REVIEW PAPER

Effectiveness of novel iron regulators in the treatment of diabetic nephropathy

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ABSTRACT

Introduction and aim. The novel advancements of upcoming iron regulators used to treat diabetic nephropathy have implicated a common manifestation of combination chelation therapy used to eliminate end-stage renal disease associated with inflammation and iron imbalance that is altered by renal iron absorption. However, iron accumulation in the clustered kidneys that filter blood may cause problems that affect diabetic blood sugar regulation.

Material and methods. A well-designed method was employed to discover relevant research publications on iron chelators and their potential to treat diabetic nephropathy. "Iron chelators", "diabetic nephropathy", "end-stage renal disease", and "chelation therapy" were searched in Google Scholar, Web of Science, PubMed, and EMBASE.

Analysis of literature. Although the specific etiology and development have not been fully explored, emerging evidence on iron pathophysiology helps comprehend the pathogenesis of acute kidney damage and chronic kidney disease, which crucially provides novel iron chelation therapy techniques. Ferroptosis and hepcidin marker proteins increase oxidative/nitrifying stress and kidney injury. Iron chelator medicines including deferoxamine, deferasirox, and deferiprone were tested as prophylactic strategies.

Conclusion. This article covers both preclinical and clinical aspects of iron chelators to avoid diabetic nephropathy, including novel iron therapies that must be reviewed when selecting dosing regimens.

Keywords. acute kidney injury, chronic kidney disease, end-stage renal disease, iron chelators, renal iron handling

Introduction

Diabetic nephropathy (DN), the most common complication of type II diabetes mellitus and the leading cause of end-stage renal disease (ESRD) globally, are caused by the microvascular barriers of diabetes and causes kidney injury that is significantly more likely to cause morbidity and mortality.[1] It was discovered ten years ago that 40% of diabetic patients have type II diabetes mellitus which is characterized by declined glomerular filtration rate (GFR) and persistent presence of albuminuria (or an albuminuria excretion rate of >300 mg/d or 200 g/min), which eventually results in ESRD.[2]

It is also predicted that 4.39×10^8 individuals by 2030 will get diabetes mellitus worldwide, which has a varied etiology and is characterized by hyperglycemia resulting from abnormalities in insulin action, insulin secretion, or both. Many organs, particularly the eyes, nerves, feet, blood vessels, kidneys, and heart, are related to damage, dysfunction, and failure in chronic diabetes. Microvascular problems like retinopathy, neuropathy, and nephropathy have been linked to long-term diabetes.[3] Globally there has been an increase in the burden of chronic diseases like hypertension and diabetes. With a frequency of 3.8% and 11.8% in rural adults and in urban adults, respectively, India has the highest cases of diabetes worldwide. Between 25 and 40 % of them go on to acquire ESRD, often known as chronic kidney disease (CKD). Type I and type II diabetes both result in ESRD which raises the risk of acute kidney infection (AKI). Unlike polycystic kidney disease, when their size is reduced, glomeruli and kidneys are often larger in diabetic nephropathy.[4]

For improved disease control, it is essential to cure individuals that have more chance to develop DN. Many variables and mechanisms are associated to the onset and progression of DN. Renal damage and elevated iron (Fe) content have been linked and it has been fundamentally seen that people with diabetic nephropathy are more frequently found to have CKD and AKI which alters iron control for absorption.[5] In a previous study, it was observed that diabetes increased the levels of Fe regulating proteins and elevated the Fe concentration in kidney of type I and II diabetic mouse models. The increased renal Fe induced the renin-angiotensin system in the kidney leading to the development of diabetic nephropathy which can be overcome by the use of Fe chelator deferiprone.[6] Additionally, this contributes to illnesses like anemia, nephrotic syndrome, lupus nephritis, and Wegner's disease. In conclusion, Fe deposition occurs frequently in CKD but less frequently in acute kidney disease, which may be due to changed molecular levels of Fe management that induce renal damage.[7] The term "renal Fe handling" basically refers to the process by which circulating Fe can be filtered by the kidney's glomerulating function and almost reabsorbed by tubules of epithelial tissue to prevent urinary Fe waste.[8] One key obstacle in the pathogenesis of many kidney disorders, including diabetic nephropathy is related with the association of hepcidin serum concentrations along with C-reactive proteins (CRP) wherein the high level of hepcidin concentrations in the body produced by inflammation.[9]

Aim
It is a narrative review that reveals the therapeutic potential of novel iron chelators to treat diabetic nephropathy.

Material and methods
A well-designed method was employed to discover relevant research publications on iron chelators and their potential to treat diabetic nephropathy. "Iron chelators", "diabetic nephropathy", "end-stage renal disease", and "chelation therapy" were searched in Google Scholar, Web of Science, PubMed, and EMBASE.

Analysis of literature
Molecular pathways
The Fe transporter protein transferrin transports Fe from the plasma, where it is bound, to the majority of bodily tissues and cells. Afterward, Fe-free transferrin is exposed to extracellular fluid for a subsequent cycle of Fe binding and administration by selective absorption of Fe transferrin via hepcidin and ferroportin.[10] Less than 0.1 percent, or about 2-3 mg, of the body's total Fe, is associated with transferrin. The key factor causing the transferrin and its associated Fe to shift after two to three hours is nearly 20 or about 25 mg of Fe absorption. Fe is accumulated within cells as ferritin and Fe-regulated processes control each cell's Fe requirements are met via a reciprocal relationship between the quantity of Fe-storing ferritin and the number of transferrin receptors.[11]

Iron abnormalities in acute kidney injury
No intervention has been found to certainly and consistently prevent AKI despite years of investigation. Increasing our knowledge of AKI pathophysiology is therefore required in order to find novel treatment targets.[12] AKI could be a significant public health concern that makes a variety of hospital admissions more challenging globally. The ability of Fe to catalyze the Fenton and Haber-Weiss reactions, which result in the application of oxidative damage to cell membranes, proteins, and DNA, makes Fe essential for many physiological processes but harmful to the kidneys and other organs when present in excess.[13] AKI is majorly responsible for higher patient death. Fe's crucial role in AKI is supported by a large body of evidence from diagnostic models.[14] Fe content is noticeably elevated within the kidneys of animals exposed to a variety of toxic stimuli, exogenous Fe infusion exacerbates nephritic injury, and most importantly specialized Fe chelation in medicine is protective. Additionally, exogenous hepcidin administration, the chief regulator of overall Fe equilibrium protects against AKI conditions while genetic engineering of essential proteins associated with the regulation, transport, and metabolism of Fe (such as heme oxygenase-1, ferritin, and ferroportin) has an impact on these processes.[15] A small number of human researchers have looked into the viability of using such animal models in therapeutic settings, and the early findings are undeniably positive.

The majority of animal studies on the therapeutic effects of Fe chelation mainly focused on preventing AKI. The mechanism of actions of different Fe chelators is shown in Figure 1. In particular, Fe chelators were typically given before (or concurrently with) the injury to the urinary organ.[16] Contrarily, only a little amount of research has been done on the usage of Fe chelators as a kind of therapeutic for the cure of AKI after the harm to the urinary organ has already occurred.[17] The therapeutic effects of DFP which was used alone or combined with deferoxamine (DFO) were seen within 30 minutes of the onset of urinary organ injury in a mouse model of AKI caused by aluminium chloride. However, no study has looked into how well Fe chelators work to treat AKI if their administration is put off for many hours or more.[18] Idiopathic reactions exist regarding the mechanisms supporting DFO's preventive benefits in AKI-prone animals. One apparent justification, however, is that virulent forms of non-transferrin safe Fe are removed from the circulation and chelated by DFO which prevents downstream detrimental effects including supermolecule Fe-dependent oxidative deaths such as peroxidation and ferroptosis.[19] Additionally, DFO inhibits lysosomal Fe-mediated death induced by H_2O_2 and artesunate via the ferroptosis freelance pathway, indicating that it may have completely diverse effects on various Fe pools (such as lysosomal, mitochondrial, cytosolic, or extracellular Fe), which remains partly active in triggering different death phenotypes in response to different lethal stressors. DFO may also affect cell survival and proliferation by scavenging superoxide free radicals, among other impacts on cells.[20]
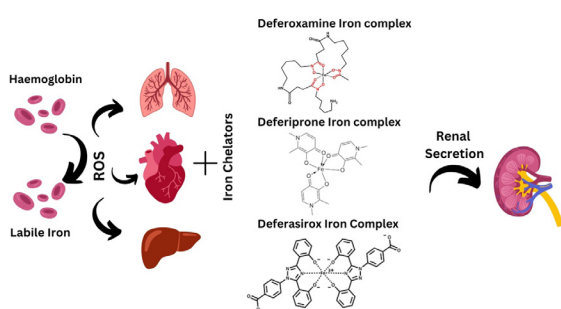

Fig. 1. Mechanism of actions of iron chelators to sequester the free iron and combat the kidney injury

Iron abnormalities in chronic kidney disease

Multiple pathways seriously decrease Fe metabolism in advanced renal disease. Fe deficiency is now discovered in the vast majority of individuals along with dialysis co-dependent CKD, despite the fact that a thorough review of each patient's development over time has not been conducted.[21] High hepcidin concentrations may result in reduced Fe absorption and elevated levels of Fe loss, especially in cases of gastrointestinal bleeding, in Fe insufficiency (Fig. 2). It has been shown that serum hepcidin concentrations correlate with CRP, which measures the correlation between hepcidin and the estimated glomerular filtration rate, and shows that high concentrations of hepcidin are partially caused by inflammation linked to the development of many kidney disorders.[22] Hepcidin levels are also elevated after hemodialysis or peritoneal dialysis by additional inflammatory stimuli such as intermittent infection and blood interaction with foreign objects like catheters or dialysis membranes.[23] Hepcidin is expelled via the membrane and its concentration in the plasma declines during hemodialysis, however, because of the rapid hepcidin formation, the concentration of hepcidin is returned within an hour of the procedure being finished.[24]

Inflammation-induced regulation of hepcidin secretion

Hepcidin synthesis is greatly boosted in infections and other inflammatory situations, which causes distinctive inflammatory hypoxia.[25] Hepcidin transcription is typically induced by inflammation through a second inflammatory mechanism that stimulates hepcidin via activin B, the BMP receptor, and the Smad signaling pathway and it also relies on the interleukin-6,14 receptor and the JAK2-STAT3 pathway (Figure 2).[25] The JAK2-STAT3 pathway and hepcidin have been implicated in the development and progression of diabetic nephropathy. The JAK2-STAT3 pathway is activated in response to cytokines and growth factors, including interleukin-6 (IL-6), which is known to be upregulated in diabetic nephropathy. It works by signaling and transcriptional regulation.[26]

Signaling: Upon ligand binding, JAK2 is activated, leading to the phosphorylation of STAT3.[27]

Transcriptional Regulation: Phosphorylated STAT3 forms dimers and translocates to the nucleus, where it acts as a transcription factor, regulating the expression of target genes.[28] The JAK2-STAT3 pathway is associated with inflammation and fibrosis, which are prominent features of diabetic nephropathy. Activation of the pathway leads to the production of pro-inflammatory cytokines and the promotion of fibrotic processes.[29]

– renal injury: The activation of JAK2-STAT3 pathway in diabetic nephropathy contributes to renal injury by promoting oxidative stress, inflammation, and fibrosis, ultimately leading to kidney dysfunction.[30]

– hepcidin and iron metabolism: Hepcidin dysregulation in diabetic nephropathy affects iron metabolism. Increased hepcidin levels lead to decreased iron absorption and release, resulting in disrupted iron homeostasis. Altered iron metabolism has been implicated in the pathogenesis of diabetic nephropathy.[31]
Therapeutic Implications:

– targeting JAK2-STAT3 Pathway: Modulating the JAK2-STAT3 pathway has emerged as a potential

therapeutic strategy for various diseases, including diabetic nephropathy. Inhibitors targeting JAK2 or STAT3 have shown promise in preclinical studies, but further research is needed to assess their efficacy and safety.[32]

– hepcidin manipulation: Considering the involvement of hepcidin dysregulation in diabetic nephropathy, therapies aimed at modulating hepcidin levels or iron metabolism might have therapeutic potential. However, specific interventions targeting hepcidin in diabetic nephropathy are still under investigation.[33]
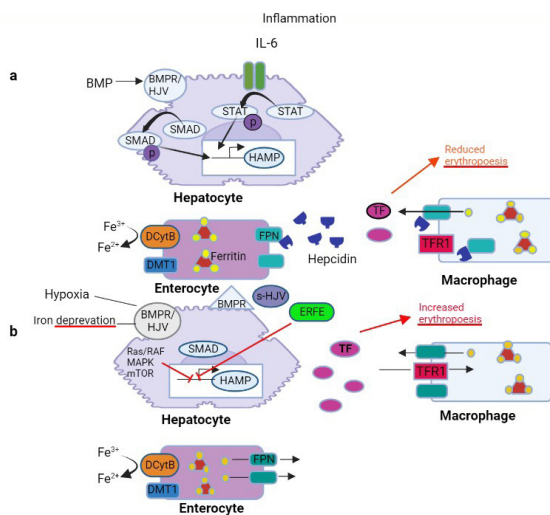

Fig. 2. Hepcidin regulation in diabetic nephropathy; BMP – bone morphogenetic proteins; SMAD –suppressor of mothers against decapentaplegic; DMT1-divalent metal (Ion) transporter 1; ERFE – erythroferrone; hepcidin antimicrobial peptide; IL-6 – interleukin-6; DCYTB – duodenal cytochrome b

Therapeutic approaches to treat diabetic nephropathy
For acute kidney injury

In individuals with diabetic nephropathy, AKI can occur as a complication. Several factors can contribute to AKI in these cases, including infections, medications (e.g., certain antibiotics or contrast agents), and dehydration. Diabetic nephropathy weakens the kidneys over time, making them more susceptible to acute injury. Severe or recurrent episodes of AKI can accelerate the progression of diabetic nephropathy.[34] AKI episodes may cause additional damage to the already compromised kidneys, leading to a decline in kidney function and worsening of the underlying diabetic nephropathy.[35] Both AKI and diabetic nephropathy are commonly associated with diabetes. Diabetic nephropathy develops in individuals with diabetes, particularly those with poorly controlled blood sugar levels. Prompt recognition and management of AKI are crucial to prevent further kidney damage. Treatment focuses on addressing the underlying

cause, maintaining fluid and electrolyte balance, and providing supportive care. In severe cases, dialysis may be necessary.[36] Intracellular and systemic systems help to keep the equilibrium of Fe under normal circumstances. Fe excess may exist when this intricate homeostatic mechanism malfunctions. It is challenging to identify Fe excess. Even though it is intrusive and risky, liver biopsies continue to be the gold standard. With little danger to the patient, the ability to identify Fe using non-invasive approaches let researchers better grasp the rate of Fe overload in various organs.[37]

Even though it may not be a precise procedure, estimating serum ferritin (mg/L) is the simplest and, as a result, the most frequently used diagnostic tool for determining body Fe reserves. Myelodysplastic syndromes, sickle cell disease, and thalassemia are the most prevalent haematological conditions that lead to Fe overload. Deferiprone, deferoxamine, and deferasirox are the three medications that have been authorised for the cure of Fe excess in all of these disorders.[38] These chelators have been shown to improve event-free survival (EFS) by lowering tissue Fe levels and preventing Fe overload problems. "The U.S. Food and Drug Administration (FDA) have given the go-ahead for the use of DFO, deferasirox (DFX), and diisopropyl fluorophosphate (DFP) as three Fe chelators for the treatment of acute kidney disease". These medications need to vary in terms of pharmacokinetics, methods of administration, and side effects.[39] The novel Fe chelators used frequently for AKI has been discussed further and the upcoming Fe chelators are mentioned in Table 1.

Deferoxamine (DFO)
DFO has the longest clinical history because previously it was the main Fe chelator that was initially tested and approved by the FDA.[40] Compared to DFP or DFX, DFO has a greater affinity for binding to Fe, and it was employed in large quantities of animal models of acute kidney injury and extrarenal organ injury. In a chronic situation, DFO is supplied parenterally via a blood vessel infusion or an infinite hypodermic pump (in the acute setting).[41] The DFO-Fe advanced (ferrioxamine) is removed through the feces and urine when DFO binds to Fe first and then the binding takes place. Ocular toxicity and hypotension are the most severe possible side effects of DFO, and they virtually exclusively affect people who get extremely high dosages (for example, 60 mg/kg).[42]

Deferasirox (DFX)
A second Fe chelator, DFX, wasn't approved for almost 40 years (between 1968 and 2005). With a half-life of 8 to 16 hours, DFX, an oral Fe chelator, enables a simple once-daily dosage. Moreover, DFX causes a 38% increase in blood serum creatinine. As a result, DFX is not

recommended for people with adequate to advanced chronic kidney disease (eGFR, 40 ml/min).[43]

Deferiprone (DFP)

DFP is another oral Fe chelator that is given three times daily and has a $t_{1/2}$ of about two hours. DFP has an advantage over other Fe chelators in that it has a higher lipophilicity and higher intracellular penetrance, which makes it easier to chelate intracellular Fe [33]. This DFP characteristic has been used to increase cardiac Fe chelation in patients with hypochromic anemia.[44]

Outcomes from evaluation of the iron chelators

DFO was found to be a good candidate for use in clinical trials due to a variety of qualities for the prevention of AKI. The logistical difficulties that can arise due to enteral injection of DFP in the context of acute disorders, as well as problems with aspiration and reduced gastrointestinal absorption, are avoided with epithelial duct administration of DFO.[45] DFO has been used by both people and animals for the longest time. Even at doses as high as 32 mg/kg, it is also well tolerated acutely. So, small to adequate variance doses of DFO (10–20 mg/kg) would probably be enough to sustain the action because Fe chelation therapy in this scenario primarily aims to eliminate the current chemical change in Fe.

Treatment for chronic kidney disease

CKD and DN are closely related conditions, and the hormone hepcidin plays a role in their connection. Diabetic nephropathy is a type of kidney disease that occurs as a complication of diabetes. It is characterized by damage to the small blood vessels in the kidneys, resulting in impaired kidney function. Over time, this can lead to chronic kidney disease.[46] Hepcidin is a hormone primarily produced in the liver. Its main function is to regulate iron levels in the body. However, emerging research suggests that hepcidin may also play a role in kidney disease, including CKD and DN. In CKD, hepcidin levels are often increased. This leads to a condition known as "anemia of chronic kidney disease" (CKD-associated anemia). Hepcidin acts by inhibiting the release of iron from cells, including the iron required for the production of new red blood cells.[47] As a result, CKD patients with high levels of hepcidin may experience lower red blood cell counts and anemia.

In the case of diabetic nephropathy, hepcidin may contribute to the development and progression of the disease. Research suggests that hepcidin levels are increased in diabetic nephropathy, and this increase is associated with impaired iron metabolism and kidney damage. Elevated hepcidin levels can lead to increased iron retention within the kidneys, promoting inflammation and oxidative stress, which are factors contributing to the progression of DN.[48]

Oral administration of iron

It is advised to begin treatment with oral Fe in CKD individuals who are not presently following dialysis or peritoneal dialysis. The optimal time to provide 200 mg of elemental Fe to an adult patient is during a fast (ferrous salts are suggested for better absorption). The most prevalent issues with oral Fe therapy in CKD- which may need hospitalisation to get Fe intravenously – involve gastrointestinal intolerance, intestinal absorption issues, or a non-compliance.[49]

Iron infusion

In individuals with CKD who are not receiving dialysis, intravenous Fe therapy is advised if:
- After three months of oral Fe therapy, or in cases of unable to tolerate oral Fe or malabsorption, Fe parameter targets are not fulfilled.
- In patients who need a rapid Hb response and have severe anaemia and Fe shortage.[50]

Considerations for treatment strategies currently applied to CKD

Ferrous citrate (FC): The negative effects of bronzed diabetes, which are a problem with IV formulations, may not occur when Fe replacement is done orally with preparations like FC since there may be additional physiological constraints on Fe absorption. FC is permitted to be used in ESRD patients as a phosphate binder. In more recent times, the FDA authorised FC for the treatment of CKD patients who weren't receiving chemical analysis. Recent studies without the use of chemical analysis show that FC increases Hgb in CKD patients while also lowering phosphorus (stage 3–5).[51]

Ferric maltol: In the United Kingdom and the United States, ferric maltol is authorised for the cure of people with inflammatory bowel disease and has a low risk of side effects. It has shown quick anemia repair. Individuals with CKD stages 3–4 performed phase three of the study with oral ferrous maltol for the cure of United Nations agency in subjects with CKD in order to compare the budding implications of ferrous maltol on Hgb vs. placebo (AEGIS-CKD). The outcomes of the experiment are still being finalized.[52]

Ferric salt change state (FPC): In 2015, the FDA gave the drug its green light to be utilized in individuals undergoing chemical analysis. It is a complex, carbohydrate-free, soluble Fe salt that is given to hemodialysis patients through the dialysate. It prevents Fe sequestration inside the reticuloendothelial macrophages and gives Fe to transferrin. In the continuous replacement exploitation Fe soluble equivalents (CRUISE) one and two trials, FPC was compared to placebo in individuals with ESRD receiving hemodialysis. When compared to a placebo, FPC administered by dialysate was analysed to well preserve Hgb, TSAT, and protein while significantly reducing the need for ESA dose.[53]

Liposomal/Sucrosomial Fe: A lipid bilayer encircles the ferrous salt core in sucrosomial Fe, which also has a layer of sucrosomes (sucrester, a chemical agent, and extra amyloid compounds). By doing this, Fe can dodge the effects of hepcidin's downregulation and be consumed by microfold cells through the systema lymphaticum, limiting any adverse consequences that could otherwise occur. According to preliminary research, liposomal Fe increases Hgb in CKD individuals while lowering the chance of toxic effects. Sucrosomial Fe has also been demonstrated to lower the anaemia in individuals suffering from cancer, disturbed patients, and people having bariatric surgery. The effectiveness and safety of sucrosomial Fe in CKD patients have not been studied.[54]

All the novel Fe supplements and their effective doses are discussed in Table 1.

Table 1. Upcoming novel iron therapies used for treatment of DN

Therapeutic molecule	Chemical class	Development phase	Exposure time	Hb, g/dl	Hepcidin concentration, µg/l	Refs
Daprodustat	HIF-PH inhibitor	Phase II	24 weeks	~0.1	−20.6	56
		Phase III	24 weeks	Increased 0.79	Decreased −55.67%	
Desidustat	HIF-PH inhibitor	Phase II	6 weeks	Increased 1.57 to 2.92	Decreased −59.24 to −91.36	57
Enarodustat	HIF-PH inhibitor	Phase II	6 weeks	Increased	Decreased	58
Molidustat	HIF-PH inhibitor	Phase II	16 weeks	Increased 1.4 to 2.0	Decreased −18	59
Roxadustat	HIF-PH inhibitor	Phase II	4 weeks	Increased 0.4 to 1.8	Decreased −225 to −70	60
		Phase III	8 weeks	Increased 1.9	Decreased −56.14	
Vadadustat	HIF-PH inhibitor	Phase II	20 weeks	Increased	Decreased	61
PRS-080#22	Hepcidin antagonist	Phase I	Single dose	Unaffected	Decreased	62
LY2928057 (monoclonal antibody against ferroportin)	Abrogated interaction with hepcidin	Phase I	6 weeks	–	Increased	
LY3113593 (monoclonal Antibody against BMP6)	Decreased expression of hepcidin	Phase I	Single dose	Increased	Decreased	
Vitamin D2	Decreased expression of hepcidin	Phase IV	6 months	–	–	63
Vitamin D3	Decreased expression of hepcidin	Phase I	6 weeks	Stable	Stable	

Future prospects

The essential and upcoming future prospect treatment strategies used for the treatment for CKD and AKI are described here in Table 1 and Table 2. Renal Vitamin

D dysregulations, oxidative stress, inflammation, and apoptosis were all linked to Fe-induced nephrotoxicity. Although, DFX decreased the amount of systemic Fe in the body, vitamin D3 monotherapy demonstrated very low renal Fe concentrations and tissue destruction. The co-therapy strategy however demonstrated the greatest therapeutic benefits through increased variation of renal Fe-homeostatic molecules.[55] Daprodustat boosts HIF-levels by inhibiting HIF-PH, stabilising HIF-1 which raises EPO levels and lowers hepcidin levels (Table 1). An assay using recombinant ferroportin-expressing HEK 293 cells and the novel humanised IgG4 monoclonal antibody LY2928057 demonstrates strong inhibition of hepcidin activity. It inhibits ferroportin-hepcidin binding with high affinity towards human ferroportin.

Table 2. Novel iron supplements used for CKD

	Formulations	References
Ferrous Compounds (Fe²⁺)		
Ferroglycine sulfate	Ferro Sanol®: 100 mg (capsule), Glutaferro Drops: 30 mg/mL	64
Fe gluconate	Losferron: 80 mg (tablet)	65
Fe latate	Cromatonbic Ferro: 37.5 mg (drinkable vial)	66
Fe sulfate	FeroGradumet: 105 mg (tablet); Tradyferon: 80 mg (tablet)	66
Ferric compounds (Fe³⁺)		
Ovalbumin	Kilor, Syron 600, Profer, Ferroprotin: 80 mg (packet)	67
Ferrimannitol	Kilor, Syron 300, Profer, Ferroprotin: 40 mg (packet)	68
Ferrocolinate	Podertoinc adults: 112 mg (packet)	69
Succinylcasein Fe	Lactoferrin, Ferrocurir, Ferplex: 40 mg (drinkable vial)	69

Conclusion

In conclusion, the hepcidin level presents a complex and significant clinical challenge in the treatment of diabetic nephropathy associated with CKD and AKI. Hepcidin dysregulation can contribute to iron metabolism abnormalities, leading to iron overload or iron deficiency, both of which can adversely affect kidney function and overall health. Dysregulation of hepcidin levels during AKI and CKD could potentially impact renal iron handling, oxidative stress, and inflammation, further exacerbating kidney injury. Managing the interplay between diabetic nephropathy, CKD, AKI, and hepcidin requires a multifaceted approach. Additionally, this review discusses about the interventions to modulate hepcidin levels and iron metabolism which may hold promise in improving outcomes. Further research is needed to elucidate the precise mechanisms underlying hepcidin's role in the context of diabetic nephropathy, CKD and AKI, with the ultimate goal of developing targeted therapies and personalized treatment plans for affected individuals. In summary, the association between diabetic

nephropathy, CKD, AKI, and hepcidin underscores the intricate interplay between various pathological processes. In individuals with CKD and in cases of AKI, Fe scarcity and Fe overload is a frequent and treatable cause. Given the limits of hepcidin and ferritin in determining Fe shortage and Fe overload in patients with anaemia of CKD, innovative therapy is weighed against the possible advantages of circumventing or limiting blood transfusions. For the treatment of CKD and AKI, a variety of approved medications are available, including both oral and intravenous formulations are suitable for patients with stable CKD, and Fe chelation therapy for AKI is advised globally leading to a wealth of clinical data. DFP, DFO, and DFX are just a few of the Fe chelators medications that are commonly used to treat acute kidney injury. Additional medications that are currently undergoing clinical trials may also be combined with Fe chelators to treat diabetic nephropathy. Fe modulators can demonstrate their therapeutic effects by acting on the hepcidin and ferritin modulators. Understanding these relationships can contribute to the development of novel therapeutic approaches and improve patient outcomes in this complex clinical scenario. So, for novel approach Fe modulators play an important role in treating CKD and AKI by enhancing good renal properties used in the treatment of renal disease.

Declarations

Funding
No funding was received to carry out this work.

Author's contributions
Conceptualization, G.K. and D.B.; Methodology, B.C.; Software, H.J. and S.R.; Validation, G.K., H.S.T., B.C. and S.R.; Formal Analysis, G.K.; Investigation, D.B.; Resources, H.j.; Data Curation, S.R.; Writing – Original Draft Preparation, D.B.; Writing – Review & Editing, G.K.; Visualization, G.K.; Supervision, G.K.

Conflicts of interest
The authors declare no conflicts of interest.

Data availability
Not applicable.

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