

Hypophosphatemia after Treatment of Iron Deficiency with Intravenous Ferric Carboxymaltose or Iron Isomaltoside -A Systematic Review and Meta-Analysis

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Abstract

Background: Hypophosphatemia is an increasingly recognized side-effect of ferric carboxymaltose (FCM) and possibly iron isomaltoside/ferric derisomaltose (IIM), which are used to treat iron deficiency. Objective: To determine frequency, severity, duration and risk factors of incident hypophosphatemia after treatment with FCM and IIM. Data Sources: A systematic literature search for articles indexed in EMBASE, PubMed and Web of Science in years 2005 to 2020 was carried out using the search terms ‘ferric carboxymaltose’ OR ‘iron isomaltoside’. Study Selection: Prospective clinical trials reporting outcomes on hypophosphatemia rate, mean nadir serum phosphate and/or change in mean serum phosphate from baseline were selected. Data Extraction: Hypophosphatemia rate and severity were compared for studies on IIM vs. FCM after stratification for chronic kidney disease. Meta-regression analysis was used to investigate risk factors for hypophosphatemia. Results: Across the 42 clinical trials included in the meta-analysis, FCM induced a significantly higher incidence of hypophosphatemia than IIM (47%, 95% CI 36-58% vs. 4%, 95% CI 2-5%), and significantly greater mean decreases in serum phosphate (0.40 versus 0.06 mmol/L). Hypophosphatemia persisted at the end of the study periods (maximum 3 months) in up to 45% of patients treated with FCM. Meta-regression analysis identified low baseline serum ferritin and transferrin saturation, and normal kidney function as significant predictors of hypophosphatemia. Interpretation: FCM is associated with a high risk of hypophosphatemia, which does not resolve for at least 3 months in a large proportion of affected patients. More severe iron deficiency and normal kidney function are risk factors for hypophosphatemia.

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Abstract

Background : Hypophosphatemia is an increasingly recognized side-effect of ferric carboxymaltose (FCM) and possibly iron isomaltoside/ferric derisomaltose (IIM), which are used to treat iron deficiency.

Objective: To determine frequency, severity, duration and risk factors of incident hypophosphatemia after treatment with FCM and IIM.

Data Sources : A systematic literature search for articles indexed in EMBASE, PubMed and Web of Science in years 2005 to 2020 was carried out using the search terms ‘ferric carboxymaltose’ OR ‘iron isomaltoside’.

Study Selection : Prospective clinical trials reporting outcomes on hypophosphatemia rate, mean nadir serum phosphate and/or change in mean serum phosphate from baseline were selected.

Data Extraction : Hypophosphatemia rate and severity were compared for studies on IIM vs. FCM after stratification for chronic kidney disease. Meta-regression analysis was used to investigate risk factors for hypophosphatemia.

Results : Across the 42 clinical trials included in the meta-analysis, FCM induced a significantly higher incidence of hypophosphatemia than IIM (47%, 95% CI 36-58% vs. 4%, 95% CI 2-5%), and significantly greater mean decreases in serum phosphate (0.40 versus 0.06 mmol/L). Hypophosphatemia persisted at the end of the study periods (maximum 3 months) in up to 45% of patients treated with FCM. Meta-regression

analysis identified low baseline serum ferritin and transferrin saturation, and normal kidney function as significant predictors of hypophosphatemia.

Interpretation : FCM is associated with a high risk of hypophosphatemia, which does not resolve for at least 3 months in a large proportion of affected patients. More severe iron deficiency and normal kidney function are risk factors for hypophosphatemia.

Keywords: anaemia, phosphate, FGF23, ferric derisomaltose

Introduction

Introduction of the intravenous iron preparations ferric carboxymaltose (FCM) and iron derisomaltose/iron isomaltoside 1000 (IIM) represented major advances in intravenous iron therapy because both preparations allow rapid correction of total iron deficit in one or two infusions, while exhibiting low rates of hypersensitivity reactions^{1,2}. Both drugs are frequently used to treat iron deficiency of various causes. The commonest indications include iron deficiency due to gastrointestinal blood loss, inflammatory bowel disease (IBD), heavy uterine bleeding and post-partum hemorrhage^{3,4}. Iron infusions are also frequently given to correct pre- or postoperative iron deficiency anemia. In patients with chronic kidney disease (CKD), i.v. iron increases response to erythropoiesis stimulating agents, while in patients with chronic heart failure, FCM improves exercise performance⁵⁻⁷.

Despite their overall favorable safety profile and simple administration schedule, hypophosphatemia is a side-effect of both iron preparations^{8,9}. Reporting of this side effect in clinical trials is inconsistent, leading to a remarkable variability in the documentation of hypophosphatemia rates. The severity of hypophosphatemia in affected patients is also underestimated when only mean phosphate concentrations across all patients is reported, including those who remain free from hypophosphatemia. The finding that hypophosphatemia persists in a subgroup of patients through the end of study follow-up, illustrates that the true duration of hypophosphatemia is unknown and can only be estimated from uncontrolled, retrospective studies¹⁰.

An increasing number of case reports suggests that hypophosphatemia after i.v. iron can cause acute, severe and/or chronic and potentially irreversible complications especially after repeated administration. Reported clinical manifestations include asthenia, fatigue, myopathy, respiratory failure, osteomalacia, bone pain and fractures, which are all recognized symptoms and signs of prolonged or severe hypophosphatemia¹¹.

The mechanism of hypophosphatemia after i.v. iron is renal phosphate wasting; impaired kidney function partially protects against hypophosphatemia. Urinary phosphate excretion is regulated by the phosphaturic hormone, fibroblast-growth factor-23 (FGF23)¹²⁻¹⁴. Accordingly, the severity and risk of hypophosphatemia correlates with the magnitude of iron-induced increases in circulating concentrations of full-length, intact FGF23 (iFGF23) and with higher glomerular filtration rate¹¹. Besides its effects as phosphaturic hormone, FGF23 also inhibits activation of 25(OH)vitamin D to 1,25(OH)₂vitamin D (calcitriol), which could explain the mild hypocalcemia and subsequent increase in circulating parathyroid hormone (PTH) concentration following intravenous iron treatment. Due to the phosphaturic effects of PTH, this mechanism may further prolong hypophosphatemia long after the increase in FGF23 returns towards normal¹⁵.

Differences in incidence, severity and possibly duration of hypophosphatemia, suggest that the specific pharmacological properties of the iron-carbohydrate complex may influence risk of hypophosphatemia¹¹. Among i.v. iron preparations, saccharated iron oxide, iron sucrose and iron polymaltose, have been reported to induce hypophosphatemia¹⁶⁻¹⁹.

The diversity in the underlying etiology and variation in the severity of iron deficiency in patients included in different clinical trials limits direct comparison of safety data from prospective studies. To define the frequency and severity of hypophosphatemia after treatment with the internationally available high-dose intravenous iron preparations FCM and IIM, a systematic literature review and meta-analysis was carried out²⁰.

Methods

The rationale for this systematic review was to determine the incidence of hypophosphatemia after administration of FCM or IIM. To assess the incidence, we included prospective studies reporting on phosphate as a safety outcome. The search strategy is described in Figure 1 and the supplementary material. For the meta-analysis, data were extracted from each study by two authors independently. In case of inconsistent data entry, agreement was reached by discussion among authors. For each study included we recorded study drug and dose, the threshold for the definition of hypophosphatemia, the number of patients developing hypophosphatemia and the absolute number in whom phosphate was measured (safety analysis set) or, if available, hypophosphatemia rate and mean or median nadir phosphate. In addition, the following trial data were collected: the time point after administration of the study drug at which phosphate was measured, hypophosphatemia rate at the end of the study period and study duration. The following pre-treatment parameters were assessed in the FCM or IIM treatment arms: median or mean concentration of ferritin, hemoglobin, transferrin saturation and phosphate concentration. A single study reported on relevant outcomes from a direct head to head comparison of IIM and FCM. For this meta-analysis of safety outcomes data on hypophosphatemia for the FCM or IIM treatment arm were assessed for each study individually. Due to the wide range of treatments in the comparator arms (placebo, standard medical care, various oral iron preparations, ferrumoxytol, iron dextran, iron sucrose, saccharated iron oxide) odds ratios are not comparable between studies. Criteria for risk bias assessment were predefined to consider potential limitations in study design and reporting that could potentially affect observed hypophosphatemia rate or severity. Each of studies included was assessed according to the criteria listed in Figure S1. According to these criteria each study was graded and the overall score correlated with outcomes reported by Spearman rank correlation analysis. Risk of publication bias was assessed by funnel plot analysis.

The meta-analysis was performed using the metafor package (version 2.1-0) in R (R version, 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio (version 1.2.5001, RStudio, Inc., Boston, MA, USA) as described by Viechtbauer et al²¹. Effect sizes of frequencies and counts were calculated as raw proportions. In case of zeroes, a value of 0.01 was added to the respective value to avoid division by zero; all other values remained unmodified. Effect sizes of mean phosphate levels and mean change of phosphate were calculated as mean differences of reported mean post-treatment phosphate minus mean pre-treatment phosphate concentration. For subgrouping, studies were stratified by iron preparation and the presence or absence of chronic kidney disease in the study population. Heterogeneity between studies was estimated by a restricted maximum-likelihood estimator and reported using the Cochrane Q and the I^2 statistic. Additional details of the statistical methods can be found in the supplementary material.

For meta-regressions, mean serum ferritin, mean transferrin saturation, and mean age were extracted from the studies' baseline characteristics. For ferritin, a log-linear weighted regression was performed, whereas transferrin saturation was treated as a potential linear modifier. The respective R syntax is given in the appendix. Serum ferritin values were log10 transformed for further computations, as this parameter follows a log-normal distribution.

Frequencies were either calculated by dividing the number of patients developing hypophosphatemia by the number of patients in whom phosphate concentrations were available or the hypophosphatemia rate as reported in the study.

For original data, please contact the corresponding author.

Results

Hypophosphatemia rates in prospective studies

The systematic literature search identified 224 prospective studies. After manual selection, 42 clinical trials that used either FCM or IIM and reported relevant outcomes on phosphate were included in the meta-analysis

(Figure 1). Outcomes were inconsistently reported (Table 1). Seventeen of 42 studies defined hypophosphatemia as a serum phosphate concentration <0.64 mmol/L or <2.0 mg/dL) and 8 of 42 studies used serum phosphate up to 0.84 mmol/L (2.56 mg/dl) as cutoff. To assess if the frequency of hypophosphatemia depended on the threshold applied, this variable was included in the risk-bias assessment (Figure S1). Twenty-five of 42 studies included in the final analysis reported a threshold for the definition of hypophosphatemia. Other criteria that were included in the risk-bias assessment were the point in time when the phosphate was measured, mean nadir phosphate and hypophosphatemia rate at the end of follow-up. Only four studies reported all relevant definitions and outcomes on hypophosphatemia (Figure S1). Risk bias assessment showed that studies with higher risk score reported significantly lower hypophosphatemia rates ($r = 0.348$, $p = 0.021$). No significant correlation between overall risk score, mean change in phosphate or mean nadir phosphate was found. Independent analysis of studies on FCM and IIM by funnel blot analysis showed no evidence of publication bias (Figure S2).

Hypophosphatemia rates ranged from 0% to 92%. To assess to what extent heterogeneity could be explained by use of IIM or FCM, studies were grouped by study population (CKD vs. non-CKD). The pooled hypophosphatemia rate after FCM was significantly higher than after IIM (47% vs. 4%; $p < 0.001$). Since reduced glomerular filtration rate impairs urinary phosphate excretion, we next assessed kidney function as a cause of heterogeneity, which was reduced by analyzing CKD patients independently. In CKD patients, hypophosphatemia rates were 27% after FCM vs. 2% after IIM (Figure 2). Despite significant heterogeneity among studies in non-CKD-patients, pooled hypophosphatemia rates were significantly higher after FCM than after IIM treatment (51 vs 5%; $p < 0.001$).

Studies reporting mean nadir plasma phosphate concentrations in the treatment arms after administration of FCM or IIM are shown in Figure 3A. Pooled analysis shows that in few studies mean nadir phosphate reaches a concentration <0.6 mmol/L. The overall pooled mean nadir phosphate concentration after FCM was 0.69 mmol/L (95% CI 0.60 - 0.78) in patients without CKD vs. 1.11 mmol/L (95% CI 0.96 - 1.27) in the subgroup of patients with CKD.

Figure 3B shows analysis of mean change in phosphate from baseline. The pooled analysis of reported results across etiologies shows that the mean decrease in phosphate after FCM is -0.40 (95% CI -0.50 - -0.31) mmol/L vs. 0.06 (95% CI -0.14 - 0.02) mmol/L after IIM.

The duration of hypophosphatemia was not reported in any of the studies, but hypophosphatemia rate at the end of the study period ranged from 0-45 % after a follow-up of up to 3 months (Table 1).

Meta-regression analysis was carried out to test if serum iron parameters are predictors of hypophosphatemia. As shown in Figure 4, serum ferritin and transferrin saturation at baseline showed a significant association with a hypophosphatemia rate after stratification of trials by study drug. In trials on both study drugs, more severe iron deficiency was associated with a greater risk of post-treatment hypophosphatemia, but the overall risk for hypophosphatemia was lower for IIM. A stronger negative association between hypophosphatemia rate and $\log(\text{ferritin})$ was noted for FCM than for IIM. The same was observed for the association between transferrin saturation and hypophosphatemia rate (Figure 4, Table S1). No association between mean total iron dose and hypophosphatemia rate was found when studies using FCM or IIM were analyzed independently. When mean total iron dose was correlated with nadir phosphate concentration, a significant association was found on meta-regression analysis (Figure S3).

Discussion

Despite the advantages of latest generation intravenous preparations FCM and IIM, which allow safe correction of total iron deficit in 1-2 infusions in the majority of patients, hypophosphatemia is increasingly recognized as a delayed adverse drug reaction. Although listed in the drug label as a potential side effect, the overall incidence and the clinical relevance of this adverse event are largely unknown.^{11,22,23}

This systematic review and meta-analysis show that the reported incidence of hypophosphatemia after

infusion of FCM or IIM ranges from 0% to 92% of in prospective clinical trials. Our systematic review and meta-analysis show that this wide range is in part attributable to inconsistent assessment and reporting of hypophosphatemia in clinical studies. As determinants and predictors of hypophosphatemia we have identified preserved renal function, the severity of iron deficiency and possibly dose.

The present analysis highlights inconsistencies in reporting of relevant endpoints. Some studies only report on mean phosphate concentrations before and after treatment or relative changes. Incidence of hypophosphatemia and the proportion of patients developing severe hypophosphatemia (<0.3 mmol/L) are much more relevant for the care of individual patients. Study protocols of ongoing clinical trials, which include assessment of the prevalence of the different degrees of hypophosphatemia (<0.3 mmol/L, 0.3 - 0.6 mmol/L, 0.6 - 0.8 mmol/L) during follow up visits are preferable and should become standard in reporting this side effect, because the risk for complications of hypophosphatemia increases with its severity²⁴.

Further, the duration of hypophosphatemia should be prospectively assessed by following-up on patients who develop hypophosphatemia during the study. Accordingly, the description of ‘i.v. iron-induced hypophosphatemia’ as ‘transient decrease of phosphate levels’ may be applicable to a study population but inappropriate in describing the side-effect in individual patients, because recovery is unpredictable for individual patients. Retrospective studies have suggested that the median time to recovery is 40-80 days, but this is insufficient to assess the true duration of hypophosphatemia in individual patients, who developed this side-effect¹⁰. None of the prospective studies reported on the actual duration of hypophosphatemia. Hence, the risk of long-term complications is also unknown.

Among patients with impaired renal function, the pooled risk of hypophosphatemia was significantly lower when compared with studies in other patient populations. The result supports previous findings that FCM and to a lesser degree IIM cause hypophosphatemia by renal wasting. Urinary phosphate excretion is controlled by the hormone intact FGF23, which is induced by FCM through incompletely defined mechanisms²⁵.

The difference in incidence between FCM and IIM across etiologies supports the notion that hypophosphatemia is not a class effect of all i.v. irons, but rather a specific effect of FCM. This conclusion is supported by clinical trials confirming that despite comparable dosing of FCM and the comparator (iron dextran or ferumoxytol), hypophosphatemia was far more common after FCM^{15,26}. Pharmacologically, i.v. iron preparations are ‘non-biological complex drugs (NBCD)’, where the active drug is not a homo-molecular structure but consists of different closely related structures. The composition, characteristics and in-vivo effects of NBCD are highly dependent on manufacturing processes, which limits the possibilities to study the carbohydrate moiety independently of iron²⁷.

The clinical manifestations of inappropriately high FGF23 with consequent hypophosphatemia are diverse and best known from patients with defects in genes regulating phosphate homeostasis and patients with tumor-induced osteomalacia. Weakness of proximal muscles, dental problems, bone pain and osteomalacia are typical manifestations of these diseases. As treatment with certain i.v. iron preparations is a novel cause of inappropriate FGF23 elevation, it can be expected that severely and chronically affected patients could also develop symptoms mimicking TIO or genetic hypophosphatemia²⁸. Accordingly, a number of cases with clinical complications of hypophosphatemia has been reported¹¹.

In conclusion, this systematic review and meta-analysis shows that hypophosphatemia is a common medical problem after administration of FCM, especially in patients with preserved kidney function and more severe iron deficiency. The incidence is higher, severity and duration are more severe after FCM as compared to IIM.

Abbreviations: FCM, ferric carboxymaltose; IIM, iron isomaltoside; FS, ferric sucrose; SIO, saccharated iron oxide; ID, iron dextrane; FO, ferumoxytol, na, not available; GYN, gynecology; IDA, iron deficiency anemia; PBM, patient blood management; CKD, chronic kidney disease; NDD-CKD, non-dialysis dependent chronic kidney disease; HD-CKD, hemodialysis-dependent chronic kidney disease; RLS, restless leg syndrome

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Tables

Table 1: Characteristics of the 42 prospective clinical trials Included in the meta-analysis.

First author (year)	Study type	Therapeutic area	Threshold for hypophosphatemia	S
Allen et al. (2011) ²⁹	RCT	RLS	na	1
Auerbach et al. (2019) ³⁰	RCT	mixed IDA	2 mg/dL (0.65 mmol/L)	1
Bailie et al. (2010) ³¹	RCT	mixed IDA	na	1
Barish et al. (2012) ³² - multiple dose arm	RCT	mixed IDA	2 mg/dL (0.65 mmol/L)	4
Barish et al. (2012) ³² - single dose arm	RCT	mixed IDA	2 mg/dL (0.65 mmol/L)	3
Bhandari et al. (2015) ³³	RCT	HD-CKD	2 mg/dL (0.65 mmol/L)	4
Bhandari et al. (2020) ³⁴	RCT	NDD-CKD	2 mg/dL (0.65 mmol/L)	5
Biggar et al. (2016) ³⁵	SAT	HD-CKD	na	2
Birgegard et al. (2016) ³⁶ - bolus arm	RCT	malignancy	2 mg/dL (0.65 mmol/L)	1
Birgegard et al. (2016) ³⁶ - infusion arm	RCT	malignancy	2 mg/dL (0.65 mmol/L)	1
Breymann et al. (2017) ³⁷	RCT	GYN	0.6 mmol/L	8

First author (year)	Study type	Therapeutic area	Threshold for hypophosphatemia	S
Charytan et al. (2013) ³⁸ - HD-arm	RCT	HD-CKD	na	3
Charytan et al. (2013) ³⁸ - NDD-HD arm	RCT	NDD-CKD	na	3
Dahlerup et al. (2016) ³⁹	SAT	IDA digestive diseases	2 mg/dL (0.65 mmol/L)	1
Detlie et al. (2019) ⁴⁰ - FCM arm	RCT	IDA digestive diseases	0.8 mmol/L	4
Detlie et al. (2019) ⁴⁰ - IIM arm	RCT	IDA digestive diseases	0.8 mmol/L	4
Ding et al. (2020) ⁴¹ - 1000 mg cohort	RCT	mixed IDA	0.8 mmol/L	6
Ding et al. (2020) ⁴¹ - 500 mg cohort	RCT	mixed IDA	0.8 mmol/L	6
Drexler et al. (2019) ⁴²	RCT	IDA/blood donation	0.84 mmol/L	8
Evstatiev et al. (2011) ⁴³	RCT	IDA digestive diseases	na	8
Favrat et al. (2014) ⁴⁴	RCT	mixed IDA	0.8 mmol/L	5
Gybel-Brask et al. (2018) ⁴⁵	RCT	IDA/blood donation	2 mg/dL (0.65 mmol/L)	1
Holm et al. (2017) ⁴⁶	RCT	GYN	2 mg/dL (0.65 mmol/L)	8
Huang et al. (2018) ⁴⁷ - CKD arm	SAT	NDD-CKD	na	4
Huang et al. (2018) ⁴⁷ - control arm	SAT	mixed IDA	na	4
Huang et al. (2018) ⁴⁷ - pregnant arm	SAT	GYN	na	4
Hussain et al. (2013) ⁴⁸	RCT	mixed IDA	2 mg/dL (0.65 mmol/L)	4
Ikuta et al. (2018) ⁴⁹	SAT	mixed IDA	2.5 mg/dL (0.81 mmol/L)	8
Ikuta et al. (2019) ⁵⁰	RCT	GYN	0.81 mmol/L	8
Ikuta et al. (2019) ⁵¹	SAT	IDA digestive diseases	2.5 mg/dL (0.81 mmol/L)	8
Johannsson et al. (2015) ⁵²	RCT	PBM	2 mg/dL (0.65 mmol/L)	2
Kalra et al. (2016) ⁵³ - bolus arm	RCT	NDD-CKD	2 mg/dL (0.65 mmol/L)	5
Kalra et al. (2016) ⁵³ - infusion arm	RCT	NDD-CKD	2 mg/dL (0.65 mmol/L)	5
Macdougall et al. (2014) ⁵⁴ - high ferritin arm	RCT	NDD-CKD	na	3
Macdougall et al. (2014) ⁵⁴ - low ferritin arm	RCT	NDD-CKD	na	3
Mahey et al. (2016) ⁵⁵	RCT	GYN	na	8
Onken et al. (2014) ¹ - cohort 1	RCT	mixed IDA	na	3
Onken et al. (2014) ¹ - cohort 2	RCT	mixed IDA	na	3
Onken et al. (2014) ⁵⁶	RCT	NDD-CKD	na	5
Prats et al. (2013) ¹³	RCT	NDD-CKD	na	8
Qunibi et al. (2011) ⁵⁷	RCT	NDD-CKD	na	5
Reinisch et al. (2013) ⁹	RCT	IDA digestive diseases	2 mg/dL (0.65 mmol/L)	5
Roberts et al. (2016) ¹⁴	RCT	HD-CKD	na	4
Seid et al. (2008) ⁵⁸	RCT	GYN	na	4
Seid et al. (2017) ⁵⁹ - heavy menstrual bleeding arm	RCT	GYN	na	3
Seid et al. (2017) ⁵⁹ - post-partum anemia arm	RCT	GYN	na	3
Stohr et al. (2019) ⁶⁰ - CKD arm	SAT	NDD-CKD	0.8 mmol/L	2
Stohr et al. (2019) ⁶⁰ - heart failure arm	SAT	heart failure	0.8 mmol/L	2
Toledano et al. (2016) ⁶¹	SAT	malignancy	na	9
Van Wyck et al. (2007) ⁸	RCT	GYN	na	4
VanWyck et al. (2009) ⁶²	RCT	GYN	2 mg/dL (0.65 mmol/L)	6
Wolf et al. (2013) ¹⁵	RCT	GYN	2 mg/dL (0.65 mmol/L)	5
Wolf et al. (2018) ²⁶	RCT	mixed IDA	2 mg/dL (0.65 mmol/L)	3
Wolf et al. (2020) ⁶³ - trial A FCM	RCT	mixed IDA	2 mg/dL (0.65 mmol/L)	3
Wolf et al. (2020) ⁶³ - trial A IIM	RCT	mixed IDA	2 mg/dL (0.65 mmol/L)	3
Wolf et al. (2020) ⁶³ - trial B FCM	RCT	mixed IDA	2 mg/dL (0.65 mmol/L)	3
Wolf et al. (2020) ⁶³ - trial B IIM	RCT	mixed IDA	2 mg/dL (0.65 mmol/L)	3

Figure legends

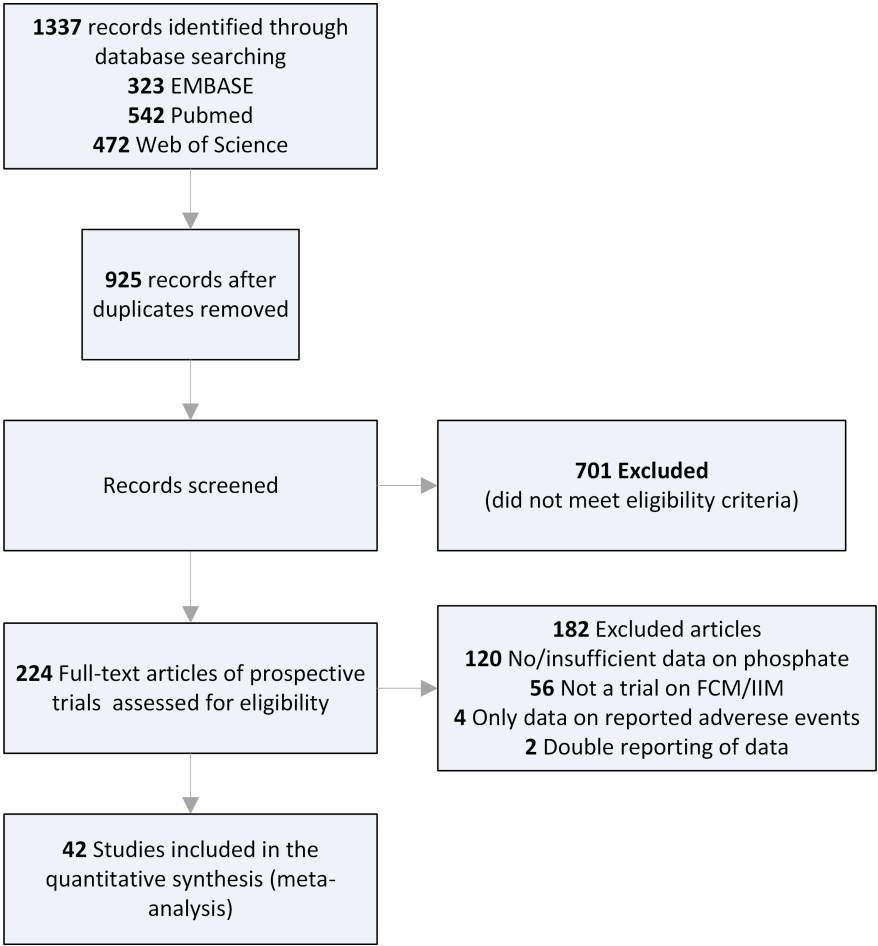
Figure1: PRISMA diagram. The search strategy and study selection for the meta-analysis of clinical trials.

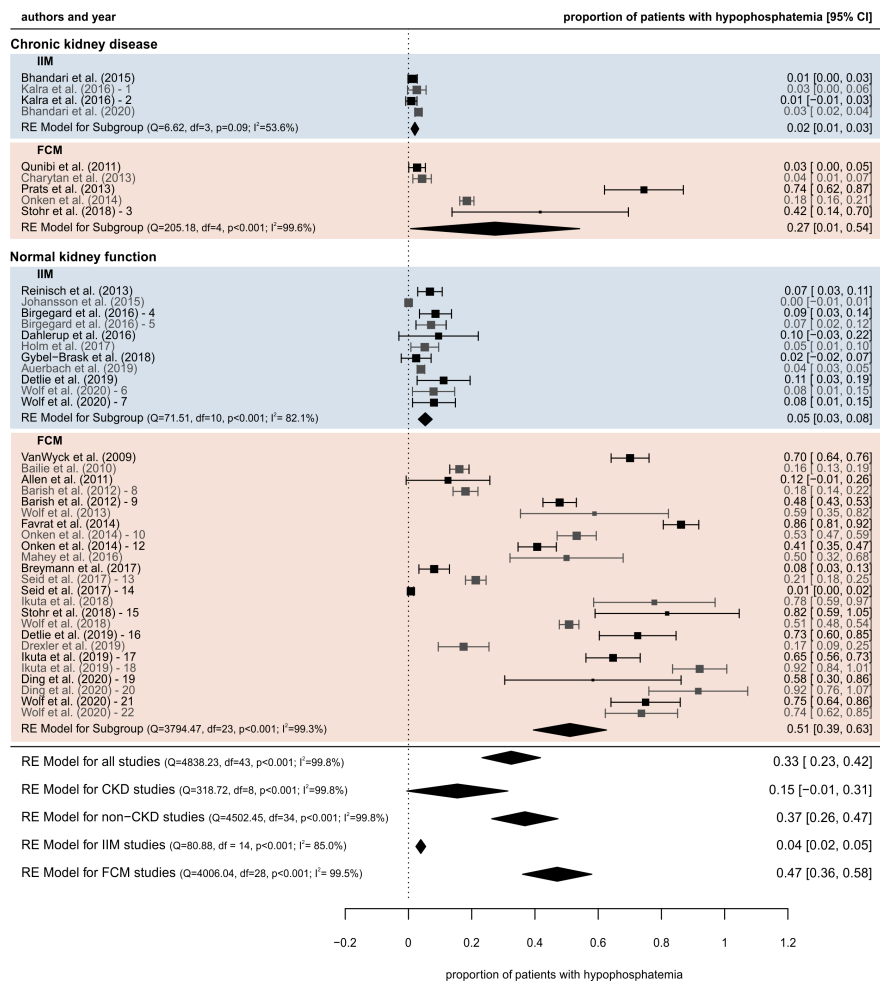
Figure 2: Forest plot on hypophosphatemia rate according to iron preparation and presence of chronic kidney disease.

1 - infusion arm; 2 - bolus arm; 3 - NDD-CKD arm; 4 - bolus arm; 5 - infusion arm; 6 - IIM arm; 7 - trial A; 8 - trial B; 9 - single dose arm; 10 - multiple dose arm; 11 - cohort 1; 12 - cohort 2; 13 - heavy menstrual bleeding arm; 14 - post-partum anemia arm; 15 - non-CKD/heart-failure arm; 16 - FCM arm; 17 - Ref:⁵⁰; 18 - Ref.⁵¹; 19 - 500 mg dose; 20 - 1000 mg dose; 21 - trial A; 22 - trial B

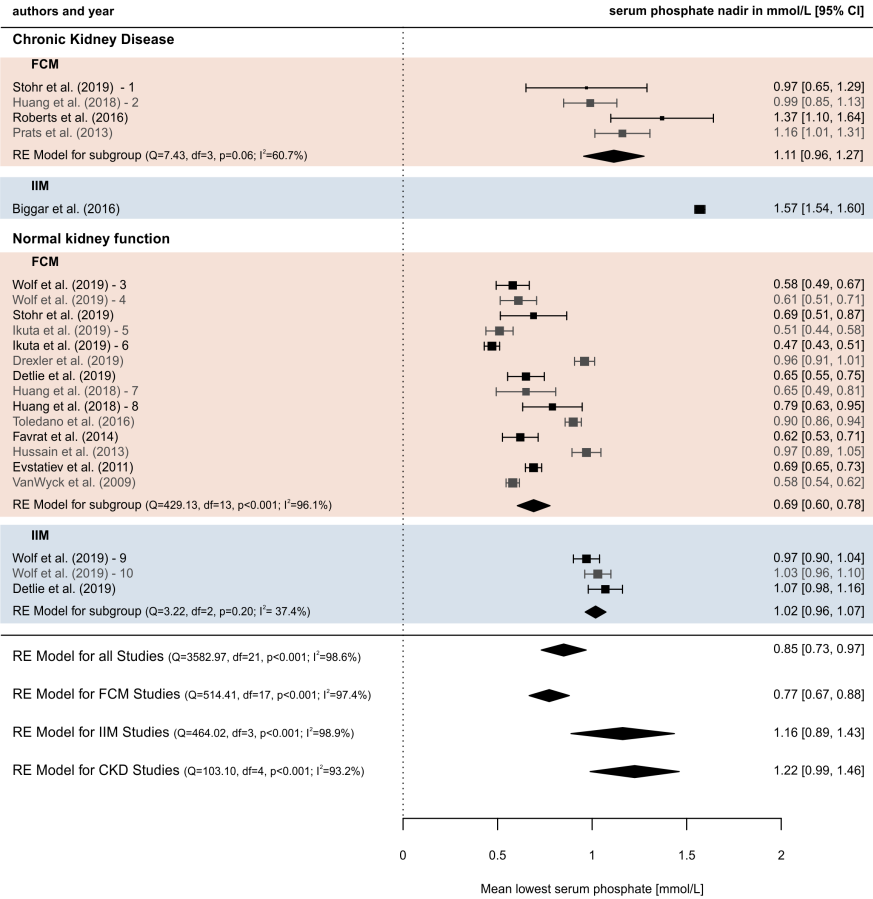
Figure 3: Forest plot on severity of hypophosphatemia rate according to iron preparation and presence of chronic kidney disease. (A) Mean lowest serum phosphate concentration. 1 - NDD-CKD arm; 2 - *NDD-CKD arm* ; 3 - trial B; 4 - trial A; 5 - Ref: ⁵¹; 6 - Ref:⁵⁰; 7 - control arm; 8 - pregnant arm; 9 - *trial A*; 10 - *trial B*(B) Mean changes in serum phosphate from baseline. 1 - NDD-CKD arm; 2 - NDD-CKD arm; 3 - trial B; 4 - trial A; 5 - pregnant arm; 6 - control arm; 7 - non-CKD/heart-failure arm; 8 - trial A; 9 - trial B

Figure 4: Meta regression of hypophosphatemia rate in relation to either log(mean ferritin) (A,B) or mean transferrin saturation (C,D) in studies on FCM (A,C) or IIM (B,D). Numerical outputs are reported in Table S2.





A



B

