In-Depth Topic Review

American Journal of Nephrology

Am J Nephrol 2007;27:565–571
DOI: 10.1159/000107927

Received: July 10, 2007
Accepted: July 23, 2007
Published online: September 5, 2007

Nonhematological Benefits of Iron

Rajiv Agarwal

Division of Nephrology, Department of Medicine, Indiana University School of Medicine, and Richard L. Roudebush VA Medical Center, Indianapolis, Ind., USA

Key Words

Anemia · Iron deficiency · Chronic kidney disease · Quality of life · Cognitive function · Physical performance · Thermoregulation

Abstract

Iron deficiency anemia is common in people with chronic kidney disease (CKD) and its importance in supporting erythropoiesis is unquestioned especially in those patients treated with erythropoietin. Clinical symptomatology such as fatigability, cold intolerance, failure to concentrate and poor effort intolerance is often attributed to anemia or uremia. That iron deficiency, per se, can cause these symptoms is poorly recognized. Clinical and animal studies that support the benefits of iron supplementation, independent of increasing hemoglobin, such as those on immune function, physical performance, thermoregulation, cognition, and restless leg syndrome and aluminum absorption is the subject of this narrative review.

Iron deficiency anemia is common in people with chronic kidney disease (CKD). Clinical symptomatology such as fatigability, cold intolerance, failure to concentrate and poor effort intolerance is often attributed to anemia or uremia. That iron deficiency, per se, can cause these symptoms is poorly recognized. Clinical and animal studies that support the benefits of iron supplementation, independent of increasing hemoglobin, is the subject of this brief review.

The putative nonhematological benefits of iron supplementation are outlined in table 1 and discussed below.

Physical Performance

Elegant studies performed more than 30 years ago by Finch et al. [1] in experimental iron deficiency in rats provides the best evidence of an independent role of iron on physical performance. Rats fed an iron-deficient chow became anemic and exchange transfusion was performed to adjust hemoglobin in the iron-deficient group. In a control iron-replete group hemoglobin was dropped to 6 g/dl by means of exchange transfusion as well. Physical perfor-

Table 1. Putative nonhematological effects of iron deficiency

1	Physical performance
2	Thermoregulation
3	Cognitive function
4	Restless leg syndrome
5	Immune function
6	Aluminum absorption

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0250–8095/07/0276–0565$23.50/0

Accessible online at:
www.karger.com/ajn

Rajiv Agarwal, MD
VAMC, 111N
1481 West 10th Street
Indianapolis, IN 46202 (USA)
Tel. +1 317 554 0000, ext. 82241, Fax +1 317 988 2171, E-Mail ragarwal@iupui.edu

mance of these rats was assessed by exercising on a treadmill and recording the time before the rats fell off the treadmill. By exchange transfusions, the hemoglobin concentration was then raised in all groups at the same rate of 1 g/dl/day. The question being posed was the impact of repairing anemia without correcting iron deficiency on physical performance. At baseline, most animals regardless of the group ran <10 min. Correction of anemia in the iron-replete animals increased the running time to about 20 min. In contrast, correction of anemia in iron-deficient animals did not increase the running ability at all even after their hemoglobin levels have been raised to the nonanemic level of 12 g/dl. Thus, iron deficiency without anemia may impair physical performance.

In a separate set of experiments, the investigators clamped the hemoglobin concentration at 10 g/dl in all groups of rats. The control group was fed an iron-replete diet; the experimental groups were maintained on an iron-deficient diet for either 3 or 4 weeks. Rats that were on an iron-deficient diet for 4 weeks could run for only 3 min. whereas the iron-replete rats could run for about 20 min. This physical impairment was somewhat less severe in the rats that had been on an iron-deficient diet for only 3 weeks.

Contrary to popular belief, myoglobin was not the cause of physical impairment. Muscle myoglobin level remained low in both the iron-deficient and iron-treated groups of animals but was higher in the controls [1]. Since the animals that were iron-treated had good physical performance, but their myoglobin levels remain low, this suggests that myoglobin level was not the cause for physical impairment. Similar results are found for other iron-requiring proteins such as cytochromes a, b and c excluding them as candidates for physical impairment as well. A mitochondrial enzyme of skeletal muscle, α-glycerophosphatase, important in oxidative phosphorylation was found to correlate with physical impairment. Its level was seen to fall in the iron-deficient animals and rise in the iron-treated animals. Thus, iron deficiency may impact oxidative phosphorylation which, in turn, impairs physical performance. This is compelling experimental evidence that iron deficiency – in rodents – per se can impair physical performance.

Human Studies on Physical Performance

Hinton et al. [2] randomized 42 iron-deficient, nonanemic young women (18–33 years of age) to either ferrous sulfate or placebo for 6 weeks in a double-blind manner. After 2 weeks, subjects trained on a cycle ergometer. In the iron-supplemented group the time to complete a 15-km cycle ergometer test, respiratory exchange ratio and work rate were decreased to a greater extent compared to the placebo group. These results support the notion that iron deficiency per se impairs favorable adaptation to aerobic exercise.

Using an identical study design as above, Brownlie et al. [3] randomized 41 untrained, iron-depleted, nonanemic women to either 100 mg ferrous sulfate or a placebo for 6 weeks in a double-blind manner. Significant treatment effects were observed for time to complete the 15-km time trial, work rate, and percentage of maximal oxygen uptake in subjects with a baseline serum transferrin receptor concentration >8.0 mg/l. No significant treatment effects were observed in subjects with a normal baseline transferrin receptor concentration. These data suggest that iron deficiency without anemia impairs adaptation in endurance capacity after aerobic training in previously untrained women.

In further studies from Hinton et al. [4], iron supplementation in men and women with iron deficiency without anemia for 6 weeks in a double-blind, randomized trial prevented the decline in ventilatory threshold observed in the placebo group from pre- to postsupplementation; this effect was greater in individuals with lower serum ferritin before intervention. Changes in serum ferritin from pre- to posttreatment were positively correlated with changes in ventilatory threshold, independent of supplementation.

Friedmann et al. [5] randomized 40 young elite athletes (13–25 years of age) with low serum ferritin and normal hemoglobin to 12-week treatment with either twice a day ferrous iron (equivalent to 2 × 100 mg elemental iron) or with placebo using a double-blind method. Aerobic and anaerobic capacity was measured using an intensive treadmill test. Aerobic capacity improved only in the iron-treated group. In contrast, the anaerobic capacity or maximal capillary lactate concentration remained unchanged in both treatment groups. The authors conclude that in young elite athletes with low serum ferritin and normal hemoglobin concentration iron supplementation leads to an increase in maximal aerobic performance capacity without an augmentation of red blood cell volume.

Other small studies have had mixed success in demonstrating the salutary effects of iron on exercise performance. For example, LaManca et al. [6] randomized 20 active women (19–35 years) to oral iron or placebo in a double-blind manner for 8 weeks and performed a per-

centage of maximal oxygen uptake (VO_2-max) test and an endurance test (80% VO_2-max) on a cycle ergometer. After treatment the iron group's VO_2-max was significantly greater than the placebo group's value; postendurance blood lactate also decreased in the iron group. Although the point estimate of endurance time to exhaustion increased by 38% (37.28 ± 5.03 to 51.4 ± 7.45 min) following iron treatment, this change was not statistically significant. Similarly, Klingshirn et al. [7] found that 8 weeks of oral iron supplementation in 18 iron-deficient, nonanemic women distance runners, improves iron status, but does not enhance endurance capacity. Both groups increased their time to exhaustion (25.5 and 22.2% for the iron and placebo groups, respectively) but they were not significantly different ($p = 0.72$) from each other. There were also no differences between the groups with respect to lactate concentrations and physiological measures taken during the two exercise tests. Small samples, differences in outcome measurement and study protocols may account for these negative studies. For example, it is possible that lower-intensity endurance exercise is tightly correlated with tissue iron deficiency, whereas a brief intense exercise may be more tightly correlated with severity of anemia [8].

In a double-blind randomized placebo-controlled trial, women who were not anemic but complained of unexplained fatigue were randomized to ferrous sulfate (80 mg/day of elemental iron) or placebo [9]. Overall, 136 (94%) women completed the study. The level of fatigue after 1 month decreased by –1.82/6.37 points (29%) in the iron group compared with –0.85/6.46 points (13%) in the placebo group (difference 0.95 points, 95% CI 0.32–1.62; $p = 0.004$). Subgroup analysis showed that only women with ferritin concentrations 50 ng/ml or less improved with iron supplementation.

Haas and Brownlie [10] reported a systematic review of animal and human studies to establish the causal relationship between iron deficiency and physical work capacity. Iron deficiency was examined along a continuum from severe iron-deficiency anemia to moderate iron-deficiency anemia to iron deficiency without anemia. They concluded that iron-deficiency anemia has a strong causal effect on aerobic capacity in animals and humans. The presumed mechanism for this effect is the reduced oxygen transport associated with anemia; tissue iron deficiency may also play a role through reduced cellular oxidative capacity. Although endurance capacity was also compromised in iron-deficiency anemia, the poor cellular oxidative capacity observed in animals has not been demonstrated in humans. Efficient energy utilization was affected at all levels of iron deficiency in humans, in the laboratory and the field. They concluded that the biological mechanisms for the effect of iron-deficiency anemia on work capacity are sufficiently strong to justify interventions to improve iron status as a means of enhancing health. This may also extend to the segment of the population experiencing iron deficiency without anemia in whom the effects on work capacity may be more subtle, but the number of individuals thus affected may be considerably more than those experiencing iron-deficiency anemia. Indeed, in an Australian epidemiologic survey among 14,762 young (18–23 years) and 14,072 middle-aged (45–50 years) women, a history of iron deficiency within the past 2 years was associated with worsening of mental composite score (–2.1), physical composite score (–3.2) and vitality (–4.2) on the Medical Outcome Study short-form survey (SF-36) compared to women who had no history, or past history, of iron deficiency [11]. These results suggest that iron deficiency is associated with decreased general health and well-being and fatigue.

Thermoregulation

Iron-deficient patients with normal hemoglobin levels may have an impaired ability to maintain core body temperature in response to cold-stress. Martinez-Torres et al. [12] submersed 3 groups of volunteers in a cold water bath and studied them for several hours. The 3 groups were nonanemic controls, iron-deficient anemic and iron-deficient nonanemic subjects. Oral temperature, norepinephrine and oxygen consumption were measured at baseline and every 15 min for 60 min. Mean serum hemoglobin level was 7.5 g/dl in the iron-deficient anemic group of subjects and within the normal range for the other two groups. Although oral temperature dropped in all groups in response to cold water immersion, the drop in oral temperature was most marked in the iron-deficient anemic and iron-deficient nonanemic groups compared to the control group. Time-dependent, plasma norepinephrine response was accelerated in both iron-deficient groups compared to controls. Oxygen consumption was increased in iron-deficient subjects whether they had normal or low hemoglobin levels. The results of this study indicate that iron-deficient individuals, despite an increased oxygen consumption and sympathetic activity, had falling body temperature suggesting heat loss with iron deficiency – not anemia per se. The increase in oxygen consumption and plasma catecholamine was similar in anemic and nonanemic indi-

viduals with iron deficiency. The authors suggest that this may be due to a defect in the mitochondria of these individuals involving an uncoupling of oxidative phosphorylation.

Cognitive Function

An extensive literature supports an important role of iron for neurotransmitter synthesis, uptake and degradation [13]. Iron is important for mitochondrial function which is richly distributed in the metabolically active brain tissue. The role of iron in the brain in normal and diseased states is discussed elsewhere [14].

A randomized trial evaluated the independent role of iron deficiency in adolescent girls in four Baltimore high schools on verbal learning [15]. These girls had iron deficiency without anemia, with hemoglobin of 13 g/dl and serum ferritin concentration of 9 ng/ml. The investigators randomly assigned these 81 girls to either ferrous sulfate by mouth or placebo, and they measured cognitive function by standard instruments at baseline and at eight weeks. In the iron-treated girls the hemoglobin increased by about 0.4 g/dl, and in control girls it fell somewhat. The girls treated with iron recalled more words at baseline, and at subsequent trials compared to untreated controls. There was improvement in verbal learning in nonanemic adolescent girls with only minimal improvement in hemoglobin. This suggests an independent role of iron deficiency in cognitive performance.

In a more recent randomized controlled trial in women with iron deficiency with or without anemia, it was found that serum ferritin concentration increase was associated with improvements in performance on attention, memory, and learning tasks, but that the time to complete the task was unaffected [16]. This relation of changes in ferritin concentrations and in cognitive performance is a highly important relation because it shows that persons do not have to be anemic to have alterations in attention, memory, and learning. In contrast, anemia was significantly related to speed of processing in the cross-sectional analysis, and a change in hemoglobin was significantly related to improvement in the speed of processing for the attention and memory tasks in the longitudinal analysis. This study demonstrates a relation between iron status and information processing in adult women of reproductive age. This study challenges the traditionally held viewpoint that iron deficiency does not have functional consequences until it has reached the level of anemia.

McCann and Ames [17] reviewed evidence of a causal relationship between dietary iron deficiency with or without anemia during development and deficits in subsequent cognitive or behavioral performance. Based on their review, they concluded that although most of the 5 conditions of causality (association, plausible biological mechanisms, dose response, ability to manipulate the effect, and specificity of cause and effect) are partially satisfied in humans, animals, or both, a causal connection has not been clearly established. In children >2 years of age and in adolescents with iron deficiency without anemia, evidence suggests cognitive or behavioral deficits. Given the small number of studies conducted in either humans or animals, a firm conclusion is not possible.

Restless Leg Syndrome

In an intriguing study, Earley et al. [18] found no differences in serum iron, serum ferritin levels and transferrin saturation between people who have restless leg syndrome versus controls. However, evidence for iron deficiency was found in the cerebrospinal fluid. Patients with restless leg syndrome actually have reduced iron stores in the substantia nigra compared to normal controls on specialized magnetic resonance imaging studies [19]. This suggests a state of regional iron deficiency. In fact, if only serum measurements of iron markers are used to define iron deficiency, no relationship between iron deficiency and restless leg syndrome is found [20].

Sloand et al. [21] treated 11 hemodialysis patients with restless leg syndrome with i.v. iron. The RLS symptoms score in 14 controls that get placebo shows no change from baseline to 4 weeks. The iron-treated group showed improvement. This study suggests that iron deficiency may actually be mediating some of the movement disorders that we see in patients on hemodialysis.

Immune Function

Many bacteria and other pathogens, such as the malarial parasite, require iron for growth and have developed sophisticated strategies to acquire iron from the host; iron is also required to mount an effective immune response.

Mackler et al. [22] reported the effects of iron deficiency in the rat on neutrophil activation and on levels of neutrophil myeloperoxidase and cytochrome b. The period of time required for neutrophil activation was not

significantly affected by iron deficiency, but the maximum rates of respiration attained after activation were markedly lower (60% decrease) in iron-deficient neutrophils than in control cells. The myeloperoxidase activity of neutrophils from iron-deficient rats was also markedly decreased (approximately 75%) compared with the activity of control cells; however, the concentration of cytochrome b in the neutrophils was unaffected by iron deficiency.

Beard [8] summarized the abnormalities in immune function with iron deficiency to consist of reduced bactericidal activity of macrophages, reduced myeloperoxidase activity of neutrophils, decreased T lymphocyte number, blastogenesis, mitogenesis and migration abnormalities. In addition, activated lymphocytes produce less interleukin-2. Humoral immunity appears to be less affected.

Chandra studied children with moderate iron deficiency and severe iron deficiency, and a matched group of normal controls with no anemia or iron deficiency [23]. Patients had measurement of in vitro neutrophil function by examining the ability of neutrophils to kill bacteria. Neutrophils were exposed to *Staphylococcus aureus*, and then the number of remaining *S. aureus* colonies at 20 min were compared to baseline. This was used as a measure of intracellular bacterial killing. The nitroblue tetrazolium test was used to study the ability of neutrophils to mounting an oxidative response. Bacterial killing was impaired in children with moderate iron deficiency and those with severe iron deficiency. They had a large number of bacterial colonies remaining at 20 min, compared to the control group of children. After treatment with i.v. iron for 4–7 days, there was a significant reduction in the number of *S. aureus* colonies remaining in the moderate and severe iron deficiency groups at 20 min. Nitroblue tetrazolium test was impaired at baseline in the moderate and severe deficiency groups compared to the controls, but after treatment with iron, oxidative burst achieved a level similar to that in controls.

The relationship between iron and infection is complex as demonstrated in a randomized, placebo-controlled trial of oral iron and folic acid with or without zinc in 24,076 preschool children in Zanzibar, a country with a high malaria transfer setting [24]. Those treated with active drug were 12% more likely to die or need treatment in a hospital for an adverse event and 11% more likely to be admitted to the hospital than the placebo group. Infection or malaria-related causes were the most likely reasons for admission to the hospital. Notably, those who were iron deficient and anemic had half the event rate when treated with active drug when compared to placebo. Thus, the evidence of harm was mainly seen in those children who were iron replete but received iron.

Aluminum Absorption

Cannata et al. [25] have reported the effect of iron status on aluminum absorption in vivo using an animal model and in vitro using an intestinal mucosal cell line. Rats were iron overloaded by intraperitoneal injection of iron dextran or iron deficient by phlebotomy. These rats, and normal controls, were then dosed with aluminum hydroxide (40 mg/day) for 30 days. Urinary excretion of aluminum was significantly greater in the iron-deficient group than in the other two groups throughout the study period, and brain aluminum at the end of the experiment was significantly increased in the iron-depleted group (1.93 μg/g) and decreased in the iron-overloaded group (0.73 μg/g) compared with controls (1.42 μg/g). In fact, the brain aluminum levels in iron-overloaded rats were not higher than those in normal rats that had not been dosed with aluminum hydroxide (0.61 μg/g). In the in vitro experiments cultures of a rat intestinal cell line were iron overloaded or iron depleted prior to pulsing with aluminum transferrin (0.5 mg/ml) for 24 h. Uptake of aluminum was significantly greater in the iron-depleted cells (2.3 ng/μg cell DNA) than in iron-overloaded (0.81 ng) or untreated (0.83 μg) cells. These studies show that iron depletion markedly increases absorption and cellular uptake and suggest that susceptible individuals, such as renal failure patients, run an increased risk of toxicity if they are iron deficient.

Conclusions

In fact, health-related quality of life as measured by the Kidney Disease Quality of Life (KDQoL) instrument has been reported in anemic patients with nondialysis CKD who were randomized to either oral iron or intravenous iron gluconate [26]. No patient was receiving erythropoietin. There was 0.4 g/dl increase in hemoglobin in the iron group and 0.2 g/dl increase in the placebo group. There was no significant difference in the increments in hemoglobin. In comparison to oral iron, intravenous iron achieved greater improvements in ferritin (232.0 ± 160.8 vs. 55.9 ± 236.2 ng/ml, $p < 0.001$) and transferrin saturation (8.3 ± 7.5 vs. 2.9 ± 8.8%, $p = 0.007$). Despite no significant difference in hemoglobin between the two

Table 2. Quality of life at baseline and change from baseline to day 43 or early termination

Subscale	i.v. iron (n = 36)		p.o. iron (n = 39)		p value
	baseline	within-group CFB	baseline	within-group CFB	i.v. iron vs. p.o. iron
SF-12 physical health composite	35.9 ± 10.5	4.8 ± 8.6*	36.4 ± 9.8	0.7 ± 8.6	0.080
SF-12 mental health composite	49.8 ± 11.8	3.3 ± 9.8	49.8 ± 12.8	−0.8 ± 15.1	0.114
Burden of kidney disease	72.7 ± 23.6	6.4 ± 19.6	71.5 ± 28.5	−3.6 ± 25.9	0.056
Symptoms/problems of kidney disease	78.1 ± 16.3	3.0 ± 11.6	75.6 ± 19.1	−2.7 ± 17.5	0.025
Effects of kidney disease	86.2 ± 16.6	2.7 ± 14.5	80.5 ± 20.7	−2.3 ± 13.13	0.048

Values are subscale scores ± SD. CFB = Change from baseline.
* Within-group change significant at the $p < 0.01$ level. From Agarwal et al: Am J Nephrol 2006;26:445–454.

groups, the physical composite score improved by 4.8% with intravenous iron ($p < 0.01$) but did not change with oral iron (table 2). Due to improvements in scores with intravenous iron, and worsening with oral iron, specific differential effects favoring intravenous iron were seen for the symptoms/problem list ($p = 0.025$) and the effect of kidney disease on patients ($p = 0.048$). Although the bias introduced as a result of open label nature of this study cannot be discounted, these data suggest an independent effect of achieving better iron stores on quality of life in patients with CKD.

In conclusion, iron is important for continued RBC production in patients treated with erythropoietin. However, iron may have a variety of nonhematological benefits such as on immune function, physical performance, thermoregulation, cognition, and restless leg syndrome and aluminum absorption. These observations generally made in the population of patients without CKD suggest the nonhematological benefits of iron supplementation. Whether patients with CKD would have similar benefits is largely unknown. It is time to test the hypothesis that common clinical symptoms traditionally attributed to anemia such as feeling cold, impaired cognitive function, or fatigue may in fact be due to iron deficiency and not the anemia. If this hypothesis is confirmed, correction of iron deficiency may become a simple and attractive option to enhance the well-being of patients with CKD independent of correction of anemia.

References

1 Finch CA, Miller LR, Inamdar AR, Person R, Seiler K, Mackler B: Iron deficiency in the rat: physiological and biochemical studies of muscle dysfunction. J Clin Invest 1976;58:447–453.
2 Hinton PS, Giordano C, Brownlie T, Haas JD: Iron supplementation improves endurance after training in iron-depleted, nonanemic women. J Appl Physiol 2000;88:1103–1111.
3 Brownlie T, Utermohlen V, Hinton PS, Haas JD: Tissue iron deficiency without anemia impairs adaptation in endurance capacity after aerobic training in previously untrained women. Am J Clin Nutr 2004;79:437–443.
4 Hinton PS, Sinclair LM: Iron supplementation maintains ventilatory threshold and improves energetic efficiency in iron-deficient nonanemic athletes. Eur J Clin Nutr 2007;61:30–39.
5 Friedmann B, Weller E, Mairbaurl H, Bartsch P: Effects of iron repletion on blood volume and performance capacity in young athletes. Med Sci Sports Exerc 2001;33:741–746.
6 LaManca JJ, Haymes EM: Effects of iron repletion on VO_{2max}, endurance, and blood lactate in women. Med Sci Sports Exerc 1993;25:1386–1392.
7 Klingshirn LA, Pate RR, Bourque SP, Davis JM, Sargent RG: Effect of iron supplementation on endurance capacity in iron-depleted female runners. Med Sci Sports Exerc 1992;24:819–824.
8 Beard JL: Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr 2001;131:568S–579S.
9 Verdon F, Burnand B, Stubi CL, Bonard C, Graff M, Michaud A, Bischoff T, de Vevey M, Studer JP, Herzig L, Chapuis C, Tissot J, Pecoud A, Favrat B: Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. BMJ 2003;326:1124.
10 Haas JD, Brownlie T: Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 2001;131:676S–688S.
11 Patterson AJ, Brown WJ, Powers JR, Roberts DC: Iron deficiency, general health and fatigue: results from the Australian Longitudinal Study on Women's Health. Qual Life Res 2000;9:491–497.
12 Martinez-Torres C, Cubeddu L, Dillmann E, Brengelmann GL, Leets I, Layrisse M, Johnson DG, Finch C: Effect of exposure to low temperature on normal and iron-deficient subjects. Am J Physiol 1984;246:R380–R383.

13 Youdim MB, Yehuda S: The neurochemical basis of cognitive deficits induced by brain iron deficiency: involvement of dopamine-opiate system. Cell Mol Biol (Noisy-le-grand) 2000;46:491–500.
14 Connor JR, Menzies SL, Burdo JR, Boyer PJ: Iron and iron management proteins in neurobiology. Pediatr Neurol 2001;25:118–129.
15 Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J: Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. Lancet 1996;348:992–996.
16 Murray-Kolb LE, Beard JL: Iron treatment normalizes cognitive functioning in young women. Am J Clin Nutr 2007;85:778–787.
17 McCann JC, Ames BN: An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. Am J Clin Nutr 2007;85:931–945.
18 Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP: Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology 2000;54: 1698–1700.
19 Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ: MRI measurement of brain iron in patients with restless legs syndrome. Neurology 2001;56:263–265.
20 Berger K, von Eckardstein A, Trenkwalder C, Rothdach A, Junker R, Weiland SK: Iron metabolism and the risk of restless legs syndrome in an elderly general population: the MEMO-Study. J Neurol 2002;249:1195–1199.
21 Sloand JA, Shelly MA, Feigin A, Bernstein P, Monk RD: A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. Am J Kidney Dis 2004;43: 663–670.
22 Mackler B, Person R, Ochs H, Finch CA: Iron deficiency in the rat: effects on neutrophil activation and metabolism. Pediatr Res 1984; 18:549–551.
23 Chandra RK: Reduced bactericidal capacity of polymorphs in iron deficiency. Arch Dis Child 1973;48:864–866.
24 Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, Dhingra U, Kabole I, Deb S, Othman MK, Kabole FM: Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. Lancet 2006;367:133–143.
25 Cannata JB, Fernandez-Soto I, Fernandez-Menendez MJ, Fernandez-Martin JL, McGregor SJ, Brock JH, Halls D: Role of iron metabolism in absorption and cellular uptake of aluminum. Kidney Int 1991;39:799–803.
26 Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehey DJ, Besarab A: A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. Am J Nephrol 2006;26:445–454.