary hormone deficiency (MPHD). This complicates both the clinical presentation and interpretation of treatment effects, as QoL impairments may stem from deficiencies in other pituitary axes, such as gonadal or thyroid function (8, 16). However, data from rare populations with isolated GHD, such as individuals with genetic defects in the GH-releasing hormone receptor, provide valuable insights into the direct impact of GH deficiency independent of other hormonal disruptions (18).

Diagnostic criteria for AGHD have evolved significantly over the past two decades. The diagnosis is currently based on a combination of biochemical tests and clinical context. Measurement of insulin-like growth factor I (IGF-I) alone is insufficient due to its low sensitivity, particularly in older adults and those with comorbidities (10). Therefore, dynamic stimulation tests remain the gold standard. These include the insulin tolerance test (ITT) and the glucagon stimulation test (GST).

Importantly, the timing of GH deficiency onset may influence symptom profile and response to therapy. Patients with CO-GHD often exhibit psychosocial consequences, including reduced education and employment status, which may impact long-term QoL (12, 19). In contrast, AO-GHD may present with more metabolic or somatic features, such as increased central adiposity, fatigue, and dyslipidemia (1, 6). These differences must be accounted for when evaluating therapeutic outcomes.

Concept and Measurement of Quality of Life in AGHD

Quality of life is a multidimensional construct that encompasses an individual's physical health, psychological state, level of independence, social relationships, and relationship to salient features of their environment (20). In the context of AGHD, QoL is significantly impaired and often serves as a primary outcome for evaluating treatment efficacy (10). Despite the widespread recognition of its clinical relevance, the accurate measurement of QoL in AGHD remains challenging due to conceptual, methodological, and practical limitations.

One important distinction in the literature is between quality of life, health status, and well-being. While these terms are often used interchangeably, they represent different constructs. While QoL is typically associated with overall life satisfaction and perceived functioning, health status refers more narrowly to physical capabilities and limitations, and well-being emphasizes psychological states such as anxiety, depression, and energy levels (16). Misclassification of these dimensions in studies has led to inconsistent findings regarding the effects of rhGH therapy.

A range of tools have been developed to assess QoL in AGHD, broadly divided into generic and disease-specific instruments:

Generic Instruments

Generic tools such as the Short Form-36 Health Survey (SF-36), the Nottingham Health Profile (NHP), and

the Psychological General Well-Being Schedule (PGWB) are widely used across populations with chronic diseases (15, 21). These instruments allow for comparisons across different disease states but may lack sensitivity to detect improvements specific to AGHD, especially in patients with mild-to-moderate impairment (7).

Disease-Specific Instruments

To overcome the limitations of generic tools, disease-specific instruments have been developed. The most widely validated is the Quality of Life Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA), a self-administered questionnaire that covers 25 items related to energy, social isolation, emotional reactions, and coping (15). Its utility has been demonstrated in large international databases such as KIMS and HypoCCS, showing good sensitivity to change and internal consistency (1, 9). KIMS (Pfizer International Metabolic Database), was launched in 1994 to monitor the outcomes and safety of long-term rhGH replacement therapy in hypopituitary adults with GHD and it contains data on more than 14,000 patients from 31 countries. The study indicates that most (78%) adult patients had AO-GHD. GHD in adults most frequently results from tumors in the hypothalamic-pituitary region or as a consequence of their treatment e.g., surgery or radiotherapy (9). The Hypopituitary Control and Complications Study "HypoCCS" was a prospective, open label, global, multicenter, observational study on routine clinical care of adults with growth hormone deficiency occurring either isolated or in combination with other pituitary hormone deficiencies. The study contains data on 10673 patients from 16 countries.

Another instrument, the Questions on Life Satisfaction-Hypopituitarism (QLS-H), offers a semi-quantitative assessment of life satisfaction across work, physical condition, mood, and sexual functioning (15). This tool has been particularly helpful in long-term observational studies.

However, each instrument has limitations. Generic tools may overlook subtle yet clinically meaningful improvements, while disease-specific tools cannot be used to compare AGHD with other conditions.

Beyond self-reports, efforts have been made to correlate QoL measures with biochemical (e.g., IGF-I levels) and functional outcomes (e.g., body composition, cognitive testing), with mixed results (5). While some studies have identified associations between IGF-I levels and mood or anxiety, others have found no clear correlation between biochemical normalization and improved subjective well-being (6, 11).

Finally, newer studies have highlighted the need to consider psychological and behavioral variables such as coping style, health beliefs, and treatment expectations, which may influence QoL independently of GH deficiency or its correction (13). For instance, patients with high belief in medication necessity and active coping strategies are more likely to report adherence and improved well-being, regardless of objective changes (13).

Baseline Quality of Life in Untreated AGHD

Adults with untreated AGHD consistently report a reduced QoL across multiple studies and populations. This reduction is evident in both physical and psychological domains and frequently persists even in patients receiving adequate replacement of other pituitary hormones (1). Common complaints include fatigue, social withdrawal, anxiety, low mood, reduced physical endurance, impaired sexual function, and cognitive dysfunction such as forgetfulness and decreased concentration (10, 11).

Several observational studies and cross-sectional analyses have confirmed that QoL in untreated AGHD patients is significantly lower than in the general population, as measured by both generic and disease-specific questionnaires (15, 16). One of the earliest consistent findings, reported by McGauley and others, was that patients with hypopituitarism and GH deficiency experience profound psychological burden even when other hormone deficiencies are adequately managed (10).

More recent analyses reinforce these conclusions. For example, the HypoCCS and KIMS observational cohorts showed that AGHD patients reported severe impairments in domains such as energy levels, emotional reactions, and social functioning prior to the initiation of rhGH therapy (9, 21). According to Kołtowska-Häggström et al. the most burdensome symptoms at baseline were tiredness, memory problems, low self-confidence, tenseness, and poor socialization, with the first two contributing most significantly to impaired daily functioning (9).

Interestingly, baseline QoL impairment appears to vary by etiology and age of onset. Individuals with CO-GHD transitioning into adulthood often report psychosocial difficulties such as lower educational attainment, reduced employment and marital rates, and lower income compared to peers (12, 19). A study by Kao et al. confirmed that adults with CO-GHD secondary to panhypopituitarism had lower QoL scores, more childhood behavioral problems, and impaired psychosexual function, despite no increased psychological distress compared to controls (12).

In contrast, adults with isolated lifelong untreated GHD, such as those with genetic mutations affecting GH signaling, may not perceive their quality of life as impaired. Barbosa et al. reported that a genetically homogeneous group of adults with isolated GHRH receptor mutations exhibited QoL levels similar to healthy controls, suggesting that adaptation over the lifespan may play a protective role (18).

Subgroups such as individuals with TBI-induced AGHD may present with overlapping symptoms of PTSD and neurocognitive impairment, making it difficult to attribute QoL deficits exclusively to GH deficiency (4, 8). Herodes et al. found that patients with AGHD and TBI had impaired physical and cognitive function as well as elevated PTSD symptoms at baseline, despite being relatively young (4).

Furthermore, functional limitations such as reduced exercise capacity often correlate with diminished QoL. Olczyk et al. showed that GH-deficient patients had significantly worse exercise tolerance than obese or healthy controls and rated their perceived exertion higher, suggesting a mismatch between physical and mental capacity (22). However, in GHD patients, the typical correlations between functional metrics and QoL seen in healthy individuals were largely absent.

In summary, untreated AGHD is associated with clear and multidimensional impairments in QoL, particularly in emotional, cognitive, and energy-related domains. These impairments differ by age of onset, etiology, and presence of comorbidities. Recognizing these baseline patterns is essential for evaluating the true benefits of GH replacement and for identifying those who may benefit most from therapy.

Effects of Growth Hormone Replacement Therapy on Quality of Life

Recombinant human growth hormone (rhGH) replacement therapy is the cornerstone of treatment for AGHD, and one of its most studied endpoints is the improvement in patient-reported QoL. While the effects on metabolic parameters such as body composition, lipid profile, and bone mineral density are well established (1, 6), the impact of rhGH therapy on QoL has shown greater interindividual variability, and remains a topic of significant clinical interest.

Short-Term Effects

Numerous studies report that the majority of QoL improvements occur within the first 6-12 months of rhGH replacement therapy. This initial response is particularly pronounced in domains such as energy, emotional well-being, and social functioning (5, 21). In the KIMS cohort, the most substantial improvements were observed during the first year, with gains in areas such as tiredness, tenseness, and self-confidence (9). Similarly, meta-analyses show that mood status improves after 3-6 months of treatment, although the effect sizes tend to diminish over time (16).

Disease-specific instruments like QoL-AGHDA are especially sensitive to these early changes. For example, Elbornsson et al. demonstrated that most of the QoL gains occurred within the first year, although some domains, such as memory and tenseness, showed slower response (14). Interestingly, patients with more severe baseline impairments reported greater QoL gains, suggesting a ceiling effect in milder cases (14).

In contrast, some studies such as Deijen & Arwert's meta-analysis found that the placebo effect might partly explain early mood improvements, and that short-term rhGH therapy (e.g., 6 months) may not significantly outperform placebo in terms of QoL (16). These findings highlight the importance of patient selection and expectation management.

Long-Term Effects

Longitudinal studies over 5-8 years suggest that QoL improvements achieved during the first year are generally maintained over time, though the magnitude of change may plateau (14, 15). Ikeda et al. reported sustained improvements in QoL over 6 years, followed by a stabilization phase (23). However, not all dimensions remained significantly improved, particularly in older patients.

Scores in QoL-AGHDA and PGWB remained stable in patients adhering to treatment protocols, and IGF-I levels positively correlated with sustained psychological well-being (14). These findings are supported by registry data, which showed long-term improvements in well-being, though not always returning to population norms (9).

Long-term therapy is generally well tolerated, with few discontinuations due to adverse effects. Gradual titration and individualized dosing strategies help minimize common side effects such as edema, joint stiffness, or glucose intolerance (1). Individualized rhGH dosing is critical for optimizing QoL response. Underdosing may lead to suboptimal symptom control, whereas overdosing can increase the risk of side (2, 23). Most guidelines recommend titrating rhGH to achieve IGF-I levels in the upper half of the age-adjusted normal range, which has been associated with better subjective well-being (5).

However, the relationship between IGF-I levels and QoL is not linear. While some patients report improvements in parallel with IGF-I normalization, others show no clear correlation, suggesting that QoL effects are multifactorial and not solely biochemically driven (7, 8).

Patient Subgroups and Predictors of Response

Certain patient subgroups appear to derive disproportionate benefit from rhGH therapy:

- women, particularly those with adult-onset GHD, often report greater improvements in QoL compared to men (14)
- patients with low baseline QoL experience the most substantial gains (14,15).
- those with childhood-onset GHD may respond differently, with some studies suggesting limited improvements, possibly due to lifelong adaptation to the deficiency (18).
- patients with TBI-induced AGHD have shown mixed results. In a pilot study, Herodes et al. reported improvements in lean body mass and PTSD symptoms, although statistically significant QoL gains were not achieved in the small cohort (4).
- patients with strong beliefs in treatment necessity and active coping strategies show better adherence and more consistent QoL improvement (13).

It is also important to consider psychological mediators. Patients with poor mental QoL or passive coping styles may struggle to translate physiological gains into perceived improvements (13). These findings support the integration of behavioral support and expectation management into routine AGHD care.

Conclusions

Growth hormone replacement therapy in AGHD leads to significant and sustained improvements in quality of life for many – but not all – patients. Benefits are most consistently observed in domains such as energy, emotional well-being, and social functioning, particularly in patients with low baseline QoL or strong psychological engagement with treatment (1, 9, 14).

However, outcomes are highly individualized and depend on multiple interacting factors, including etiology, age, sex, comorbidities, psychological profile, and adherence. Therefore, GH replacement should not be viewed as a "one-size-fits-all" intervention but rather as part of a comprehensive, personalized management strategy.

Clinicians should carefully assess baseline QoL, patient expectations, and mental health status prior to initiating rhGH therapy. Regular re-evaluation using validated tools can guide dosing, identify non-responders, and support shared decision-making.

Ultimately, future advances in trial design, psychological profiling, and healthcare policy will be essential to ensure that rhGH therapy in adults is not only biochemically effective, but also meaningful to patients' lives.

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