The Role of Insulin-Like Growth Factor-1 in Anemia Among Adults Undergoing Maintenance Hemodialysis: A Comprehensive Review

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Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Anemia remains one of the most common and clinically significant complications of chronic kidney disease (CKD), particularly among adults receiving maintenance hemodialysis (MHD). Although impaired renal erythropoietin production is considered the principal mechanism, anemia in this population is multifactorial and is influenced by iron dysregulation, chronic inflammation, uremic toxins, nutritional deficiencies, shortened erythrocyte survival, and resistance to erythropoiesis-stimulating agents (ESAs). Emerging evidence suggests that insulin-like growth factor-1 (IGF-1), a key mediator of the growth hormone axis, may contribute to erythropoiesis through both erythropoietin-dependent and independent pathways. Reduced circulating IGF-1 concentrations are frequently observed in CKD and may reflect the combined effects of growth hormone resistance, protein-energy wasting, chronic inflammation, and metabolic disturbances. Consequently, IGF-1 has gained increasing attention as a potential biomarker of hematologic status and a possible therapeutic target in patients undergoing maintenance hemodialysis.

Aim: This review aims to comprehensively summarize current evidence regarding the physiological role of IGF-1 in erythropoiesis, alterations of the growth hormone–IGF-1 axis in CKD, and the relationship between serum IGF-1 concentrations and anemia in patients receiving maintenance hemodialysis. Furthermore, it explores the interactions between IGF-1, inflammation, nutritional status, iron metabolism, and ESA responsiveness, while highlighting the potential clinical implications of IGF-1 as a biomarker and future therapeutic target.

Conclusion: Current evidence indicates that reduced serum IGF-1 levels are consistently associated with lower hemoglobin concentrations, impaired erythropoiesis, protein-energy wasting, chronic inflammation, and adverse clinical outcomes in patients undergoing maintenance hemodialysis. Beyond its anabolic and metabolic actions, IGF-1 appears to play an important regulatory role in erythroid progenitor proliferation, differentiation, and survival, suggesting that dysfunction of the growth hormone–IGF-1 axis may contribute to the complex pathogenesis of renal anemia. Although available studies support the potential value of serum IGF-1 as a marker of nutritional and hematologic status, the existing evidence remains limited by relatively small sample sizes and predominantly observational designs. Large prospective studies and randomized clinical trials are required to establish causality, determine clinically relevant cutoff values, and evaluate whether therapeutic modulation of the GH/IGF-1 axis can improve anemia management and long-term outcomes in maintenance hemodialysis patients.

Keywords: Chronic kidney disease; Maintenance hemodialysis; End-stage kidney disease; Anemia; Insulin-like growth factor-1; Erythropoiesis; Growth hormone; Protein-energy wasting; Erythropoiesis-stimulating agents.

Introduction

Chronic kidney disease (CKD) is a progressive systemic disorder associated with multiple metabolic, cardiovascular, endocrine, nutritional, and hematological complications. Among these, anemia is one of the most frequent and clinically important complications, particularly in patients reaching end-stage kidney disease and requiring maintenance hemodialysis. Its presence is strongly associated with fatigue, reduced exercise tolerance, impaired quality of life, cardiovascular complications, hospitalization, and increased mortality. Therefore, anemia is not only a laboratory abnormality but also a major determinant of clinical outcomes in patients undergoing long-term dialysis. [1]

The pathogenesis of anemia in CKD is multifactorial. Although reduced renal erythropoietin production remains the central mechanism, several additional factors contribute to impaired erythropoiesis, including absolute or functional iron deficiency, inflammation, increased hepcidin activity, shortened red blood cell survival, uremic toxin accumulation, nutritional deficiencies, and bone marrow suppression. This complexity explains why many hemodialysis patients continue to have suboptimal hemoglobin levels despite treatment with iron supplementation and erythropoiesis-stimulating agents. [2]

Maintenance hemodialysis further amplifies the burden of anemia through recurrent blood loss, dialysis-related inflammation, reduced red cell survival, altered iron handling, and frequent comorbid conditions. In this population, anemia management requires more than correction of erythropoietin deficiency alone. Persistent anemia or poor response to erythropoiesis-stimulating agents often indicates the presence of additional biological disturbances, including malnutrition, chronic inflammation, mineral bone disease, and endocrine dysfunction. [3]

Insulin-like growth factor-1 (IGF-1) is a peptide hormone mainly produced by the liver under growth hormone stimulation, but it is also synthesized locally in many tissues. It has important anabolic, metabolic, and cellular effects, including stimulation of protein synthesis, cell proliferation, differentiation, and survival. Beyond its classical role in growth and metabolism, IGF-1 has been implicated in hematopoiesis through its ability to support erythroid progenitor proliferation and enhance erythropoietic activity. [4]

In patients with CKD and those undergoing maintenance hemodialysis, the growth hormone–IGF-1 axis is frequently disturbed. Despite normal or increased growth hormone levels, IGF-1 bioavailability may be reduced because of growth hormone resistance, inflammation, uremia, altered IGF-binding proteins, metabolic acidosis, and protein-energy wasting. These abnormalities suggest that reduced IGF-1 may reflect a broader state of endocrine and nutritional dysfunction in dialysis patients. [5]

The relationship between IGF-1 and anemia is biologically plausible because effective erythropoiesis requires not only erythropoietin and iron but also adequate nutritional, hormonal, and inflammatory balance. IGF-1 may contribute to red blood cell production by promoting erythroid progenitor survival, improving bone marrow responsiveness, and interacting with erythropoietin signaling pathways. Therefore, reduced IGF-1 may represent one of the overlooked contributors to persistent anemia in maintenance hemodialysis patients. [6]

Clinical studies have suggested that lower serum IGF-1 concentrations are associated with lower hemoglobin levels and worse hematological status in selected populations, including older adults, diabetic CKD patients, and patients receiving hemodialysis. However, evidence specifically addressing serum IGF-1 and anemia in maintenance hemodialysis remains limited, and the direction of causality is still uncertain. IGF-1 may be a direct erythropoietic modulator, a marker of nutritional status, or an integrated biomarker reflecting inflammation, malnutrition, and metabolic dysfunction. [7]

Therefore, this review aims to summarize the current evidence regarding the role of IGF-1 in anemia among adults undergoing maintenance hemodialysis. It discusses the physiology of the growth hormone–IGF-1 axis, its alteration in CKD, the mechanisms of renal anemia, the biological role of IGF-1 in erythropoiesis, available clinical evidence, and the interaction of IGF-1 with inflammation, protein-energy wasting, iron metabolism, and erythropoiesis-stimulating agent responsiveness. The ultimate

goal is to clarify whether IGF-1 may serve as a clinically useful biomarker or future therapeutic target in renal anemia. [8]

Physiology of the Growth Hormone–IGF-1 Axis

The growth hormone–insulin-like growth factor-1 (GH–IGF-1) axis is a central endocrine system regulating growth, metabolism, cellular repair, and tissue homeostasis. Growth hormone is secreted from the anterior pituitary gland under hypothalamic control by growth hormone–releasing hormone and somatostatin. After secretion, GH acts mainly on the liver to stimulate synthesis of IGF-1, although IGF-1 is also produced locally in several tissues where it functions through autocrine and paracrine mechanisms. This dual endocrine and local activity allows IGF-1 to influence multiple biological systems, including skeletal muscle, bone, kidney, vascular tissue, and hematopoietic cells. [9]

Circulating IGF-1 is not present as a free hormone alone; most of it is bound to insulin-like growth factor-binding proteins, particularly IGFBP-3, which regulate its stability, tissue delivery, and biological availability. These binding proteins prolong the half-life of IGF-1 but also determine how much active hormone is available to interact with IGF-1 receptors. Therefore, serum IGF-1 concentration reflects only part of the biological activity of the GH–IGF-1 system, because changes in binding proteins, nutrition, inflammation, liver function, and renal clearance may significantly alter IGF-1 bioavailability. [10]

At the cellular level, IGF-1 acts mainly through the IGF-1 receptor, a transmembrane tyrosine kinase receptor expressed in many tissues. Activation of this receptor stimulates intracellular pathways such as PI3K/Akt and MAPK signaling, which promote cell survival, proliferation, differentiation, and resistance to apoptosis. These signaling effects explain why IGF-1 is considered an anabolic and cytoprotective hormone rather than only a mediator of linear growth. In adults, IGF-1 contributes to maintenance of muscle mass, metabolic balance, vascular integrity, and tissue repair. [11]

The GH–IGF-1 axis is strongly influenced by nutritional status. Adequate protein and energy intake are required for normal hepatic IGF-1 synthesis, while fasting, inflammation, chronic illness, and protein-energy wasting reduce IGF-1 levels even when GH secretion is preserved. This makes IGF-1 a clinically relevant marker of anabolic reserve and nutritional health, particularly in chronic diseases such as CKD. In patients undergoing maintenance hemodialysis, reduced IGF-1 may therefore indicate not only endocrine disturbance but also malnutrition, inflammation, and catabolic stress. [12]

IGF-1 also has an important relationship with hematopoiesis. Experimental and clinical evidence suggests that IGF-1 can stimulate erythroid progenitor cell proliferation, support differentiation, and protect developing erythroid cells from apoptosis. These effects may occur independently or synergistically with erythropoietin. Therefore, normal erythropoiesis depends not only on erythropoietin and iron availability but also on a favorable hormonal and nutritional environment in which IGF-1 may play a supportive role. [13]

In the context of maintenance hemodialysis, understanding the GH–IGF-1 axis is clinically important because this pathway connects several major problems in dialysis patients: malnutrition, sarcopenia, inflammation, frailty, cardiovascular risk, and anemia. A low IGF-1 level may therefore represent an integrated biological signal of impaired anabolic function and reduced erythropoietic potential. This makes IGF-1 an attractive candidate biomarker for evaluating anemia beyond conventional parameters such as hemoglobin, ferritin, transferrin saturation, and erythropoietin-stimulating agent dose. [14]

Alterations of the GH–IGF-1 Axis in CKD and Maintenance Hemodialysis

Patients with chronic kidney disease frequently develop disturbances in the growth hormone–IGF-1 axis, particularly as renal function declines and uremic burden increases. Although growth hormone secretion may be normal or even elevated, its biological action becomes impaired because of growth hormone resistance, altered receptor signaling, and reduced hepatic responsiveness. As a result, circulating IGF-1 activity may decline despite preserved hormonal stimulation, creating a state of functional anabolic resistance. [15]

In maintenance hemodialysis, this endocrine disturbance is intensified by chronic inflammation,

oxidative stress, metabolic acidosis, insulin resistance, and accumulation of uremic toxins. These factors interfere with post-receptor signaling and reduce the anabolic effects of IGF-1 in peripheral tissues. Therefore, low IGF-1 in hemodialysis patients should not be interpreted as an isolated endocrine abnormality, but rather as part of a wider metabolic syndrome associated with chronic kidney failure. [16]

Protein-energy wasting is one of the strongest clinical conditions linked to reduced IGF-1 in dialysis patients. Inadequate dietary intake, dialysis-related amino acid losses, inflammation, and catabolic illness all contribute to loss of muscle and protein stores. Because IGF-1 synthesis is highly nutrition-sensitive, reduced serum IGF-1 may reflect impaired anabolic reserve and worsening nutritional status, both of which are common among adults undergoing long-term hemodialysis. [17]

Altered IGF-binding proteins also contribute to abnormal IGF-1 bioavailability in CKD. Since the kidney participates in the metabolism and clearance of several binding proteins, advanced renal failure can change the balance between bound and biologically active IGF-1. This means that total serum IGF-1 may not fully represent tissue-level IGF-1 activity, especially in uremic patients with inflammation, hypoalbuminemia, or malnutrition. [18]

The clinical importance of GH–IGF-1 axis dysfunction extends beyond growth and nutrition. Low IGF-1 has been associated with reduced muscle strength, sarcopenia, frailty, cardiovascular risk, and mortality in CKD and hemodialysis populations. These associations are highly relevant to anemia because the same inflammatory and catabolic pathways that reduce IGF-1 may also impair erythropoiesis and decrease responsiveness to erythropoiesis-stimulating agents. [19]

Thus, GH–IGF-1 axis dysfunction may represent a mechanistic bridge between malnutrition, inflammation, endocrine dysregulation, and anemia in maintenance hemodialysis. Rather than being only a nutritional marker, IGF-1 may help identify patients with impaired erythropoietic capacity and poor anabolic status. This concept supports the need to evaluate IGF-1 within a broader clinical framework that includes hemoglobin, iron indices, inflammatory markers, albumin, muscle status, and ESA responsiveness. [20]

Pathophysiology of Anemia in Maintenance Hemodialysis

Anemia in patients undergoing maintenance hemodialysis is a complex disorder resulting from the interaction of multiple pathological mechanisms rather than erythropoietin deficiency alone. Progressive loss of functioning renal tissue reduces the number of erythropoietin-producing fibroblasts within the renal cortex, leading to inadequate stimulation of erythroid progenitor cells in the bone marrow. As kidney disease advances, this endocrine defect becomes increasingly severe and represents the principal mechanism underlying renal anemia. Nevertheless, numerous additional factors coexist and contribute to the persistence and severity of anemia in the dialysis population. [21]

Iron dysregulation is another major contributor to anemia in maintenance hemodialysis. Repeated blood loss during dialysis sessions, frequent laboratory testing, vascular access procedures, and gastrointestinal bleeding may produce absolute iron deficiency. At the same time, chronic inflammation promotes increased hepatic hepcidin production, which inhibits ferroportin-mediated iron export from enterocytes and macrophages, thereby limiting iron availability for erythropoiesis despite adequate or increased iron stores. Consequently, many dialysis patients develop functional iron deficiency characterized by reduced iron utilization rather than depleted body iron reserves. [22]

Chronic systemic inflammation plays a central role in the development of renal anemia and contributes significantly to resistance to erythropoiesis-stimulating agents. Elevated concentrations of inflammatory cytokines, including interleukin-6 and tumor necrosis factor-α, suppress erythroid progenitor proliferation, reduce endogenous erythropoietin production, impair iron mobilization through hepcidin activation, and shorten red blood cell survival. Persistent inflammation therefore establishes a chronic inhibitory environment that compromises effective erythropoiesis and reduces treatment response. [23]

Uremic toxin accumulation further aggravates anemia by impairing bone marrow function and reducing

the responsiveness of erythroid precursor cells to erythropoietin. These toxins may directly inhibit cellular proliferation, increase oxidative stress, and promote premature erythrocyte destruction. Furthermore, shortened red blood cell lifespan, which is commonly observed in advanced CKD, increases the rate of erythrocyte turnover and further contributes to declining hemoglobin concentrations despite ongoing erythropoiesis. [24]

Several additional factors may exacerbate anemia in maintenance hemodialysis, including deficiencies of vitamin B12 and folate, secondary hyperparathyroidism, aluminum toxicity, occult blood loss, inadequate dialysis, and medications that interfere with erythropoiesis. Protein-energy wasting and hypoalbuminemia further impair bone marrow activity by reducing the availability of nutrients required for effective red blood cell production. The coexistence of these abnormalities explains why anemia severity often varies considerably among adults with similar degrees of renal dysfunction. [25]

The multifactorial nature of renal anemia has important therapeutic implications. Although iron supplementation and erythropoiesis-stimulating agents remain the cornerstone of treatment, correction of hemoglobin cannot always be achieved by these interventions alone. Identifying additional contributors—including inflammation, malnutrition, endocrine disturbances, and altered anabolic signaling—is increasingly recognized as an essential component of individualized anemia management. Within this context, the GH–IGF-1 axis has emerged as a potential link between nutritional status, chronic inflammation, and impaired erythropoiesis, providing a biological rationale for investigating its role in patients undergoing maintenance hemodialysis. [26]

Figure 1. Pathophysiology of anemia in chronic kidney disease. CKD—chronic kidney disease; EPO—erythropoietin; ACE—angiotensin converting enzyme; RBC—red blood cells.

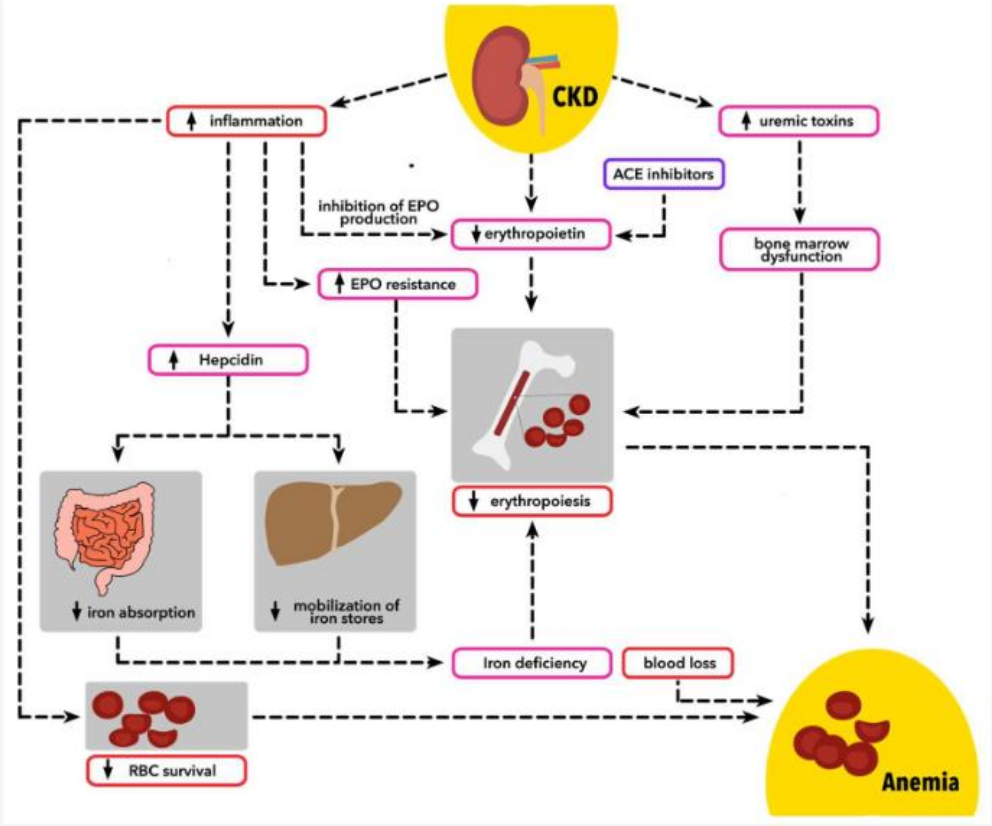

Figure 1: Pathophysiology of anemia in chronic kidney disease [26]

Role of IGF-1 in Erythropoiesis and Red Blood Cell Homeostasis

Insulin-like growth factor-1 (IGF-1) has emerged as an important regulator of hematopoiesis beyond its established roles in growth and metabolism. Experimental evidence demonstrates that IGF-1 directly

stimulates the proliferation, differentiation, and maturation of erythroid progenitor cells within the bone marrow. Through activation of the IGF-1 receptor, it enhances intracellular signaling pathways that promote cell cycle progression and inhibit apoptosis, thereby increasing the survival of erythroid precursors and supporting effective red blood cell production. These actions suggest that IGF-1 contributes to maintaining normal erythropoiesis under both physiological and pathological conditions. [27]

The interaction between IGF-1 and erythropoietin is particularly important in regulating erythropoiesis. Rather than replacing erythropoietin, IGF-1 appears to enhance the sensitivity of erythroid progenitor cells to erythropoietin stimulation, facilitating a more efficient proliferative response. Experimental studies have demonstrated that the combined action of erythropoietin and IGF-1 produces greater erythroid expansion than either factor alone, indicating a synergistic relationship between these two hormonal pathways. Consequently, reduced IGF-1 concentrations may diminish bone marrow responsiveness even when erythropoietin levels or ESA therapy are adequate. [28]

Beyond its direct effects on erythroid cells, IGF-1 indirectly supports erythropoiesis by improving the metabolic environment required for bone marrow function. As a potent anabolic hormone, IGF-1 promotes protein synthesis, preserves skeletal muscle mass, improves nutritional status, and reduces cellular apoptosis. Since protein-energy wasting and chronic inflammation are common among maintenance hemodialysis patients and both negatively influence erythropoiesis, reduced IGF-1 may contribute to anemia through multiple interconnected pathways rather than through a single direct mechanism. [29]

Experimental and clinical observations also suggest that IGF-1 may influence red blood cell survival. By reducing oxidative stress and promoting cellular integrity, IGF-1 may help maintain erythrocyte membrane stability and decrease premature erythrocyte destruction. Although these mechanisms remain incompletely understood, preservation of red blood cell lifespan may represent another pathway through which adequate IGF-1 concentrations contribute to maintaining hemoglobin levels in patients with chronic kidney disease. [30]

The biological relevance of IGF-1 is supported by observations in several clinical populations. Lower circulating IGF-1 concentrations have been associated with lower hemoglobin levels in older adults, diabetic patients with chronic kidney disease, and individuals receiving maintenance hemodialysis. These findings suggest that impaired IGF-1 activity may be linked to defective erythropoiesis across different chronic disease states, although the magnitude of its contribution likely varies according to nutritional status, inflammatory burden, and underlying renal dysfunction. [31]

Taken together, current evidence indicates that IGF-1 participates in erythropoiesis through both direct stimulation of erythroid progenitor cells and indirect modulation of nutritional, inflammatory, and metabolic pathways. This multifaceted role provides a strong biological rationale for investigating serum IGF-1 as a potential biomarker of hematological status and as a possible therapeutic target in patients undergoing maintenance hemodialysis, particularly those with persistent anemia despite conventional treatment. [32]

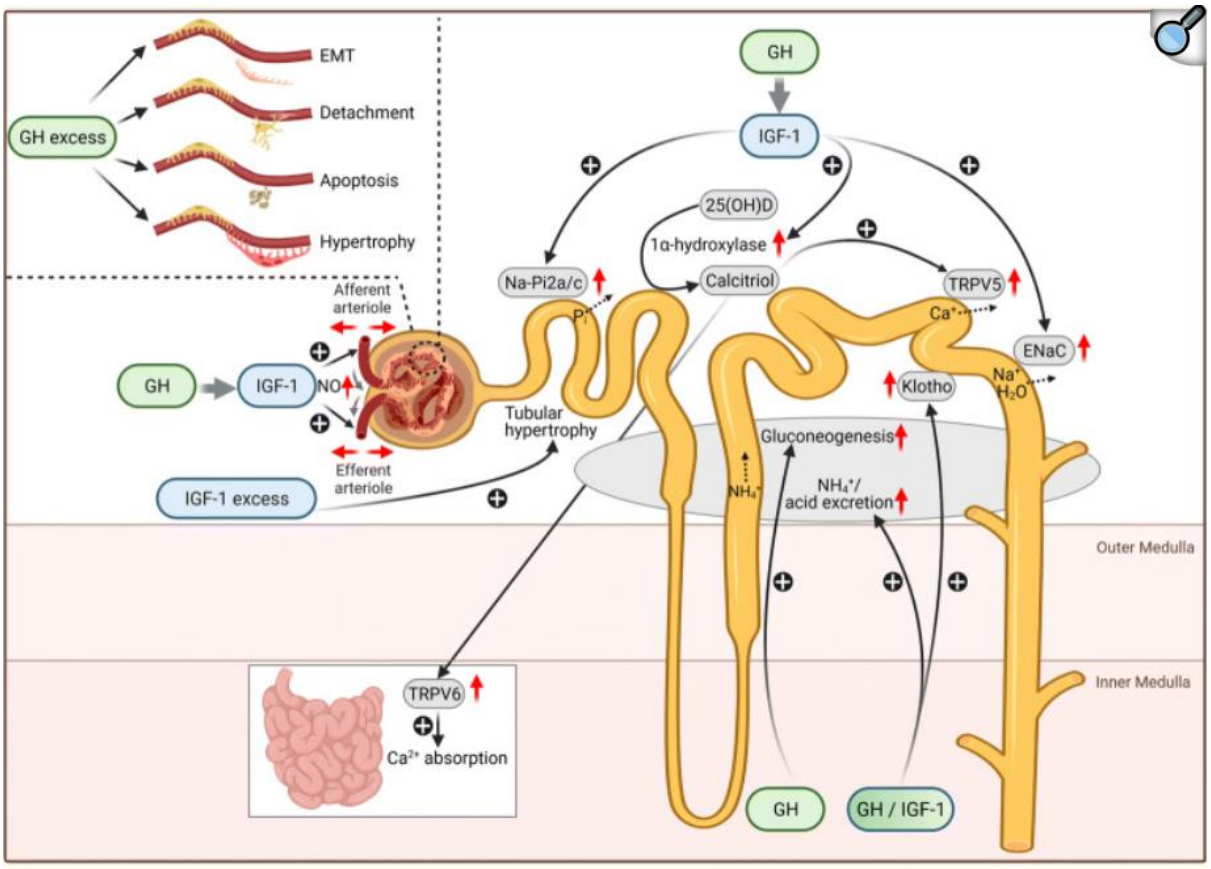

Figure 2: Physiological and pathophysiological actions of growth hormone and its mediator insulin-like growth factor-1 (IGF-1) on the kidneys: GH and IGF-1 receptors (GHR/IGF-1R) are widely expressed in the glomerular and tubular cells. GH can act on the kidneys, either directly via activation of the GHR/Janus kinase-2 (JAK2)-signal transducer and activator of transcription 5 (STAT5) and ERK1/2 pathways, or indirectly via circulating or paracrine-synthesized IGF-1 by activating IGF-1R. Most of the glomerular and tubular effects of GH are mediated by IGF-1 and include the following: (1) dilation of the afferent and efferent arterioles via increased synthesis of the endogenous vasodilator nitric oxide (NO), resulting in enhanced glomerular filtration rate and renal plasma flow; (2) stimulation of phosphate (Pi) reabsorption in the proximal tubules via up-regulation of the sodium-phosphate transporters (Na-Pi2a/2c; (3) stimulation of sodium (Na+) and water (H2O) reabsorption in the distal nephron via up-regulation of the epithelial sodium channel (ENaC); and (4) stimulation of the 1α-hydroxylase and thereby, calcitriol synthesis in the proximal tubule, with subsequent increases in calcium (Ca+) absorption via up-regulation of the epithelial calcium channels TRPV6 and TRPV5 in the intestine and distal renal tubule, respectively. Some GH effects may also be mediated by IGF-1, including stimulation of (1) net acid secretion via increased ammonia (NH4+) production in the proximal tubule and a Na+-dependent mechanism in the distal tubule and (2) renal Klotho synthesis in the distal renal tubule. GH was shown to directly enhance renal gluconeogenesis in proximal tubular cells. In states of GH excess, GH can directly induce glomerulosclerosis and podocyte injury, characterized by podocyte hypertrophy, apoptosis, dedifferentiation of podocytes (epithelial–mesenchymal transition, EMT), and/or cross-linking of the basement membrane resulting in increased podocyte permeability to albumin and detachment of podocytes from the glomerular basement membrane. By contrast, IGF-1 excess results in tubular hypertrophy only. The kidneys of patients with chronic kidney disease (CKD) are protected from the potentially negative effects of long-term GH-treatment on the glomerulus, likely due to the CKD-associated GH insensitivity of the kidneys and/or the much lower GH exposure in GH-treated patients, compared to those with the abovementioned conditions. [32]

Clinical Evidence Linking Serum IGF-1 with Anemia in Maintenance Hemodialysis

Interest in the relationship between serum IGF-1 and anemia has increased over the past decade as evidence has emerged linking reduced IGF-1 concentrations with impaired erythropoiesis in chronic diseases. Although the number of studies specifically involving maintenance hemodialysis patients remains relatively limited, available clinical data consistently suggest that lower circulating IGF-1 levels are associated with lower hemoglobin concentrations and a higher prevalence of anemia. These findings support the hypothesis that IGF-1 may influence erythropoiesis beyond its established metabolic and anabolic functions. [33]

Evidence from non-dialysis populations first demonstrated the association between IGF-1 and hematological status. Studies involving older adults reported that individuals with higher serum IGF-1 concentrations had significantly higher hemoglobin levels independent of erythropoietin concentrations and several traditional anemia risk factors. Similarly, investigations in patients with diabetic chronic

kidney disease identified low IGF-1 as an independent predictor of anemia, suggesting that impaired IGF-1 activity may contribute to declining hemoglobin before the initiation of dialysis therapy. These observations provided the biological foundation for evaluating IGF-1 in maintenance hemodialysis patients. [34]

Subsequent studies in maintenance hemodialysis populations have demonstrated similar findings. Patients with lower serum IGF-1 concentrations generally exhibit lower hemoglobin values and poorer nutritional indicators than patients with higher IGF-1 levels. Because serum IGF-1 is closely associated with nutritional status, muscle mass, and inflammatory burden, it may serve as an integrated biomarker reflecting the combined effects of these factors on erythropoiesis. Consequently, reduced IGF-1 may identify patients at greater risk of persistent anemia despite standard treatment. [35]

Several investigators have also examined the relationship between IGF-1 and other laboratory parameters relevant to anemia. Lower IGF-1 concentrations have been associated with hypoalbuminemia, reduced transferrin saturation, elevated inflammatory markers, and poorer overall nutritional status. These associations suggest that the relationship between IGF-1 and hemoglobin is unlikely to be isolated but rather reflects the broader interaction between endocrine regulation, nutrition, inflammation, and iron metabolism in patients undergoing maintenance hemodialysis. [36]

Patients without anemia demonstrated significantly higher serum IGF-1 concentrations than anemic patients, while serum IGF-1 showed a significant positive correlation with hemoglobin concentration. Furthermore, multivariable regression analysis identified higher IGF-1 levels as an independent protective factor against anemia after adjustment for relevant clinical variables. These findings support the concept that serum IGF-1 is independently associated with better hematological status in maintenance hemodialysis patients and may provide additional prognostic information beyond conventional anemia markers.

Despite these encouraging findings, the available literature remains limited by relatively small sample sizes, cross-sectional study designs, and heterogeneity in patient characteristics and laboratory methods. Most published studies demonstrate an association rather than causation, making it difficult to determine whether reduced IGF-1 directly contributes to impaired erythropoiesis or primarily reflects the underlying inflammatory and nutritional disturbances common in advanced CKD. Large prospective studies and interventional trials are therefore required to clarify the causal relationship and to determine whether therapeutic modulation of the GH–IGF-1 axis can improve anemia management in patients receiving maintenance hemodialysis. [37]

Interactions Between IGF-1, Protein-Energy Wasting, Inflammation, and ESA Resistance

Protein-energy wasting is highly prevalent among adults undergoing maintenance hemodialysis and represents one of the most important clinical contexts in which low IGF-1 should be interpreted. Reduced dietary intake, dialysis-related nutrient losses, metabolic acidosis, inflammation, hormonal resistance, and catabolic comorbidities all contribute to progressive loss of protein stores and muscle mass. Because IGF-1 production is strongly dependent on adequate protein and energy availability, low serum IGF-1 may serve as a marker of impaired anabolic reserve in dialysis patients. [38]

The relationship between IGF-1 and anemia may therefore be partly mediated by nutritional status. Adequate erythropoiesis requires sufficient amino acids, micronutrients, iron availability, and marrow metabolic activity. In patients with protein-energy wasting, reduced IGF-1 may reflect a catabolic environment in which erythroid progenitor proliferation is impaired and hemoglobin synthesis becomes less efficient. This explains why anemia in hemodialysis often coexists with hypoalbuminemia, sarcopenia, weight loss, and poor functional status. [39]

Inflammation is another major pathway connecting low IGF-1 with anemia. Chronic kidney disease and hemodialysis are associated with persistent inflammatory activation caused by uremic toxins, vascular access-related factors, oxidative stress, comorbid disease, and dialysis membrane bioincompatibility. Inflammatory cytokines suppress hepatic IGF-1 production, impair GH receptor signaling, increase hepcidin expression, and inhibit erythroid progenitor activity. Thus, inflammation can simultaneously

reduce IGF-1 bioavailability and worsen anemia. [40]

ESA resistance is one of the most clinically relevant consequences of this inflammatory and catabolic state. Patients with low IGF-1 may have reduced marrow responsiveness because of malnutrition, cytokine-mediated suppression, impaired iron mobilization, and defective anabolic signaling. In such patients, escalating ESA doses may produce limited hemoglobin improvement unless the underlying nutritional and inflammatory disturbances are addressed. Therefore, IGF-1 may help identify a subgroup of patients in whom anemia reflects broader biological dysfunction rather than isolated erythropoietin deficiency. [41]

The interaction between IGF-1 and iron metabolism is also clinically important. Functional iron deficiency is common in maintenance hemodialysis and is often driven by hepcidin-mediated iron restriction. Since inflammation both increases hepcidin and suppresses IGF-1 activity, low IGF-1 may coexist with reduced transferrin saturation and poor iron utilization. This combined disturbance may limit erythropoietic response despite apparently adequate ferritin levels, emphasizing the need to interpret iron indices within the broader inflammatory and nutritional context. [42]

Overall, IGF-1 appears to occupy a central position linking protein-energy wasting, inflammation, iron dysregulation, and ESA hyporesponsiveness. Its clinical value may not lie in replacing conventional anemia markers, but in complementing them by reflecting the patient's anabolic, inflammatory, and erythropoietic reserve. This integrated interpretation may improve individualized anemia assessment in maintenance hemodialysis patients. [43]

Clinical Implications and Therapeutic Perspectives

Serum IGF-1 may have clinical value as an additional biomarker in patients undergoing maintenance hemodialysis, particularly when anemia persists despite apparently adequate iron supplementation and ESA therapy. Unlike hemoglobin, ferritin, or transferrin saturation, IGF-1 reflects a broader biological state involving nutrition, inflammation, endocrine function, and anabolic reserve. Therefore, measuring IGF-1 may help identify patients in whom anemia is driven partly by protein-energy wasting, chronic inflammation, or impaired GH–IGF-1 signaling. [44]

From a practical clinical perspective, low IGF-1 should not be interpreted as an isolated abnormality. Instead, it should prompt broader evaluation of nutritional status, serum albumin, muscle mass, inflammatory markers, dialysis adequacy, iron indices, mineral metabolism, and ESA responsiveness. This approach is particularly relevant because increasing ESA dose alone may be ineffective or potentially harmful when the underlying cause of anemia is inflammation, malnutrition, or impaired marrow responsiveness rather than pure erythropoietin deficiency. [45]

Nutritional intervention is one of the most relevant therapeutic strategies for improving the IGF-1 axis in hemodialysis patients. Adequate protein and energy intake, correction of metabolic acidosis, management of inflammation, and prevention of dialysis-related nutrient losses may improve anabolic signaling and potentially support erythropoiesis. Although nutritional therapy should not be viewed as a direct treatment for anemia, improving nutritional status may enhance marrow function and increase responsiveness to conventional anemia therapy. [46]

Exercise-based interventions may also have theoretical value because physical activity can improve muscle mass, reduce frailty, enhance insulin sensitivity, and stimulate anabolic pathways. In maintenance hemodialysis patients, exercise programs may improve functional capacity and nutritional status, and these effects could indirectly support IGF-1 activity. However, evidence specifically proving that exercise-induced changes in IGF-1 improve hemoglobin levels in dialysis patients remains limited. [47]

Pharmacologic modulation of the GH–IGF-1 axis remains an area of interest but cannot yet be recommended for routine anemia management. Growth hormone therapy and ghrelin receptor agonists have been explored in dialysis patients mainly for anabolic and nutritional indications, with some evidence of increased IGF-1 concentrations. Nevertheless, concerns regarding cost, safety, glucose metabolism, fluid retention, cardiovascular risk, and uncertain hematological benefit limit their clinical

application at present. [48]

Therefore, the current role of IGF-1 is best understood as a promising biomarker and mechanistic link rather than an established therapeutic target. In the future, IGF-1 may contribute to individualized anemia management by helping distinguish patients with true iron or erythropoietin deficiency from those with broader inflammatory, nutritional, and endocrine dysfunction. This may support a more integrated treatment strategy combining optimized dialysis care, iron therapy, ESA use, nutritional rehabilitation, inflammation control, and metabolic correction. [49]

Although accumulating evidence supports an association between serum IGF-1 and anemia in maintenance hemodialysis, several important knowledge gaps remain. Most available studies are cross-sectional, limiting the ability to establish temporal or causal relationships. Consequently, it is still uncertain whether reduced IGF-1 directly contributes to impaired erythropoiesis or primarily reflects the effects of chronic inflammation, protein-energy wasting, and advanced kidney disease. Well-designed prospective cohort studies are needed to clarify the prognostic significance of serum IGF-1 in the progression and management of renal anemia. [50]

Another important area for future investigation is the standardization of IGF-1 measurement and interpretation in patients with chronic kidney disease. Variability among laboratory assays, age-related physiological changes, sex differences, nutritional status, liver function, and alterations in IGF-binding proteins may all influence circulating IGF-1 concentrations. Establishing standardized reference ranges and clinically meaningful cutoff values specific to maintenance hemodialysis patients would improve the utility of IGF-1 as a biomarker in both research and clinical practice.

Future research should also explore whether integrating serum IGF-1 with conventional anemia markers—including hemoglobin, ferritin, transferrin saturation, albumin, inflammatory biomarkers, and indices of nutritional status—can improve risk stratification and predict responsiveness to erythropoiesis-stimulating agents. Such multimarker approaches may better reflect the multifactorial pathophysiology of renal anemia than reliance on individual laboratory parameters.

Finally, randomized clinical trials are required to determine whether interventions capable of improving the GH–IGF-1 axis—including nutritional optimization, exercise rehabilitation, correction of metabolic acidosis, anti-inflammatory strategies, or targeted endocrine therapies—can translate into meaningful improvements in hemoglobin levels, ESA responsiveness, quality of life, and long-term clinical outcomes. These investigations may ultimately determine whether IGF-1 evolves from a promising biomarker into a therapeutic target for individualized anemia management in patients undergoing maintenance hemodialysis.

Conclusion

Serum insulin-like growth factor-1 appears to have an important relationship with anemia in patients undergoing maintenance hemodialysis. Although renal anemia has traditionally been explained mainly by erythropoietin deficiency and iron dysregulation, current evidence supports a broader pathophysiological model that includes inflammation, protein-energy wasting, endocrine dysfunction, impaired marrow responsiveness, and altered anabolic signaling.

IGF-1 may contribute to erythropoiesis through direct stimulation of erythroid progenitor proliferation, enhancement of cell survival, and possible synergism with erythropoietin. In maintenance hemodialysis patients, reduced IGF-1 may also reflect malnutrition, inflammation, sarcopenia, and impaired metabolic reserve, all of which can worsen anemia and reduce ESA responsiveness.

Therefore, IGF-1 should be viewed as a promising integrative biomarker linking nutritional, inflammatory, endocrine, and hematological status in dialysis patients. However, available evidence remains insufficient to support routine IGF-1-guided anemia management. Future prospective and interventional studies are required to determine whether improving IGF-1 activity can enhance hemoglobin levels, reduce ESA resistance, and improve outcomes in maintenance hemodialysis.

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