Transpl Int (2003) 16: 642–647
DOI 10.1007/s00147-003-0568-4

ORIGINAL ARTICLE

Stefan Herget-Rosenthal
Guido Gerken
Thomas Philipp
Gerald Holtmann

Serum ferritin and survival of renal transplant recipients: a prospective 10-year cohort study

Received: 24 April 2002
Revised: 9 December 2002
Accepted: 28 January 2003
Published online: 6 May 2003

S. Herget-Rosenthal · G. Gerken
T. Philipp · G. Holtmann (✉)
Division of Gastroenterology
and Hepatology, Medizinische Klinik,
Universitätsklinikum Essen,
Hufelandstrasse 52,
45122 Essen, Germany
E-mail: g.holtmann@uni-essen.de
Tel.: +49-201-7233618
Fax: +49-201-7235970

Abstract Increased serum ferritin is frequent in renal transplant recipients. This reflects iron overload due to blood transfusions given to treat renal anaemia. Previous studies suggested excess mortality in non-renal transplant recipients with iron overload. We hypothesized that serum ferritin levels above 1,100 ng/ml may be associated with increased long-term mortality in renal transplant recipients. Twenty consecutive renal transplant recipients with high levels of serum ferritin and 20 renal transplant recipients with normal serum ferritin levels, matched for age and gender, were prospectively studied for 10 years. Nine patients (45%) with increased serum ferritin died during follow-up, compared to four controls (20%). Univariate and multivariate analysis identified multiple blood transfusions (>40 units) prior to transplantation as being associated with higher mortality in renal transplant recipients (risk ratio (RR): 3.1, confidence interval (CI): 1.1–9.2; $P=0.03$). These data suggest that serum ferritin levels above 1,100 ng/ml due to multiple blood transfusions causing iron overload is a relevant factor that increases mortality.

Introduction

Elevated levels of serum ferritin are frequently found in renal transplant recipients [15] and may be due to hepatocellular disease, infection, inflammation or malignancies [9, 21, 32]. Renal transplant recipients with excessively high serum ferritin levels generally received large numbers of blood transfusions for treatment of renal anaemia before recombinant human erythropoietin became available [15]. In these patients excessively elevated serum ferritin levels predominantly reflected iron overload [11, 26, 33], and a serum ferritin level above 1,100 ng/ml has high sensitivity and positive predictive value for indicating iron overload [33, 35]. Previous studies suggested excess mortality in non-renal transplant patients with iron overload [2, 5, 22]. However, it has been questioned whether high serum ferritin levels are a risk factor for increased mortality [7, 13, 37]. Consequently, we aimed to determine whether serum ferritin levels above 1,100 ng/ml are associated with

excess mortality of renal transplant recipients during long-term follow-up.

Patients and methods

In 1990 we prospectively identified 20 renal transplant recipients with serum ferritin levels above 1,100 ng/ml and 20 age-matched and gender-matched renal transplant recipients with normal serum ferritin levels as controls [15]. According to previous reports, [33, 35] iron overload is to be assumed when the serum ferritin level measured 6 weeks after successful transplantation is above 1,100 ng/ml. The reference range for serum ferritin was 60–220 ng/ml for men and 40–180 ng/ml for women. The study was performed in accordance with the ethical standards of the Declaration of Helsinki, and informed consent was obtained from all patients prior to their being enrolled. We reviewed the medical records at the beginning of the study (referred to as "baseline") and after 10 years, or at the last visit preceding death (referred to as "end of follow-up") to record underlying renal disease, human leukocyte antigen (HLA) A3 [14], time from its diagnosis to transplantation, number of blood units used prior to transplantation, diabetes mellitus, cirrhosis, infection, inflammation, malignancy or vascular disease, desferrioxamine treatment or iron supplementation, and date and cause of death when appropriate. Cirrhosis was diagnosed by clinical examination, biochemistry, ultrasound and CT studies. Vascular disease was defined as the presence of cardio-vascular, cerebro-vascular and/or peripheral vascular disease. The Khan score, assessing co-morbidity in chronic dialysis patients, was derived from data directly preceding renal transplantation [17]. In addition, the following laboratory data were recorded at baseline and at the end of the follow-up: aminotransferases, bilirubin, C-reactive protein, cyclosporin-A dose and trough levels, haemoglobin, hepatitis B and hepatitis C serology, prothrombin time, serum creatinine, and ferritin. Impaired liver function was defined as an elevation of aminotransferases or serum bilirubin to levels higher than twice the upper reference value, or a decrease of prothrombin time below the lower reference value.

Statistical analyses

We used the Wilcoxon test or Fisher's exact test for comparison of categorical data to compare subjects with high or normal levels of serum ferritin. The primary endpoint was the survival rate after 10 years of follow-up. Potentially relevant risk factors for the primary endpoint were coded as present or absent and assessed by univariate analysis with Fisher's exact test. Non-parametric tests were used for continuous variables. A two-tailed P value under 0.05 was considered to be statistically significant. All variables with a $P < 0.20$ in the univariate analyses were included in a stepwise logistic regression analysis. The risk associated with high serum ferritin levels, when other significant risk factors had been adjusted for, was calculated according to the Mantel–Haenszel method [24]. Data are reported as mean values ± SD with ranges given in parentheses, relative risk or 95% confidence intervals (CI) when appropriate. Analyses were performed with Statistical Analysis Systems (SAS), version 6.11 (SAS Institute, Cary, N.C., USA).

Results

The baseline characteristics of the 20 renal transplant recipients with high levels of serum ferritin and those of the 20 control subjects are presented in Table 1. Patients with increased serum ferritin levels received significantly more units of blood prior to renal transplantation than controls (53 ± 14 vs 4 ± 1 units; $P < 0.001$). Patients with high serum ferritin levels and controls did not differ in terms of underlying renal disease, diabetes mellitus, heterozygous HLA-A3, renal disease for longer than 10 years, and re-transplantation (Table 1). Renal allograft function at baseline and after 10 years was moderately impaired in patients with and without increased serum ferritin and did not differ substantially between either group. No anaemia was found in either group at baseline or after 10 years, as demonstrated by normal haemoglobin values (Table 2). At baseline, patients with high and normal serum ferritin levels did not significantly differ with regard to co-morbidity (Table 1). An equal number of patients in both groups had vascular disease. General co-morbidity as assessed by the Khan score was the same in both groups. No cirrhosis, severe infections, inflammation, or malignancies were detected at baseline.

After 10 years of follow-up, serum ferritin levels were still markedly elevated in patients with initially high values (Table 2). Although we noted a significant decrease of serum ferritin in this group, 12 patients with high serum ferritin at baseline maintained serum ferritin levels above 1,100 ng/ml. In control patients, serum ferritin levels were moderately higher at the end of the follow-up than at baseline, but remained within the reference range and well below 1,100 ng/ml (Table 2). No patient had received treatment with desferrioxamine or iron supplementation after renal transplantation. At the end of the follow-up, vascular disease was diagnosed in seven patients with high levels of serum ferritin and in

Table 1 Baseline characteristics of patients with high levels and normal levels of serum ferritin

Characteristic	High serum ferritin level	Normal serum ferritin level	P
Female/male (*n*)	6/14	6/14	
Age above 45 years	4	6	
Underlying renal disease (*n*)			n.s.
Glomerulonephritis	11	8	
Interstitial nephritis	–	2	
Chronic pyelonephritis	3	4	
Other/undetermined	6	6	
HLA-A3 positive[a] (*n*)	5	4	n.s.
Renal disease for more than 10 years	16	11	n.s.
Khan score			n.s.
Low risk (*n*)	9	10	
Medium risk (*n*)	11	10	
Vascular disease (*n*)	4	4	n.s.
Diabetes mellitus (*n*)	2	1	n.s.
Blood transfusions > 40 units (*n*)	10	0	< 0.001
First/second renal transplantation (*n*)	15/5	17/3	n.s.

[a]All positive patients were heterozygous with regard to HLA-A3

Table 2 Serum ferritin, liver function tests, viral-hepatitis marker and other laboratory parameters at baseline and at the end of the follow-up (*ALT* alanine transferase, *AST* aspartate transferase)

Parameter	High serum ferritin level		Normal serum ferritin level	
	Baseline	End of follow-up[a]	Baseline	End of follow-up[a]
Serum ferritin (ng/ml)	2.788 ± 280[d]	1.528 ± 341[d,e]	88 ± 25	186 ± 73
ALT (U/l)	23 ± 4[c]	35 ± 10[d,e]	15 ± 6	11 ± 2
AST (U/l)	15 ± 2[c]	24 ± 7[c,e]	13 ± 5	9 ± 1
Total serum bilirubin (μmol/l)	9 ± 2	12 ± 1	12 ± 2	10 ± 2
Prothrombin time (%)	87 ± 6	92 ± 4[c]	95 ± 2	101 ± 2
Serum creatinine (μmol/l)	274 ± 97	221 ± 44	256 ± 71	177 ± 35
Haemoglobin (g/dl)	13.5 ± 0.5	12.7 ± 0.4	13.4 ± 0.5	13.5 ± 0.5
C-reactive protein > 10 mg/l (*n*)	6/20		3/20	
HbsAg (positive/tested)	5/20		1/20	
Anti-HCV (positive/tested)[b]	8/17		4/17	
HCV-PCR (positive/tested)[b]	3/8		3/4	

[a]Last value measured during the follow-up
[b]Hepatitis C serology results were not from baseline records but were taken from initial measurement in the records, as they were not available in 1990
[c]$P < 0.05$ for patients with high ferritin vs patients with normal ferritin
[d]$P < 0.001$ for patients with high ferritin vs patients with normal ferritin
[e]$P < 0.05$ at baseline vs at the end of follow-up

six control patients. Cirrhosis was found in one patient with high serum ferritin. No severe infections, inflammation, or malignancies were recorded at the end of the follow-up period for surviving patients with and without high serum ferritin levels.

C-reactive protein was only mildly elevated at baseline and did not significantly differ between patients with and without high serum ferritin (8 ± 4 vs 6 ± 3 mg/l). C-reactive protein at baseline of all 40 patients studied was grouped in quartiles. Three patients in the quartile with the highest, and two patients in the quartile with the lowest, C-reactive protein values, died. Of the second and third quartile, four patients each died. Patients with high ferritin levels had significantly higher serum aminotransferases levels at baseline and at the end of the follow-up, than patients with normal serum ferritin ($P < 0.05$) (Table 2). However, we noted only moderate elevations of aminotransferases in patients with high ferritin. Serum bilirubin was normal and did not differ between both groups. Prothrombin time was shorter in patients with high ferritin levels than that in controls, but all values were within the reference range. More patients with high serum ferritin levels had impaired liver function (six vs two; $P = 0.13$).

As shown in Table 2, hepatitis B surface antigen was found in more patients with high serum ferritin than in controls. During the 10 years of follow-up, data on hepatitis-C (HCV) testing became available and hepatitis-C status was assessed for the majority of patients. Although more patients with high serum ferritin levels tested positive for hepatitis-C antibodies than controls did, HCV-polymerase chain reaction confirmed active hepatitis C in equal numbers of patients with and without high serum ferritin. At the end of the follow-up, the daily cyclosporin-A dose was significantly lower in patients with high serum ferritin levels (199 ± 18 vs 261 ± 20 mg/day; $P < 0.05$), while cyclosporin-A trough levels were similar for both groups (170 ± 16 vs 164 ± 10 ng/ml; $P = 0.60$).

Overall, 27 of 40 patients (68%; CI: 51–81%) were alive after 10 years of follow-up. In nine patients (45%; CI: 23–69%), substantially more with increased serum ferritin died during the follow-up, compared to four with normal serum ferritin levels (20%; CI: 6–44%; $P = 0.18$). Patients with high serum ferritin levels died from ischaemic heart disease ($n = 3$), malignancy ($n = 2$: hepatocellular carcinoma and colon cancer), severe infections ($n = 2$: endocarditis and urosepsis), cardiac and hepatic failure ($n = 1$ each). The patient with hepatocellular carcinoma suffered from chronic hepatitis B, the patient with hepatic failure from chronic hepatitis C. Patients with normal serum ferritin levels died from severe infections ($n = 2$: sepsis and meningitis), ischaemic heart disease ($n = 1$), and malignancy ($n = 1$: colon cancer). The survival of renal transplant recipients with serum ferritin levels above 1,100 ng/ml and patients with normal serum ferritin at baseline is illustrated in Fig. 1. Serum ferritin levels were significantly higher in patients who did not survive (1,967 ± 493 ng/ml) than in patients who survived the 10-year follow-up (1,284 ± 297 ng/ml, $P < 0.01$). Univariate analysis showed a statistically significant association between transfusion of more than 40 units of blood prior to transplantation and mortality (Table 3). Multivariate analysis revealed polytransfusion above 40 units to be the only independent predictor of death during the 10-year follow-up (RR: 3.1, CI: 1.1–9.2; $P = 0.03$).

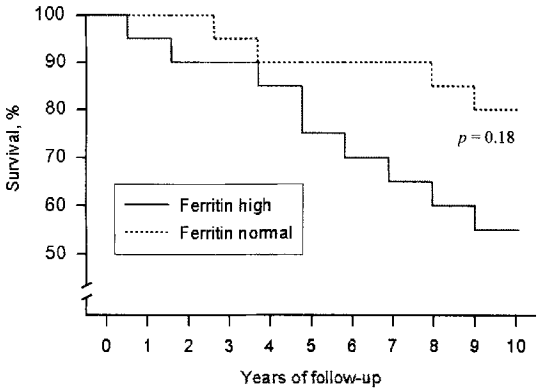

Fig. 1 Survival rates of renal transplant recipients with serum ferritin levels above 1,100 ng/ml and with serum ferritin within the normal range

Discussion

This is the first prospective long-term study assessing excessively high serum ferritin levels as a prognostic factor of mortality in renal transplant recipients. The main finding is that the mortality rate of renal transplant recipients with serum ferritin levels above 1,100 ng/ml is higher than that of renal transplant recipients with normal levels of serum ferritin, during the follow-up of 10 years, although the difference just failed to reach statistical significance. However, we identified the transfusion of more than 40 units of blood prior to transplantation as being an independent factor associated with a higher mortality in renal transplant recipients. This is consistent with previous studies, which suggested that iron overload is associated with increased mortality in renal transplant recipients and in other patients [2, 5, 22, 33].

Previously, a strong correlation between excessively high serum ferritin levels and iron overload was demonstrated [35]. This association was also found in the present study, further supporting the assumption that iron overload itself was the key factor for the high mortality in patients with high serum ferritin levels. Furthermore, iron overload in our patients was due to excessively administered iron rather than hereditary haemochromatosis, hence we could not find an association with HLA-A3 [14].

Patients with excessively high serum ferritin levels died from various causes, due to the widespread organ dysfunction caused by iron overload [27, 35]. Indeed, iron overload has been associated with an increased risk of severe infection [3, 12, 29, 36, 40], cardiovascular disease [34, 39], and malignancy [19, 23, 42]. The increased susceptibility to infection, and the increased proliferation of malignant cells in iron overload may be due to depressed phagocytic function of neutrophils and to impaired cell-mediated immunity [30, 42, 43]. The higher incidence of cardiovascular disease may be explained by enhanced atherosclerotic plaque formation during iron overload [1, 44]. The association of iron overload with infection, cardiovascular disease and malignancy could well contribute to the excess mortality and various causes of death in our patients with highly elevated serum ferritin. However, other studies reached conflicting results regarding the association of iron overload with cardiovascular disease, infection and malignancy [7, 13, 37]. In contrast to our cohort, these studies investigated patients with only moderately elevated serum ferritin levels, far below 1,100 ng/ml. Thus, severe iron overload may not be the predominant cause of ferritin elevation in these studies. Iron overload, as reflected by excessively elevated serum ferritin, is predominantly due to multiple blood transfusions. Additionally, blood transfusions exert an immunosuppressive effect [6, 20]. In patients awaiting renal transplantation, blood transfusions induced a long-lasting suppression of cell-mediated immunity [6, 41]. This may impair host resistance to infection and immune control of malignant cells, and may therefore be a factor causing increased mortality due to infection and malignancy in patients receiving multiple blood transfusion.

The present case–control study is based on 20 cases with high levels of serum ferritin and 20 controls with normal levels. This small sample size emphasizes the relevance of our findings, though independent confirmation is required. In addition, there are a number of factors independent of the iron overload that may influence the serum ferritin level [9, 21, 32]. Nevertheless, we did not find an increased rate of severe infections, inflammation, malignancies, vascular disease or other

Table 3 Univariate analysis of risk factors for death in renal transplant recipients during the 10 years of follow-up (RR and 95% CI)

Risk factors	RR	CI	*P*
Serum ferritin > 1,100 ng/ml	1.7	0.9–3.2	0.08
Age > 45 years	2.1	0.7–6.0	0.17
Blood transfusions > 40 units	3.1	1.1–8.9	0.04
Renal disease for more than 10 years	1.1	0.7–1.8	0.49
C-reactive protein > 10 mg/l	1.6	0.5–5.3	0.31
HbS-Ag positivity	1.0	0.2–5.1	0.65
Diabetes mellitus	1.2	0.6–2.3	0.39
Impaired liver function at baseline[a]	1.6	0.4–6.1	0.41

[a]Defined as elevation of aminotransferases or serum bilirubin > twice the upper reference value or decrease of prothrombin time < lower reference value

co-morbidity as additional causes of ferritin elevations. In addition, C-reactive protein, used to adjust to severe infections and inflammation, was only moderately elevated in patients with excessively high serum ferritin, and similar to patients with normal serum ferritin levels. Furthermore, higher C-reactive protein values were not associated with increased mortality. However, the higher prevalence of chronic hepatitis-B antibodies and hepatitis-C antibodies in patients with elevated serum ferritin may explain the occurrence of more hepatocellular diseases and higher overall mortality rate in this cohort. Furthermore, moderately elevated aminotransferases and smaller dosage requirement of the hepatic metabolized cyclosporin A in patients with high serum ferritin levels suggest mild hepatocellular injury. However, only fulminant hepatocellular injury is associated with increases in serum ferritin of the magnitude determined in our patients [32]. Additionally, PCR data show equal numbers of patients with replicating hepatitis C in both groups, although limitations in the sensitivity of HCV antibody testing may have affected our results. Thus, the mild hepatocellular injury observed in our patients is unlikely to be the cause of elevated serum ferritin levels in our patients. Contrary to a previous study, the association of elevated aminotransferases and serum ferritin seems not to be evidence of an aggravating effect of iron overload on hepatitis-C infection, as patients with high and normal ferritin levels did not differ in regard to replicating hepatitis C [38].

Although some studies have shown chronic hepatitis B and hepatitis C to be associated with increased mortality in renal transplant recipients [25, 31], the impact of chronic hepatitis B and hepatitis C on the long-term survival of renal transplant recipients remains controversial [4, 8, 16, 18]. Later data suggest that it is predominantly cirrhosis due to hepatitis B and hepatitis C that increases mortality in these patients [8, 18]. There was no significantly higher incidence of cirrhosis in patients with high serum ferritin levels, indicating that cirrhosis does not account for the increase in mortality. However, a limitation is that cirrhosis was diagnosed indirectly, not by histology.

Therefore, we consider iron overload and not hepatocellular disease, severe infections, inflammation, malignancies, vascular disease or other co-morbidity to be the crucial factor for excessive elevation of serum ferritin levels in our study. Although serum ferritin slightly decreased during our study period, values remained far above the normal range, despite adequate transplant function. This is of interest, as functioning renal transplants provide adequate erythropoietin to compensate for renal anaemia. This has been associated with normalization of serum ferritin [7, 28]. Contrary to our study, these patients presented only moderately elevated serum ferritin levels. This suggests that iron overload was not the predominant cause of serum ferritin, in previous studies. As serum ferritin levels remained high in our patients, despite rapid improvement of renal anaemia, we assume that iron overload persisted. This is consistent with studies in chronic haemodialysis patients showing persistence of iron overload even when anaemia was adequately controlled by erythropoietin [10].

In summary, renal transplant patients with markedly elevated serum ferritin levels after transplantation demonstrated higher mortality than renal transplant recipients with normal serum ferritin levels. As excessively high serum ferritin levels predominantly reflected iron overload, these data indicate that increased mortality may be attributed to iron overload.

Acknowledgments The authors thank the staff of the renal transplant outpatients department for their co-operation and help.

References

1. Araujo JA, Romano EL, Brito BE, Parthe V, Romano M, Bracho M, Montano RF, Cardier J (1995) Iron overload augments the development of atherosclerotic lesions in rabbits. Arterioscler Thromb Vasc Biol 15: 1172–1180
2. Ballas SK (2001) Iron overload is a determinant of morbidity and mortality in adult patients with sickle cell disease. Semin Hematol 38 [Suppl 1]:30–36
3. Boelaert JR, Daneels RF, Schurgers ML, Matthys EG, Gordts BZ, Van Landuyt HW (1990) Iron overload in haemodialysis patients increases the risk of bacteraemia: a prospective study. Nephrol Dial Transplant 5:130–134
4. Breitenfeldt MK, Rasenack J, Berthold H, Olschewski M, Schroff J, Strey C, Grotz WH (2002) Impact of hepatitis B and C on graft loss and mortality after kidney transplantation. Clin Transplant 16:130–136
5. Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, Allen CJ, Farrell DE, Harris JW (1994) Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. N Engl J Med 331:567–573
6. Brunson ME, Alexander JW (1990) Mechanisms of transfusion-induced immunosuppression. Transfusion 30:651–658

7. Eschbach JW, Adamson JW (1999) Iron overload in renal failure patients: changes since the introduction of erythropoietin therapy. Kidney Int 55 [Suppl 69]:35–43
8. Fabrizi F, Martin P, Ponticelli C (2002) Hepatitis B virus and renal transplantation. Nephron 90:241–251
9. Gabay C, Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 340: 448–454
10. Gastaldello K, Vereerstraeten A, Nzame-Nze T, Vanherweghem JL, Tielemans C (1995) Resistance to erythropoietin in iron-overloaded haemodialysis patients can be overcome by ascorbic acid administration. Nephrol Dial Transplant 10 [Suppl 6]:44–47
11. Gungor T, Rohrbach E, Solem E, Kaltwasser JP, Kornhuber B (1996) Logarithmic quantitation using serum ferritin to estimate iron overload in secondary haemochromatosis. Arch Dis Child 74:323–327
12. Hoen B, Kessler M, Hestin D, Mayeux D (1995) Risk factors for bacterial infections in haemodialysis adult patients: a multicentre prospective survey. Nephrol Dial Transplant 10:377–381
13. Hoen B, Paul-Dauphin A, Hestin D, Kessler M (1998) Epibacdial: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. J Am Soc Nephrol 9:869–876
14. Hohler T, Gerken G (2000) Genetic hemochromatosis—from molecular genetics to the clinical diagnosis. Z Gastroenterol 38:509–515
15. Holtmann G, Anlauf M, Wagner K, Holtmann M, Kolbel CBM, Philipp T, Goebell H (1990) Prevalence, causes and effects of iron overload in patients with allogeneic renal grafts. Med Klin 85:517–522
16. Huo TI, Yang WC, Wu JC, King KL, Loong CC, Lin CY, Chang FY, Lee SD (2001) Kidney transplantation in patients with chronic hepatitis B virus infection: is the prognosis worse? Dig Dis Sci 46:469–475
17. Khan IH, Catto GRD, Edward N, Fleming LW, Henderson IS, Macleod AM (1993) Influence of coexisting disease on survival on renal-replacement therapy. Lancet 341:415–418
18. Kliem V, Van der Hoff U, Brunkhorst R, Tillmann HL, Flik J, Man MP, Pichlmayr R, Koch KM, Frei U (1996) The long-term course of hepatitis C after kidney transplantation. Transplantation 62:1417–1421
19. Knekt P, Reuanen A, Takkunen H, Aromas A, Heliovaara M, Hakulinen T (1994) Body iron stores and risk of cancer. Int J Cancer 56:379–382
20. Landers DF, Hill GE, Wong KC, Fox IJ (1996) Blood transfusion-induced immunomodulation. Anesth Analg 82:187–204
21. Lee MH, Means RT (1995) Extremely elevated serum ferritin levels in a university hospital: associated diseases and clinical significance. Am J Med 98: 566–571
22. MacPhail AP, Mandishona EM, Bloom PD, Paterson AC, Rouault TA, Gordeuk VR (1999) Measurements of iron status and survival in African iron overload. S Afr Med J 89:966–972
23. Mandishona E, MacPhail AP, Gordeuk VR, Kedda MA, Paterson AC, Rouault TA (1998) Dietary iron overload as a risk factor of hepatocellular carcinoma in black Africans. Hepatology 27: 237–245
24. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719–748
25. Mathurin P, Mouquet C, Poynard T, Sylla C, Benalia H, Fretz C, Thibault V, Cadranel JF, Bernard B, Opolon P, Coriat P, Bitker MO (1999) Impact of hepatitis B and C virus on kidney transplantation outcome. Hepatology 29:257–263
26. Moreb J, Popovtzer MM, Friedlaender MM, Konijn AM, Hershko C (1983) Evaluation of iron status in patients on chronic hemodialysis: relative usefulness of bone marrow hemosiderin, serum ferritin, transferrin saturation, mean corpuscular volume and red cell protoporphyrin. Nephron 35:196–200
27. Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G (1996) Long-term survival in patients with hereditary hemochromatosis. Gastroenterology 110:1107–1119
28. Park SB, Kim HC, Lee SH, Cho WH, Park CH (1994) Evolution of serum ferritin levels in renal transplant recipients with severe iron overload. Transplant Proc 26:2054–2055
29. Patruta SI, Hoerl WH (1999) Iron and infection. Kidney Int 55 [Suppl 69]: 125–130
30. Patruta SI, Edlinger R, Sunder-Plassmann G, Hoerl WH (1998) Neutrophil impairment associated with iron therapy in hemodialysis patients with functional iron deficiency. J Am Soc Nephrol 9:655–663
31. Pereira BJG, Natov SN, Bouthot BA, Murthy BVR, Ruthazer R, Schmid CH, Levey AS (1998) Effect of hepatitis C infection and renal transplantation on survival in end-stage renal disease. Kidney Int 53:1374–1381
32. Prieto J, Barry M, Sherlock S (1975) Serum ferritin in patients with iron overload and with acute and chronic liver disease. Gastroenterology 68:525–533
33. Rao KV, Anderson WR (1985) Hemosiderosis and hemochromatosis in renal transplant recipients. Am J Nephrol 5:418–430
34. Salonen JT, Nyysonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R (1992) High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. Circulation 86:803–811
35. Schafer AI, Cheron RG, Dluhy R, Cooper B, Gleason RE, Soeldner JS, Bunn HF (1981) Clinical consequences of acquired transfusional iron overload in adults. N Engl J Med 304:319–324
36. Seifert A, Von Herrath D, Schaefer K (1987) Iron overload, but not treatment with desferrioxamine favours the development of septicemia in patients on maintenance hemodialysis. Q J Med 65:1015–1024
37. Sempos CT, Looker AC, Gillum RF, McGee DL, Vuong CV, Johnson CL (2000) Serum ferritin and death from all causes and cardiovascular disease: the NHANES II mortality study. Ann Epidemiol 10:441–448
38. Sezer S, Ozdemir FN, Guz G, Ozdemir BH, Sengul S, Arat Z, Turan M, Demirhan B, Haberal M (2001) Ferritin levels can be a good predictor for HCV viremia in potential renal transplant candidates. Transplant Proc 33: 2796–2798
39. Sullivan JL (1996) Iron versus cholesterol: perspective on the iron and heart disease debate. J Clin Epidemiol 49:1345–1352
40. Tielemans CL, Lenclud CM, Wens R, Collart FE, Dratwa M (1989) Critical role of iron overload in the increased susceptibility of haemodialysis patients to bacterial infections: beneficial effects of desferrioxamine. Nephrol Dial Transplant 4:883–887
41. Van Twuyver E. Mooijaart RJD, Ten Berge IJM, Van Der Horst AR, Wilmink JM, Kast WM, Melief CJM, De Waal LP (1991) Pretransplantation blood transfusion revisited. N Engl J Med 325:1210–1213
42. Weinberg ED (1996) The role of iron in cancer. Eur J Cancer Prev 5:19–36
43. Weiss G (2002) Iron and immunity: a double-edged sword. Eur J Clin Invest 32 [Suppl 1]:70–78
44. Yuan XM, Brunk UT (1998) Iron and LDL-oxidation in atherogenesis. APMIS 106:825–842