Diabetes mellitus refers to a group of metabolic and hormonal disorders characterized by elevated blood glucose resulting from inadequate insulin secretion or impaired insulin action. In some cases, the primary defect is the synthesis, release or action of insulin; in other instances, a metabolic defect beyond insulin is responsible (Taylor et al, 1994). The chronic hyperglycemia that results, may eventually lead to dysfunction, damage and eventual failure of various organ systems, especially the heart, kidneys, blood vessels, nerves and eyes. Although most health care providers primarily associate diabetes mellitus with abnormal carbohydrate metabolism, protein and lipid metabolism are also adversely affected by the inadequate insulin secretion or decreased tissue responsiveness to insulin (insulin resistance) (DeFranzo et al, 1992).

The central identifying feature of diabetes is chronic and substantial elevation of circulating glucose concentration. This ‘minimum identifying feature’ may be accompanied by a plethora of other biochemical disturbances and clinical manifestations, nature and severity of which depend upon the pathogenesis of the diabetic state, the degree of insulin action, co-existent environmental or co-morbid conditions, and the presence of progressive diabetic tissue damage. The metabolic abnormalities associated with diabetes mellitus are determined primarily by the degree of hyperglycemia resulting from the interplay between variable degree of insulin deficiency and insulin resistance in various tissues notably skeletal muscles, adipose tissue and liver (Martin et al, 1992).
Interest in trace elements has been steadily increasing over the last 25 years. A growing number of trace elements have been found to be of immense nutritional importance to mammals and a few of these elements are considered to be of physiological significance in human (Aggett, 1985). The major recognized functions of the trace elements relate to several crucial metabolic pathways. They serve as a variety of catalytic, structural and regulatory functions in which they interact with macromolecules such as enzymes, pro-hormones, pre-secretory granules and biological membranes (Aikawa, 1963). Disorders of mineral metabolism are among the less well-understood clinical problems encountered by clinicians and magnesium deficiency is one of them (Razz & Havivi, 1989).

Many studies have suggested an association between diabetes mellitus and alterations in concentration of intracellular electrolytes including magnesium, sodium, potassium and calcium. It is still contentious whether disturbances in ionic imbalance occur after the development of diabetes mellitus or whether diabetes is the result of altered ionic environment. Several large observational studies have demonstrated strong cross-sectional association between low serum magnesium levels and type 2 diabetes (Kao et al, 1999). In vitro studies have also shown an effect of magnesium on the secretion of insulin by pancreas and on the responsiveness to insulin by peripheral tissues (Moles & McMullen, 1982).

Hypomagnesemia has been suggested to probably be the 'most under diagnosed electrolyte deficiency in current medical practice' (Whang, 1987). Despite the known frequency of this metabolic disorder in diabetic patients, little is known about the clinical complications of hypomagnesemia in diabetes. Until recently, hypomagnesemia was a poorly recognized feature of diabetes mellitus. There are conflicting reports on plasma/serum magnesium concentration in diabetic patients. Although most of
the studies seem to stress the presence of low plasma and tissue levels of magnesium, yet several different reports have supported the presence of normal and or even higher mean serum and intracellular magnesium levels. Numerous physiological and clinical variables are probably able to modify the status of magnesium in diabetic patients. In particular, the type of diabetic disease, the duration, the severity of impairment of glucose metabolism, presence of obesity, the kind of therapy practiced and renal function can explain the heterogeneity of the results obtained (Yajnik et al, 1984; Mather et al, 1982). With the more accurate techniques and comparatively large-scale studies, diabetes has been found to be most frequent chronic disorder associated with hypomagnesemia in patients attending a general medical clinic (Mooradian & Morley, 1987).

Magnesium is essential ion involved in glucose homeostasis at multiple levels. A complex interplay exits between magnesium and glucose metabolism. Magnesium plays an important role in activities of various enzymes involved in glucose oxidation and may play a role in the release of insulin. Magnesium has been reported to be mainly intracellular and its intracellular uptake is stimulated by insulin (Paolisso et al, 1986). Magnesium influences insulin secretion by altering the sensitivity of β cells of islets of Langerhans to glucose (Dzurik et al, 1991).

Magnesium is the most abundant intracellular divalent cation present in living organisms. Magnesium is also involved in amino acid activation, protein synthesis and is required for ribosomal integrity, DNA replication, transcription into RNA and translation into proteins (Vernon, 1988).

All enzymatic reactions that involve ATP show an absolute requirement for Magnesium (Ingraham & Green, 1958). Magnesium co-ordinates with ATP molecule to form true substrate and in addition may labilize the terminal phosphate bond of ATP to facilitate the transfer of phosphate to other molecule. It may also
serve to neutralize the negative charge density on the ATP molecule and facilitate its binding to the enzyme participating in biochemical reactions. The almost universal involvement of magnesium in a wide variety of cellular processes critical to glucose metabolism, insulin action and cardiovascular function and has been well appreciated (Gomez, 1998). Intracellular free magnesium (Mg) exists in the regulatory concentration range for most magnesium-dependent enzymes, channels and pump mechanisms.

Physicians are now recognizing Magnesium deficiency frequently due to increased clinical awareness and greater frequency of assessment of magnesium status. In the recent years there has been a growing interest in magnesium and its correlation with development of various age related diseases viz: hypertension, diabetes mellitus, cardiovascular diseases, atherosclerosis, myocardial damage, cardiac arrhythmias through free radical oxidation of cellular components. Linkage between magnesium deficiency and insulin resistance, carbohydrate intolerance, accelerated atherosclerosis, dyslipidemia, hypertension and adverse outcomes in pregnancies complicating diabetes have been observed or postulated (Resnick et al, 1991).

Magnesium deficiency is unlikely to occur in man from simply lack of foods containing this mineral, except in advanced forms of malnutrition (Hamilton & Minski, 1972). Diabetic patients may develop hypomagnesemia possibly because of excessive urinary loss of magnesium accompanied with glycosuria or due to decreased intestinal absorption or both. Recent reports have also suggested that it may involve some specific defect at the tubular level in renal reabsorption (Garland, 1992). It is proposed that hypomagnesemia might be a risk factor in the development of diabetic complications. Long-term hypomagnesemia may exert deleterious effect on vascular diseases. Epidemiological surveys, clinical investigations and experimental studies have currently reported that magnesium may play an important role in the
Oxidative stress, resulting both from over-production of reactive oxygen radicals and decreased efficiency of antioxidant defenses is now considered a factor contributing to chronic diabetic complications. The strict relation between the known pathogenic factors involved in the development of these complications (non-enzymatic protein glycation, activation of polyol pathway, changes in lipid metabolism, haemostatic abnormalities) and oxidative stress has been examined in the light of recent studies (Baynes, 1991).

There is a large volume of literature suggesting that magnesium deficit contributes to aging process and to the vulnerability to age-related diseases (Fehlinger, 1989; Durlach et al, 1993, Rayssiguier et al, 1993). One of the biological changes associated with aging is an increase in free radical formation and subsequent damage to cellular processes. Prime targets of these reactive free radicals are unsaturated lipids in the cell membranes, amino acids in proteins and nucleotides in DNA.

It has recently been suggested that mammalian tissue contains numerous defenses against oxidative stress some of which may be compromised during magnesium deficiency (Weglicki et al 1996). Furthermore, magnesium itself possesses antioxidant properties, scavenging oxygen radicals, possibly by affecting the rate of spontaneous dismutation of the superoxide ion. Free radical oxidation of cellular components is a well-established mechanism in cellular injury in many of the age related diseases including diabetes mellitus and hypertension. There has recently been interest in the hypothesis that oxidative stress may contribute to the development of complications in diabetes mellitus.
Keeping in view the above stated observations, the present study was planned with an objective to find out the interrelationship between magnesium status and oxidative stress in diabetes and to evaluate the effect of magnesium supplementation on oxidative stress in diabetes. Following studies were carried out to achieve the objective:

- To induce magnesium deficiency in rats by synthetic diet and evaluate its effect on magnesium status (in serum, RBC, urine and tissues), blood glucose and plasma insulin.
- Whether magnesium deficiency exists in experimental diabetes induced in the rats by diabetogenic agent i.e. alloxan and time taken for magnesium deficiency.
- To study the parameters of oxidative stress (vitamins C & E, uric acid, total thiols, MDA and RBC GSH) and total radical trapping antioxidant parameter (TRAPc) in experimental rats as compared to control rats.
- To study the effect of magnesium deficiency and diabetes on lipid profile, other related ions (Na+, K+ & Ca2+) and ATPases (Na+ K+ ATPase and Ca2+ ATPase), and tissue antioxidant enzymes (SOD and GST).
- To evaluate the effect of magnesium supplementation on above stated parameters in experimentally induced diabetic rats as compared to non-supplemented diabetic rats.
- To study the magnesium status of human diabetic subjects and its relation to glucose, oxidative stress, TRAPc and other parameters.
- To find out the effect of duration of diabetes i.e. newly diagnosed to up to 20 years on magnesium status.