Prevalent iron parameters among haemodialysis patients in insurance haemodialysis centers

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by

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PROTOCOL

Introduction

Anemia is common in patients with chronic kidney disease **(Frei *et al*., 2009)** and end stage renal disease patients receiving hemodialysis **(Akhtar *et al*., 2003)**.

Anemia in end stage renal disease is not a trivial problem. There is a strong association between haemoglobin and risk of death in end stage renal disease **(Levy. *et al*., 2004a).**

Functional and absolute iron deficiencies are important causes of anemia in end stage renal disease. True iron deficiency is found in up to 40% of patients with end stage renal disease **(Levy. *et al*., 2004b).**

(Fishbane., 2007) stated that causes of iron deficiency in hemodialysis patients include:

- Depletion of iron stores.
- Chronic blood loss:
    1. Blood retention by the dialysis lines and filters.
    2. Blood sampling for laboratory testing.
    3. Accidents related to the vascular access.
    4. Surgical blood loss.
    5. Occult gastrointestinal bleeding.
- Decreased dietary iron absorption:
    1. Phosphate binders inhibit iron absorption.
    2. Histamine-2 blockers, proton pump blockers and functional achlorhydria impair iron absorption.
    3. Uremic gut does not absorb iron optimally.
- Increased iron demand:
    1. Due to increased rate of erythropoiesis induced by erythropoiesis-stimulating agents.
    2. Impaired release of iron from storage tissues (reticuloendothelial blockade).

There are many tests that investigate anemia in end stage renal disease, such as: (haemoglobin level, red blood cell indices, blood film, white blood cells and platelets, reticulocyte count, serum iron and total iron binding capacity, transferrin saturation, serum ferritin, C-reactive protein and stool occult blood) **(Levy. *et al.*, 2004c).**

Aim of the work

To study the prevalent iron parameters (serum iron, total iron binding capacity, transferrin saturation and serum ferritin) among hemodialysis patients in insurance hemodialysis centers.

Patients and methods

This study will include 200 hemodialysis patients on regular hemodialysis in El-Dokki 6th October Insurance Hospital, El-Mokattam Insurance Hospital and El-Suez Insurance Hospital.

All patients will be subjected to the following:

1- **Full history taking:**
   Especially history of: (blood loss, blood transfusion, iron administration and erythropoiesis stimulating agents administration).
2- **Full clinical examination.**
3- **Laboratory investigations:**
   a) Serum iron, total iron binding capacity, transferrin saturation and serum ferritin.
   b) Complete blood count.
   c) Other investigations as appropriate.

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LIST OF ABBREVIATIONS

apo	Apoprotein	Hct	Hematocrite
BM	Bone marrow	HCV Ab	Hepatitis C virus antibody
BMP6	Bone morphogenetic protein 6	HD	Hemodialysis
CBC	Complete blood count	HH	Hereditary hemochromatosis
CHr	Reticulocyte hemoglobin content	HIF	Hypoxia inducible factor
CI	Confidence interval	HIV Ab	Human immune-diffency virus antibody
CKD	Chronic kidney disease	HJV	Hemojuvelin
Cp	Ceruloplasmin	HO-1	Heme oxygenase 1
CRP	C-reactive protein	I.V.	Intravenous
DcytB	Duodenal cytochrome B	ID	Iron deficiency
DMT-1	Divalent metal transporter-1	IDA	Iron-deficiency anemia
ELISA	Enzyme-linked immunosorbent assay	IMP	Integrin-mobilferrin paraferritin
EPO	Erythropoietin	IREs	Iron-responsive elements
ESAs	Erythropoiesis stimulating agents	IRPs	Iron regulatory proteins
ESRD	End-stage renal disease	Jak2	Janus kinase 2
FID	Functional iron deficiency	KDOQI	Kidney Dialysis Outcomes Quality Initiative
FLVCR	Feline leukemia virus subgroup C receptor	LC/MS-MS	Liquid chromatography tandem mass spectrometry
FPN	Ferroportin	LHD%	Low haemoglobin density
GFR	Glomerular filtration rate	LVH	Left ventricular hypertrophy
GIT	Gastrointestinal tract	MCH	Mean cell hemoglobin
Hb	Hemoglobin	MCHC	Mean cell hemoglobin concentration
HBVsAg	Hepatitis B virus surface antigen	MCV	Mean cell volume

Nramp1	Natural resistance-associated macrophage protein 1	SELDI-TOF MS	Surface-enhanced laser desorption/ionization time-of-flight mass spectrometry
PHRC	Percentage of hypochromic red cells	SI	Serum iron
RBCs	Red blood cells	sTfR	Soluble transferrin receptor
RDW	Red blood cell distribution width	Tf	Transferrin
RE	Reticuloendothelial	TfR	Transferrin receptor
rHuEPO	Recombinant human erythropoietin	TIBC	Total iron-binding capacity
RPM	Round per minute	TSAT	Transferrin saturation
RR	Relative risk	WBCs	White blood cells
SD	Standard deviation	ZnPP	Zinc protoporphyrin

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REVIEW

CHAPTER 1

ANEMIA OF CHRONIC KIDNEY DISEASE

Anemia in chronic kidney disease

Definition of anemia:

Anemia is defined by the World Health Organization as a hemoglobin (Hb) concentration of less than 13 g/dL in adult men and non-menstruating women and less than 12 g/dL in menstruating women **(Wish.**, **2009).**

Epidemiology of anemia in chronic kidney disease:

Anemia in patients with renal disease has been known for more than 170 years **(Besarab. *et al*., 2009).** In general, there is a progressive increase in the incidence and severity of anemia with declining renal function. The reported prevalence of anemia by (CKD) stage varies significantly and depends to a large extent on the definition of anemia and on whether study participants are selected from the general population, are at high risk of (CKD), are diabetic or are already under the care of a physician **(Macdougall. *et al*., 2007).**

Hemoglobin levels in patients on dialysis						
	Among patients on dialysis>180 days			**Among patients new to ESRD, at start of dialysis**		
Country	n	Mean Hb (g/dl)	Hb <11 g/dl (% of patients)	n	Mean Hb (g/dl)	Hb <11 g/dl (% of patients)
Sweden	466	12.0	23	168	10.7	55
United States	1690	11.7	27	458	10.4	65
Spain	513	11.7	31	170	10.6	61
Belgium	442	11.6	29	213	10.3	66
Canada	479	11.6	29	150	10.1	70
Australia and New Zealand	423	11.5	36	108	10.1	70
Germany	459	11.4	35	142	10.5	61
Italy	447	11.3	38	167	10.2	68
United Kingdom	436	11.2	40	93	10.2	67
France	341	11.1	45	86	10.1	65
Japan	1210	10.1	77	131	8.3	95

Table 1: Mean hemoglobin (Hb) levels and percentage of patients with Hb levels <11 g/dl who have been on dialysis therapy for more than 180 days and at the time of starting dialysis, by country **(Macdougall. *et al*., 2007).**

Population studies such as the National Health and Nutrition Examination Survey (NHANES) by the National Institutes of Health and the Prevalence of Anemia in Early Renal Insufficiency (PAERI) Study suggest that the incidence of anemia is less than 10% in CKD stages 1 and 2, 20% to 40% in CKD stage 3, 50% to 60% in CKD stage 4 and more than 70% in CKD stage 5 **(Wish.**, **2009).** If anemia is not treated in end-stage renal disease (ESRD) patients, hematocrit values of 18%-24% are typical **(Fishbane., 2007).**

Target level of hemoglobin (Hb) in chronic kidney disease:

The target (Hb) level for anemic patients with (CKD) treated with erythropoiesis stimulating agents (ESAs) has been a subject of considerable controversy, because observational studies have disagreed with the results of interventional trials **(Wish.**, **2009).**

The 2001 version of the NKF-K/DOQI anemia guidelines recommended a target (Hb) of 11 to 12 g/dL in ESA-treated anemic patients with CKD **(Wish.**, **2009).** The UK Renal Association guidelines recommended a target (Hb) level above 10 g/dL, but the upper limit is not specified. The European guidelines recommended a target (Hb) level above 11 g/dL (but not above 14 g/dL). They recommended aiming for (Hb) level of (11-12) g/dL if risk of cardiac failure or ischemic heart disease is present **(Steddon. *et al*., 2006).**

Although higher targets of hemoglobin that had been thought as early fears about increased thrombotic risks and loss of vascular access in hemodialysis patients were dispelled, it is now thought that over-zealous correction (above 12 g/dL) of (Hb) leads to increased mortality in patients with ischemic heart disease and heart failure **(Steddon. *et al*., 2006).** Recent studies, the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE), have suggested that targeting higher hemoglobin levels (generally above 12.5 g/dL) may result in higher cardiovascular adverse events **(Provenzano., 2009).**

Based on the results of the (CHOIR) and (CREATE) studies, the Food and Drug Administration (FDA) changed the package insert for epoetin and darbepoetin to state that the physician should "individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL" in patients with CKD. The