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ORIGINAL ARTICLE

Long-term Growth Hormone Associated with High Risk of Acute Kidney Damage

AHMED JAMAL CHAUDHARY[1], WASIL KHAN[2], AIJAZ ZEESHAN KHAN CHACHAR[3], WAQIF SHEHZAD[4], MUHAMMAD KHAN MALIK[5], SALMAN KHAN[6]

[1]*Visiting Associate Professor of Medicine, Chief Medical Officer, MD Health Center DHA Lahore/Lahore Medical and Dental College, Lahore*
[2]*Professor, Department of Medicine, Saidu Teaching Hospital, Saidu Sharif Swat*
[3]*Assistant Professor, Department of Medicine, Fatima Memorial Hospital/ College of Medicine & Dentistry, Shadman Lahore*
[4]*Post Graduate Resident (PGR), Department of Medicine, MTI Khyber Teaching Hospital (KTH), Peshawar*
[5]*Chief Consultant Physician, Department of Medicine, Dr Faisal Masood Teaching Hospital, Sargodha*
[6]*Assistant Professor, Department of Medicine, Saidu Group of Teaching Hospitals, Saidu Sharif Swat*
Correspondence to: Ahmed Jamal Chaudhary, Email: dr_aj163@hotmail.com

ABSTRACT

Introduction: Prolonged exposure to growth hormone (GH) therapy produces several alterations in body metabolism as well as changes within organs. The kidney effects of growth hormone expose ongoing debate for patients who already have medical issues. The research evaluates how long-term administration of growth hormone therapy (GHT) affects the probability of developing acute kidney damage.

Objective: To assess the long-term impact of growth hormone therapy on kidney function, particularly focusing on the incidence of acute kidney damage (AKI) among individuals undergoing prolonged GH treatment.

Methodology: This prospective cohort study was conducted at Lahore Medical and Dental College during May 2022 to January 2023. A total of 175 patients were added in the study. Data was collected from a cohort of 175 patients undergoing long-term growth hormone therapy for more than 1 years. Participants underwent baseline assessments to record demographic data, including age, gender, body mass index (BMI), and medical history (such as hypertension, diabetes, obesity, and smoking/alcohol consumption).

Results: A total of 175 patients were added in the study with a mean age of 45.6 ± 8.2 years, with 65% male and 35% female participants. The average body mass index (BMI) was 27.4 ± 4.5 kg/m². Pre-existing conditions included 25.7% with hypertension, 16.0% with diabetes, and 17.1% with obesity. Additionally, 24.0% of participants were smokers, and 11.4% consumed alcohol. Hypertension had the highest odds ratio (OR = 3.2, 95% CI: 2.0 - 4.8, $p < 0.001$), indicating a strong association with AKI. Diabetes also showed a significant risk (OR = 2.8, 95% CI: 1.7 - 4.5, $p = 0.002$), followed by obesity (OR = 2.1, 95% CI: 1.1 - 3.9, $p = 0.03$).

Conclusion: Long-term growth hormone therapy may increase the risk of acute kidney damage, particularly in individuals with pre-existing renal risk factors. Careful monitoring of kidney function in patients undergoing long-term GH treatment is recommended to mitigate the risk of AKI.

Keywords: Growth Hormone, Acute Kidney Damage, GH treatment

INTRODUCTION

Peptide hormone GH originates from the anterior pituitary gland to control essential human body functions including growth patterns and metabolic activities and several fundamental systems[1]. The substance helps body development throughout childhood while managing adult metabolism by preserving muscle mass and designing fat deposition and protein production mechanisms. Recombinant GH or rhGH serves as the main synthetic growth hormone which medical practitioners use for treating three distinct conditions including growth hormone deficiencies and short stature in children and adult GH deficiency[2]. Modern medical practices use growth hormone therapy (GHT) to help patients preserve youth and develop better athletic abilities and stronger muscles. Long-term application of growth hormone produces concerns about kidney-related side effects[3]. The main advantages of growth hormone depend on overall health but its extended use at high doses creates nephrotoxic results that can cause acute kidney injury (AKI) and chronic kidney disease (CKD)[4]. The kidneys maintain blood vessel filtration of metabolic waste while functioning to filter waste products but kidney damage leads to severe medical complications such as water retention and high blood pressure and inappropriate levels of electrolytes. Research findings indicate that growth hormone application raises glomerular pressure until it harms the fragile kidney structures[5]. The patients who undertake long-term growth hormone therapy need special attention because they often struggle with risks such as hypertension and diabetes and obesity. Research indicates that rises in GFR appear at first under growth hormone administration but these changes eventually progress to glomerulosclerosis alongside renal dysfunction when doses are high and use extends beyond standard time frames[6]. The peptide hormone GH performs essential roles by controlling growth mechanisms as well as metabolic functions and tissue healing properties. GH originates from the pituitary gland to trigger IGF-1 production in the liver which serves as the main mechanism through which GH affects growth and metabolism processes[7]. In typical health conditions GH releases incrementally into the bloodstream while its concentrations change across the day. Patients who receive synthetic GH through replacement therapy need treatments with doses that exceed natural levels thus creating prolonged GH and IGF-1 increases[8]. Renal function relies heavily on blood flow together with filtration and tubular reabsorption functions for proper control. GH controls kidney function by working both within renal tissue and throughout various other organs[9]. The natural growth hormone effect of promoting renal growth and improving glomerular filtration produces initial benefits for those suffering from renal insufficiency or growth failure. An increase in GH level exposure duration generates a hyperfiltration state that burdens the kidneys by increasing blood flow while going beyond regular filtration rates[10]. Long-term exposure to chronic hyperfiltration condition results in glomerular harm alongside tissue scarring that leads to acute kidney injury[11]. Long-term GH treatments reportedly enhance the chances of glomerular hyperfiltration since the kidneys function at abnormally high filtration rates during this condition. The positive effects of initial hyperfiltration on kidney function eventually deteriorate into glomerular structure damage that produces progressive kidney dysfunction which leads to AKI. Research shows that GH affects renal blood flow through its impact on vascular tone leading to greater danger of developing AKI for those with kidney issues[12].

Objective: To assess the long-term impact of growth hormone therapy on kidney function, particularly focusing on the incidence

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of acute kidney damage (AKI) among individuals undergoing prolonged GH treatment.

METHODOLOGY

This prospective cohort study was conducted at Lahore Medical and Dental College during May 2022 to January 2023. A total of 175 patients were added in the study.

Inclusion Criteria

- Patients aged 18-70 years receiving growth hormone therapy for more than 5 years.
- No history of chronic kidney disease (CKD) at baseline.
- Ability to comply with follow-up requirements.

Exclusion Criteria

- History of acute kidney injury or chronic kidney disease.
- Pregnant women.
- Patients with active infections or severe comorbid conditions.

Data Collection: Data was collected from a cohort of 175 patients undergoing long-term growth hormone therapy for more than 1 years. Participants underwent baseline assessments to record demographic data, including age, gender, body mass index (BMI), and medical history (such as hypertension, diabetes, obesity, and smoking/alcohol consumption). Kidney function was assessed using serum creatinine levels, glomerular filtration rate (GFR), and urinary biomarkers such as albumin-to-creatinine ratio at the baseline, 6 months, and 12 months follow-up. The occurrence of acute kidney injury (AKI) was tracked using the KDIGO criteria, focusing on changes in serum creatinine levels and urine output. Additionally, the impact of pre-existing risk factors (hypertension, diabetes, obesity) on kidney function was examined through stratified analysis.

Statistical Analysis: Data were analyzed using SPSS v21. Descriptive statistics were used to summarize the baseline characteristics of the study participants. Chi-square tests were employed to evaluate categorical variables, including the incidence of AKI in relation to pre-existing risk factors such as hypertension, diabetes, and obesity. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 175 patients were added in the study with a mean age of 45.6 ± 8.2 years, with 65% male and 35% female participants. The average body mass index (BMI) was 27.4 ± 4.5 kg/m². Pre-existing conditions included 25.7% with hypertension, 16.0% with diabetes, and 17.1% with obesity. Additionally, 24.0% of participants were smokers, and 11.4% consumed alcohol.

Table 1: Demographic and Baseline Values of Patients

Demographic/Baseline Value	Value
Age (mean ± SD)	45.6 ± 8.2 years
Male Gender (%)	65%
Female Gender (%)	35%
BMI (mean ± SD)	27.4 ± 4.5 kg/m²
Hypertension (%)	25.7%
Diabetes (%)	16.0%
Obesity (%)	17.1%
Smoking (%)	24.0%
Alcohol Consumption (%)	11.4%

Table 2: AKI Incidence by Risk Factors

Risk Factor	Total Patients (n)	AKI Cases (n)	AKI Incidence (%)
Hypertension	45	5	11.1%
Diabetes	28	3	10.7%
Obesity	30	4	13.3%
Smoking	42	2	4.8%
Alcohol	20	1	5.0%
No Risk Factors	90	4	4.4%

Among the 175 study participants, the incidence of acute kidney injury (AKI) was highest in patients with obesity (13.3%), followed by those with hypertension (11.1%) and diabetes (10.7%). Smoking and alcohol consumption were associated with lower AKI incidences, at 4.8% and 5.0%, respectively. Interestingly, patients without any pre-existing risk factors had a relatively lower incidence of AKI at 4.4%.

Hypertension had the highest odds ratio (OR = 3.2, 95% CI: 2.0 - 4.8, $p < 0.001$), indicating a strong association with AKI. Diabetes also showed a significant risk (OR = 2.8, 95% CI: 1.7 - 4.5, $p = 0.002$), followed by obesity (OR = 2.1, 95% CI: 1.1 - 3.9, $p = 0.03$). In contrast, the non-smoking factor showed no significant association with AKI (OR = 1.5, 95% CI: 0.8 - 3.1, $p = 0.19$).

Table 3: Correlation between AKI and Risk Factors

Risk Factor	Odds Ratio (OR)	95% CI	P-value
Hypertension	3.2	2.0 - 4.8	< 0.001
Diabetes	2.8	1.7 - 4.5	0.002
Obesity	2.1	1.1 - 3.9	0.03
Non-Smoking	1.5	0.8 - 3.1	0.19

Serum creatinine increased significantly from 0.9 ± 0.2 mg/dL at baseline to 1.2 ± 0.4 mg/dL at 12 months, indicating kidney dysfunction. GFR decreased from 91.5 ± 12.3 mL/min/1.73m² to 86.1 ± 9.5 mL/min/1.73m², further confirming the decline in kidney function. The urinary protein level showed a significant increase from 12.3 ± 4.1 mg/dL to 17.3 ± 5.2 mg/dL, suggesting the development of proteinuria over the course of growth hormone therapy.

Table 4: Effect of Growth Hormone on Kidney Biomarkers

Biomarker	Pre-treatment (Mean ± SD)	Post-treatment (Mean ± SD)	P-value
Serum Creatinine (mg/dL)	0.9 ± 0.2	1.2 ± 0.4	< 0.05
GFR (mL/min/1.73m²)	91.5 ± 12.3	86.1 ± 9.5	< 0.05
Urinary Protein (mg/dL)	12.3 ± 4.1	17.3 ± 5.2	< 0.01

Hypertension (β = 0.98) and diabetes (β = 0.75) were the strongest predictors of AKI, with odds ratios of 2.7 and 2.1, respectively. Obesity (β = 0.55) also showed a significant association with AKI (OR = 1.8), while smoking and alcohol consumption did not significantly affect AKI incidence.

Table 5: Multivariate Regression Analysis of Factors Associated with AKI

Factor	Beta Coefficient (β)	Odds Ratio (OR)	95% CI	P-value
Hypertension	0.98	2.7	2.0 - 3.9	< 0.001
Diabetes	0.75	2.1	1.5 - 3.1	0.002
Obesity	0.55	1.8	1.2 - 2.6	0.03
Age > 50 years	0.47	1.6	1.1 - 2.4	0.05
Smoking	0.32	1.4	0.9 - 2.2	0.18
Alcohol Consumption	0.15	1.2	0.8 - 1.7	0.32

DISCUSSION

The researchers assessed both short-term and long-term kidney function changes among patients receiving growth hormone therapy (GHT) to determine acute kidney injury (AKI) incidence rates among these patients. The data from this research shows that long-term administration of growth hormone (GH) therapy may promote the development of acute kidney injury (AKI) among those who have comorbidities such as hypertension, diabetes, and obesity. These results suggest that there is an increased risk of renal function impairment in patients on prolonged GH therapy and comorbidity looms in such patients[13]. In the context of existing literature that has been reviewed, the relationship with GH therapy and the AKI greatly elevates the concern of adverse outcomes after chronic exposure to high levels of GH and, as a consequence, poor kidney health. Regarding kidney functions, patients did not exhibit significant alteration in renal functioning during the initial stage, but over time, an abnormal decline was recorded[14]. At the 6th and 12th months, serum creatinine rose and

glomerular filtration rate (GFR) was found lowered, which indicated progression in renal impairment. Patients diagnosed with hypertension, diabetes, or obesity appeared to have worse outcomes and greater decline in renal functions as these existing illnesses worsened the Acute Kidney Injury[15]. The data also suggested that among those patients with hypertension, the incidence of AKI was higher as compared to patients without renal issues, clearly indicating hypertension posed as the major risk for the cohort population. This evidence stems from already known research, which emphasizes that high blood pressure potentially damages the kidneys, which later causes kidneys to function poorly[16]. Diabetes is one of the important risk factors to develop CKD or AKI, especially when combined with long-standing growth hormone therapy. Studies suggest that hyperglycemia associated with diabetes tends to injure the systemic vasculature along with increasing the likelihood of renal failure, and coupling this with extensive periods of growth hormone treatment can lead to dire consequences for the kidneys[17]. The results of this study indicate that those with diabetes may react differently to GH than others leading to renal impairment and possibly necessitating closer surveillance for AKI. Obesity is another important risk factor where patients with a higher body mass index (BMI) have a greater chance of developing AKI[18]. As deteriorating as both smoking and alcohol related activities are to general kidney health, interventional long-term GH therapy may not significantly stand out in terms of risk in comparison to other variables like high blood pressure or obesity. On the other hand, this one is tricky because smoking and alcohol's effect is multifaceted, and in conjunction with certain clinical factors, it may be really complicated[19]. Longitudinal Cox regression indicated these as well, suggesting that prolonged time in the use of GH therapy combined with hypertension, diabetes, and obesity were potent predictors of AKI. The hazard ratios for each of these factors indicated that the study patients were at higher risk of developing AKI during the study period. This suggests that any health status prior to commencing GH therapy must be carefully evaluated. The study is limited by the fact that the follow up period was only 12 months and it was not possible to study the long-term cumulative effects of GH therapy.

CONCLUSION

It is concluded that long-term growth hormone (GH) therapy is associated with an increased risk of acute kidney injury (AKI), particularly in patients with pre-existing risk factors such as hypertension, diabetes, and obesity. This study highlights the importance of careful monitoring of kidney function in patients receiving prolonged GH treatment, especially those who exhibit these comorbid conditions. The findings suggest that GH therapy, while beneficial for treating growth hormone deficiency and related conditions, may exacerbate renal stress and increase the likelihood of kidney damage in susceptible individuals.

REFERENCES

1. Haffner, D., Schaefer, F., Nissel, R., Wühl, E., Tönshoff, B. and Mehls, O., 2000. Effect of growth hormone treatment on the adult height of children with chronic renal failure. New England Journal of Medicine, 343(13), pp.923-930.
2. Bell, J., Parker, K.L., Swinford, R.D., Hoffman, A.R., Maneatis, T. and Lippe, B., 2010. Long-term safety of recombinant human growth hormone in children. The Journal of Clinical Endocrinology & Metabolism, 95(1), pp.167-177.
3. Kellum, J.A., Romagnani, P., Ashuntantang, G., Ronco, C., Zarbock, A. and Anders, H.J., 2021. Acute kidney injury. Nature reviews Disease primers, 7(1), pp.1-17.
4. Moore, P.K., Hsu, R.K. and Liu, K.D., 2018. Management of acute kidney injury: core curriculum 2018. American Journal of Kidney Diseases, 72(1), pp.136-148.
5. Murugan R, Kellum JA. Acute kidney injury: what's the prognosis?. Nature Reviews Nephrology. 2011 Apr;7(4):209-17.
6. Rein, J.L. and Coca, S.G., 2019. "I don't get no respect": the role of chloride in acute kidney injury. American Journal of Physiology-Renal Physiology, 316(3), pp.F587-F605.
7. Sharfuddin, A.A. and Molitoris, B.A., 2011. Pathophysiology of ischemic acute kidney injury. Nature Reviews Nephrology, 7(4), pp.189-200.
8. Poston JT, Koyner JL. Sepsis associated acute kidney injury. Bmj. 2019 Jan 9;364.
9. Andreoli SP. Acute kidney injury in children. Pediatric nephrology. 2009 Feb;24(2):253-63.
10. Amdur, R.L., Chawla, L.S., Amodeo, S., Kimmel, P.L. and Palant, C.E., 2009. Outcomes following diagnosis of acute renal failure in US veterans: focus on acute tubular necrosis. Kidney international, 76(10), pp.1089-1097.
11. Ostermann, M. and Joannidis, M., 2016. Acute kidney injury 2016: diagnosis and diagnostic workup. Critical care, 20, pp.1-13.
12. Wang, Y. and Bellomo, R., 2017. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. Nature Reviews Nephrology, 13(11), pp.697-711.
13. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clinical journal of the American Society of Nephrology. 2006 Jan 1;1(1):19-32.
14. Levey AS, Coresh J. Chronic kidney disease. The lancet. 2012 Jan 14;379(9811):165-80.
15. ad-hoc working group of ERBP:, Danilo Fliser, Maurice Laville, Adrian Covic, Denis Fouque, Raymond Vanholder, Laurent Juillard, and Wim Van Biesen. "A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy." Nephrology Dialysis Transplantation 27, no. 12 (2012): 4263-4272.
16. Joannidis, M., Druml, W., Forni, L.3., Groeneveld, A.B.J., Honore, P.4., Hoste, E., Ostermann, M., Oudemans-van Straaten, H.7. and Schetz, M., 2017. Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017: Expert opinion of the Working Group on Prevention, AKI section, European Society of Intensive Care Medicine. Intensive care medicine, 43, pp.730-749.
17. Becherucci F, Roperto RM, Materassi M, Romagnani P. Chronic kidney disease in children. Clinical kidney journal. 2016 Aug 1;9(4):583-91.
18. Grams ME, Rabb H. The distant organ effects of acute kidney injury. Kidney international. 2012 May 2;81(10):942-8.
19. Carel, J.C., Ecosse, E., Landier, F., Meguellati-Hakkas, D., Kaguelidou, F., Rey, G. and Coste, J., 2012. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. The Journal of Clinical Endocrinology & Metabolism, 97(2), pp.416-425.

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