Chapter 1

Introduction
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Chronic renal failure (CRF) represents a progressive, irreversible decline in the glomerular filtration rate. Progressive renal function loss is a common phenomenon in renal failure, irrespective of the underlying cause of the kidney disease. Most chronic nephropathies lack specific treatment and progress relentlessly to end-stage renal disease (ESRD) prevalence of which is increasing worldwide (Locatelli et al., 2001; Moeller et al., 2002).

Chronic renal failure is associated with an extensive and complex set of pathological consequences that can result in a number of irreversible, but preventable complications affecting every organ of the body. Chronic renal failure is associated with insulin resistance, hypertension, increased glycation of proteins, proteinuria, anemia, cardiovascular diseases and hypothyroidism. Even though, these disorders have a multifactorial etiology, there is now strong correlative evidence implicating the formation of reactive oxygen species (ROS) and the accompanying increase in oxidative stress as key contributors to these biological perturbation and thereby contributing significantly to the progressive decline in renal function in CRF (Locatelli et al., 2003).

Studies in the past have demonstrated the pathophysiological importance of the metabolites of partially reduced oxygen molecules or reactive oxygen species (ROS) in various experimental renal diseases, including several animal models of primary glomerulopathy and acute renal failure, both ischemic and nephrotoxic (Shah., 1989). Accumulating evidences from clinical studies have also suggested that CRF is associated with enhanced oxidative stress (Himmelfarb and Hakim, 2003).

The consequences of oxidative stress are multiple and invariably ominous. A normochromic, normocytic anemia secondary to decreased erythropoietin production and shortened erythrocyte survival is seen in more than 90% of patients. Recently, an anemia
identification and intervention strategy for patients with chronic renal insufficiency was proposed for the Renal Anemia Management Period (RAMP) (Besarab and Levin, 2000). RAMP is defined as “that critical period in the evolution of progressive kidney disease when anemia may be subclinical or asymptomatic, but during which correction of anemia has the potential to alter the complications of chronic renal insufficiency” (Besarab and Levin, 2000). Although the benefits of such a program have yet to be evaluated the conceptual framework represents a rational approach that addresses current treatment strategies and their economic implications. Correction of anemia in CRF patients, besides its beneficial effects, represents an effective approach to reduce oxidative stress (Lahera et al., 2006).

Chronic renal failure with and without nephrotic syndrome is frequently accompanied by abnormalities in lipoprotein metabolism. Cardiovascular death is the most commonly reported cause of mortality in the ESRD population. Hyperlipidemia has been reported to be associated with progressive renal disease in both animal and human studies (Mackenzie and Brenner, 1998). In animal models, use of lipid-lowering agents decreases the extent of glomerular injury when both underlying renal disease and hyperlipidemia are present (Scanferla et al., 1992; Walker, 1993). Among the examined nontraditional risk factors, an increase in oxidative stress has been postulated to contribute to excessive uremic cardiovascular risk (Yeun and Kaysen, 2000). Therefore, the correction of lipid abnormalities in patients with renal insufficiency may have a beneficial effect on the rate of progression of renal disease.

Nonenzymatic glycation of both circulating and structural proteins is a process of particular physiopathological relevance for the development and progression of many pathological conditions like diabetes and atherosclerosis (Lapolla and Traldi, 2005). Non-enzymatic glycation is a common posttranslational modification of proteins in which reducing sugars bind covalently to the free amino groups (Lapolla and Traldi, 2005). This
non-enzymatic modification of proteins alters not only the structure, but also the biological properties of proteins. This can lead to a variety of chemical entities and induce structural changes in enzymes starting from conformational alterations, progressing to thiol oxidation, aggregation, formation of disulphide and other covalent cross-links, and inactivation of enzymes. Excessive generation of nonenzymatic glycated products has been reported as one of the mechanisms proposed in the pathogenesis of progressive renal injury (Wells-Knecht et al., 1996). Consequently, the inhibition of glycation reaction could be of great interest to prevent the progression of renal insufficiency.

Apart from these perturbations, a variety of endocrine and metabolic abnormalities are common in CRF. Many aspects of carbohydrate metabolism are impaired in patients with chronic renal failure (CRF). These derangements lead to glucose intolerance in these patients (Alvestrand, 1997; Mak, 1989). Patients with chronic renal failure have been reported to have mild fasting hyperglycemia and an abnormal response to an oral and intravenous glucose tolerance test, and some maintain normoglycaemia in the presence of hyperinsulinaemia. Several lines of evidence suggest that hyperglycemia and hyperinsulinemia may be important risk factors for the development of atherosclerosis, accumulation of advanced glycosylation end products in various tissues, and dyslipidemia, and may, in addition, have adverse effects on protein metabolism in chronic renal failure patients (Alvestrand, 1997; Mak, 1989). Impaired insulin action occurs at early stages of renal disease (Sechi et al., 2002), and the prevalence of IR increases as the glomerular filtration rate decreases (Sit et al., 2006). A number of different factors have been suggested to contribute to IR in chronic renal failure, including hormonal imbalances, chronic metabolic acidosis, anemia, and physical inactivity (Zanetti et al., 2008).

Although the relationship between oxidative stress and uremic complications has been extensively investigated, the possible role of oxidative stress in glycemic regulation is still a
neglected area. However, there are evidences in the literature that enhanced free radical concentrations may impair insulin action, thus contributing to the generation of hyperglycemia (Hansen et al., 1999; Rudich et al., 1997). Previous report from our laboratory has indicated that vitamin E can improve the insulin sensitivity in L-6 cell lines exposed to oxidative stress (Vinayaga Moorti et al., 2006). Even though results of in vitro experiments have suggested that oxidative stress per se can cause decreased glucose uptake, controversial reports are still documented in the literature regarding the effects of hydrogen peroxide on insulin signaling machinery (Hayes and Lockwood, 1987; Heffetz et al., 1990).

Given the plausible imperative role of oxidative stress in the development of various pathological processes associated with chronic renal failure, it is of interest to evaluate the beneficial effect of antioxidants in ameliorating these pathological processes. It was therefore deemed pertinent to study whether oxidative stress per se can modify insulin sensitivity, glycation. Efforts were also made to explore the possible beneficial effects of green tea and taurine in preventing these pathological processes. The lack of information in literature with respect to the relationship of oxidative stress with these pathological processes in chronic renal failure prompted the search for the same in patients with chronic renal failure.