Causes of anemia in the uremic milieu

- Reduced **production** of erythropoietin
- **Shortened erythrocyte lifespan** caused by uremic toxins and oxidative stress
- **Impaired iron availability** due to inflammation-driven production of hepcidin, which inhibits intestinal iron absorption
- Occult **blood loss** due to uremic platelet dysfunction

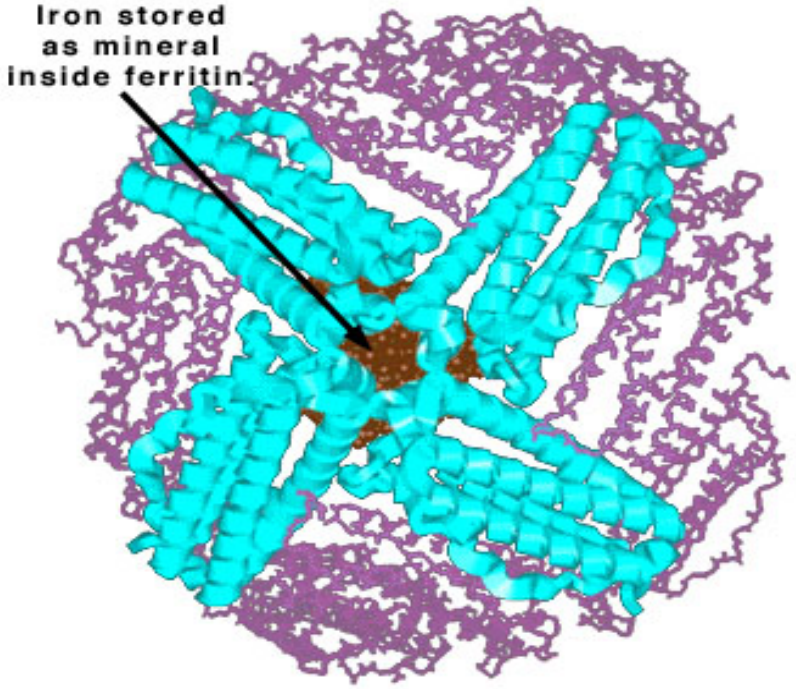
Hemodialysis patients lose 7-15 ml (3-10 mg iron) of blood per day due to blood trapped in dialysis machine, sampling for lab tests, bleeding etc.

Complex **properties**

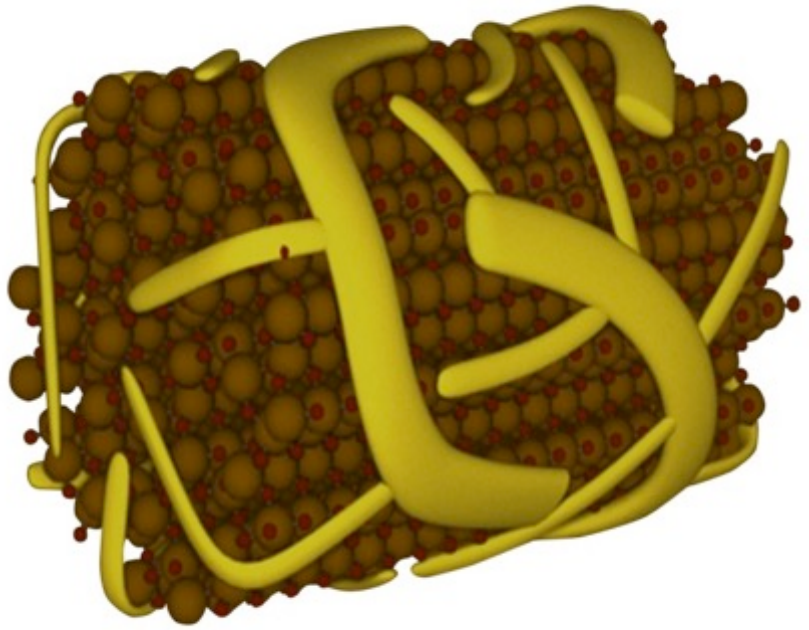
Sodium fe accharide
in sucrose haride

Iron sucros haride
(**Venofer,**

Ferric hydroxide core encased in a carbohydrate shell designed to act like ferritin and prevent rapid release of its iron content



Crystal structure of ferritin
(storage protein with antioxidative properties)



Carbohydrate shell

Fenton reaction:

$H_2O_2 + Fe^{2+} \rightarrow .OH + OH^- + Fe^{3+}$

The hydroxyl radical is the most reactive and cytotoxic free radical known

Haber Weiss reaction:

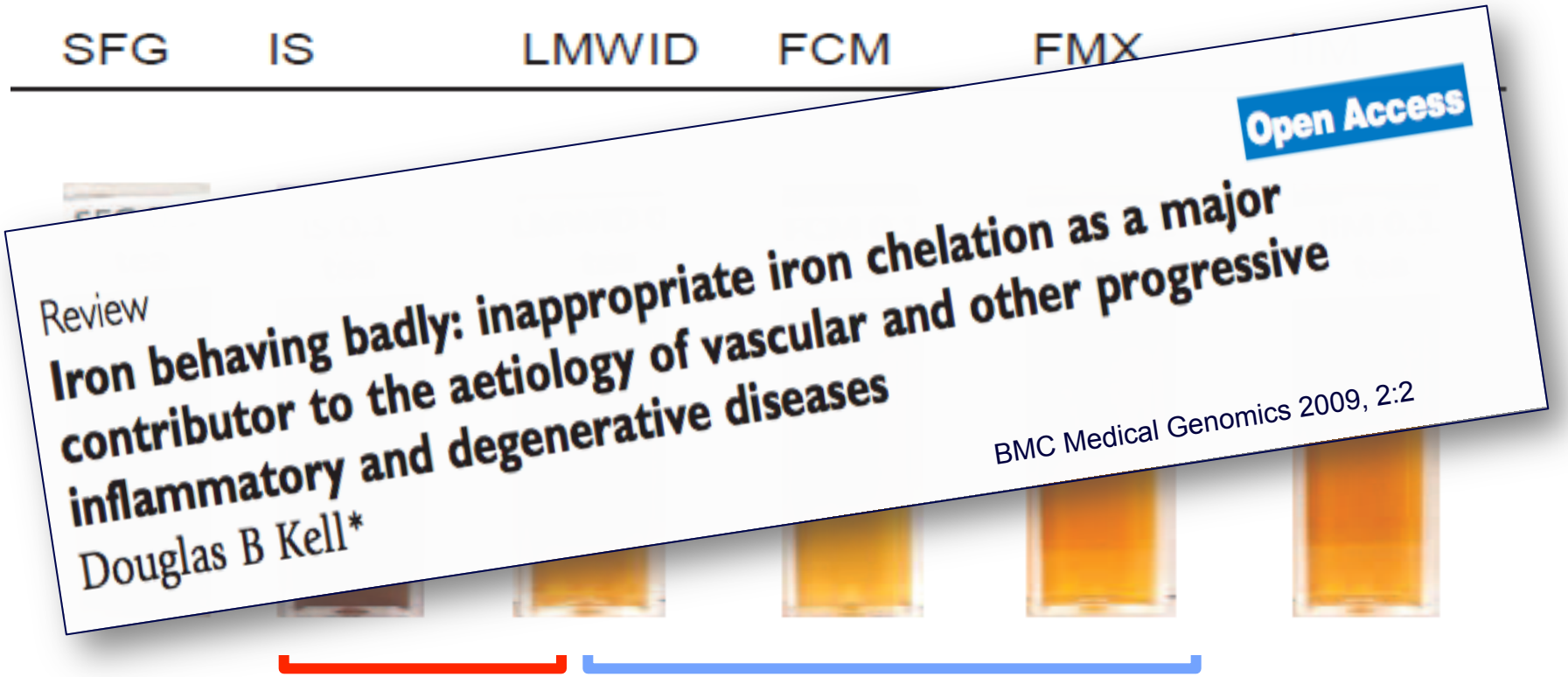
$Fe^{3+} + O_2^{\cdot -} \longrightarrow Fe^{2+} + O_2$

These two reactions supply the fuel for continuous iron-catalyzed hydroxyl radical production and perpetuation of oxidative stress. ***Does this occur in vivo?***

O_2; superoxide; H_2O_2; hydrogen perioxide.

Simple Visual Qualitative Assessment of Amount of Labile Iron in i.v. Iron Preparations

Reaction with tea (polyphenols):



SFG: Sodium ferric gluconate in sucrose; **IS**: Iron sucrose
LMWID: Low molecular weight iron dextran; **FCM**: Ferric carboxymaltose
FMX: Ferumoxytol; **IIM**: Iron isomaltoside 1000

Neiser et al. *Eur. J. Pharm. Biopharm.* (2013), submitted.

Efficacy and Safety of Intravenous Iron Therapy for Functional Iron Deficiency Anemia in Hemodialysis Patients: A Meta-Analysis

2658 participants

Am J Nephrol 2014

Paweena Susantitaphong[a, b, d] Fahad Alqahtani[c] Bertrand L. Jaber[a, b]

Table 3. Summary effect of intravenous iron therapy on anemia parameters and markers of oxidative stress and inflammation in RCT

Outcome variables	Studies, n	Patients, n	Mean net change[a]	p	Assessment of		Assessment of ion bias
						st, p	
Anemia param							
Hemoglobi							
Serum ferri							
Serum iron,							
TIBC, µg/dl						1.00	–
Transferrin,	2	68	−1.55 (−14.85, 11.75)	0.82	0	0.94	–
TSAT, %	4	499	4.02 (0.48, 7.57)	0.026	91	<0.001	0.11
Reticulocyte hemoglobin content, pg	2	359	1.01 (0.47, 1.55)	<0.001	0	0.60	–
Erythropoietin dose, units/week	2	224	−4,850 (−13,113, 3,412)	0.25	79	0.03	–
Markers of oxidative stress							
Plasma TBARS, µmol/l	2	20	0.30 (0.07, 0.53)	0.01	0	1.00	–
Plasma MDA, µmol/l	2	147	0.07 (−0.32, 0.46)	0.74	0	1.00	–
Neutrophil respiratory burst, RLU	2	28	262.96 (−142.97, 668.89)	0.20	0	1.00	–
Markers of inflammation							
β_2-Microglobulin, mg/dl	2	56	4.81 (1.35, 8.27)	0.006	0	1.00	–

Data in parentheses denote 95% confidence limits. RLU = Relative light units.

[a] By random-effects model meta-analysis. [b] An I^2 index ≥75% indicates medium-to-high heterogeneity.

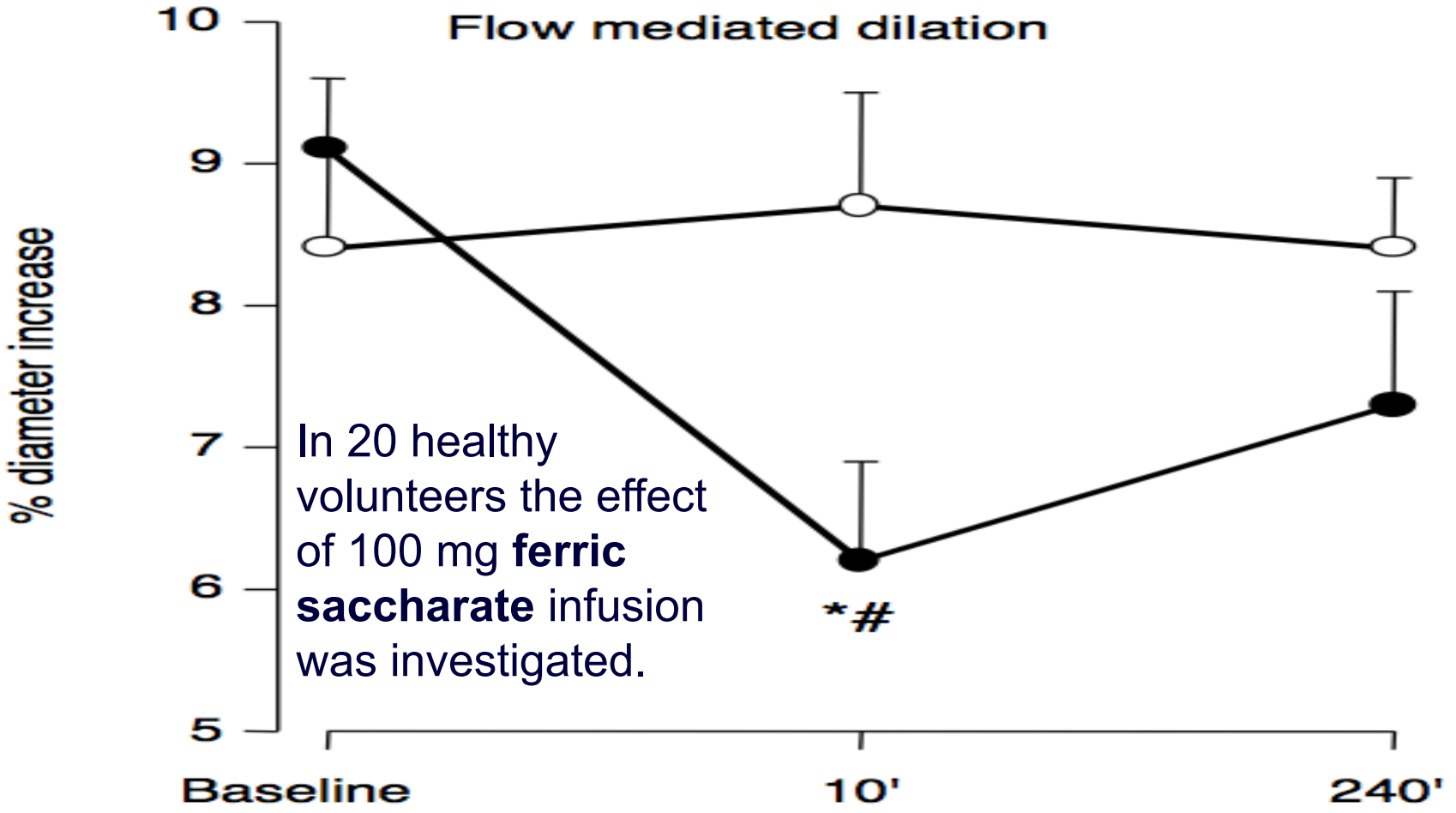
"Intravenous iron exerts some effects on markers of oxidative stress that are of unclear clinical significance"

European Journal of Clinical Investigation (2002) **32** (Suppl. 1), 9–16

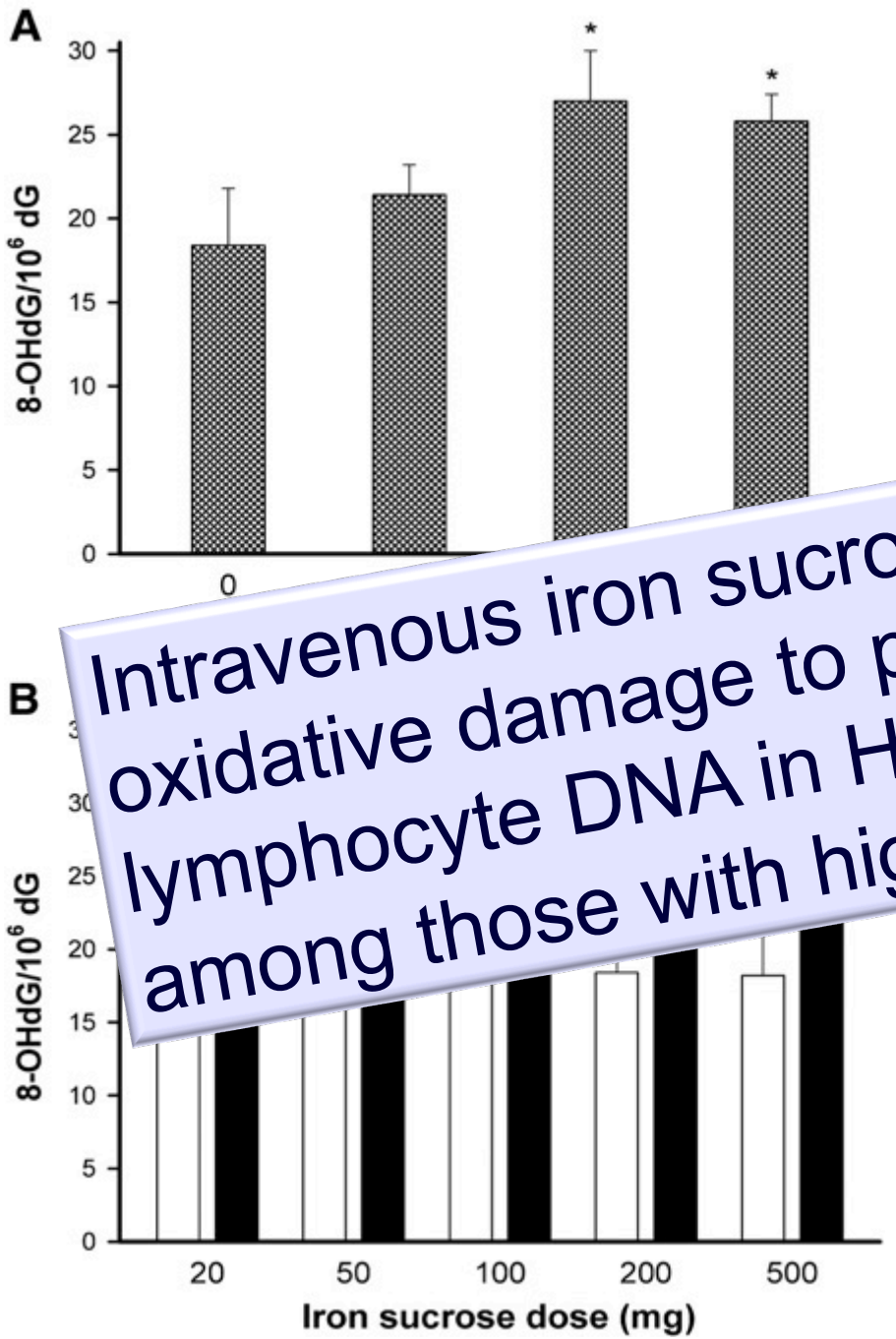
Ferric saccharate induces oxygen radical stress and endothelial dysfunction *in vivo*

T. M. Rooyakkers[*¶], E. S. G. Stroes[*], M. P. Kooistra[†], E. E. van Faassen[‡], R. C. Hider[§], T. J. Rabelink[*] and J. J. M. Marx[¶]

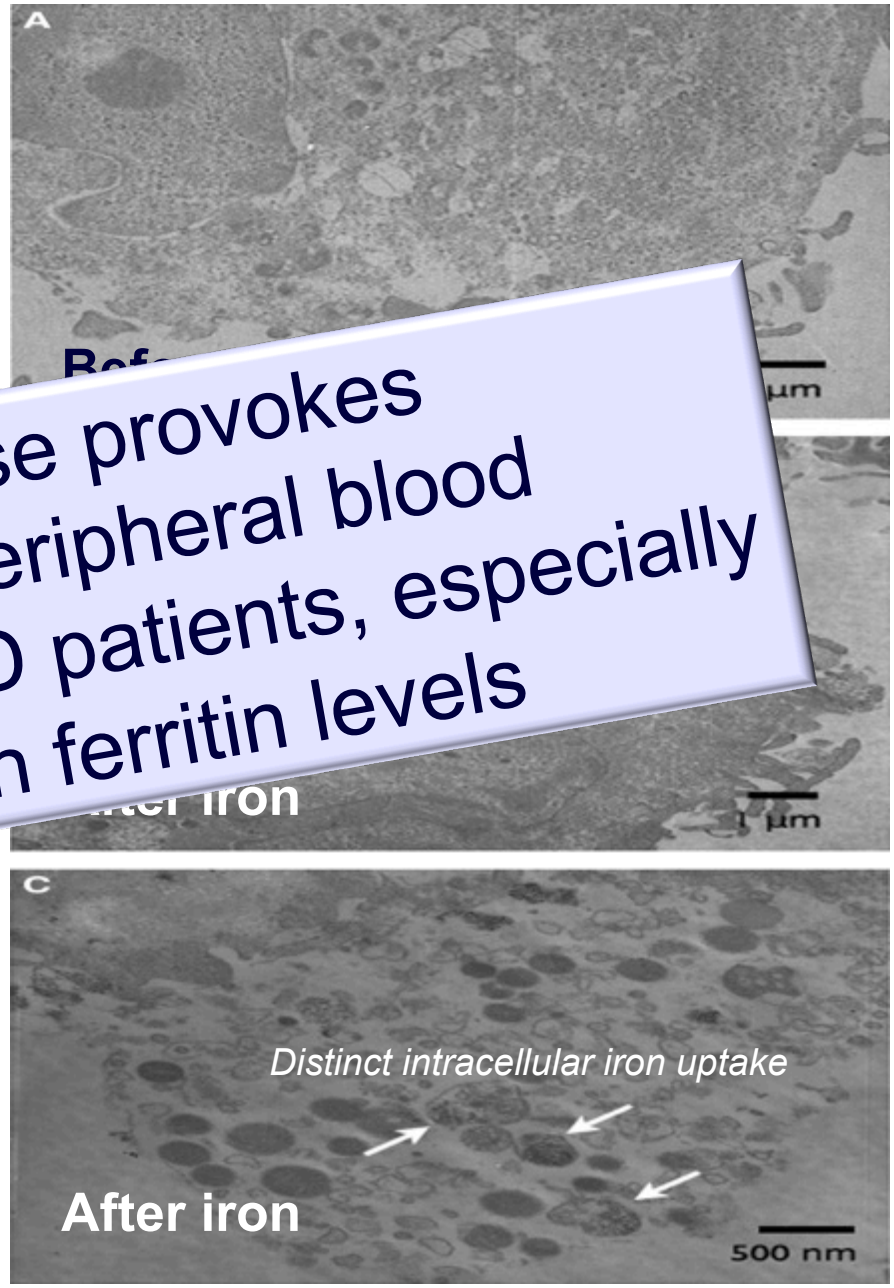
[*]Department of Internal Medicine, University Medical Center, Utrecht, The Netherlands, [†]Dianet, Utrecht, The Netherlands, [‡]Debye Institute, University Utrecht, The Netherlands, [§]Department of Pharmacy, School of Health and Life Science, King's College London, UK, [¶]Eijkman-Winkler Institute, University Medical Centre, Utrecht, The Netherlands



In 20 healthy volunteers the effect of 100 mg **ferric saccharate** infusion was investigated.



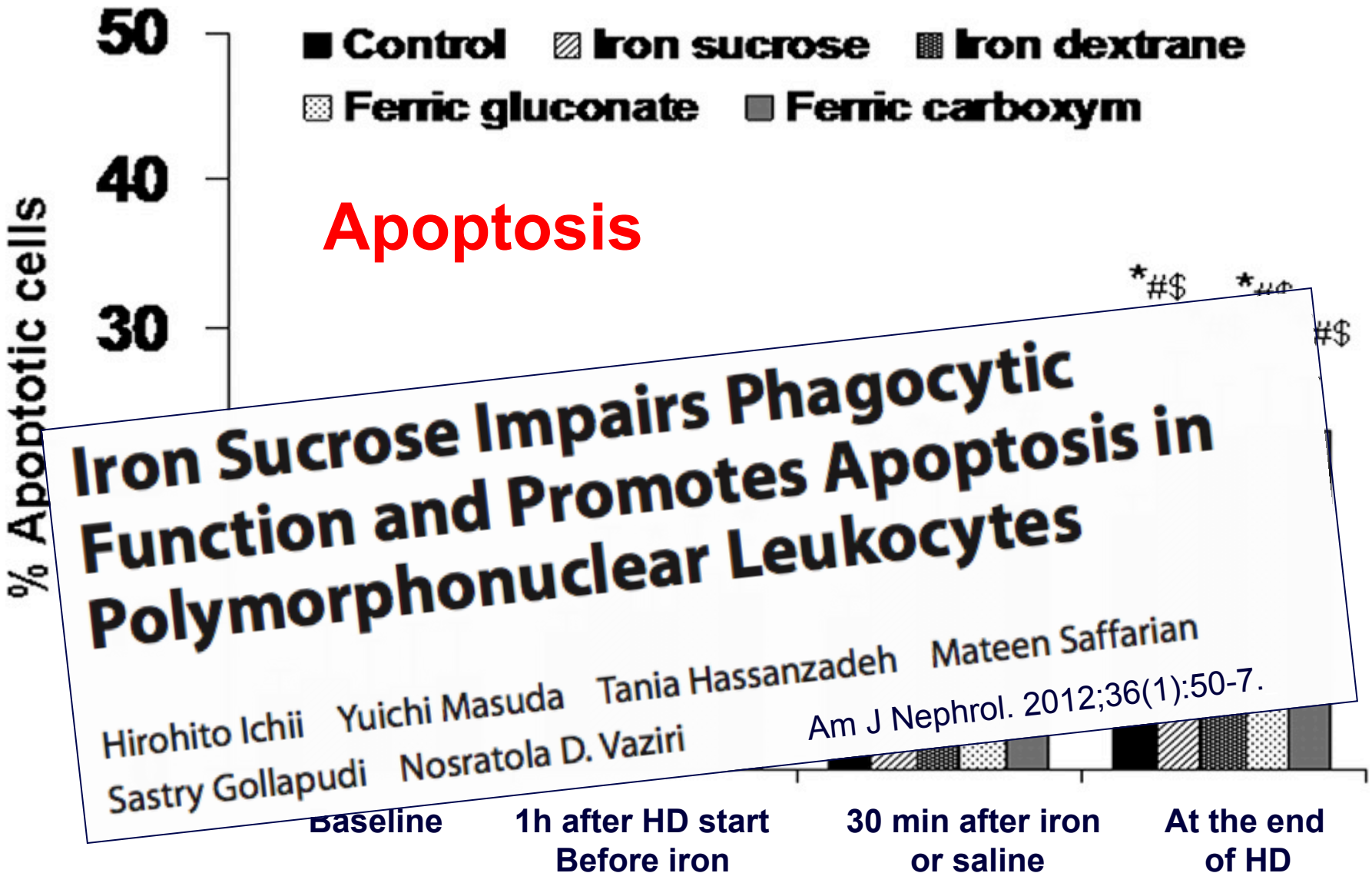
Electron micrographs of human lymphocytes



Intravenous iron sucrose provokes oxidative damage to peripheral blood lymphocyte DNA in HD patients, especially among those with high ferritin levels

Kuo K et al. JASN 2008;19:1817-1826 JASN

Deleterious Effects of i.v. Iron on Mononuclear Cells



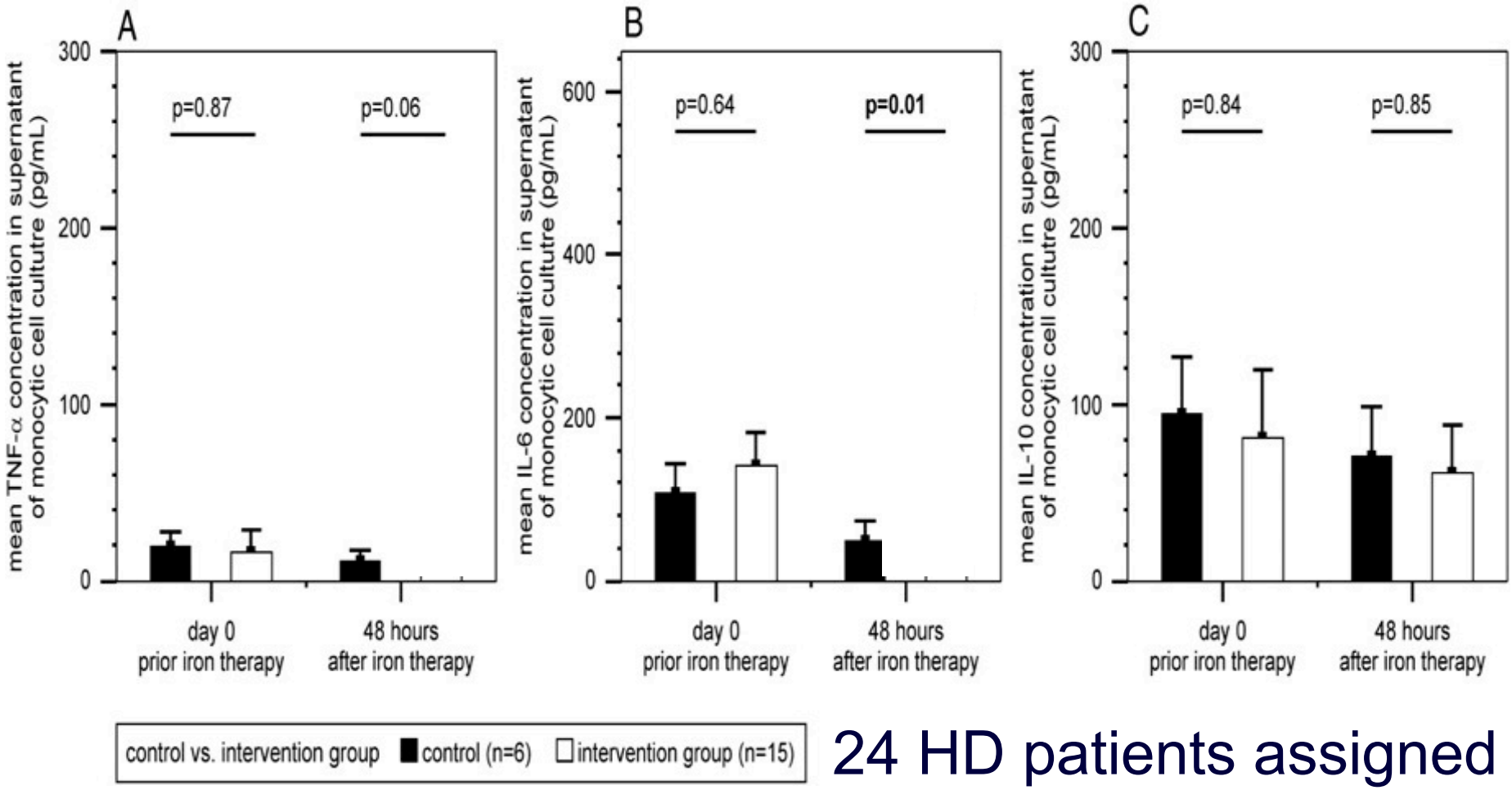
Iron Sucrose Impairs Phagocytic Function and Promotes Apoptosis in Polymorphonuclear Leukocytes

Hirohito Ichii Yuichi Masuda Tania Hassanzadeh Mateen Saffarian
Sastry Gollapudi Nosratola D. Vaziri

Am J Nephrol. 2012;36(1):50-7.

Martin-Malo A et al. Nephrol. Dial. Transplant. 2012;27:2465-2471

Intravenous Iron Treatment Promotes Monocyte Cytokine Formation *ex vivo*

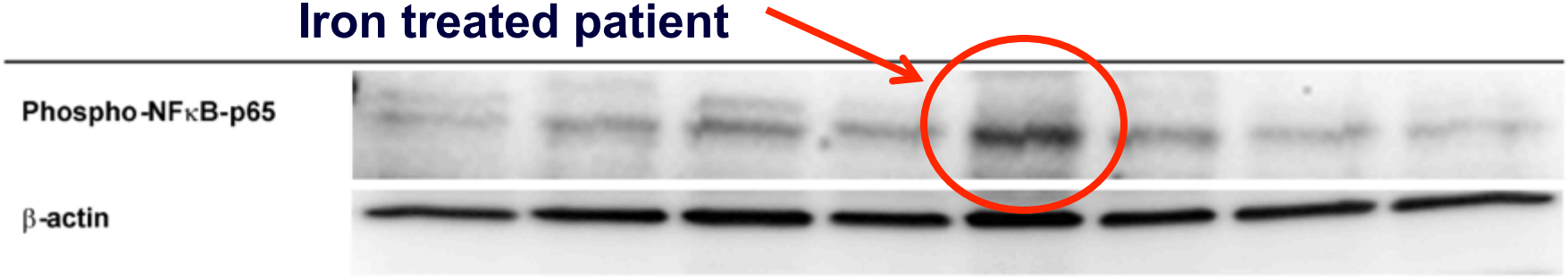


24 HD patients assigned to i.v. **iron surcose** or saline

Sonnweber T et al. Nephrol. Dial. Transplant. 2011;26:977-987

Iron Stimulates NF-κB

Iron treated patient



Iron activates NF-κB in Kupffer cells

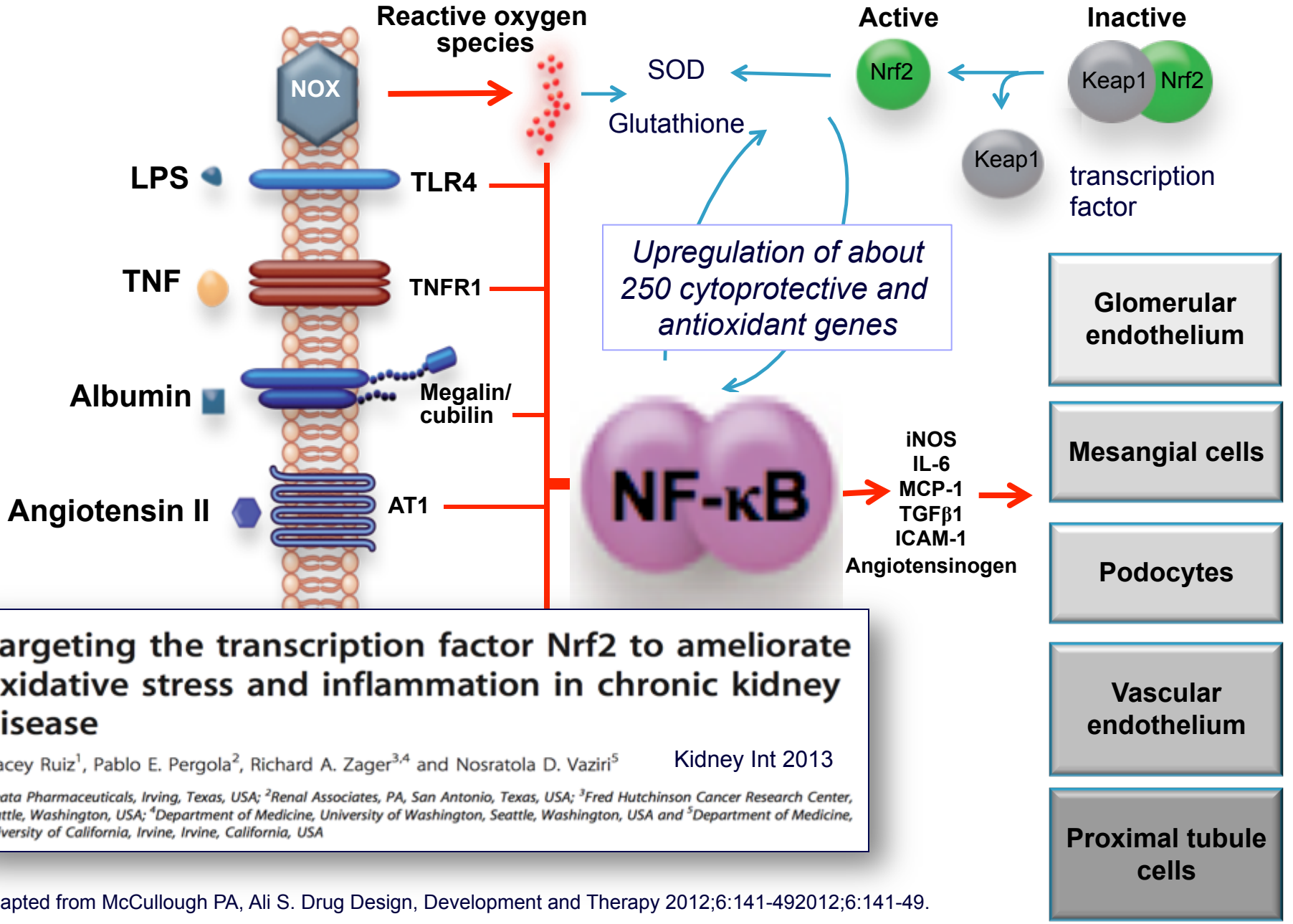
Am J Physiol Gastrointest Liver Physiol 283: G719–G726, 2002

HONGYUN SHE,[1] SHIGANG XIONG,[1] MIN LIN,[1] EBRAHIM ZANDI,[2]
CECILIA GIULIVI,[3] AND HIDEKAZU TSUKAMOTO[1]
[1]*Departments of Pathology and* [2]*Molecular Microbiology and Immunology, Keck School of Medicine of the University of Southern California, Los Angeles, California 90033-9141; and* [3]*Department of Chemistry, University of Minnesota, Duluth, Minnesota 55812*

Intravenously administered iron is taken up by monocytes and activate the NF-κB pathway.

Sonnweber T et al. Nephrol. Dial. Transplant. 2011;26:977-987

Multiple pathways stimulate NF-κB in the uremic milieu



Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease

Stacey Ruiz[1], Pablo E. Pergola[2], Richard A. Zager[3,4] and Nosratola D. Vaziri[5]

Kidney Int 2013

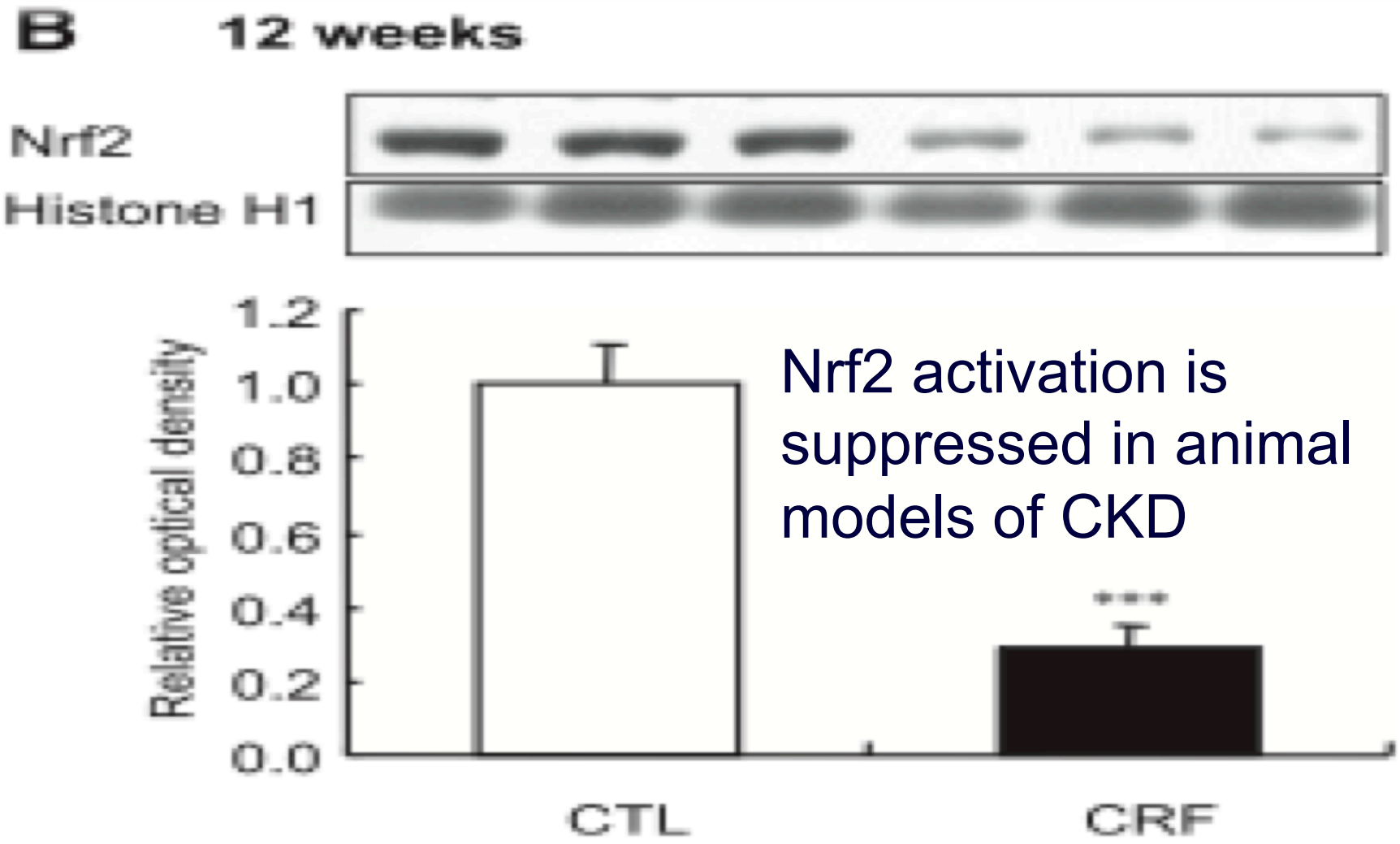
[1]Reata Pharmaceuticals, Irving, Texas, USA; [2]Renal Associates, PA, San Antonio, Texas, USA; [3]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA; [4]Department of Medicine, University of Washington, Seattle, Washington, USA and [5]Department of Medicine, University of California, Irvine, Irvine, California, USA

Adapted from McCullough PA, Ali S. Drug Design, Development and Therapy 2012;6:141-492012;6:141-49.

Contribution of impaired Nrf2-Keap1 pathway to oxidative stress and inflammation in chronic renal failure

Am J Physiol 2010;298:F662-F671

Hyun Ju Kim and Nosratola D. Vaziri
Division of Nephrology and Hypertension, University of California, Irvine, California



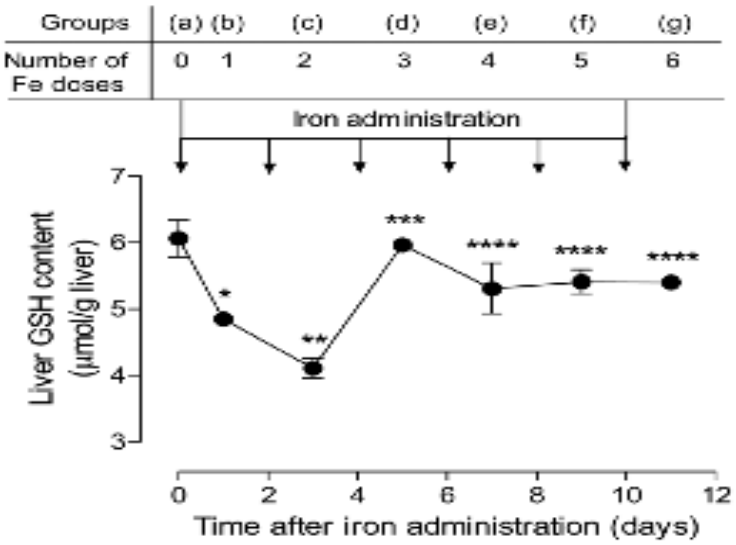
Nrf2 activation is suppressed in animal models of CKD

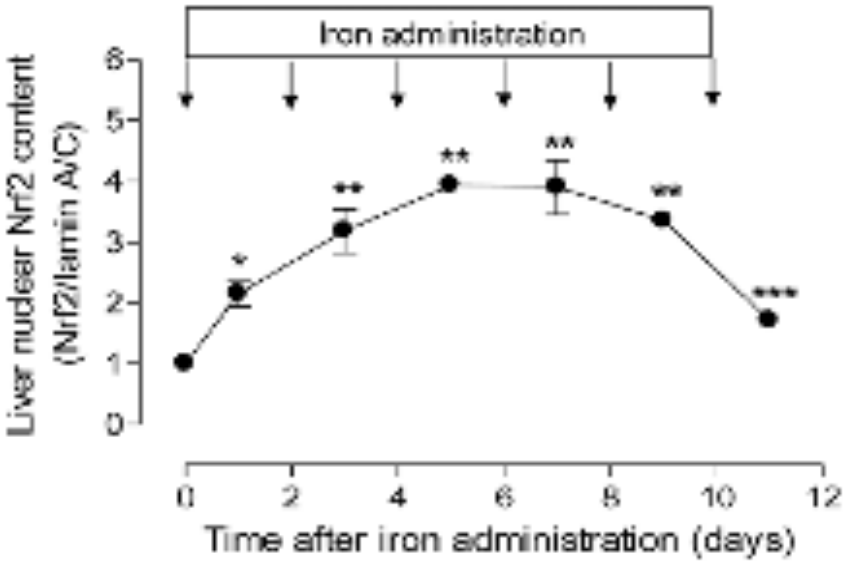
Nrf2 activation in the liver of rats subjected to a preconditioning sub-chronic iron protocol

Paula Morales, Romina Vargas, Luis A. Videla and Virginia Fernández*

Food Funct. 2014, 5, 243

GSH; gluthathione





- Fe administration leads to transient liver oxidative stress development and transient Nrf2 activation.
- **Question:** What happens when iron is injected into the inflamed, pro-oxidative and Nrf2 exhausted uremic milieu?

Does iron-mediated oxidative stress translate into increased risk for atherosclerotic lesions?

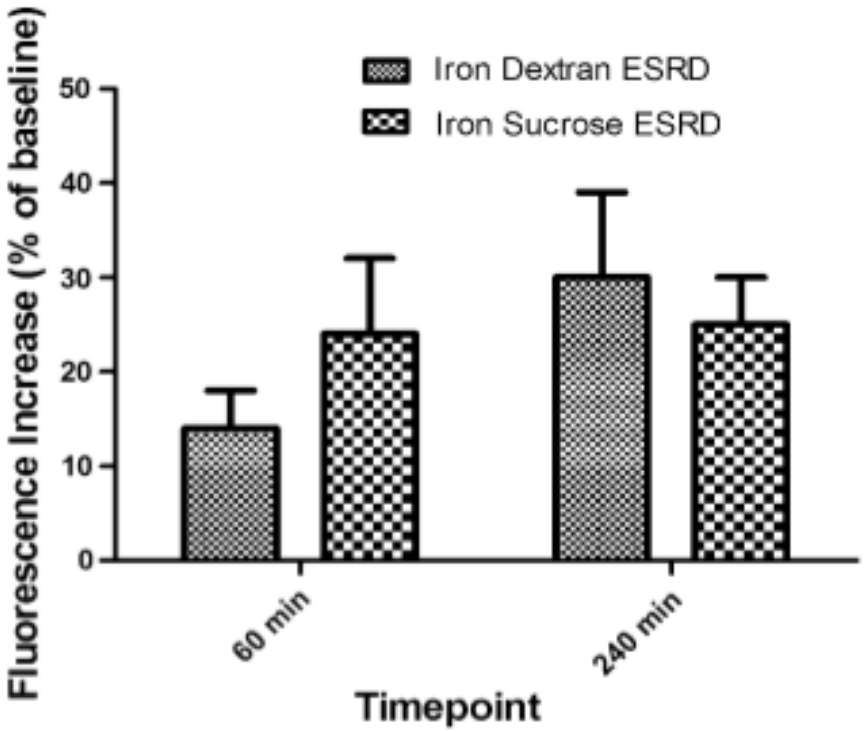


Fig. 3 Intracellular ROS generation after IV Iron in ESRD patients

- **Iron sucrose** administration was associated with higher maximum serum non-transferrin bound iron concentrations compared to **iron dextrane**.
- Both compounds produced similar ROS generation and cytokine activation that was more pronounced among ESRD patients.

Review

Biochim Biophys Acta. 2009 Jul;1790(7):718-23.

Iron in arterial plaque: A modifiable risk factor for atherosclerosis

Jerome L. Sullivan *

Burnett School of Biomedical Sciences, University of Central Florida College of Medicine, Orlando, Florida, USA

- Ferrous iron leads to the generation of the hydroxyl radical, known to damage membrane lipids, oxidize low-density lipoprotein, and promote atherogenesis.

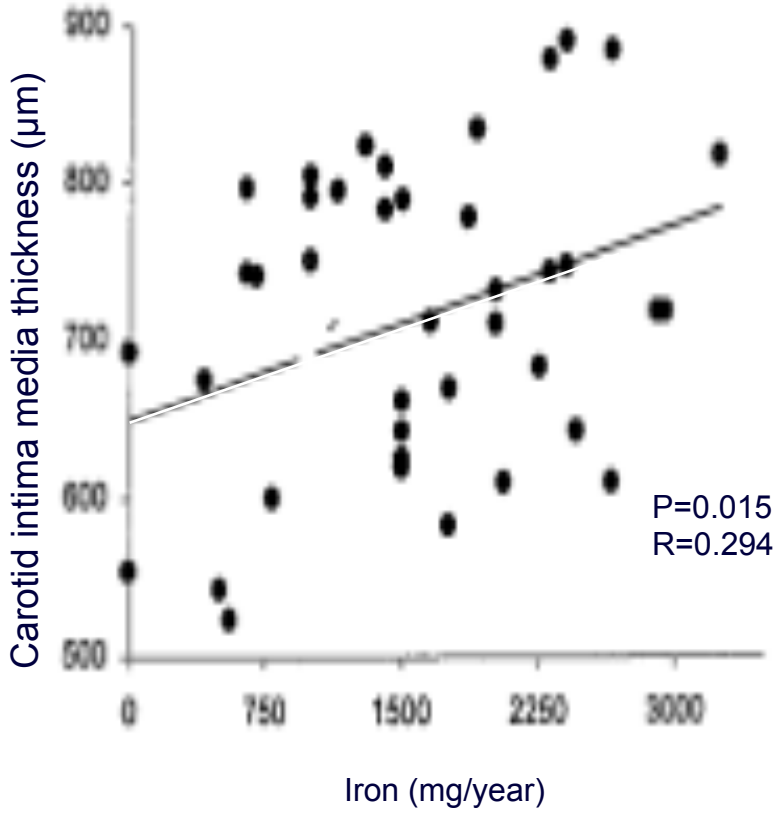
- It is believed that most intravenous iron formulations release bioactive iron, especially if given rapidly enough to over-saturate receptors.

- Under the influence of the increased concentrations of hepcidin, iron is primarily sequestered in macrophages and that iron-laden macrophages within the plaque promote atherosclerosis.

Iron Therapy, Advanced Oxidation Protein Products, and Carotid Artery Intima-Media Thickness in End-Stage Renal Disease

Tilman Drüeke, MD; Véronique Witko-Sarsat, PhD; Ziad Massy, MD; Béatrice Descamps-Latscha, MD, PhD; Alain P. Guerin, MD; Sylvain J. Marchais, MD; Valérie Gausson, MS; Gérard M. London, MD

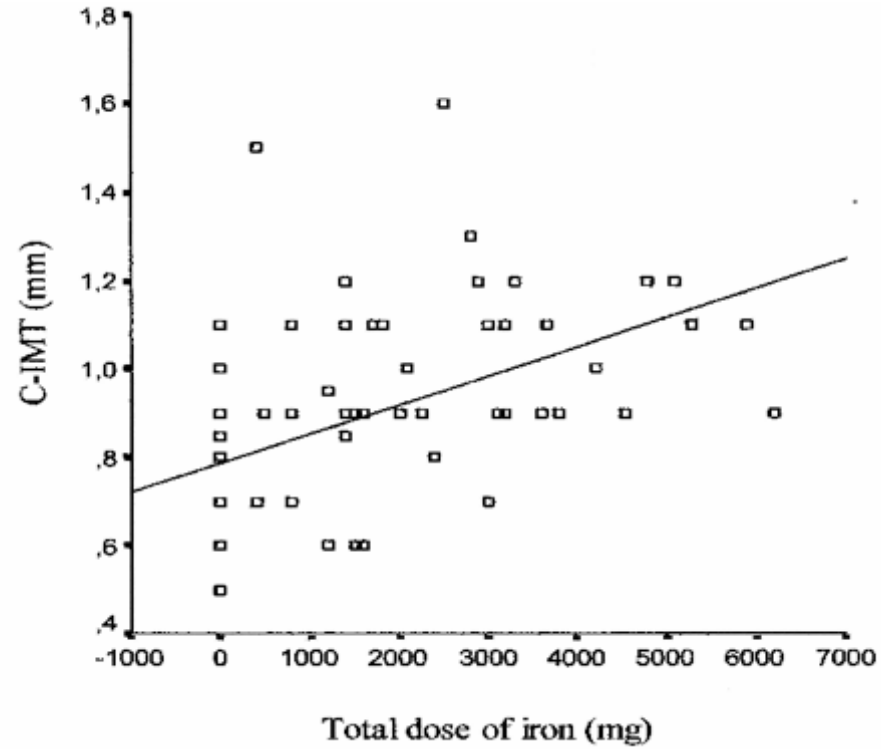
Circulation 2002



Intravenous Iron Therapy as a Possible Risk Factor for Atherosclerosis in End-stage Renal Disease

Kadriye Altok REIS,[1] MD, Galip GUZ,[1] MD, Hakan OZDEMIR,[2] MD, Yasemin ERTEN,[1] MD, Veli ATALAY,[1] MD, Zerrin BICIK,[1] MD, Zubeyde Nur OZKURT,[1] MD, Musa BALI,[1] MD, *and* Sukru SINDEL,[1] MD

Int Heart J 2005



Hypothesis: Atherosclerosis may be increased by the usually recommended doses of intravenous iron.

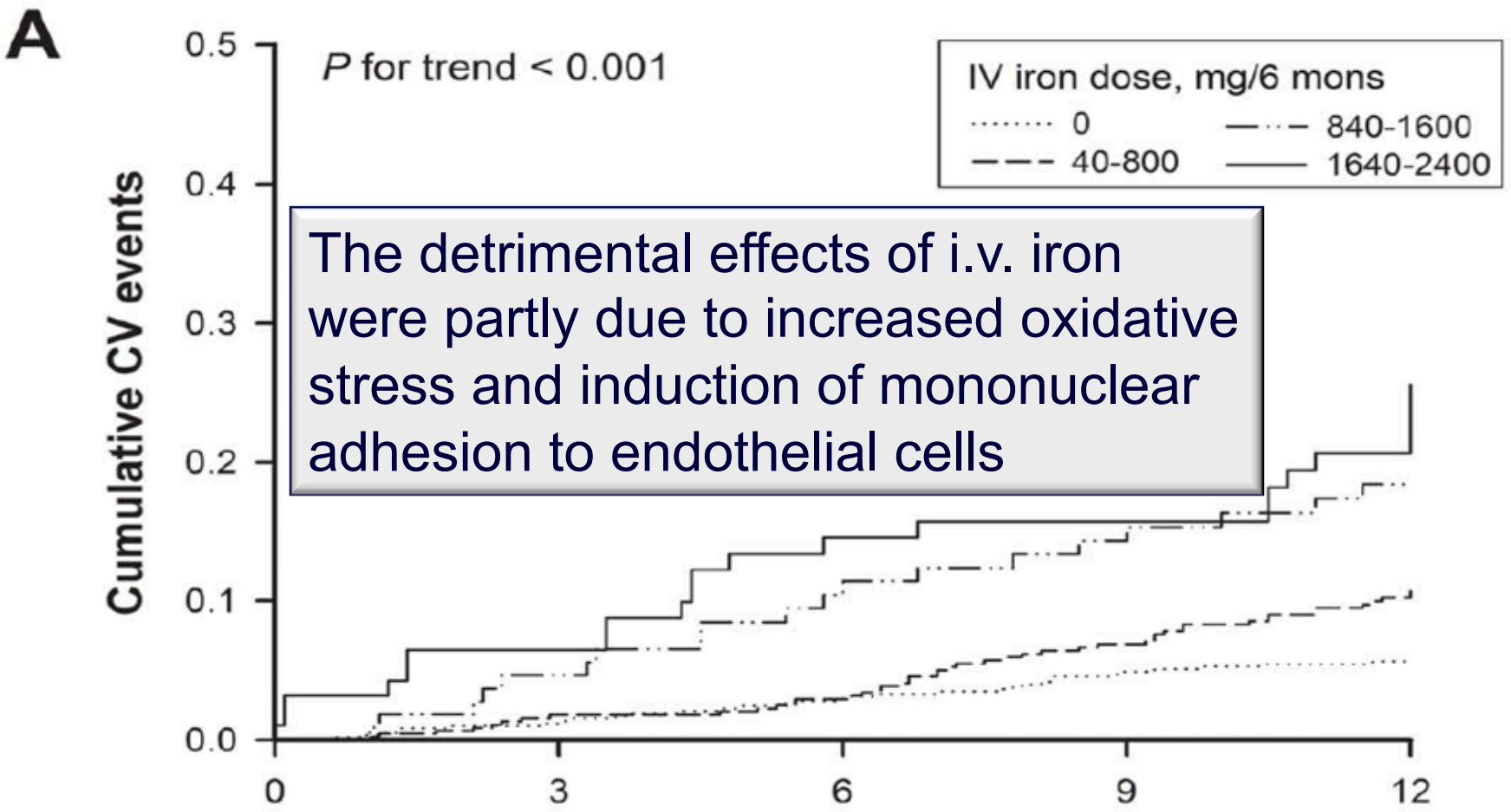
OPEN ACCESS Freely available online

PLOS | ONE

Dec 2012

Intravenous Ferric Chloride Hexahydrate Supplementation Induced Endothelial Dysfunction and Increased Cardiovascular Risk among Hemodialysis Patients

Ko-Lin Kuo[1,4,5], Szu-Chun Hung[4,5], Yao-Ping Lin[7], Ching-Fang Tang[7], Tzong-Shyuan Lee[1], Chih-Pei Lin[3,6]*, Der-Cherng Tarng[1,2,7]*



The detrimental effects of i.v. iron were partly due to increased oxidative stress and induction of mononuclear adhesion to endothelial cells

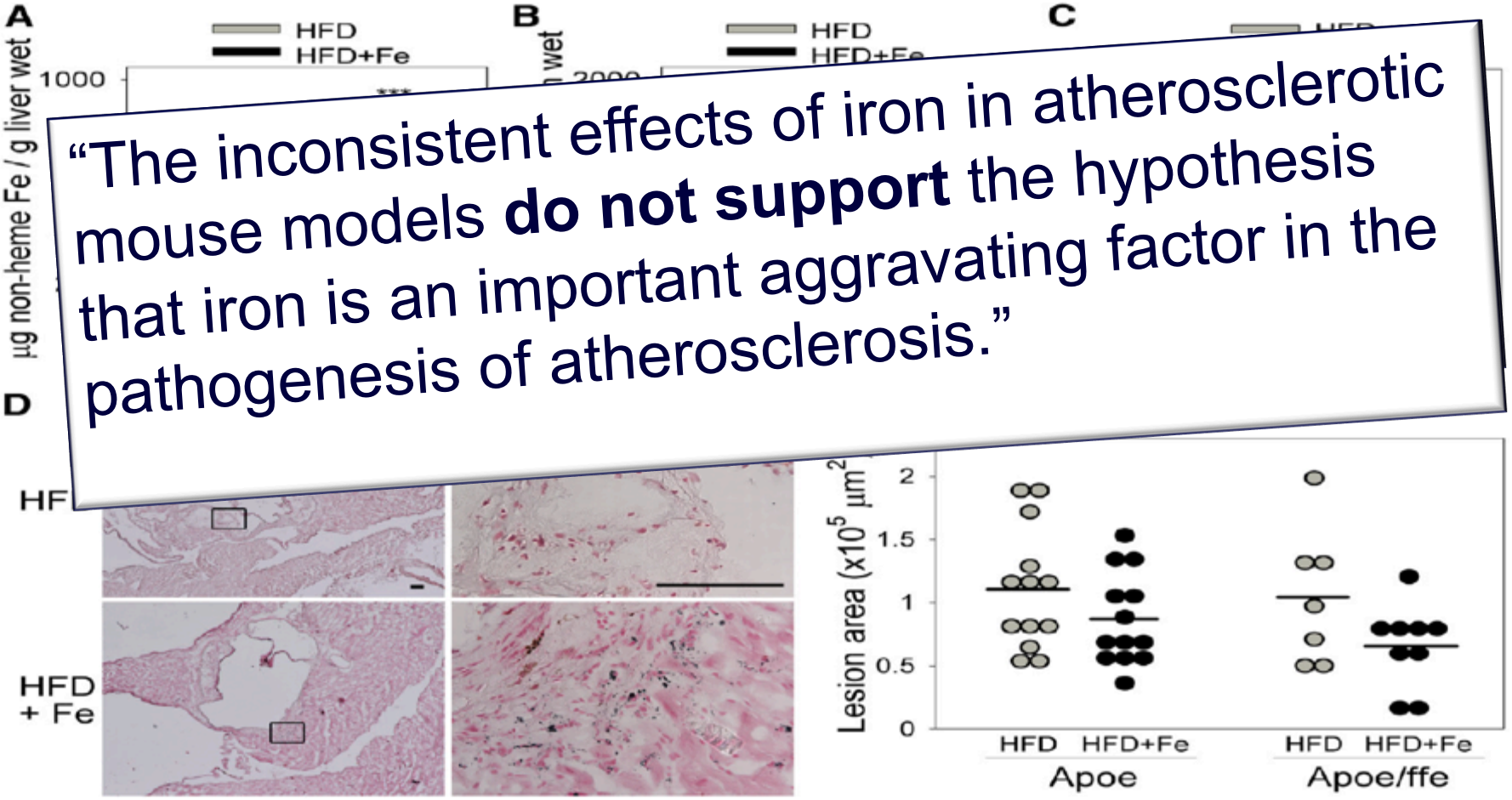
Testing the Iron Hypothesis in a Mouse Model of Atherosclerosis

Cell Reports Dec 2013

Léon Kautz,[1] Victoria Gabayan,[1] Xuping Wang,[1] Judy Wu,[1] James Onwuzurike,[1] Grace Jung,[1] Bo Qiao,[1] Aldons J. Lusis,[1,2,3] Tomas Ganz,[1,4] and Elizabeta Nemeth[1,*]

HFD; high fat diet

"The inconsistent effects of iron in atherosclerotic mouse models **do not support** the hypothesis that iron is an important aggravating factor in the pathogenesis of atherosclerosis."



The flatiron (ffe) mouse accumulates iron in macrophages without other confounding abnormalities

Intravenous Iron Supplementation Practices and Short-Term Risk of Cardiovascular Events in Hemodialysis Patients

Abhijit V. Kshirsagar[1*], Janet K. Freburger[2], Alan R. Ellis[2], Lily Wang[2], Wolfgang C. Winkelmayer[3], M. Alan Brookhart[2,4]

PLoS One. 2013 Nov 1;8(11):e78930

- A **retrospective cohort** was created from the clinical database of a large dialysis provider merged with data from the USRDS.
- 117,050 patients contributed 776,203 unique iron exposure periods.
- There were **no consistent associations** of either high or bolus dose vs. low or maintenance respectively among pre-specified subgroups.

Strategies favoring large doses of intravenous iron were not associated with increased short-term cardiovascular morbidity and mortality. Investigation of the long-term safety of the various intravenous iron supplementation strategies may still be warranted.

Emerging Links Between Iron and Vascular Calcification and Bone Mineral Metabolism

Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial

TRANSFUSION Volume 49, December 2009

David B. Van Wyck, Antoinette Mangione, John Morrison, Phillip Earl Hadley, Judi A. Jehle, and Lawrence Tim Goodnough for the Ferric Carboxymaltose Study Group

The most common adverse event associated with **ferric carboxymaltose** was asymptomatic hypo-phosphatemia.

TABLE 3. Serum phosphate, calcium, and potassium at baseline, at the lowest value observed (nadir), and at the final study examination in patients after treatment with IV ferric carboxymaltose or oral ferrous sulfate*

		Change from baseline			
Variable	Baseline mean	To nadir	p Value†	To final value	p Value†
Phosphate (mg/dL)					
IV ferric carboxymaltose	3.7 ± 0.5	−1.9 ± 0.6	<0.001	−1.0 ± 0.9	<0.001
Oral ferrous sulfate	3.7 ± 0.5	−0.3 ± 0.5	<0.001	0.1 ± 0.6	0.097
p Value‡	0.795	<0.001		<0.001	
Calcium (mEq/L)					
IV ferric carboxymaltose	9.2 ± 0.4	−0.5 ± 0.4	<0.001	0.0 ± 0.4	0.169
Oral ferrous sulfate	9.2 ± 0.4	−0.2 ± 0.3	<0.001	0.1 ± 0.4	<0.001
p Value‡	0.448	<0.001		<0.001	
Potassium (mg/dL)					
IV ferric carboxymaltose	4.2 ± 0.4	−0.4 ± 0.3	<0.001	−0.2 ± 0.4	<0.001
Oral ferrous sulfate	4.2 ± 0.3	−0.3 ± 0.3	<0.001	−0.1 ± 0.4†	0.013
p Value‡	0.949	0.008		0.012	

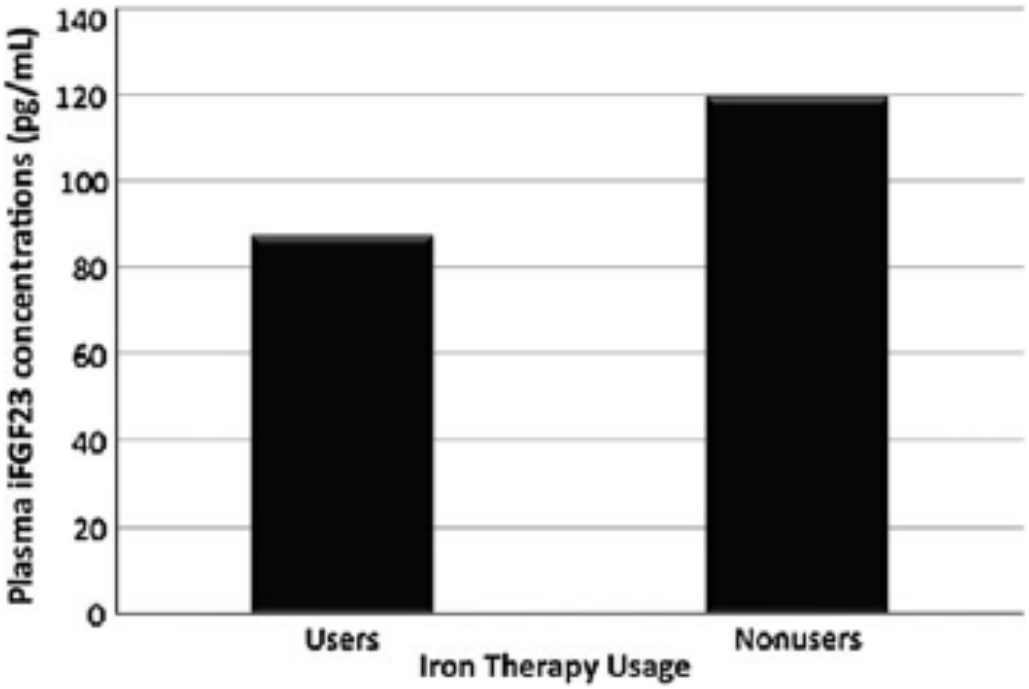
* Results are given as mean ± SD for the safety population.
† Within-group comparison.
‡ Between-group comparison.

Proc Natl Acad Sci U S A. 2011;108:E1146-55.

Iron deficiency drives an autosomal dominant hypophosphatemic rickets (ADHR) phenotype in fibroblast growth factor-23 (Fgf23) knock-in mice

Emily G. Farrow[a], Xijie Yu[b], Lelia J. Summers[a], Siobhan I. Davis[a], James C. Fleet[c], Matthew R. Allen[d], Alexander G. Robling[d], Keith R. Stayrook[a], Victoria Jideonwo[a], Martin J. Magers[a], Holly J. Garringer[e], Ruben Vidal[e], Rebecca J. Chan[f], Charles B. Goodwin[f], Siu L. Hui[g], Munro Peacock[g], and Kenneth E. White[a,1]

Iron deficiency stimulates FGF23 transcription in osteocytes



- A negative relationship between iron administration and serum iFGF23 level in a dialysis population.
- If high levels of FGF23 are harmful, iron therapy may have a beneficial effect on bone metabolism by reducing FGF23 levels in a dialysis population.

Clin Exp Nephrol (2013) 17:416–423

Effect of ferric carboxymaltose on serum phosphate and C-terminal FGF23 levels in non-dialysis chronic kidney disease patients: post-hoc analysis of a prospective study

Merche Prats[1,3*], Ramon Font[1], Carmen García[1], G...

BMC Ne...

- **Ferric carboxymaltose** induces reduction in serum phosphate levels that persists for three months.
- **Ferric carboxymaltose** causes a significant decrease in C-terminal FGF23 levels

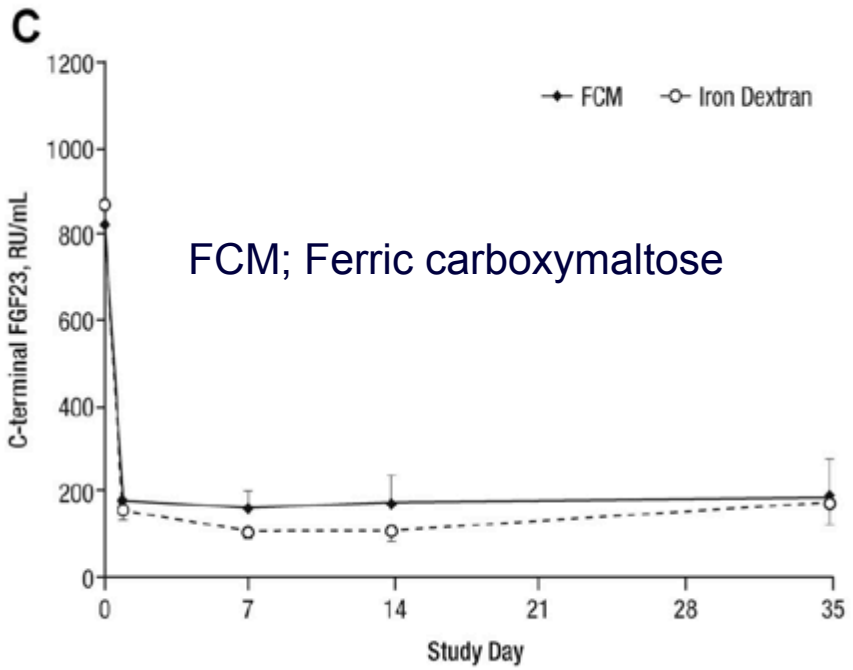
				<0.0001
		28.9(10)	25.6(12.7)	<0.0001
	67.8(61.7)	502.5(263.3)	230(144.6)	<0.0001
Calcium, mg/dl	9.3(0.4)	9.3(0.5)	9.3(0.5)	ns
Phosphate, mg/dL	4.2(0.8)	3.6(1.1)	3.8(0.6)	<0.0001
PTH, pg/ml	138.1(2.5-600)	124(2.5-736)	106.5(2.5-613)	ns
1,25(OH)$_2$ D, pg/mL	9.7(4.4)	10(3.7)	10.4(5.4)	ns
FGF23, RU/mL	442(44.9-4079.2)	340(68.5-2603.3)	191.6(51.3-2465.9)	<0.0001

TAST: transferrin saturation.

Effects of Iron Deficiency Anemia and Its Treatment on Fibroblast Growth Factor 23 and Phosphate Homeostasis in Women

Journal of Bone and Mineral Research, Vol. 28, No. 8, August 2013,

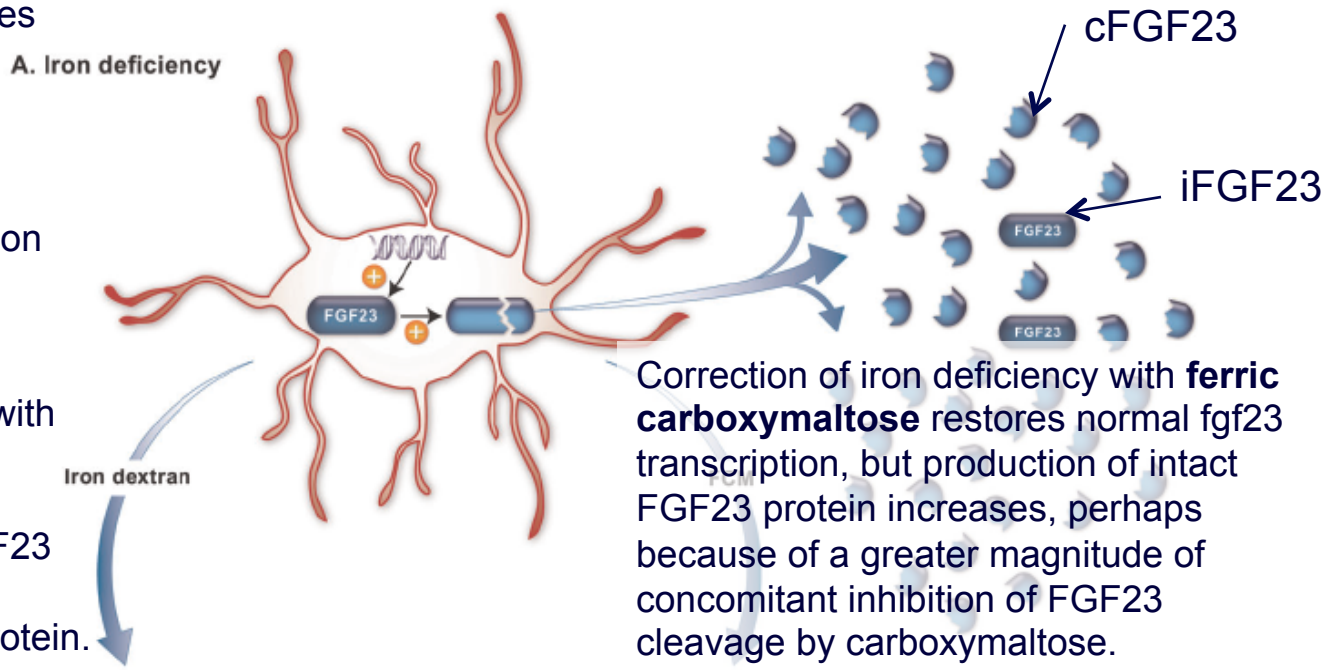
Myles Wolf,[1] Todd A Koch,[2] and David B Bregman[2,3]



FCM; Ferric carboxymaltose

- Iron deficiency associated with normal intact FGF23 but markedly higher c-terminal FGF23.
- I.v. iron lowers c-terminal FGF23 in humans by reducing fgf23 transcription.

fgf23 transcription in osteocytes is up-regulated by **iron deficiency**, but a counter-balancing increase in post-translational FGF23 cleavage maintains normal net production of intact protein.



Correction of iron deficiency with **iron dextran** restores normal fgf23 transcription, thereby decreasing production of FGF23 fragments while maintaining normal production of intact protein.

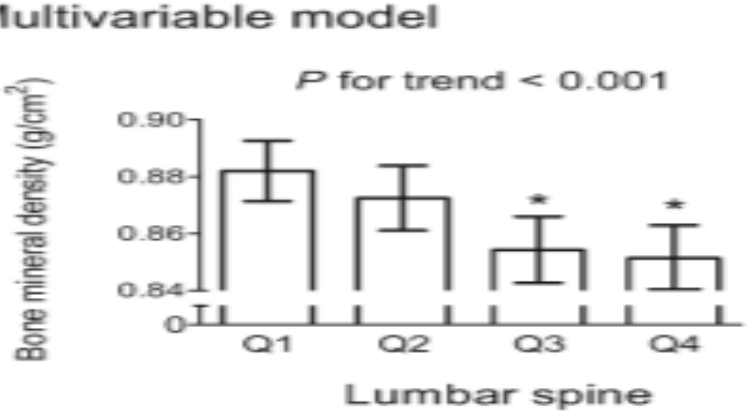
Correction of iron deficiency with **ferric carboxymaltose** restores normal fgf23 transcription, but production of intact FGF23 protein increases, perhaps because of a greater magnitude of concomitant inhibition of FGF23 cleavage by carboxymaltose.

Conclusion: We need to learn more about the interactions between iron deficiency and effects of different iron solutions on mineral metabolism and vascular calcification

Journal of Bone and Mineral Research, Vol. 28, No. 8, August 2013, pp 1793–1803

The association between higher serum ferritin level and lower bone mineral density is prominent in women ≥45 years of age (KNHANES 2008–2010)

Osteoporos Int. 2013 Oct;24



Ferritin Ferroxidase Activity: A Potent Inhibitor of Osteogenesis

Abolfazl Zarjou,[1] Viktória Jeney,[1] Paolo Arosio,[2] Maura Poli,[2] Erzsébet Zavaczki,[1] György Balla,[3] and József Balla[1]

Journal of Bone and Mineral Research, Vol. 25, 2010, pp 164–172

Iron overload in
mice results in
increased bone
oxidative stress,
leading to bone
loss.

J Nephrol. 2014 Feb 6. [Epub ahead of print]

Suppressive effects of iron overloading on vascular calcification in uremic rats.

Seto T[1], Hamada C, Tomino Y.

Iron dextran reduced Runx2 and the phosphate transporter Pit-1

Ferritin Prevents Calcification and Osteoblastic Differentiation of Vascular Smooth Muscle Cells

Induction of heme oxygenase/ferritin system prevented phosphate mediated calcification

Abolfazl Zarjou,* Viktória Jeney,* Paolo Arosio,† Maura Poli,† Péter Antal-Szalmás,‡ Anupam Agarwal,§ György Balla,‖ and József Balla*

J Am Soc Nephrol. 2009 Jun;20(6):1254-63.

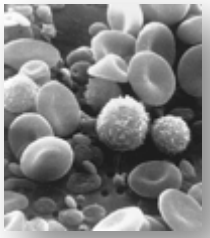
On the other hand…

Serum ferritin levels are associated with vascular damage in patients with nonalcoholic fatty liver disease☆

Iron compartmentalization into macrophages

L. Valenti [a], D.W. Swinkels [b], L. Burdick [a], P. Dongiovanni [a], H. Tjalsma [b], B.M. Motta [a], C. Bertelli [a], E. Fatta [a], D. Bignamini [a], R. Rametta [a], S. Fargion [a,*], A.L. Fracanzani [a]

Nutr Metab Cardiovasc Dis. 2011 Aug;21(8):568-75.



Inflammation
(IL-6)

Hepcidin inhibits iron efflux from ferroportin-expressing cells, such as duodenal enterocytes, reticuloendothelial macrophages and hepatocytes

Spleen

STAT3 +

Hepcidin

FPN

Liver

FPN

Hepcidin

Plasma iron

Hepcidin

Red blood cells

Hypoxia
HIF-2

EPO

Bone marrow

Hypoxia
HIF-2

Increased hepcidin may increase iron deposition in macrophages which enhance oxidative stress in atherosclerotic plaques

Stenvinkel and Barany. Contrib Nephrol. 2012;178:35-9.

Is Increased Hepcidin Pro-atherogenic?

Serum Hepcidin Is Associated With Presence of Plaque in Postmenopausal Women of a General Population

Tessel E. Galesloot, Suzanne Holewijn, Lambertus A.L.M. Kiemeney, Jacqueline de Graaf, Sita H. Vermeulen,* Dorine W. Swinkels*

Arterioscler Thromb Vasc Biol 2014

Arterioscler Thromb Vasc Biol. 2011

Serum Hepcidin and Macrophage Iron Correlate With MCP-1 Release and Vascular Damage in Patients With Metabolic Syndrome Alterations

Luca Valenti, Paola Dongiovanni, Benedetta Maria Motta, Dorine W. Swinkels, Paola Bonara, Raffaela Rametta, Larry Burdick, Cecelia Frugoni, Anna Ludovica Fracanzani, Silvia Fargion

Pharmacological Suppression of Hepcidin Increases Macrophage Cholesterol Efflux and Reduces Foam Cell Formation and Atherosclerosis

Arterioscler Thromb Vasc Biol 2012

Omar Saeed, Fumiyuki Otsuka, Rohini Polavarapu, Vinit Karmali, Daiana Weiss, Talina Davis, Brad Rostad, Kimberly Pachura, Lila Adams, John Elliott, W. Robert Taylor, Jagat Narula, Frank Kolodgie, Renu Virmani, Charles C. Hong, Aloke V. Finn

Hepcidin-25 is related to cardiovascular events in chronic haemodialysis patients

Nephrol Dial Transplant. 2013 Dec;28(12):3062-71

405 pts in CONTRAST study

Neelke C. van der Weerd[1,2],
Muriel P.C. Grooteman[1,3],
Michiel L. Bots[4],

[1]Department of Nephrology, VU Medical Centre, Amsterdam, The Netherlands,
[2]Department of Nephrology, University Medical Centre Utrecht, Utrecht, The Netherlands,

Table 3. Relationship between hepcidin-25 and cardiovascular events

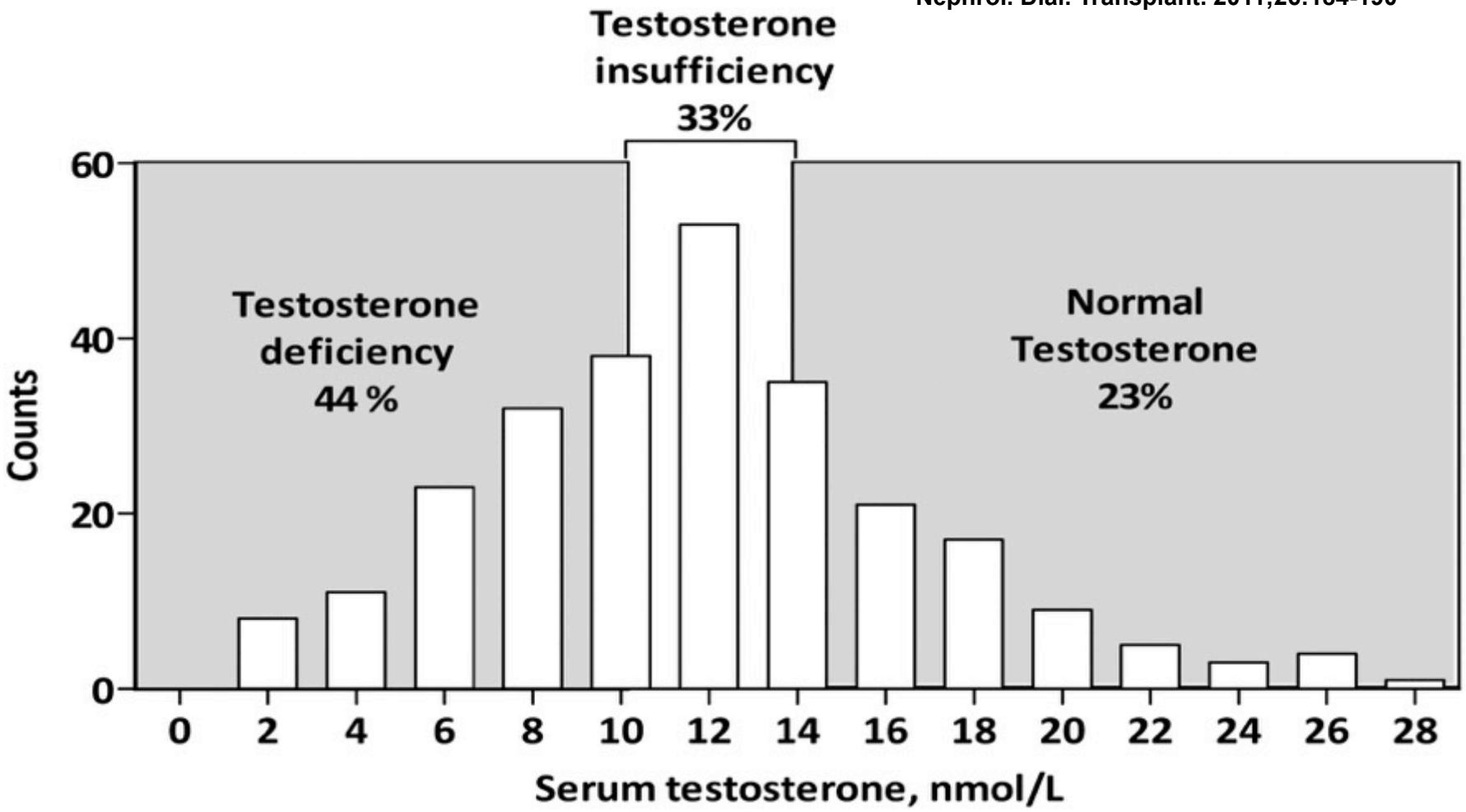
	Hazard ratio[a]	95% CI	P-value
Model 1: crude analysis	1.11	0.99–1.24	0.053
Model 2: adjustment for demographic and clinical parameters related to all-cause mortality[b]	1.16	1.04–1.29	0.011
Model 3: additional adjustment for demographic and clinical parameters related to hepcidin-25[c]	1.15	1.02–1.29	0.026
Model 4a: additional adjustment for biochemical parameters[d]	1.24	1.09–1.42	0.002
Model 4b: additional adjustment for ferritin	1.32	1.13–1.54	<0.001
Model 4c: additional adjustment for hsCRP	1.24	1.05–1.46	0.013

- Hepcidin-25 was associated with fatal and non-fatal CV events
- Inflammation appears to be a significant confounder in the relation between hepcidin and mortality

Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease

Juan Jesús Carrero[1,2,3,*], Abdul Rashid Qureshi[1,*], Ayumu Nakashima[1], Stefan Arver[4], Paolo Parini[5], Bengt Lindholm[1], Peter Bárány[1], Olof Heimbürger[1] and Peter Stenvinkel[1]

Nephrol. Dial. Transplant. 2011;26:184-190



Testosterone deficiency is a cause of anaemia and reduced responsiveness to erythropoiesis-stimulating agents in men with chronic kidney disease

Nephrol Dial Transpl 2012

Juan Jesús Carrero[1,2,3,4], Peter Bárány[1], Mahmut Ilker Yilmaz[5], Abdul Rashid Qureshi[2], Alper Sonmez[6], Olof Heimbürger[1], Tanez Ozgurtas[7], Mujdat Yenicesu[5], Bengt Lindholm[2] and Peter Stenvinkel[1]

Model	Prediction of ESA dose (U/kg/week)	β (SE)	P-value
1	Total testosterone (in nmol/L)	−0.28 (2.3)	0.007
2	1 + Age (in years) and SHBG (in nmol/L)	−0.28 (2.5)	0.004
3	2 + Davies comorbidity score	−0.27 (2.4)	0.006
4	3 + CRP (in mg/L) and albumin (in g/L)	−0.26 (2.6)	0.02

Probability to poor ESA responsiveness (ESA wk/Kg<121) in ESA treated hemodialysis men.

	Odds Ratio	95% CI	P value
Testosterone deficiency <10 nmol/L	2.68	1.17-6.14	0.001

Adjusted for age, SHBG, co-morbidities, albumin, CRP

ORIGINAL ARTICLE

Endocrine Research

Testosterone Suppresses Hepcidin in Men: A Potential Mechanism for Testosterone-Induced Erythrocytosis

Eric Bachman, Rui Feng,* Thomas Travison,* Michelle Li, Gordana Olbina, Vaughn Ostland, Jagadish Ulloor, Anqi Zhang, Shehzad Basaria, Tomas Ganz, Mark Westerman, and Shalender Bhasin

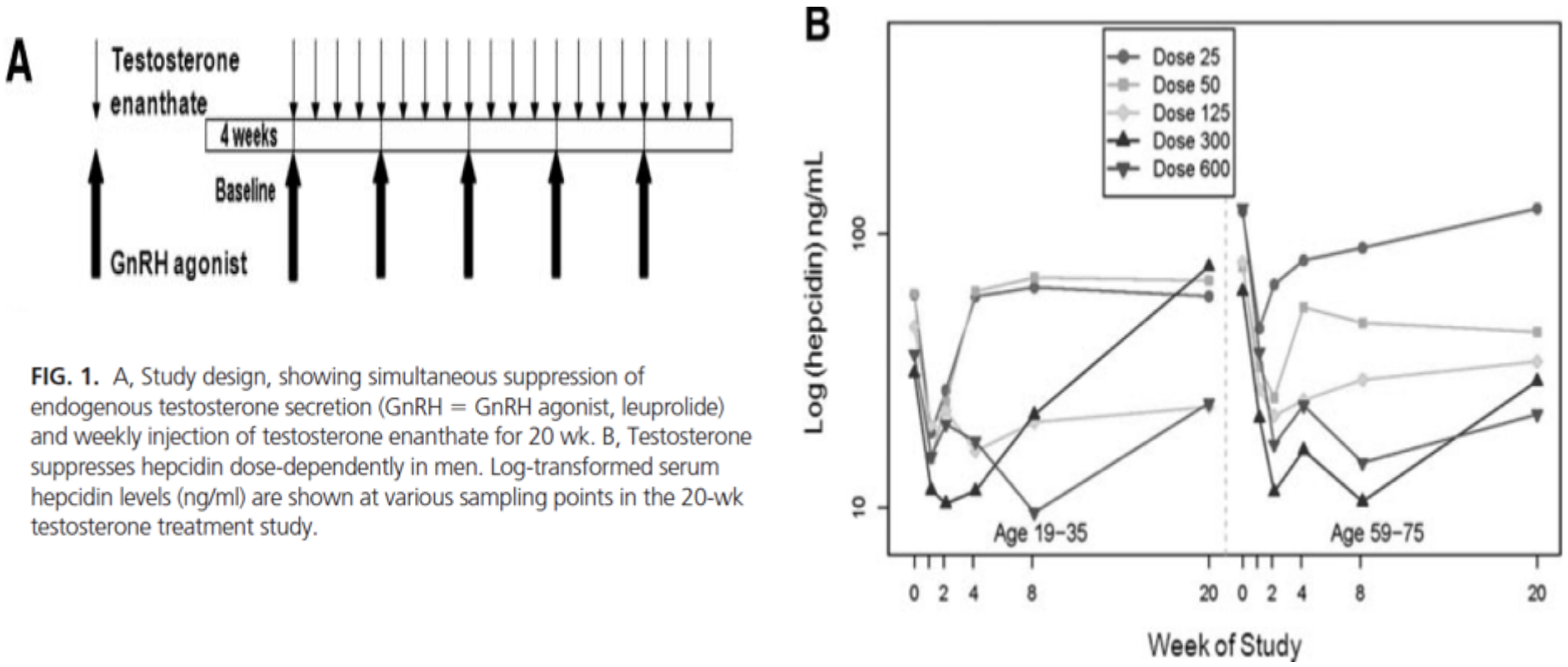
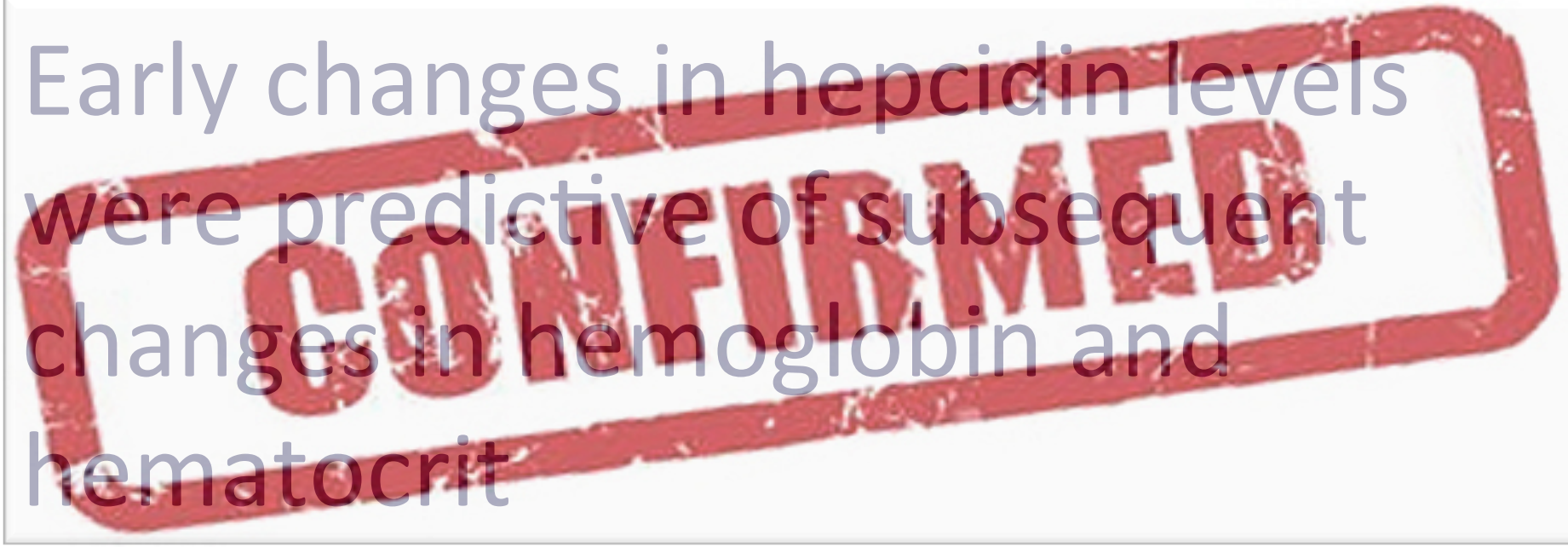


FIG. 1. A, Study design, showing simultaneous suppression of endogenous testosterone secretion (GnRH = GnRH agonist, leuprolide) and weekly injection of testosterone enanthate for 20 wk. B, Testosterone suppresses hepcidin dose-dependently in men. Log-transformed serum hepcidin levels (ng/ml) are shown at various sampling points in the 20-wk testosterone treatment study.

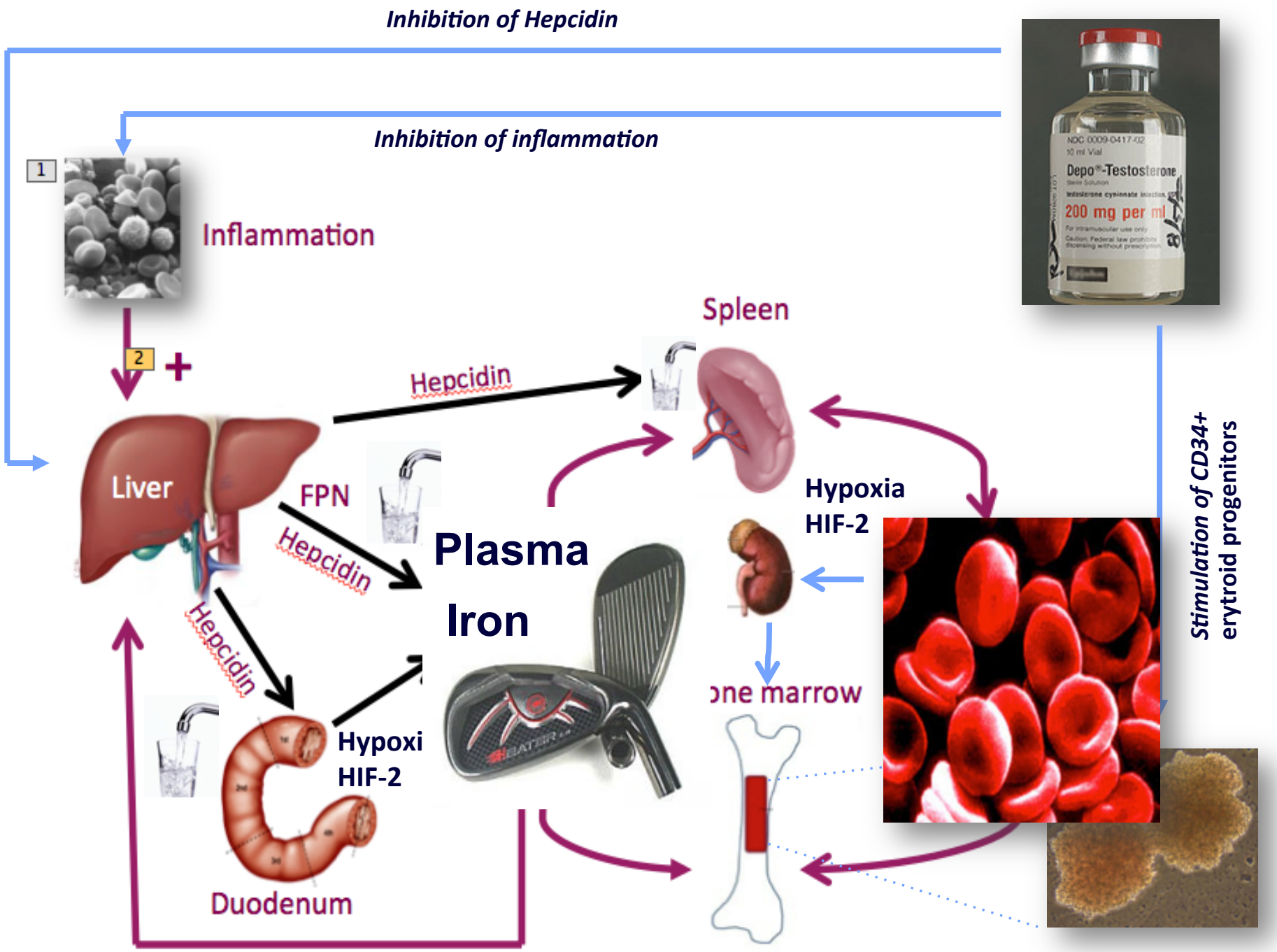
J Clin Endocrinol Metab. 2010 Oct;95(10):4743-7.

Early changes in hepcidin levels were predictive of subsequent changes in hemoglobin and hematocrit



Aging Cell (2013) **12**, pp280–291 Doi: 10.1111/acel.12052

Testosterone administration inhibits hepcidin transcription and is associated with increased iron incorporation into red blood cells


Inhibition of Hepcidin
Inhibition of inflammation
1
Inflammation
2
+
Hepcidin
Spleen
Liver
FPN
Hepcidin
Plasma
Iron
Hepcidin
Hypoxia
HIF-2
Hypoxi
HIF-2
one marrow
Duodenum
Stimulation of CD34+
erytroid progenitors
Depo®-Testosterone
200 mg per ml