5. Renal Complications

Principles

- To prevent renal complications associated with thalassemia both transfusion and non-transfusion dependent thalassemias.
- To provide effective monitoring and treatment for patients with evidence of renal disease.
- To provide effective monitoring of renal function for patients on iron chelation

Recommendation

- Renal abnormalities, both tubular and glomerular, are frequent in patients with TDT and NTD.
- Contributing factors likely include chronic anemia and hypoxemia, iron overload, and iron chelators.
- Serum creatinine needs to be checked monthly to every 3 months according to iron chelator and baseline creatinine.
- Proteinuria needs to be monitored on regular basis.
- Refer to a nephrologist with expertise in the thalassemia management need to be considered when appropriate.

Background

Advances in the management of thalassemia patients have improved morbidity and mortality. Previously under-recognized end organ complications are becoming more apparent. Emerging data have demonstrated that renal abnormalities, both tubular and glomerular, are common in patients with both transfusion dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT).

Low-molecular weight proteinuria is nearly universal in patients with TDT.[392-394] Other tubular abnormalities described include increased urinary excretion of N-acetyl-β-D-glucosamide (NAG) and/ or β2-microglobulin (indicators of proximal tubular damage), calcium, phosphate, magnesium, uric acid, amino acids, and malondialdehyde.[392-402] In addition to tubular changes, glomerular abnormalities have also been reported ranging from hyperfiltration, overt proteinuria, to long-term decrease in glomerular filtration rate. [394,395,397, 401-407]

Diverse mechanisms are thought to contribute to renal dysfunction although these need to be further elucidated. These factors include chronic hypoxia and anemia, iron overload, and medication effect from iron chelators.[407] In vitro and animal studies have suggested that tubular and endothelial cells are susceptible to apoptosis under hypoxic stress with resulting tubular dysfunction and interstitial fibrosis. [409-414] In comparison, anemia appears to contribute to glomerular dysfunction by altering renal vascular flow and inducing renal hyperperfusion and glomerular hyperfiltration.[400, 406,415] In the longer-term this may result in progressive renal damage. Quinn et al also speculated on the role of hemolysis through the release of free heme and resulting decreased nitric oxide bioavailability on renal dysfunction as opposed to chronic anemia alone.[406] Supporting this hypothesis is the effect of free heme on renal injury.[416]

Various studies support the nephrotoxicity of iron. An animal model demonstrated iron deposition in the glomeruli, proximal tubules and interstation with associated proteinuria. [417] Similarly, there appears to be a correlation between increased serum ferritin and the urinary excretion of N-acetyl-β-D-glucosaminidase and β2-microglobulin, markers of proximal tubule damage.[397, 418] With adequate iron chelation, there was reversal in the observed tubular defects. [399, 418] In another study, a decreased MR T2* value was the only independent predictor of nephropathy.[404] The mechanism proposed for this iron toxicity to kidneys is similar to that seen in other target organs: 1) production of reactive oxygen species 2) lipid peroxidation and mitochondrial stress resulting in cell injury and death 3) release of cytokines and growth factors 4) fibrosis and sclerosis.[392, 419, 420]

Acute renal injury and even failure requiring dialysis have been demonstrated in a few patients receiving

deferoxamine.[421-425] Fortunately, the kidney injury was reversible in these patients. Significant renal dysfunction has also been described in some patients with bone marrow failure taking deferasirox.[426-430] In TDT patients; an increase in creatinine from baseline has been seen in patients receiving deferasirox or deferoxamine with some requiring dose modifications for normalization of their creatinine whereas others resolved spontaneously without intervention. [405,431] The prospective EPIC study which monitored patients for up to five years did not show any progressive increase in serum creatinine.[432, 433] It remains unclear how iron chelators affect the kidney. It has been suggested that over-chelation and relative iron depletion may be implicated in the renal changes observed during chelation therapy perhaps by affecting energy metabolism and/or altering prostaglandin production impacting renal hemodynamics.[392, 408]

Interventions

- There is a paucity of data in terms of kidney-specific management. One might infer from the proposed pathophysiology that renal injury may be reduced by simultaneously 1) minimizing hypoxia and anemia by regularly transfusing TDT patients 2) preventing iron overload through adequate chelation therapy 3) while avoiding over-chelation. Various other measures have been suggested but are lacking clinical data in thalassemia patients: prolyl hydroxylase inhibitors, renin angiotensin system blockage, antioxidants such as vitamin E and acetylcysteine, VEGF, arginine.[408] Additionally, one study has suggested that renal tubule function may improve in beta-thalassemia patients after hematopoietic stem cell transplant.[434]

- Baseline screening:

    - Serum creatinine levels should be assessed before initiating iron chelation therapy

- Monitoring:

    - Serum creatinine monthly deferasirox, q3 months deferoxamine
    - Patients who with additional renal risk factors should be monitored weekly during the first month after initiation or modification of deferasirox therapy, and monitored monthly thereafter. Consider GFR measurement
    - Monitor regularly for proteinuria. Fluctuations are expected; however, upward trend in the protein/creatinine, interruption or dose reduction should be considered.
    - Other causes of increasing creatinine should also be considered, example concomitant nephrotoxic medication, renal stones, etc.

- Iron chelation adjustment

    - Refer to iron chelation chapter