Summary
Metabolic syndrome, which occurs commonly in populations around the world, has been associated with an increased risk for developing cardiovascular disease and diabetes. Typically, measures of excess weight, elevated blood pressure, dyslipidemia, hyperglycemia, and inflammation are considered key elements of the syndrome. In addition to these abnormalities, oxidative stress, which is an imbalance between prooxidants and antioxidants, has also been implicated in the pathogenesis of cardiovascular disease and diabetes and serves as a common feature of metabolic syndrome. This has at least two possible implications. First, oxidative stress may be involved in the pathogenesis of metabolic syndrome. Second, oxidative stress may contribute to the complications that arise from the syndrome. Thus, understanding factors that serve to maintain the balance between prooxidants and antioxidants may help to increase the understanding about its pathophysiology and to define possible avenues for prevention and treatment.

The etiology of metabolic syndrome is multi-factorial and the reports of National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) recognized the importance of cardiovascular risk factors of what they referred to as a “constellation of lipid and non-lipid risk factors of metabolic origin” and designated this cluster as metabolic syndrome. The allied lipid disorder consists of elevations of serum triglycerides, apolipoprotein B (apo B) and small LDL particles, and low levels of HDL. These multiple abnormalities almost certainly promote the development of atherosclerosis. All of the steps in the progression of atherosclerosis in one way or another are inflammatory and it is well documented that inflammatory mediators (such as CRP and TNF-α) play a paramount role in the initiation, progression and rupture of atherosclerotic plaques. Thus markers of inflammation and endothelial dysfunction may provide additional information about a patient’s risk of developing metabolic syndrome and may become new targets for treatment.

On the other hand, evidence has emerged suggesting that the free radical generation or inadequate antioxidant defenses may lead to alteration in
structure and function of fat, protein, carbohydrate, RNA or DNA molecule. As far as the management of these disturbances in the body itself is concerned, an HDL-associated enzyme paraoxonase (PON-1) has emerged as one of the best prototypes in context of metabolic syndrome. In this regard, an understanding to the mechanism and potential role played by antioxidants, gained an outstanding importance. This has further stimulated intense research efforts to validate the beneficial effects of exogenous antioxidants or certain medicinal interventions against diabetes, hypertension and metabolic syndrome.

The first chapter of the thesis highlights and reaffirms the involvement of abnormal lipid profile together with the elevated waist circumference and inflammatory markers in prediction of metabolic syndrome in diabetic and hypertensive population. It has been established that CRP levels >3.0 mg/l adds a prognostic evidence for metabolic syndrome. Subsequently, our findings demonstrating such higher values of CRP put both diabetic and hypertensive subjects at a higher risk to develop metabolic syndrome. However, the comparatively lowered PON-1 activity and significantly lesser time for oxidation of sLDL among hypertensive subjects reflected them to be a much easier prey. This adds to a novel finding in the field of metabolic syndrome suggesting and giving an idea to find urgent preventive measures to control hypertension as well as diabetes.

The second chapter of the thesis therefore accounts for the strategies involved in the treatment of diabetes and hypertension. To explain the depth of its significance, this chapter has been bifurcated in two divisions. The treatment modalities for diabetic subjects included monotherapy with either metformin or insulin. Our aim was to scrutinize all the traits of metabolic syndrome before and after the supplementation of these hypoglycemics with the recommended doses for a considerable period of time. It was noticed that despite of beneficial changes in lipoprotein profile, such a monotherapy was not able to recompense for increased inflammatory markers and the DNA damage incurred in diabetic population. The second unit to this chapter throws light on the efficacy of
antihypertensive drugs over the various abnormal parameters of metabolic syndrome. Our results have demonstrated a significant elevation in PON-1 activity together with a reduction in lipid peroxidation as well as levels of inflammatory markers in hypertensive subjects treated with either ramipril or losartan as a once-daily anti-hypertensive agent. Besides, it was also witnessed that none of the two therapies could prevent the DNA damage up to any conspicuous level.

If oxidative stress is the pathogenic mechanism leading to metabolic syndrome as well as diabetes, the ability of a drug to prevent or reverse oxidant stress can account for its clinical usefulness. In view of this, the third chapter discusses the role of antioxidants, particularly vitamin C and vitamin E in prevention of the metabolic abnormalities aroused in the alloxan-induced diabetic rabbits. Our results with vitamin C and E clearly demonstrated significant improvement in each of the component of metabolic syndrome, the former showing much favorable results however. In addition, the DNA damage was also recovered partially, when they were supplemented with vitamin C. Such a favorable effect with antioxidants may be attributed to their ability to maintain the balance between excess free radicals and reduced antioxidant defenses.

Hitherto, it has been recognized that metabolic syndrome represents a very heterogeneous cluster of components that need a tailored but integrated approach. Moreover, the challenge for developing a new drug that will substantially reduce multiple risk factors is formidable. In this direction, the present study successfully highlights the importance of antioxidants in ameliorating the complications of metabolic syndrome. It may thus be implicated that antioxidants might provide a better prevention to metabolic syndrome as compared to that conferred by hypoglycemics or antihypertensives. This may also suggest a strong association between diabetes, oxidative stress and metabolic syndrome.