CHAPTER II

BACKGROUND RATIONALE

A large body of evidence indicates that an alteration of glomerular endothelial function has been encountered in renal patients associated with nephrotic syndrome. The glomerular endothelial surface alters from the anticoagulant expression in the normal state to becoming procoagulant activity during nephrotic syndrome[32]. Such a change in the expression of glomerular endothelium induces platelet aggregation and local intravascular coagulation in the glomerular microcirculation which is supported by the presence of shortened platelet halflife, fibrin and fibrin degradation product in the kidney and in serum and urine, and altered hemorheology namely blood hypercoagulability and hyperviscosity[33-38]. In addition, a determination of renal plasma flow which reveals a progressive reduction in renal perfusion as the disease severity progresses also implies that the ability of endothelial cell to normally dilate and maintain the perfusion is impaired and becomes provasoconstrictive in the state of severe nephrotic syndrome. Such a *dysfunctioning glomerular endothelium* in relevant to the reduction in renal perfusion has recently been delineated to represent a hemodynamic mechanism crucial to the pathogenesis of renal disease progression[39]. In essence, 2 specific issues are addressed (1) the reduction in renal perfusion precedes the development of tubulointerstitial fibrosis in severe form of idiopathic

nephrotic syndrome. (2) There is a spatial relationship between the degree of 2 reduction in renal perfusion and the magnitude of tubulointerstitial fibrosis. This simply implies its cause – and – effect relationship[40]. Similar observation was also denoted by Bohle and associates that the degree of tubulointerstitial fibrosis correlated inversely with the intensity of post glomerular capillary patency[41].

The *specific issue concerning the plausible cause of glomerular endothelial dysfunction* remains to be further elucidated. In this regard, the spontaneous and progressive reduction in renal perfusion as the disease severity progresses renders a supportive view that there should be certain toxic factor in the serum of such patient. To confirm this, it is therefore important to know whether sera from nephrotic patients are capable of inducing endothelial cell cytotoxicity in vitro ?. If so what in the sera of such patients is responsible for such phenomenon ?. By virtue of its location at the interface between the circulating blood and capillary wall, the glomerular endothelial cell is likely to be influenced by a number of hormonal as well as noxious or metabolic substances namely vasoconstrictive substances, reactive oxygen species and cytokines[42].

Reactive oxygen species in excessive amount is considered as one of the pivotal toxic product that is able to oxidise the cellular component and induce oxidative metabolic product capable of damaging the structure and function of the endothelial cell. Several

lines of investigation suggest that the production of reactive oxygen species and the resultant oxidative stress plays a key role in mediating the pathological manifestation of endothelial dysfunction[42]. It is capable of not only inducing proteinuria and nephronal damage in experimental model of puromycin aminonucleoside in animal[43], but also participating in a variety of clinical settings of glomerulo-nephritides[44-47]. It is therefore of interest to perform in this study an assessment of oxidant and antioxidant status in nephrotic patients. If there would be any evidence of oxidative stress, it would also be interested to see whether a correction of oxidant and antioxidant imbalance would improve the endothelial cell cytotoxicity, the renal function and prevent or retard the progression of renal disease in these severe form of nephrotic patients.