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REVIEW

Endocrinological disorders in acute kidney injury: an often overlooked field of clinical research

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Abstract

Acute kidney injury (AKI) is a common comorbidity, affecting approximately one in five hospitalized adults. The kidney is the site for the production, metabolism or excretion of most hormones, including the production of erythropoietin (EPO), the active form of vitamin D, renin, thrombopoietin, and the excretion of insulin, catecholamines, gastrin and many other hormones. Therefore, it is reasonable to say that AKI can have a considerable impact on the endocrine system. Although the effects of AKI on various parameters, including cardiovascular parameters, serum electrolytes and acid–base disorders, neuro-humoral mechanisms and neurological outcomes have been extensively studied, the endocrinological consequences of AKI are understudied. Thyroid dysfunction, mainly euthyroid sick syndrome, hypo/hyperglycemia, bone mineral disorders, changes in EPO and atrial natriuretic peptide (ANP) levels are commonly found in AKI. EPO, thyroxine and ANP administration have been evaluated as potential tools to prevent or treat AKI with varying success, while the effects of AKI on some key hormones, including cortisol and insulin, have never been studied. Aim of this narrative review is to illustrate what is known and what is not known about the endocrinological outcomes of AKI. Few clinical trials are ongoing: however, there is a clear need for large-scale randomized controlled trials investigating the endocrinological consequences of AKI.

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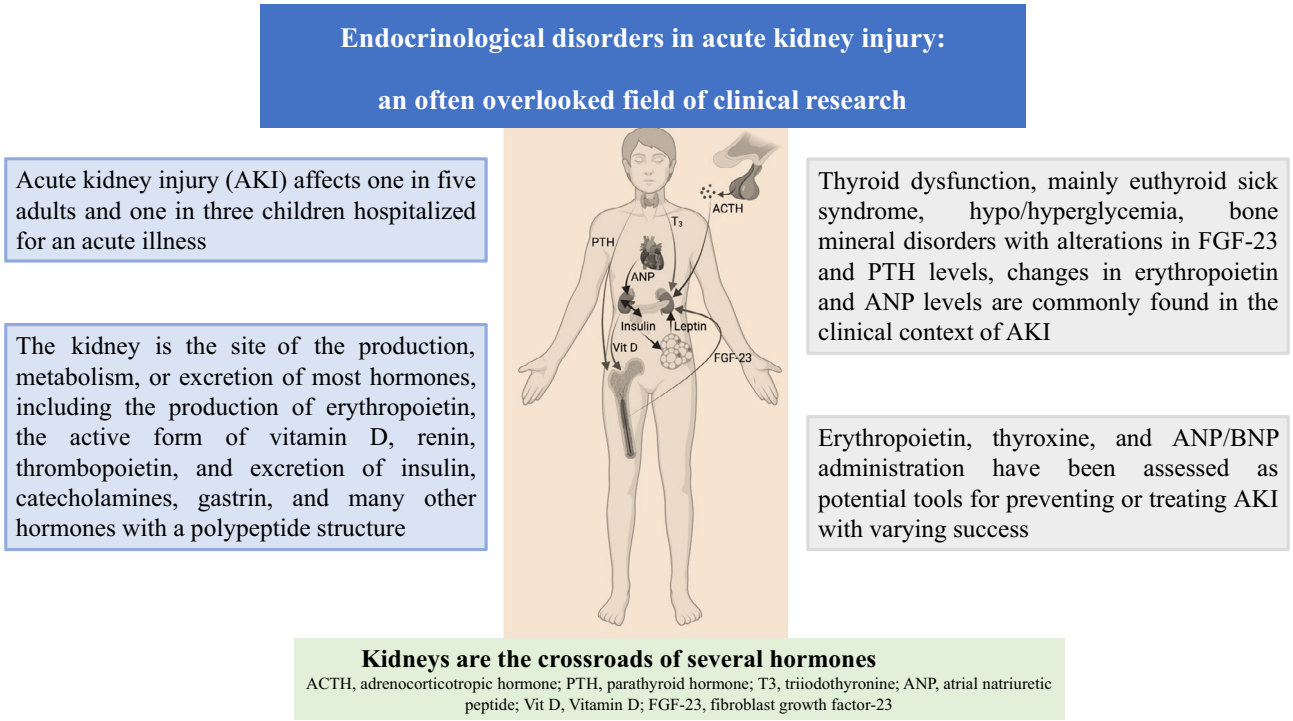
Graphical abstract



Keywords Acute kidney injury · Thyroid gland · Erythropoietin · Atrial natriuretic peptide · Bone mineral disorders

Introduction

Acute kidney injury (AKI) affects one in five adults and one in three children hospitalized for acute illness, according to a large-scale systematic review of 49 million patients, mostly from high-income countries [1]. In addition to its high prevalence, AKI predisposes to high direct medical costs, which have been found to exceed the costs of heart failure and pneumonia, both of which are more prevalent [2, 3]. Numerous consequences of AKI, including fluid and electrolyte imbalances, acid–base disorders, cardiovascular events, neurological outcomes, neuro-humoral mechanisms, liver disease and nutritional imbalances are the subject of in-depth studies; however, the potential endocrinological impact of AKI is mostly overlooked [4, 5]. Additionally, some studies have shown reduced health-related quality of life in AKI patients compared to critically ill patients without AKI or the general population [6, 7]. These effects may be attributable to reduced mobility, decreased fitness and limited energy [4]. The kidney is the site for the production, metabolism or excretion of most hormones, including the production of erythropoietin (EPO), the active form of vitamin D, renin, thrombopoietin, and the excretion of insulin, catecholamines, gastrin and many other hormones with a polypeptide structure [8]. Therefore, it is reasonable to say that AKI can have a considerable impact on the endocrine system with other potential effects on various systems and clinical outcomes.

In this narrative review, we aim to illustrate what is known and what is not known about the endocrinological outcomes of AKI, including the hypothalamic-pituitary-thyroid and adrenal axis, bone mineral disorders, and other hormones.

AKI and thyroid disorders

The complex interplay between thyroid and kidney function has long been investigated in preclinical and clinical studies. Hypothyroidism has a significant impact on kidney function through hemodynamic, glomerular and tubular mechanisms. Hypothyroidism causes a decrease in sensitivity to beta-adrenergic stimuli and a decrease in systolic cardiac function due to the reduction of the transcription of specific myocyte proteins, while mean arterial pressure increases caused by the decrease of endothelial vasodilator proteins [9, 10]. Due to a decrease in sensitivity to beta-adrenergic

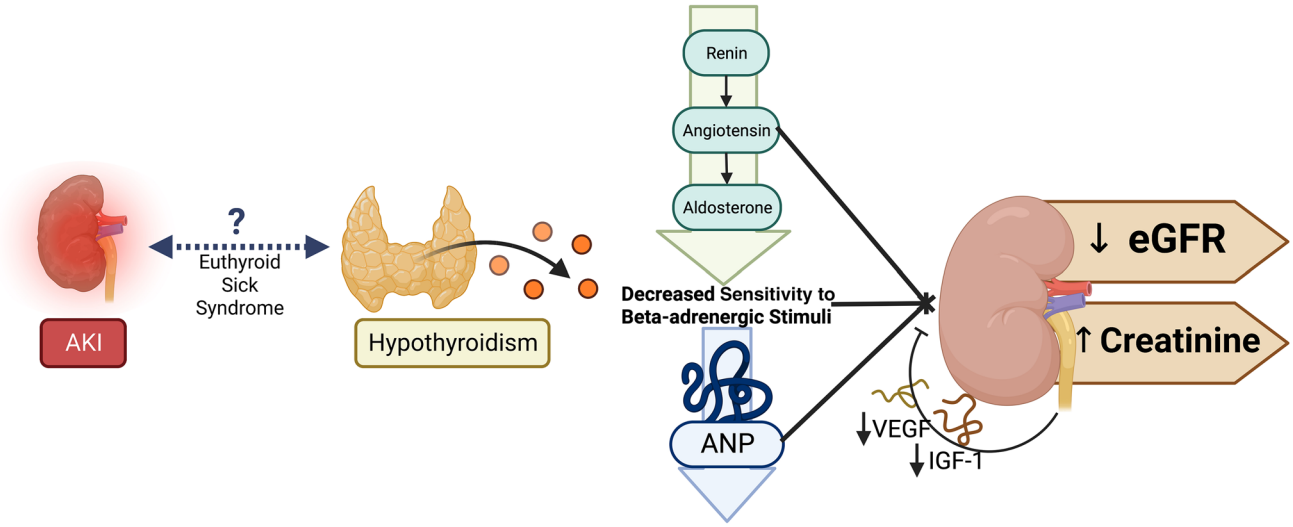


Fig. 1 Interplay between the thyroid gland and the kidneys in the setting of acute kidney injury. *AKI* acute kidney injury; *ANP* atrial natriuretic peptide; *VEGF* vascular endothelial growth factor; *IGF-1* insulin-like growth factor-1; *eGFR* estimated glomerular filtration rate

stimuli, renin secretion from the juxtaglomerular apparatus will be reduced in the context of hypothyroidism. Furthermore, decreased activation of the renin–angiotensin–aldosterone system and atrial natriuretic peptide (ANP) production cause decreased glomerular filtration rate (GFR) and kidney plasma flow [11–13]. The decline of GFR is further exacerbated by reduced secretion of kidney vasodilator proteins such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) [14] (Fig. 1). Furthermore, both production and activity of various transporters, including Na–K ATPase and Na-P exchanger, decrease with defective urinary acidification and a tendency to hyponatremia due to increased sensitivity to vasopressin [15–17]. Population-based studies have shown that higher thyroid stimulating hormone (TSH) levels are linked to a greater prevalence of chronic kidney disease (CKD) and a lower GFR regardless of various confounding factors, including demographics and medical comorbidities [16, 17]. Although hypothyroidism is linked to a drop in GFR and elevated serum creatinine levels, serum cystatin C levels are unexpectedly decreased [15]. Furthermore, a large scale meta-analysis study demonstrated that hyperthyroidism is directly linked to elevated cystatin C levels, while hypothyroidism has a directly opposite association [18]. Although in vitro studies have demonstrated that thyroid hormones have a direct role in stimulating cystatin C production, the exact underlying mechanism leading to altered cystatin C levels in patients with thyroid disorders remains unclear [19]. Therefore, cystatin C levels are not accurate indicators of glomerular function in patients with hypothyroidism. Thyroid hormone replacement has the potential to reduce the risk of progression of kidney failure to end-stage kidney disease (ESKD) [20]. Although hyperthyroidism has mostly contradictory effects on each parameter, it still predisposes to AKI, progression from AKI to CKD, and progression to kidney failure [21]. Furthermore, a considerable proportion of patients with autoimmune thyroid diseases also have proteinuria and/or glomerulonephritis, which is hypothesized to be due to shared autoimmune mechanisms [22].

Thyroid function in AKI

Thyroid function test abnormalities are prevalent in AKI patients (82.9%), while low T3 euthyroid sick syndrome (37.1%) is the most common type of imbalance according to a prospective cohort study conducted on 35 critically ill patients in whom thyroid function tests were measured on admission, hospital discharge and first outpatient visit [23]. This prospective cohort study demonstrated a negative correlation between serum TSH and urea concentrations (p value = 0.024), while thyroid function test disorders had no prognostic implications [23]. Another comparative study involving 30 participants confirmed the imbalance of the thyroid function tests in AKI patients with euthyroid sick syndrome [24]. Additionally, few clinical studies have investigated the potential therapeutic role of thyroid hormone replacement in AKI patients. Thyroxine replacement had no beneficial effect on severity or duration of AKI with a higher risk of mortality in response to TSH suppression, according to a prospective, randomized, double-blind, placebo-controlled trial in 59 patients with AKI [25]. Similar results were reported in another study investigating the effect of thyroxine therapy on post-transplant delayed graft function and acute tubular necrosis [26]. A Cochrane Library

review, including two clinical studies, concluded that thyroxine therapy had no beneficial effect on the severity or duration of AKI, the risk of renal replacement therapy, or progression to CKD [27]. In addition to changes in thyroid function in response to AKI, hypothyroidism itself can cause AKI through various mechanisms, including rhabdomyolysis and changes in renal hemodynamics [28–31].

AKI and EPO

EPO is a glycoprotein-structured hormone produced primarily by the kidneys and liver and commonly used in the treatment of anemia in ESKD and some hematological conditions [32, 33]. Although the exact underlying pathophysiology remains unclear and mostly hypothetical, treatment with EPO has been hypothesized to have beneficial effects on AKI in critically ill patients based on various results from animal studies [34–36]. EPO is involved in the post-ischemic response of the kidney via the VEGF/VEGF-receptor system leading to neovascularization involved in reperfusion [37]. Additionally, EPO levels are significantly higher in AKI patients than in healthy subjects. EPO levels correlated with length of hospital stay and levels of insulin-like growth factor binding protein-1, but not with hemoglobin concentration or arterial oxygen partial pressure [38]. Treatment with EPO had no beneficial effect on the need for transfusion (p value = 0.85) or kidney function parameters (p value = 0.67) or the need for renal replacement therapy (p value = 0.10), according to a multicenter randomized controlled trial (RCT) conducted on 134 patients with AKI and anemia [39]. Another prospective clinical study on 98 patients undergoing complex cardiac valve surgery demonstrated that EPO administration had no beneficial effect on postoperative AKI or urinary biomarker levels, such as cystatin C or neutrophil gelatinase-associated lipocalin (NGAL) [40].

At the same time, contradictory results were shown by another observational study on 71 patients awaiting coronary artery bypass grafting in which EPO treatment was associated with lower risk of AKI, progression from AKI to CKD, and all-cause mortality [41]. Individual studies investigating the role of prophylactic administration of EPO on kidney function before or during major surgery have reported various findings [42–46]. Similarly, studies investigating the role of prophylactic administration of EPO in critically ill patients or in those in the intensive care unit (ICU) reported inconsistent results in terms of kidney function and all-cause mortality [47–49].

A systematic review and meta-analysis study, including 10 RCTs with a total of 2759 participants, concluded that prophylactic administration of EPO had no beneficial impact on the incidence of AKI (p value = 0.78), need for renal replacement therapy (p value = 0.45) or all-cause mortality (p value = 0.70) [50]. Therefore, the prophylactic administration of EPO in critically ill patients or patients awaiting major surgery does not have strong scientific evidence and the need for future large-scale studies in this field is clear.

AKI and bone mineral disorders

The effects of CKD on serum levels of calcium, phosphorus, fibroblast growth factor-23 (FGF-23), Klotho, parathyroid hormone (PTH) and sclerostin are well established in multiple clinical studies, while only a few have examined such changes in patients with AKI. Significant acid–base and electrolyte disturbances may be observed in patients with AKI, including hypocalcemia, hyperphosphatemia and decreased vitamin D levels; however, critically ill patients may instead exhibit hypophosphatemia. Although CKD has been considered a risk factor for bone fractures due to associated high- and low-turnover bone disease, AKI has not been linked to bone disorders other than changes in serum levels of some bone-related peptides. Potentially, altered serum levels of such bone-related peptides, including FGF-23 and sclerostin, can lead to bone diseases that may increase the risk of future bone fractures. However, there is a clear need for future studies in this research field to reach a definitive conclusion.

FGF-23

FGF-23 is a hormone of bone origin whose concentration is regulated by serum levels of phosphate, calcium, PTH and vitamin D, and is involved in the suppression of active vitamin D synthesis and in the reabsorption of phosphate [51]. Elevated FGF-23 levels in AKI patients were first described in a case report of a patient with rhabdomyolysis, followed by a case series study of critically ill patients [52, 53]. A study involving 60 patients showed that serum levels of FGF-23 were significantly higher in patients with AKI and were associated with poor composite outcomes. In contrast, no other markers, including vitamin D metabolites or serum calcium or phosphorus levels, affected the outcome [54]. Similar findings of elevated C-terminal FGF-23 and FGF-23 levels in patients with AKI and its association with clinical outcome were reported in another clinical study, which included 250 patients undergoing cardiac surgery, and in yet another clinical study that included 20 critically ill patients [53, 55]. Other clinical studies investigating the serum levels of FGF-23 showed similar outcomes [56–58]. Further clinical and preclinical data suggest that such an increase in FGF-23 levels occurs very early in the course of AKI, potentially an early marker of AKI, and is caused by increased production rather than decreased clearance [59]. Another study on 265 ICU patients reported that the association between AKI and FGF-23 was mainly mediated by

endothelium-related biomarkers, including the vascular cell adhesion molecule -1, angiopoietin-2 and syndecan-1 [60]. To conclude, elevation of serum FGF-23 levels as an early change in the progression of AKI is associated with poor clinical outcomes which are not limited to kidney function.

Vitamin D metabolites

Through various mechanisms, hypovitaminosis D and hypervitaminosis D are potential outcomes in patients with AKI. Hyperphosphatemia or elevated levels of FGF-23, both potent inhibitors of 1-alpha hydroxylase, and malfunctioning of the 1-alpha hydroxylase enzyme due to nephron dysfunction can lead to hypovitaminosis D, while hyperparathyroidism induced by hypocalcemia can lead to hypervitaminosis D [61]. However, hypovitaminosis D is the most clinically common type of alteration and has a statistically significant association with poor clinical outcomes, including mortality [62]. According to a study on 46 patients, active vitamin D levels were statistically significantly lower in patients with AKI than in patients without AKI, while the levels were not correlated with the clinical outcome [63]. Although no clinical studies have been conducted on human subjects, vitamin D supplementation has been shown to improve cisplatin-induced AKI in animal models by inhibiting epithelial-mesenchymal transition, reducing apoptosis by increasing B-cell lymphoma 2 (Bcl-2), and increasing cell proliferation by decreasing the expression of cyclin-dependent kinase -2 and cyclin E [64, 65]. A large-scale cross-sectional study, including 219 patients with AKI (86 with acute-on-CKD and 133 with de novo AKI) admitted to the ICU because of sepsis and 219 age-matched controls, studied the serum levels of sclerostin, PTH, 25-hydroxy vitamin D (25-OH vitamin D), FGF-23, C-reactive protein (CRP), interleukin 6 (IL-6), homeostatic model evaluation for insulin resistance (HOMA-IR) and serum biochemistry. Serum levels of sclerostin, PTH, FGF-23, phosphorus, CRP, IL-6 and HOMA-IR were significantly higher in the AKI group, while serum levels of calcium and 25-OH vitamin D were reduced. Although serum levels of sclerostin and FGF-23 had a significant impact on peripheral insulin resistance, measured as HOMA-IR, neither affected the outcome of AKI. Furthermore, serum levels of sclerostin, PTH, FGF-23, 25-OH vitamin D, CRP, IL6 and HOMA-IR were similar in the de novo AKI group and in the acute-on-CKD AKI group [66]. Another case–control study on 30 AKI patients and 126 control subjects showed that serum Klotho levels were considerably higher in the AKI group without association with GFR [67]. On the other hand, the Klotho-creatinine ratio in urine was significantly lower in critically ill patients with AKI than in matched controls without AKI and was independently linked to major adverse renal outcomes [68]. In conclusion, hypovitaminosis D as a common event in the setting of either AKI or AKI-on-CKD and elevated Klotho levels do not appear to correlate with outcomes involving kidney function. Thus, it is unclear whether vitamin D supplementation or the blockade of the kidney 1-alpha hydroxylase enzyme leading to low levels of active vitamin D has clinical significance.

AKI and natriuretic peptides

Atrial natriuretic peptide, a small peptide synthesized mainly by atrial myocytes, leads to vasodilation of the afferent arteriole and inhibition of prostaglandin synthesis. Following animal studies demonstrating increased GFR after ANP administration through diuretic and natriuretic effects, human studies aimed at preventing and/or treating AKI have been conducted with variable outcomes [69, 70]. A multicenter RCT involving 77 AKI patients following cardiovascular surgery demonstrated that ANP administration had no beneficial effect on renal outcome other than increased urine output (p value = 0.018) [71]. On the other hand, another randomized placebo-controlled clinical trial conducted on 59 AKI patients following cardiovascular surgery showed that ANP infusion may have led to improved kidney excretory function, decreased risk of dialysis and improved survival free from dialysis [72]. Multiple clinical studies have investigated the potential protective role of ANP in AKI in numerous clinical circumstances. A study conducted on patients undergoing cardiovascular surgery had contradictory results with the demonstration of a decrease in urinary angiotensinogen, urinary NGAL and L-type fatty acid binding protein levels (p value < 0.01) [73]. However, another randomized placebo-controlled clinical trial conducted to evaluate the protective role of ANP in contrast-induced nephropathy did not demonstrate any beneficial effects [74]. A meta-analysis study comprising a total of 18 RCTs, of which 16 assessing the potential preventive effects of ANP, concluded that ANP may have beneficial effects. However, the evidence is not strong [75].

Studies investigating the role of brain natriuretic peptide (BNP) are limited in number and extent, while nesiritide, an analogue of human BNP, is the most valued agent. Administration of nesiritide to patients following cardiac transplantation resulted in an improvement in cardiac function and urinary output without modification of the dose of the diuretic or inotropic agent [76]. Furthermore, according to a retrospective cohort study of 940 patients, the administration of nesiritide after cardiovascular surgery appears to be a promising therapeutic alternative to prevent AKI and the need for dialysis, especially in high-risk patients [77].

Clinical studies investigating the potential protective and therapeutic role of natriuretic peptides in the context of AKI appear promising with conflicting clinical outcomes.

However, the need for future large-scale RCTs and meta-analysis studies is clear.

AKI and glycemic control

The kidney plays a significant role in glucose homeostasis by being involved in approximately 30% of daily gluconeogenesis and in 50% of insulin metabolism and clearance [78]. Furthermore, AKI patients, similarly to critically ill patients, are more prone to developing peripheral insulin resistance, which is an independent poor prognostic factor for survival in these cases. Intensive insulin therapy aimed at a plasma glucose level of 80–100 mg/dl results in a higher incidence of hypoglycemia, especially in patients with poor nutritional status, compared to conventional insulin treatment modalities and greater variability in plasma glucose levels. Among trauma patients with coexisting AKI or ESKD, the incidence of hypoglycemia with intensive insulin therapy can reach up to 76%, with cases of severe hypoglycemia defined by plasma glucose levels below 40 mg/dl reaching 29% [79]. Therefore, it is reasonable to target higher plasma glucose levels, 140–180 mg/dl, in critically ill or trauma patients with AKI or pre-existing kidney failure. However, the potentially harmful effects of hyperglycemia on kidney function, even with short-term exposure, should not be overlooked with higher plasma glucose levels.

Although glycemic control is one of the main aspects of the management of critically ill patients, studies investigating the modalities of glycemic control in patients with coexisting AKI are limited. Despite its prognostic importance, no studies have investigated the differences between the various types of insulin and the determinants of the balance between increased insulin sensitivity and peripheral insulin resistance. Future studies are needed to determine more stringent guidelines for blood glucose management in such patient groups.

AKI and other hormones

Levels of a few other hormones have been studied in clinical, preclinical and animal studies; however, the level of evidence for these hormones is low.

Insulin-like growth factor-1

Insulin-like growth factor, also called somatomedin C, is mainly produced in the liver and is the main mediator of growth hormone effects via tyrosine kinase receptors. According to a prospective cohort study of 56 ICU patients with AKI, a low serum level of IGF-1 is an independent marker of mortality (p value = 0.044) [80]. Another in vivo study demonstrated that treatment with umbilical cord mesenchymal stem cells overexpressing IGF-1 had a potential therapeutic role in gentamicin-induced AKI with regard to kidney function and histopathological characteristics [81]. Possible protective effects of IGF-1 have been demonstrated in some other preclinical studies and are involved in the regenerative capacity of stem cells [82–84]. Molecular level analysis revealed that IGF-1-mediated renoprotective mechanisms could be attributable to activation of the extracellular signal-regulated kinase-mitogen activated protein kinase pathway and upregulation of an anti-apoptotic protein Bcl-2 [85].

Leptin and adiponectin

Leptin and adiponectin are two important hormones with paracrine and endocrine effects on energy metabolism and their involvement in various medical conditions has been under study in recent years. A study conducted on a total of 81 patients, 27 healthy controls, 27 hemodialysis patients and 27 patients with AKI, showed that plasma levels of leptin were not altered in patients with AKI and had no prognostic value in the clinical outcome of AKI in contrast with hemodialysis patients [86]. However, leptin administration had a potentially beneficial role in AKI by reducing apoptosis and autophagy through interaction with the mammalian/mechanistic target of the rapamycin pathway in rats [87]. On the other hand, adiponectin-knockout mice were less likely to suffer from ischemia/reperfusion injury and AKI, which was mediated by decreased Bcl-2-associated protein X (Bax) and reduced activation of p53 and caspase-3 [88]. At the same time, contradictory results were shown in another study [89]. There is a clear need for future large-scale randomized human clinical trials to evaluate the role of adiponectin and leptin in AKI.

Adrenocorticotropic hormone

Although it is well established that adrenal insufficiency can occur in AKI, the effects of AKI on the hypothalamus–pituitary–adrenal axis are largely unknown [90]. Adrenocorticotropic hormone has been shown to have renoprotective effects on rat models of tumor necrosis factor-induced AKI through both steroid-dependent and independent mechanisms, including melanocortin-1 receptor-mediated anti-apoptotic effects on kidney tubular cells [91]. However, the results of this study require validation with further studies.

Conclusions

AKI is a common comorbidity, affecting approximately one in five adults admitted to hospital. The kidney is the site for the production, metabolism or excretion of most hormones. Therefore, it is reasonable to say that AKI can have a considerable impact on the endocrine system with other potential effects on various systems and clinical outcomes. However, the endocrinological consequences of AKI are mostly overlooked. Furthermore, it is unclear whether the endocrinological alterations observed in the setting of AKI may persist after resolution of AKI. There is clearly a need for large-scale clinical trials investigating the long-term effects of AKI on the endocrine system. Such studies can illuminate areas of endocrinological abnormalities that require therapeutic intervention or clinical follow-up. There are some ongoing clinical trials investigating the effects of alpha-melanocyte stimulating hormone (NCT00004496) and recombinant BNP (NCT01625403, NCT02095275, NCT00110201) in patients with AKI. However, there is a clear need for future large-scale RCTs investigating the endocrinological consequences of AKI.

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Data availability No data are available because this is a narrative review.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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

Research involving human participants and/or animals. (1) Statement of human rights. (2) Statement on the welfare of animals. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No verbal and written informed consent was necessary for this study.

References

1. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I et al (2013) World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol 8(9):1482–1493
2. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW (2005) Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 16(11):3365–3370
3. Rewa O, Bagshaw SM (2014) Acute kidney injury—epidemiology, outcomes and economics. Nat Rev Nephrol 10(4):193–207
4. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ (2021) Acute kidney injury. Nat Rev Dis Primers 7(1):52
5. Singbartl K, Kellum JA (2012) AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int 81(9):819–825
6. Villeneuve PM, Clark EG, Sikora L, Sood MM, Bagshaw SM (2016) Health-related quality-of-life among survivors of acute kidney injury in the intensive care unit: a systematic review. Intensive Care Med 42(2):137–146
7. Stengel B, Metzger M, Combe C, Jacquelinet C, Briançon S, Ayav C et al (2019) Risk profile, quality of life and care of patients with moderate and advanced CKD: the French CKD-REIN Cohort Study. Nephrol Dial Transpl 34(2):277–286
8. Acharya V, Olivero J (2018) The kidney as an endocrine organ. Methodist Debakey Cardiovasc J 14(4):305–307
9. Danzi S, Klein I (2003) Thyroid hormone and blood pressure regulation. Curr Hypertens Rep 5(6):513–520
10. Kotsis V, Alevizaki M, Stabouli S, Pitiriga V, Rizos Z, Sion M et al (2007) Hypertension and hypothyroidism: results from an ambulatory blood pressure monitoring study. J Hypertens 25(5):993–999
11. Vargas F, Moreno JM, Rodríguez-Gómez I, Wangensteen R, Osuna A, Alvarez-Guerra M et al (2006) Vascular and renal function in experimental thyroid disorders. Eur J Endocrinol 154(2):197–212
12. Ichihara A, Kobori H, Miyashita Y, Hayashi M, Saruta T (1998) Differential effects of thyroid hormone on renin secretion, content, and mRNA in juxtaglomerular cells. Am J Physiol Endocrinol Metab 274(2):E224–E231
13. van Hoek I, Daminet S (2009) Interactions between thyroid and kidney function in pathological conditions of these organ systems: a review. Gen Comp Endocrinol 160(3):205–215
14. Schmid C, Brändle M, Zwimpfer C, Zapf J, Wiesli P (2004) Effect of thyroxine replacement on creatinine, insulin-like growth factor 1, acid-labile subunit, and vascular endothelial growth factor. Clin Chem 50(1):228–231
15. Wiesli P, Schwegler B, Spinas GA, Schmid C (2003) Serum cystatin C is sensitive to small changes in thyroid function. Clin Chim Acta 338(1–2):87–90
16. Lo JC, Chertow GM, Go AS, Hsu C-Y (2005) Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int 67(3):1047–1052
17. Sun MT, Hsiao FC, Su SC, Pei D, Hung YJ (2012) Thyrotropin as an independent factor of renal function and chronic kidney disease in normoglycemic euthyroid adults. Endocr Res 37(3):110–116
18. Zhang D, Gao L, Ye H, Chi R, Wang L, Hu L et al (2019) Impact of thyroid function on cystatin C in detecting acute kidney injury: a prospective, observational study. BMC Nephrol 20(1):41
19. Schmid C, Ghirlanda-Keller C, Zwimpfer C, Zoidis E (2012) Triiodothyronine stimulates cystatin C production in bone cells. Biochem Biophys Res Commun 419(2):425–430
20. Shin DH, Lee MJ, Kim SJ, Oh HJ, Kim HR, Han JH et al (2012) Preservation of renal function by thyroid hormone replacement therapy in chronic kidney disease patients with subclinical hypothyroidism. J Clin Endocrinol Metab 97(8):2732–2740
21. Iglesias P, Bajo MA, Selgas R, Díez JJ (2017) Thyroid dysfunction and kidney disease: An update. Rev Endocr Metab Disord 18(1):131–144
22. Weetman AP, Tomlinson K, Amos N, Lazarus JH, Hall R, McGregor AM (1985) Proteinuria in autoimmune thyroid disease. Acta Endocrinol (Copenh) 109(3):341–347
23. Iglesias P, Olea T, Vega-Cabrera C, Heras M, Bajo MA, del Peso G et al (2013) Thyroid function tests in acute kidney injury. J Nephrol 26(1):164–172

24. Kaptein EM, Levitan D, Feinstein EI, Nicoloff JT, Massry SG (1981) Alterations of thyroid hormone indices in acute renal failure and in acute critical illness with and without acute renal failure. Am J Nephrol 1(3–4):138–143
25. Acker CG, Singh AR, Flick RP, Bernardini J, Greenberg A, Johnson JP (2000) A trial of thyroxine in acute renal failure. Kidney Int 57(1):293–298
26. Acker CG, Flick R, Shapiro R, Scantlebury VP, Jordan ML, Vivas C et al (2002) Thyroid hormone in the treatment of post-transplant acute tubular necrosis (ATN). Am J Transplant 2(1):57–61
27. Nigwekar SU, Strippoli GF, Navaneethan SD (2013) Thyroid hormones for acute kidney injury. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD006740.pub2
28. Shakoor MT, Moahi K, Shemin D (2020) Hypothyroidism-induced acute kidney ınjury and hyponatremia. R I Med J 103(7):61–64
29. Neves PD, Bridi RA, Balbi AL, Ponce D (2013) Hypothyroidism and acute kidney injury: an unusual association. BMJ Case Rep. https://doi.org/10.1136/bcr-2013-200585
30. Cai Y, Tang L (2013) Rare acute kidney injury secondary to hypothyroidism-induced rhabdomyolysis. Yonsei Med J 54(1):172–176
31. Ghayur A, Elahi Q, Patel C, Raj R (2021) Rhabdomyolysis-induced acute kidney injury in a patient with non-compliance to levothyroxine therapy. Endocrinol Diabetes Metab Case Rep. https://doi.org/10.1530/EDM-21-0034
32. Bahlmann FH, Kielstein JT, Haller H, Fliser D (2007) Erythropoietin and progression of CKD. Kidney Int Suppl 107:S21–S25
33. Hanna RM, Streja E, Kalantar-Zadeh K (2021) Burden of anemia in chronic kidney disease: beyond erythropoietin. Adv Ther 38(1):52–75
34. Bernhardt WM, Eckardt KU (2008) Physiological basis for the use of erythropoietin in critically ill patients at risk for acute kidney injury. Curr Opin Crit Care 14(6):621–626
35. Kwak J, Kim JH, Jang HN, Jung MH, Cho HS, Chang SH et al (2020) Erythropoietin ameliorates ıschemia/reperfusion-ınduced acute kidney ınjury via ınflammasome suppression in mice. Int J Mol Sci 21(10):3453
36. Chou YH, Liao FL, Chen YT, Yeh PY, Liu CH, Shih HM et al (2019) Erythropoietin modulates macrophages but not post-ischemic acute kidney injury in mice. J Formos Med Assoc 118(1 Pt 3):494–503
37. Nakano M, Satoh K, Fukumoto Y, Ito Y, Kagaya Y, Ishii N et al (2007) Important role of erythropoietin receptor to promote VEGF expression and angiogenesis in peripheral ischemia in mice. Circ Res 100(5):662–669
38. Sabatino A, Ceresini G, Marina M, Fiaccadori E (2019) Endocrine system in acute kidney injury. In: Rhee CM, Kalantar-Zadeh K, Brent GA (eds) Endocrine disorders in kidney disease: diagnosis and treatment. Springer International Publishing, Cham, pp 321–331
39. Aoun M, Sleilaty G, Boueri C, Younes E, Gabriel K, Kahwaji RM et al (2022) Erythropoietin in Acute Kidney Injury (EAKI): a pragmatic randomized clinical trial. BMC Nephrol 23(1):100
40. Kim JH, Shim JK, Song JW, Song Y, Kim HB, Kwak YL (2013) Effect of erythropoietin on the incidence of acute kidney injury following complex valvular heart surgery: a double blind, randomized clinical trial of efficacy and safety. Crit Care 17(5):R254
41. Oh SW, Chin HJ, Chae DW, Na KY (2012) Erythropoietin improves long-term outcomes in patients with acute kidney injury after coronary artery bypass grafting. J Korean Med Sci 27(5):506–511
42. Song YR, Lee T, You SJ, Chin HJ, Chae DW, Lim C et al (2009) Prevention of acute kidney injury by erythropoietin in patients undergoing coronary artery bypass grafting: a pilot study. Am J Nephrol 30(3):253–260
43. Tasanarong A, Duangchana S, Sumransurp S, Homvises B, Satdhabudha O (2013) Prophylaxis with erythropoietin versus placebo reduces acute kidney injury and neutrophil gelatinase-associated lipocalin in patients undergoing cardiac surgery: a randomized, double-blind controlled trial. BMC Nephrol 14:136
44. Dardashti A, Ederoth P, Algotsson L, Brondén B, Grins E, Larsson M et al (2014) Erythropoietin and protection of renal function in cardiac surgery (the EPRICS trial). Anesthesiology 121(3):582–590
45. Kim JE, Song SW, Kim JY, Lee HJ, Chung KH, Shim YH (2016) Effect of a single bolus of erythropoietin on renoprotection in patients undergoing thoracic aortic surgery with moderate hypothermic circulatory arrest. Ann Thorac Surg 101(2):690–696
46. de Seigneux S, Ponte B, Weiss L, Pugin J, Romand JA, Martin PY et al (2012) Epoetin administrated after cardiac surgery: effects on renal function and inflammation in a randomized controlled study. BMC Nephrol 13:132
47. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ et al (2002) Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. JAMA 288(22):2827–2835
48. Napolitano LM, Fabian TC, Kelly KM, Bailey JA, Block EF, Langholff W et al (2008) Improved survival of critically ill trauma patients treated with recombinant human erythropoietin. J Trauma 65(2):285–297 (**discussion 97-9**)
49. Endre ZH, Walker RJ, Pickering JW, Shaw GM, Frampton CM, Henderson SJ et al (2010) Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). Kidney Int 77(11):1020–1030
50. Zhao C, Lin Z, Luo Q, Xia X, Yu X, Huang F (2015) Efficacy and safety of erythropoietin to prevent acute kidney injury in patients with critical illness or perioperative care: a systematic review and meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol 65(6):593–600
51. Erben RG (2018) Physiological actions of fibroblast growth factor-23. Front Endocrinol (Lausanne) 9:267
52. Leaf DE, Wolf M, Stern L (2010) Elevated FGF-23 in a patient with rhabdomyolysis-induced acute kidney injury. Nephrol Dial Transpl 25(4):1335–1337
53. Zhang M, Hsu R, Hsu CY, Kordesch K, Nicasio E, Cortez A et al (2011) FGF-23 and PTH levels in patients with acute kidney injury: a cross-sectional case series study. Ann Intensive Care 1(1):21
54. Leaf DE, Wolf M, Waikar SS, Chase H, Christov M, Cremers S et al (2012) FGF-23 levels in patients with AKI and risk of adverse outcomes. Clin J Am Soc Nephrol 7(8):1217–1223
55. Leaf DE, Christov M, Jüppner H, Siew E, Ikizler TA, Bian A et al (2016) Fibroblast growth factor 23 levels are elevated and associated with severe acute kidney injury and death following cardiac surgery. Kidney Int 89(4):939–948
56. Chang YH, Wu CH, Chou NK, Tseng LJ, Huang IP, Wang CH et al (2020) High plasma C-terminal FGF-23 levels predict poor outcomes in patients with chronic kidney disease superimposed with acute kidney injury. Ther Adv Chronic Dis 11:2040622320964161
57. Shaker AM, El Mohamed E, Samir HH, Elnokeety MM, Sayed HA, Ramzy TA (2018) Fibroblast growth factor-23 as a predictor biomarker of acute kidney injury after cardiac surgery. Saudi J Kidney Dis Transpl 29(3):531–539
58. Gupta KL, Mohanty T, Sood V, Ramachandran R (2020) Study of FGF 23 levels in patients with acute kidney injury and its outcome. Indian J Nephrol 30(4):293–294
59. Christov M, Waikar SS, Pereira RC, Havasi A, Leaf DE, Goltzman D et al (2013) Plasma FGF23 levels increase rapidly after acute kidney injury. Kidney Int 84(4):776–785

60. de Oliveira Neves FM, Araújo CB, de Freitas DF, Arruda BFT, de Macêdo Filho LJM, Salles VB et al (2019) Fibroblast growth factor 23, endothelium biomarkers and acute kidney injury in critically-ill patients. J Transl Med 17(1):121
61. Braun AB, Christopher KB (2013) Vitamin D in acute kidney injury. Inflamm Allergy Drug Targets 12(4):262–272
62. Levin A, Bakris G, Molitch M, Smulders M, Tian J, Williams L et al (2007) Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int 71(1):31–38
63. Vijayan A, Li T, Dusso A, Jain S, Coyne DW (2015) Relationship of 1,25 dihydroxy vitamin D levels to clinical outcomes in critically ıll patients with acute kidney ınjury. J Nephrol Ther 5(1):90
64. Park JW, Cho JW, Joo SY, Kim CS, Choi JS, Bae EH et al (2012) Paricalcitol prevents cisplatin-induced renal injury by suppressing apoptosis and proliferation. Eur J Pharmacol 683(1–3):301–309
65. Hu Z, Zhang H, Yi B, Yang S, Liu J, Hu J et al (2020) VDR activation attenuate cisplatin induced AKI by inhibiting ferroptosis. Cell Death Dis 11(1):73
66. Fayed A, Abdulazim DO, Amin M, Elhadidy S, Samir HH, Salem MM et al (2021) Serum sclerostin in acute kidney injury patients. Nefrologia (Engl Ed). https://doi.org/10.1016/j.nefro.2021.01.010
67. Seibert E, Radler D, Ulrich C, Hanika S, Fiedler R, Girndt M (2017) Serum klotho levels in acute kidney injury. Clin Nephrol 87(4):173–179
68. Neyra JA, Li X, Mescia F, Ortiz-Soriano V, Adams-Huet B, Pastor J et al (2019) Urine klotho ıs lower in critically ıll patients with versus without acute kidney ınjury and associates with major adverse kidney events. Crit Care Explor 1(6):e0016
69. Conger JD, Falk SA, Hammond WS (1991) Atrial natriuretic peptide and dopamine in established acute renal failure in the rat. Kidney Int 40(1):21–28
70. Roy DR (1986) Effect of synthetic ANP on renal and loop of Henle functions in the young rat. Am J Physiol 251(2 Pt 2):F220–F225
71. Mitaka C, Ohnuma T, Murayama T, Kunimoto F, Nagashima M, Takei T et al (2017) Effects of low-dose atrial natriuretic peptide infusion on cardiac surgery-associated acute kidney injury: a multicenter randomized controlled trial. J Crit Care 38:253–258
72. Swärd K, Valsson F, Odencrants P, Samuelsson O, Ricksten SE (2004) Recombinant human atrial natriuretic peptide in ischemic acute renal failure: a randomized placebo-controlled trial. Crit Care Med 32(6):1310–1315
73. Moriyama T, Hagihara S, Shiramomo T, Nagaoka M, Iwakawa S, Kanmura Y (2017) The protective effect of human atrial natriuretic peptide on renal damage during cardiac surgery. J Anesth 31(2):163–169
74. Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS (1998) Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 31(4):674–680
75. Yamada H, Doi K, Tsukamoto T, Kiyomoto H, Yamashita K, Yanagita M et al (2019) Low-dose atrial natriuretic peptide for prevention or treatment of acute kidney injury: a systematic review and meta-analysis. Crit Care 23(1):41
76. Salzberg SP, Filsoufi F, Anyanwu A, von Harbou K, Gass A, Pinney SP et al (2005) High-risk mitral valve surgery: perioperative hemodynamic optimization with nesiritide (BNP). Ann Thorac Surg 80(2):502–506
77. Beaver TM, Winterstein AG, Shuster JJ, Gerhard T, Martin T, Alexander JA et al (2006) Effectiveness of nesiritide on dialysis or all-cause mortality in patients undergoing cardiothoracic surgery. Clin Cardiol 29(1):18–24
78. Fiaccadori E, Sabatino A, Morabito S, Bozzoli L, Donadio C, Maggiore U et al (2016) Hyper/hypoglycemia and acute kidney injury in critically ill patients. Clin Nutr 35(2):317–321
79. Stamou SC, Nussbaum M, Carew JD, Dunn K, Skipper E, Robicsek F et al (2011) Hypoglycemia with intensive insulin therapy after cardiac surgery: predisposing factors and association with mortality. J Thorac Cardiovasc Surg 142(1):166–173
80. Guimarães SM, Lima EQ, Cipullo JP, Lobo SM, Burdmann EA (2008) Low insulin-like growth factor-1 and hypocholesterolemia as mortality predictors in acute kidney injury in the intensive care unit. Crit Care Med 36(12):3165–3170
81. Liu P, Feng Y, Dong D, Liu X, Chen Y, Wang Y et al (2016) Enhanced renoprotective effect of IGF-1 modified human umbilical cord-derived mesenchymal stem cells on gentamicin-induced acute kidney injury. Sci Rep 6:20287
82. Friedlaender M, Popovtzer MM, Weiss O, Nefesh I, Kopolovic J, Raz I (1995) Insulin-like growth factor-1 (IGF-1) enhances recovery from HgCl2-induced acute renal failure: the effects on renal IGF-1, IGF-1 receptor, and IGF-binding protein-1 mRNA. J Am Soc Nephrol 5(10):1782–1791
83. Goes N, Urmson J, Vincent D, Ramassar V, Halloran PF (1996) Effect of recombinant human insulin-like growth factor-1 on the inflammatory response to acute renal injury. J Am Soc Nephrol 7(5):710–720
84. Imberti B, Morigi M, Tomasoni S, Rota C, Corna D, Longaretti L et al (2007) Insulin-like growth factor-1 sustains stem cell mediated renal repair. J Am Soc Nephrol 18(11):2921–2928
85. Wu Z, Yu Y, Niu L, Fei A, Pan S (2016) IGF-1 protects tubular epithelial cells during injury via activation of ERK/MAPK signaling pathway. Sci Rep 6:28066
86. Ficek R, Kokot F, Chudek J, Adamczak M, Ficek J, Wiecek A (2004) Plasma leptin concentration in patients with acute renal failure. Clin Nephrol 62(2):84–91
87. Li S, Zhuang K, He Y, Deng Y, Xi J, Chen J (2022) Leptin relieves ischemia/reperfusion induced acute kidney injury through inhibiting apoptosis and autophagy. Zhong Nan Da Xue Xue Bao Yi Xue Ban 47(1):8–17
88. Jin X, Chen J, Hu Z, Chan L, Wang Y (2013) Genetic deficiency of adiponectin protects against acute kidney injury. Kidney Int 83(4):604–614
89. Cheng CF, Lian WS, Chen SH, Lai PF, Li HF, Lan YF et al (2012) Protective effects of adiponectin against renal ischemia-reperfusion injury via prostacyclin-PPARα-heme oxygenase-1 signaling pathway. J Cell Physiol 227(1):239–249
90. Ahn SW, Kim TY, Lee S, Jeong JY, Shim H, Han YM et al (2016) Adrenal insufficiency presenting as hypercalcemia and acute kidney injury. Int Med Case Rep J 9:223–226
91. Si J, Ge Y, Zhuang S, Wang LJ, Chen S, Gong R (2013) Adrenocorticotropic hormone ameliorates acute kidney injury by steroidogenic-dependent and -independent mechanisms. Kidney Int 83(4):635–646