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Review Article

Heme iron polypeptide for the management of anaemia of chronic kidney disease

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SUMMARY

What is Known and Objective: **Anaemia is a common clinical finding among patients with chronic kidney disease (CKD) and is associated with significant morbidity and healthcare costs. Iron deficiency is an important contributing factor, and adequate iron supplementation is essential to optimize the management of anaemia of CKD. Oral iron is convenient and inexpensive but is poorly absorbed and associated with gastrointestinal distress. Intravenous iron overcomes these limitations but is more expensive, requires additional clinical visits for administration and is associated with serious adverse events. Oral heme iron polypeptide (HIP) is a newer dosage form that has been reported to have higher bioavailability and fewer side effects when compared with non-heme iron in healthy subjects, but data in patients with CKD are limited. The purpose of this review is to evaluate the safety and effectiveness of HIP for the management of CKD.**

Methods: **Searches for PubMed (1947–2015) and International Pharmaceutical Abstracts (1970–2015) were conducted using the following terms: heme iron, heme iron polypeptide, oral iron, anaemia and chronic kidney disease. The bibliography of each relevant article was evaluated for additional studies. Articles were selected for review if they were published in the English language and were randomized controlled trials evaluating the bioavailability, tolerability or efficacy of oral HIP in human subjects with CKD.**

Results and Discussion: **This search yielded three clinical studies. The safety and efficacy of HIP was evaluated in a total of 161 subjects with anaemia and various stages of CKD. HIP was consistently associated with lower ferritin values when compared with traditional iron supplementation. With few exceptions, the effect of HIP on haemoglobin, haematocrit, transferrin saturation and recombinant human erythropoietin dose, and adverse effects appeared similar to intravenous and oral non-heme iron supplementation. The cost of HIP is substantially more than non-heme iron and comparable to intravenous iron.**

What is New and Conclusion: **Heme iron polypeptide does not appear to confer benefit over traditional iron supplementation among patients with anaemia of CKD and is more expensive.**

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WHAT IS KNOWN AND OBJECTIVE

According to the National Kidney Foundation (NKF), 26 million Americans have chronic kidney disease (CKD) and an estimated 4 million of those individuals have anaemia.[1,2] Anaemia of CKD is associated with significant morbidity and economic burden. It is a consequence of diminished production of erythropoietin and is exacerbated by a shortened red blood cell lifespan.[1] Iron deficiency is the most common reason for resistance to recombinant human erythropoietin (rHuEPO) therapy.[3] Iron absorption, transport and utilization are altered as a result of physiological changes and interventions to manage CKD.[3] Dietary protein restriction, food/drug interactions and inflammatory processes yield less iron absorption.[4] Hepcidin, an acute phase reactant and key mediator of iron homoeostasis, is inappropriately elevated in patients with CKD in response to chronic inflammation and decreased renal elimination.[5] Hepcidin impairs absorption of dietary iron and prevents the release of iron from macrophages in the reticuloendothelial system.[3,5] Iron demand in CKD is increased in response to recombinant human erythropoietin (rHuEPO) therapy and as a result of chronic blood loss from frequent sampling and/or haemodialysis. Consequently, iron deficiency is a common finding among the CKD population and adequate iron supplementation is essential to optimize the management of anaemia of CKD.

Iron may be supplemented using the oral or intravenous routes of administration. The NKF Kidney Disease Outcomes Quality Initiative (KDOQI) recommends the intravenous route of administration in patients with haemodialysis (HD-CKD) and peritoneal dialysis CKD (PD-CKD).[2] This recommendation is based on evidence that demonstrates the superiority of intravenous iron in achieving target haemoglobin and rHuEPO dose when compared with non-heme oral iron.[4,6,7] In contrast, the increase in haemoglobin associated with intravenous iron in patient with ND-CKD is smaller and it is unclear whether a clinical benefit over non-heme oral iron offsets its risks.[2] Therefore, the recommended route of administration in ND-CKD is often based on patient-specific factors such as cost, intravenous access, prior response to iron therapy, tolerability, compliance and the severity of iron deficiency.

Dietary iron may be categorized into non-heme and heme iron based on the source of iron. Solubility and absorption vary according to the source and form of iron. Non-heme iron, such as the ferrous and ferric iron commonly found in vegetables, grains and oral iron supplements, is poorly absorbed and requires an acidic environment for optimal absorption. In contrast, heme iron is derived from haemoglobin and myoglobin found in animal food sources and is reported to have better absorption than non-heme iron.[8] The reasons for better absorption are incompletely understood but may result from fewer food interactions, a distinct

receptor rather than non-specific transporter and improved solubility at the pH values observed in the duodenum.[9,10]

Supplementation with oral non-heme iron is convenient and inexpensive, but its efficacy is limited by low bioavailability and poor tolerability, leading to non-compliance.[11] Strategies to maximize tolerability, such as administration of smaller doses with food or sustained-release dosage forms, may improve compliance and reduce side effects but diminish the bioavailability. Intravenous iron overcomes limitations of oral iron but is more costly, requires additional clinic visits for administration and is associated with more serious reactions. Oral heme iron polypeptide (HIP) is derived through the proteolytic digestion of porcine haemoglobin and is highly soluble.[9] It has been reported to have higher bioavailability and fewer side effects when compared with non-heme iron in healthy subjects.[8,9,12] These findings make HIP a promising alternative to traditional iron supplementation for anaemia of CKD. The purpose of this article is to evaluate the literature regarding the safety and effectiveness of oral HIP for the management of anaemia of CKD.

METHODS

A systematic search was conducted utilizing PubMed and International Pharmaceutical Abstracts with the following terms: *heme iron, heme iron polypeptide, oral iron, anaemia* and *chronic kidney disease*. The bibliography of each relevant article was evaluated for additional studies. Articles were selected for review if they were published in the English language and were randomized controlled trials evaluating the bioavailability, tolerability or efficacy of HIP in human subjects with CKD. This search yielded 3 clinical studies (Table 1).

RESULTS AND DISCUSSION

Non-dialysis chronic kidney disease

Nagaraju *et al.*[13] evaluated the effects of HIP on haemoglobin in adult patients with ND-CKD, anaemia and sub-therapeutic iron indices. Eligible participants were randomized to receive intravenous iron sucrose or oral HIP. The primary endpoint was median haemoglobin after 6 months of therapy. Baseline characteristics, including haemoglobin, iron indices and rHuEPO therapy, were similar between groups. Although the per cent transferrin saturation (TSAT) did increase (21·5% vs. 17%; $P = 0{\cdot}05$) after 6 months of treatment with oral HIP, haemoglobin (117 g/L vs. 110·5 g/L; $P = 0{\cdot}15$) and ferritin (85·5 mcg/L vs. 71 mcg/L; $P = 0{\cdot}81$) did not change significantly from baseline values. Those assigned to receive intravenous iron experienced an increase in ferritin (244 mcg/L vs. 67 mcg/L; $P = 0{\cdot}003$) and TSAT (21·5% vs. 17%; $P = 0{\cdot}04$) but not haemoglobin (113 g/L vs. 108·5 g/L; $P = 0{\cdot}23$) compared with baseline. At the end of treatment, there were no differences in haemoglobin, TSAT and rHuEPO dose, or adverse effects between groups, but ferritin was significantly higher in the intravenous iron group. The authors concluded oral HIP is similar in efficacy and safety to intravenous iron sucrose in maintaining haemoglobin. The limitations of this study were the single-blind design, low intravenous iron dose and small sample size (power = 0·56).

Haemodialysis chronic kidney disease

Nissenson *et al.*[14] performed a partially randomized, open-label, multisite, prospective trial of HIP for iron-replete HD-CKD patients receiving rHuEPO therapy. Participants were assigned to continue intravenous iron per study site protocol or receive either high- or low-dose HIP. The primary endpoint was mean haematocrit at 6 months compared with baseline. Data were analysed on the per-protocol population. Baseline monthly rHuEPO dose was higher (58 613 units/month vs. 35 271 units/month; $P < 0{\cdot}02$) and monthly intravenous iron dose was lower (58·3 mg/month vs. 126·6 mg/month; $P < 0{\cdot}01$) in the HIP group. Among all subjects assigned treatment with HIP, no change in haematocrit or TSAT occurred at the end of therapy, but ferritin levels decreased from baseline. Similarly, no change in haematocrit, ferritin or TSAT was observed among participants assigned to continue intravenous iron therapy. In the high-dose HIP subgroup, mean haematocrit and rHuEPO efficiency (total weekly dose divided by haemoglobin) increased, whereas the average monthly rHuEPO dose decreased after 6 months. Side effects were recorded but not reported.

These results suggest oral HIP may be a reasonable option for iron supplementation in iron-replete HD-CKD patients receiving rHuEPO therapy, but serious concerns regarding the study design confound the clinical significance of the findings. Sample size and power calculations were not reported. The open-label design, partially randomized treatment allocation and an ambiguous control intervention weaken the internal validity. Patients from a 5th study site without a reimbursement plan for intravenous iron were assigned supplementation with HIP, and subjects from this site constituted the majority of the study population (56%). This may have contributed to the observed differences in iron and rHuEPO between groups at baseline and indicates selection bias is a concern. A larger study with fewer methodological flaws is needed before HIP is widely adopted in patients with HD-CKD.

Peritoneal dialysis chronic kidney disease

The HEMATOCRIT trial was a multisite, open-label, randomized controlled trial comparing the efficacy of HIP with oral non-heme iron for the management of anaemia in patients with PD-CKD receiving rHuEPO for at least 1 month.[15] Eligible patients were randomized to receive 6 months of oral HIP or sustained-release ferrous sulphate. The primary outcome measure was median TSAT in each group at the end of therapy. Only 46% of participants were included in the per-protocol population, and the majority (66%) of protocol deviations occurred due to non-compliance, dose reduction or withdrawal due to adverse events. At the end of treatment, there were no differences in TSAT, haemoglobin, rHuEPO dose or sensitivity, and adverse effects between HIP and ferrous sulphate by univariate analysis or analysis of covariance (ANCOVA) in the intention-to-treat and per-protocol populations. Among those assigned to receive HIP, serum ferritin levels at 6 months were significantly lower. HIP treatment was independently predictive of lower ferritin using ANCOVA. Overall, few participants in either group were iron replete at the end of treatment (14% vs. 15%; $P = 0{\cdot}79$). The cost for 6 months of treatment was nearly seven times higher with HIP than with ferrous sulphate. The investigators used a lower dose of oral HIP that provided less daily elemental iron than ferrous sulphate, which may partially explain why ferritin was lower in participants assigned to HIP.

The safety and efficacy of oral HIP was evaluated in a total of 161 subjects with anaemia and various stages of CKD.[13–15] Although early clinical data in healthy volunteers suggest the bioavailability and tolerability of oral HIP is superior to non-heme

Table 1. Summary of clinical studies evaluating heme iron polypeptide for anaemia of chronic kidney disease

Citation	Participants	Study design	Intervention	Outcomes			
				Hgb/Hct	Iron indices	rHuEPO	ADE
Nagaraju *et al.*[13]	ND-CKD (N = 40) eGFR ≤ 60 mL/min 1·73 m^2 Hgb 90–120 g/L (females); 90–135 g/L (males) Serum ferritin < 100 mcg/L or TSAT < 20%	SB, RCT	HIP 11 mg PO TID ×6 mo; n = 18 Iron sucrose 200 mg IV monthly ×6 mo (IV); n = 22	Median Hgb at 6 mo: HIP = 117 g/dL, IV = 113 g/dL; P = 0·37	Median ferritin at 6 mo: HIP = 85·5, IV = 244; P = 0·004 Median TSAT at 6 mo: HIP = 21·5%, IV = 21·5%; P = 0·82	Mean rHuEPO dose (mcg/mo) at 6 mo: HIP = 60, IV = 50; P = 0·56	Overall ADE: HIP = 28, IV = 26; P = NR Symptomatic hypotension: HIP = 0, IV = 13%; P = NR Study withdrawal due to protocol non-adherence or adverse effects: HIP = 22%, IV = 13; P = NR
Nissenson *et al.*[14]	HD-CKD (N = 59)	OL*	HIP 21 mg/d** ×6 mo (LD-HIP); n = 8 HIP 36 mg/d** ×6 mo (HD-HIP); n = 20 IV iron per site protocol ×6 mo (IV); n = 31	Mean Hct at baseline and 6 mo: LD-HIP = 36·2%, 35·7%; P = NR HD-HIP = 34·2%, 35·3%; P = 0·04 IV = 35·6%, 35·6%; P = NR Combined HIP = 34·8%, 35·4%; P = 0·19	Mean ferritin at baseline and 6 mo: LD-HIP = NR HD-HIP = NR IV = 676 mcg/L, 723 mcg/L; P = NR Combined HIP: 552 mcg/L, 446 mcg/L; P < 0·01 Median TSAT at 6 mo and baseline: LD-HIP = 32·6%, 26·5%; P = 0·03 HD-HIP = NR IV = 31·6%, 30·7%; P = NR Combined HIP = 30%, 28·9%; P = NR	Mean rHuEPO dose at baseline and 6 mo: LD-HIP = NR HD-HIP = NR Combined HIP = 58 613 units/mo, 48 130 units/mo; P = 0·08 IV iron = 32 996 units/mo, 35 127; P = NR rHuEPO efficiency at baseline and 6 mo***: LD-HIP = 1227, 922; P = 0·44 HD-HIP = 1287, 1063; P = 0·016 IV = 706, 762; P = 0·68 Combined HIP = 1270, 1023; P = 0·04	Each patient was administered a monthly questionnaire to ascertain GI ADE; these data were not reported in the article Study withdrawal due to adverse effects: Combined HIP = 8%, IV = NR; P = NR
Barraclough *et al.*[15]	PD-CKD (N = 62)	OL, RCT	HIP 12 mg PO BID ×6 mo;**** n = 32 Ferrous sulphate 105 mg (elemental) PO BID ×6 mo (FS); n = 30	Median Hgb at 6 mo: HIP = 111 g/L, FS = 113 g/dL; P = 0·59	Median TSAT at 6 mo: HIP = 22%, FS = 20%; P = 0·65 Median ferritin at 6 mo: HIP = 124 mcg/L, FS = 292; P = 0·003 Frequency of iron replete***** at 6 mo: HIP = 14%. FS = 15%; P = 0·79	Median weekly darbepoetin dose at 6 mo: HIP = 20 mcg/week, FS = 20; P = 0·66 Median darbepoeitin sensitivity index ***:HIP = 0·14, FS = 0·16; P = 0·96	Overall ADE: HIP = 23, FS = 24; $P \geq 0·05$ GI ADE: HIP = 22%, FS = 13%; P = 0·51 Excluded from per-protocol analysis due to non-compliance, dose reduction, or adverse event: HIP = 70%, FS = 41%; P = NR

Hgb = haemoglobin; Hct = haematocrit; rHuEPO = recombinant human erythropoietin; ADE = adverse events; CKD = chronic kidney disease; ND-CKD = non-dialysis CKD; eGFR = estimated glomerular filtration rate; TSAT = transferrin saturation; SB = single blind; RCT = randomized controlled trial; HIP = heme iron polypeptide; PO = by mouth; TID = thrice daily; IV = intravenous; mo = month; NR = not reported; HD-CKD = haemodialysis CKD; OL = open label; *at 4 study sites, subjects were allocated using random number generation; subjects were allocated by payer source at a 5th site; **in 3 divided doses; LD-HIP = low-dose HIP; HD-HIP = high-dose HIP; ***total weekly rHuEPO dose divided by Hgb; GI ADE = gastrointestinal ADE; PD-CKD = peritoneal dialysis CKD; BID = twice daily; ****the authors specified in their published study rationale and design of the oral HIP regimen yielded 24 mg of daily elemental iron, whereas the methods of the published study stated oral HIP provided 240 mg of daily elemental iron.[15,17] The product described in the study provides 12 mg elemental iron per dose[18]; *****TSAT > 20% and ferritin > 100 mcg/L.

iron supplementation, these findings did not translate into improved outcomes in studies of patients with CKD.[9,10,12] HIP was consistently associated with lower ferritin values when compared with traditional iron supplementation. With few exceptions, the effect of HIP on haemoglobin, haematocrit, TSAT and rHuEPO dose, and adverse effects appeared similar to intravenous and oral non-heme iron supplementation. The cost of HIP is significantly more than non-heme iron and comparable to intravenous iron.[15] Overall, HIP does not appear to confer benefit over traditional iron supplementation among patients with anaemia of CKD.

The interpretation of these data must be viewed in the context of its limitations. Each study was underpowered and none were double-blinded, which increases the risk for type 2 error and bias, respectively. Some clinicians may be inclined to conclude oral HIP is equivalent to traditional iron supplementation for patients with anaemia of CKD because no significant difference in haemoglobin or rHuEPO dose was observed in any of the clinical trials. However, the absence of a statistically significant difference in a superiority trial does not establish therapeutic equivalence. Furthermore, because neither therapy improved either endpoint, the clinical significance of equivalence would remain uncertain. Although the endpoints used to assess HIP were appropriate and consistent with other studies evaluating oral non-heme iron in CKD, they are surrogate endpoints. Clinical outcomes of anaemia management, such as anaemia-related symptoms, quality of life and blood transfusions, have not been adequately assessed with iron supplementation.

The apparent difference in the bioavailability of HIP and non-heme iron between healthy volunteers and patients with CKD reflects different study methods, absorption kinetics, complex uptake regulation and chronic inflammation. The bioavailability of oral HIP in healthy subjects was assessed using serum iron concentrations, a measure that is not clinically relevant.[9,10,16] Patients with CKD have significantly higher serum hepcidin concentrations than healthy control subjects.[5] Hepcidin inhibits the movement of iron through ferroportin into systemic circulation and consequently impairs iron absorption.[5] Additionally, absorption of oral HIP is saturable and inversely associated with ferritin concentrations.[9]

The most convincing data to support the claim that HIP supplementation is associated with better tolerability were conducted in a small cohort of healthy blood donors. Frykman *et al.*[12] reported superior gastrointestinal tolerance with no difference in iron status between HIP and non-heme iron after 3 months. However, the investigators compared a lower oral HIP dose (1·2 mg HIP and 8 mg iron fumarate given twice daily) with a higher non-heme iron fumarate (60 mg given once daily) dose. Therefore, the difference in tolerability may actually reflect the effects of a larger dose of elemental iron. The safety profile of HIP in CKD conflicts with data from healthy volunteers. Overall, adverse events with HIP appear similar to intravenous and oral iron, but definitive conclusions are subject to error as a result of the open-label designs, small sample sizes and incomplete reporting. A larger trial evaluating the gastrointestinal effects of HIP is unlikely to demonstrate a benefit because a higher HIP dose may be necessary to achieve satisfactory ferritin concentrations. Moreover, a trend towards more frequent side effects and study withdrawal due to non-compliance, dose reduction or adverse events was observed with HIP when compared with a higher non-heme oral iron dose in PD-CKD.[15]

WHAT IS NEW AND CONCLUSION

Anaemia is a common complication of CKD, and iron supplementation is an important component of anaemia management. Oral iron is convenient and inexpensive but is poorly absorbed and associated with gastrointestinal distress. Intravenous iron overcomes these limitations but is more expensive and associated with serious adverse events. Early clinical data in healthy volunteers suggest the bioavailability and tolerability of oral HIP is superior to non-heme iron supplementation, but these findings did not translate into improved iron indices in studies of patients with CKD. HIP is more expensive than oral non-heme iron. Overall, HIP does not appear to confer benefit over traditional iron supplementation among patients with anaemia of CKD.

CONFLICT OF INTEREST

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