Review of Literature
REVIEW OF LITERATURE

HISTORICAL PERSPECTIVE

It was *Morgani (1682-1771)* who first of all noticed hematological derangements in association with kidney disease and described the case of a person who had odour of urine on the breath and suffered form episodes and hematemesis.

The relationship between hematopoiesis and kidney was first recognized in 1836 by a British Physician *Richard Bright*, who noted that patients with renal disease exhibited marked pallor.

In 1907, *Riesman* documented the hemorrhagic diathesis in relation to renal disease and cited the original description of Morgagni.

*Brown and Roth* in 1992 concluded that the anemia of chronic nephritis was due to decreased bone marrow production.

*Parson et al* in 1993, said that the anemia in patient with kidney disease bore a direct relationship to the degree of nitrogen retention.

In 1938, *Magner* concluded that anemia occurs regularly in cases of renal insufficiency and nitrogen retention, regardless of the nature of the renal lesion and degree of anemia is usually proportional to the degree of impairment of the excretory functions of the kidney.

*Emerson and Burrows*, in 1949, demonstrated increased destruction of erythrocytes in renal failure. They also stated that uremic sera contained one or more substances that interfered with either the growth of erythroid
precursors or with heme synthesis in tissue culture, supporting the concept that uremic suppression of erythropoises is a cause of anemia of renal failure.

In 1957, *Jacobson and coworkers* demonstrated that the kidney was the responsible organ for the control of red cell production.

“Haematopoietine” as the substance produced by kidney that regulates red cell production was first recognized many decades back and this Haematopoietine was eventually defined as an “erythropoiesis stimulating factor” by *Erslin* in 1953 and shortly thereafter, it was named “erythropoietin”.

**RECENT STUDIES**

A lot of work has been done, since the era of Morgagni, in this field, in order to understand the mechanism, as well as the consequences of renal anemia. Although still not fully understood, many aspects of anemia in CKD are now becoming clear. Management of anemia in CKD patients has always been a challenging issue for practitioners. Many studies have been carried out and some are ongoing to explore the unclear aspects of anemia in CKD patients.

*Bickford AK (2002), Fresnius Medical Care, Central Dupage Dialysis Center, USA, worked on ‘Evaluation and Treatment of Iron Deficiency in Patient with kidney Disease’ and found that serum ferritin and percent transferrin saturation, which are regarded as the best indicators of iron status, lack sensitivity and specificity to identify functional iron
deficiency, which can occur in the presence of normal or even increased iron stores.

**Firshbane S and coworkers**, *Winthrop University Hospital, Division of Nephrology, Newyork, USA* studied on ‘Evaluation of Iron status In Hemodialysis patients’, They found that a novel assay, the reticulocyte hemoglobin content (CHr) sensitively detects functional iron deficiency. They evaluated the CHr in assessment of iron status in 164 hemodialysis patients and concluded that –

- CHr is an accurate measure of iron status in hemodialysis patients.
- A reticulocyte hemoglobin content (CHr) value less than mature red cell hemoglobin content (CH) value indicates acute onset iron deficiency.
- A single dose infusion of IV iron results in correction of iron deficiency at the level of reticulocyte within 48 hours.

**Bhandari S and Coworkers**, *Renal unit leeds General Infirmary UK*, evaluated the role of RBC ferritin and reticulocyte hemoglobin content in monitoring the response to IV iron therapy. They conducted their study on 22 hemodialysis patients and concluded that these measurements provide evidence of increased iron supply for erythropoiesis during I.V iron therapy, help identify patients with functional iron deficiency, and allow more accurate monitoring of response to I/V iron therapy.
Seiler S (2000), Adam Linton Dialysis Unit London Health Sciences Centre, London, discussed newer treatment alternatives in the management of anemia of CRF. He suggested an alternate form of I.V iron, sodium ferric gluconate, to be safe and effective in the management of iron deficiency anemia in hemodialysis patients receiving erythropoietin. He also pointed out that hemodialysis patients with serum ferritin below 100ng/ml or TSAT below 20% need supplementation with parenteral iron in excess of 1000mg to achieve optimal response in Hb/Hct levels, as suggested by US NKF-DOQI clinical practice Guidelines.

Svara F et al (1996) worked on iron supplementation during erythropoietin therapy in patients on hemodialysis. They performed a comparative study on oral vs I.V iron supplementation in the treatment of secondary anemia by recombinant human erythropoietin in patient with CKD treated by hemodialysis. The study was performed on 61 patients divided into two groups of which one group received oral iron and the other group I/V iron.

After six weeks of treatment they found that –

- Rise in Hct and Se iron were comparable in both groups.

- TSAT showed a more marked increment in I.V treated group.

- S. ferritin levels declined in oral supplementation group where as increased in I.V treated group.
Thus the study conducted by these workers suggested that although the rise in Hct and serum iron may be comparable in the patients treated with oral or I/V iron, building of iron stores is much better with I/V iron and therefore from long term aspect, the study favoured the use of I/V iron supplementation in hemodialyzed patients treated with erythropoietin.

The response to oral and I/V iron supplementation in management of anemia in CKD was also discussed by Macdougall IC (1999), Department of Renal Medicine, King’s College Hospital, London (UK): He stressed that the need of I/V iron supplementation should be strongly considered when the serum ferritin level is <100µg/L or transferrin saturation is <20% or the percentage of hypochromic red cells is >10%. He also mentioned that when I.V iron supplementation is given care should be taken to prevent serum ferritin rising above 800µg/L and transferrin saturation above 50% in order to avoid iron overload.

Silverberg DS and Co-workers (1999), Department of Nephrology, Tel Aviv Medical Center, Israel evaluated the response to I.V iron for the treatment of predialysis anemia. They found that anemia in CKD patients in the predialysis period can be improved by I/V iron to a much greater extent as compared to oral iron. In addition, the advantage of maintaining adequate iron stores with I/V iron is that, when erythropoietin is needed, lower doses will be required to achieve the target Hct than if Epo were used alone.
They also claimed an I/V iron preparation, Ferric hydroxide sucrose complex, to be extremely safe with regard to the risk of anaphylactic reactions, as the authors did not see even a single anaphylactic reaction in over 20,000 infusions over a four year period.

Nissenson AR and co-workers (1999). University of California at Los Angeles Medical Center, USA, evaluated the response of I/V iron, sodium ferric gluconate complex in sucrose, in anemic CKD patients on hemodialysis and found it to be highly safe an effective in improving Hb, Hct, Iron saturation and serum ferritin level.

Faich G and Strobos J (1999), Pharmaceutical safety Assessments, Narberth, USA also assessed the safety profile of I/V iron, sodium ferric gluconate complex in sucrose and found it to be a much better alternative I/V iron preparation as compared with iron dextran.

Ahsan N (1998) Department of Medicine, Milton S Hershey Medical Centre Pennsylvania state University College of Medicine, USA, performed a comparative study on I/V vs Oral iron administration in treatment of anemia in peritoneal dialysis (PD) patients. The study was performed on 25 stable PD patients, divided into two groups, one group receiving single I/V infusion of total dose iron given on out patient basis where as the other group receiving oral iron. The study conclusively showed that the I/V iron treatment is more efficacious method of iron supplementation that oral iron in PD patients. The study also showed that
single I/V infusion of total dose iron is a safe and well tolerated method of iron administration that can be used on outpatient basis.

**Canavese C and coworkers (2004)** *Department of Internal medicine, Section of Nephrology, University of Torino, Italy* worked on low dose continuous iron therapy in chronic hemodialysis patients. Their study included 30 chronic hemodialysis patients who were put on low dose continuous iron therapy in the form of I.V iron gluconate 31.25 mg/wk for a period of 12 month followed by a 6 month withdrawal period and then again on same dose for 9 months. The study showed a significant increased in serum ferritin and TSAT during period 1 and 3. Another important observation made in the study was serum transferring level that showed a significant decrease during period 1 and 3 while increase during period 2 (i.e. negatively correlated with ferritin). Thus, this study concluded that even low dose maintenance iron therapy with only 31.25 mg weekly over one year cannot prevent the risk of iron overload in patients with moderate anemia.

*Another study published this year [Jan 2006] by Mircescu G et al, Dr Carol Davila Teaching hospital of Nephrology, Romania,* evaluated the response of I.V iron sucrose for the treatment of anemia in pre-dialysis chronic renal failure patients, who were not receiving erythropoietin. This study included 60 patients who were given 200mg of elemental iron in the form of iron sucrose preparation for a period of 12 months. The study showed a significant increase in Hb, serum iron, serum ferritin and
transferrin saturation with no worsening of renal function, no increase in blood pressure and no other side effects.

The study concluded that -

- I/V Iron therapy in pre-dialysis CKD patients not receiving erythropoietin seems to ameliorates the anemia, avoiding the necessity of erythropoietin or blood transfusion in atleast one third of patients.

- I/V iron supplementation in the form of iron sucrose appears to be effective and safe for treatment of anemia in CKD patients.

*Verma PP and co-workers (July 1999) and R&R Hospital New Delhi,* studied the types of anemia in patients with CKD and role of aluminium in hypochromic anemia of CKD. Their study was performed on 64 dialysis dependent patients of CKD with adequate dietary intake (>1500cal/day) and no apparent source of blood loss and the patients were evaluated for type of anemia. The classical normocytic normochromic picture was observed in 28.5% cases, while rest had hypochromic picture. On bone marrow study two patients had zero iron stores while all other had normal or excessive iron stores. In 10 patients with hypochromic picture, mean serum aluminium level was 170µg/lit.

This study highlights the high prevalence of hypochromic anemia in patients with adequate dietary intake and aluminium overload in Indian CRF patients.
Singh NP and Co-workers, Department of Medicine, Maulana Azad Medical College, and Associated Lok Nayak Hospitals, New Delhi assessed the efficacy of low dose erythropoietin therapy in treatment of anemia of CRF, and concluded that low dose erythropoietin (40U/Kg, biweekly) therapy is safe and effective in management of anemia of CRF.

Agarwal HK and Co-workers (2002) Department of Medicine, Nephrology and Clinical Pathology, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak (Haryana) India, performed a comparative study on use of oral and I/V iron in predialysis patients of CRF receiving recombinant human erythropoietin.

Their study was performed on 40 adult patients of CRF, who were divided into two groups – one group receiving oral iron in the form of ferrous sulphate 200mg three times a day and another group receiving 100mg of elemental iron in the form of 2ml iron dextran, twice a month intravenously. Both the groups received recombinant human erythropoietin in the dosage of 2000 units subcutaneously twice a week. The patients were followed for a period of 3 months. From the study it was concluded that I/V iron is far better than oral iron for treatment of anemia in CRF patients receiving erythropoietin, as shown by a significant rise in hematological parameters in I.V treated group as compared with oral group.