Progresion to Renal Failure

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Chronic renal failure is characterized by persistently abnormal glomerular filtration rate. It represents a developing process that is initiated by various causes, all with the common end result of persistent and usually progressive damage of varying severity to the kidneys. However the rate of progression varies significantly. I will try to discuss processes that affect progression after the initial renal insult has taken placed. Although the causes and the locations of renal insult may vary, many features are common to progression of renal failure and the final histological picture is one of glomerulosclerosis, interstitial fibrosis and loss of renal cells mainly by apoptosis.

In this context several factors play a part such as increased synthesis and decreased breakdown of extracellular matrix (ECM) and increased myofibroblasts involve the fibrinogenic process. In the process to renal progression, the balance between cell proliferation and apopitosis is also impaired. There is a loss of normal resident cell population caused by a combination of increased proapoptotic stimuli and reduced antiapopitotic stimuli. Furthermore monocytes and macrophages are recruited by cytokines which are over expressed in chronic renal failure and as a response to renal injury over expression of the macrophage colony stimulating factor by the tubules drives local macrophage proliferation in the kidney. These cells produce more cytokines which promote further fibrosis and apopitosis.

Pathophysiologic pathway to progression of renal failure is seen in Table1. Mainly the factors and processes enable renal dysfunction are hemodynamic factors, proteinuria, systemic hypertension, hypoxia, angiotensin II and other chemical mediators such as cytokines, growth factors.

Hemodynamic factors -Decreased nephron mass followed by renal insult, leads to compensatory hyperfiltration of the spared nephrons and facilitates to maintain overall GFR. However this adaptation leads to glomerular hypertension, proteinuria, and progression to renal failure. The stretching of the glomerular capillary tuft due to glomerular hypertension also stretches the neighboring mesangial cells, which induce mesangial cell proliferation followed by glomerulosclerosis. Overexpression of cytokines plays a role in this process.

Proteinuria

Glomerular capillary hypertension and the damage to permeability barrier result in proteinuria. Protein leaking from the glomerulus is taken up by proximal tubule cells. Protein loaded proximal tubular cells causes to activation of the intra renal angiotensin-converting enzyme and to abnormal production of endothelin-1 (ET-1), monocyte chemoattractant protein1 (MCP-1) and RANTES (regulated on activation, normal T cell expressed and secreted). The cytokines favor fibrosis, apoptosis and monocytic infiltration, further spreading the process.

Hypertension itself accelerates decline in renal function due to the increased glomerular capillary hypertension.

Angiotensin II (AII) is one of the key factors in progressing to renal failure. AII can be produce locally in the kidney and this local intrarenal renin-angiotensin system plays a critical task in renal auto regulation and physiologic developments. Besides its hemodynamic effects, AII stimulates expression of fibrinonectin, transforming growth factor-β (TGF-β), plasminogen activator inhibitor-1 (PAI-1), ET, aldosterone and possibly transcription factor nuclear factor κB which all favor fibrogenesis and enrollment of macrophages.

From the clinical point of view progression to renal failure has a complex and multifactorial nature (Table 2). Both renal and nonrenal predictive factors may take place and /or facilitate on the progression of renal failure. Some of the nonrenal predisposing factors both in children and adults are genetic predisposition, low birth weight, hyperlipidemia, obesity, cardiovascular diseases, lower economic status and lower educational achievement.

Primary renal disease resulting to renal insult and eventually to renal failure mainly are; congenital uropathies and glomerular diseases. Predictive factors of the progression to renal failure in children reported by North American Pediatric Renal Transplant Cooperative Study Group (NAPRTC) are low base line creatinin clearance (<50 ml/min/1.73 m^2), presenting with FSGS, low hematocrit, hypoalbuminemia, hypocalcaemia, hyperphosphatemia and hyperparathyroidism. In another study GFR under 30ml/min, severe proteinuria reported to be the independent predictors of progression to end stage renal failure (ESRF) in children.

Successful attempt at slowing down the renal progression will require a broad approach such as

treatment of primary disease, aggressive treatment of hypertension and proteinuria, early referral to a nephrologist and using potentially useful modalities

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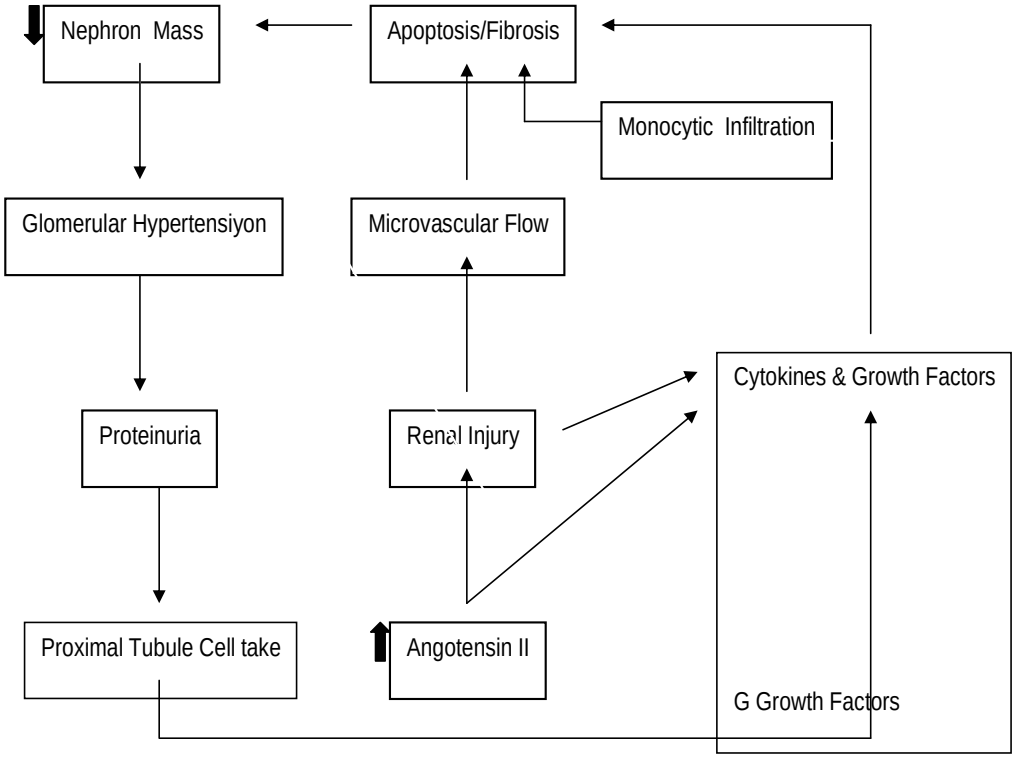
Table 1. Pathophysiologic Pathway of Chronic Renal Failure



(protein restriction in select patients, control of hyperphosphatemia, treatment of hyperlipidemia, erythropoietin, binding protein metabolites-AST-120 binds indole precursor of protein metabolite indoxyl sulfate, aldosterone antagonists).

First line primary renal disease causing renal failure in Turkish children is vesicoureteral reflux (VUR) nephropathy. I believe that it can be the similar in the Balkan area. This gives us an opportunity to reduce the progression of renal failure by diagnosing VUR in time and preventing recurrent urinary tract infections in some extend bearing in mind the other disorders which increase the risk of chronic kidney disease.

References

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