INTRODUCTION:

Diabetes mellitus is one of the main threats to human health in the 21st century (1). Changes in human behaviour and lifestyle over the last century were the main threats for dramatic increase in the incidence of diabetes worldwide [2]. Currently, over 346 million individuals worldwide suffering from Type 2 Diabetes and this number is estimated to reach 438 million by 2030 (3). Diabetes mellitus is a multifactorial disease which is characterized by chronic hyperglycemia which disturbs not only carbohydrate metabolism, but also of fat and protein metabolism due to defects in insulin secretion, action or both. Chronic exposure to elevated glucose and fatty acid concentrations can cause damage in different types of cells by a variety of mechanisms collectively known as glucolipotoxicity (4).

Diabetic Complications

Chronic complications of diabetes mellitus can be divided into vascular and nonvascular complications. The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular complications [coronary artery disease (CAD), peripheral arterial disease (PAD), cerebrovascular disease] (5).

Diabetic Retinopathy:
Retinopathy is characterized by increased vascular permeability [6], by vascular closure mediated by the formation of new blood vessels - neovascularization of the retina and posterior surface of the vitreous.
It can be classified as nonproliferative diabetic retinopathy and proliferative diabetic retinopathy or diabetic macular oedema. In diabetic retinopathy, the micro vessel supplying blood to the retina of eye is affected and can cause blindness in later stages.

Diabetic Nephropathy:
Diabetic Nephropathy [7,8] is a common and serious complication where kidneys are damaged and fails to function. The reason is due to persistent high blood sugar level in the blood. The condition when protein starts leaking in urine is called as microalbuminuria [9]. The common symptoms of kidney failure are fatigue, decreased appetite, nausea and vomiting. Anemia may also be observed in diabetic nephropathy.
Diabetic Neuropathy

Diabetic neuropathy is a chronic microvascular complication [10] affecting both somatic and autonomic peripheral nerves. It may be defined as the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes. Neuropathy and is due to high blood sugar, chemical changes that occur in the nerves. Generally it starts in the nerves of feet as they are the longest nerves and nourished with longest blood vessels of the body. This condition is called diabetic foot. Diabetic neuropathy can cause foot ulcers and foot infections as advanced complications in diabetic patients. Signs and symptoms of Diabetic Neuropathy include, decrease or no sweating, numbness, or tingling, and some sort of burning sensation, weakness and loss of reflexes.

Serum Minerals and Diabetes:

Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular cation. Magnesium acts as a cofactor in the glucose transporting mechanism of the cell and also plays an important role in glucose metabolism by acting as a cofactor for the various enzymes involved at multiple steps in insulin secretion, binding and activity (11). Magnesium deficiency has recently been proposed as a novel factor implicated in the pathogenesis of diabetic complications. Recognizing the signs of diabetes-associated magnesium deficiency is important because the deficiency can occur long before it is reflected by serum values (12). Not only hypomagnesemia has been associated with type 2 diabetes, but recent studies have reported an inverse relationship between glycemic control and serum Magnesium levels.

Zinc is the second most abundant transition metal in organisms after iron and it is the only metal which appears in all enzyme classes [13]. Zinc is an essential trace element, is useful in synthesis, storage and secretion of insulin (14). Zinc is necessary factor in a variety of “antioxidant” enzymes, particularly superoxide dismutase, catalase and peroxidase, alterations of zinc metabolism such that adequate zinc is unavailable for these enzymes might be expected to contribute to the tissue damage observed in diabetes (15).
Copper is also a vital dietary nutrient, although only small amount of the metal are needed for well-being [16]. Transition metal like copper has affinity to bind with proteins that have been glycated. Generally, serum concentration of copper and Ceruloplasmin is elevated in type 2 diabetes mellitus patients (17). Ceruloplasmin and serum albumin are the main copper binding proteins in plasma and there is some evidence that chronic hyperglycemia can damage the Copper binding properties of both (18).

Insulin resistance (IR) is a physiological condition in which cells fail to respond to the normal actions of the hormone insulin. The body produces insulin, but the cells in the body become resistant to insulin and are unable to use it as effectively, leading to hyperglycemia. Beta cells in the pancreas subsequently increase their production of insulin; further contributing hyperinsulinemia (19). This often remains undetected and can contribute to a diagnosis of Type 2 Diabetes. Insulin resistance, is the most powerful predictor of future development of type 2 diabetes, it is also a therapeutic target once hyperglycemia is present (20).

Increased oxidative stress is a widely accepted factor involved in the development and progression of diabetes and its complications [21]. Diabetes is usually accompanied by increased production of free radicals or impaired antioxidant defenses. Mechanisms by which increased oxidative stress is involved in the diabetic complications are partly known, including activation of transcription factors, advanced glycated end products (AGEs), and protein kinase C (22).

Vitamin D has a great role in glucose metabolism. These include insulin secretion, insulin exocytosis and promotes glucose uptake by peripheral tissues (23). It has got various effects such as suppression of cell mediated immunity, stimulation of neurotropic factors like nerve growth factor, regulation of cell proliferation, suppression of RAAS, Glial cell line-derived neurotrophic factor, neurotropin, reduction of albuminuria, immunomodulatory, anti-inflammatory and antiangiogenic effects (24,25).

The present study will be designed in order to estimate the alterations in the levels of serum minerals, and Vitamin D in type 2 diabetes mellitus patients with microangiopathic complications in comparison to those without these complications and their relation with oxidative stress, insulin resistance, and glycemic control.