Introduction
1. BACKGROUND

Diabetes

Diabetes Mellitus (DM) is a potentially devastating disease with high morbidity and mortality (Brownlee, 2001). Type 1 occurs in 5-10% of cases and is largely recognized as an autoimmune disease whereby the β-cells are destroyed by the body’s own antibodies. Since insulin can no longer be produced, the only effective treatment is daily insulin injection. It is estimated that 90-95% of diabetes are type 2 and is usually caused by a combination of resistance to the effects of insulin, particularly in adipose tissue, but also in liver, and its decreased production by β-cells in the pancreas. Fasting plasma glucose (FPG) concentrations are normally strictly maintained within 90-120 mg/dl but in type 2 diabetes the person is unable to maintain glucose within this range. The disease is characterized by a FPG of ≥ 126mg/dl or by a two hour oral glucose tolerance test (OGTT) of ≥200mg/dl. The onset of diabetes is preceded by a pre-diabetic state with FPG between 110-125 mg/dl and is referred to as impaired fasting glucose (IFG). Alternatively, it is recognized by a two hour OGTT of 140-200mg/dl and is referred to as impaired glucose tolerance (IGT). The American Diabetes Association (ADA) has recommended reducing the threshold for IFG to 100-125mg/dl. The WHO has chosen not to adopt this more stringent level because they believe there is no evidence to suggest any benefit in reducing adverse outcomes or progression to diabetes.

Glucose in the blood may bind to hemoglobin to give glycosylated hemoglobin (HbA1c). HbA1c is directly proportional to blood glucose level and it reflects the plasma glucose levels over the previous 2-3 months. WHO does not consider HbA1c level a suitable diagnostic test for diabetes or prediabetes for two reasons. First, this test is not readily available in many parts of the world. Secondly, HbA1c levels are influenced by other factors completely unrelated to diabetes such as anemia, pregnancy and uraemia. Because FPG and OGTT are the most applicable means of accessing glucose levels, the WHO has decided that these should remain standard for diagnosing diabetes.

Complications:

The effects of unregulated glucose control can lead to severe macro and microvascular complications. Diabetes primarily affects the heart, blood vessels, eyes, kidney and nerves. It is a leading cause of blindness and renal failure. Microvascular complications refer to those affects the heart, blood vessels, eyes, kidney and nerves. It is a leading cause of blindness and renal failure.
Microvascular complications refer to those affecting small blood vessels in the retina, kidney and peripheral nerves and can lead to retinopathy, nephropathy and neuropathy respectively. Diabetic retinopathy occurs as a result of long-term damage to blood vessels in the retinal and can lead to blindness or severe visual impairment. Diabetes can also cause the development of cataract through the formation of sorbitol deposits on the lens of the eye. Sorbitol is a product of the polyol pathway formed by the action of aldose reductase, which becomes overexpressed in type 2 diabetes, and is believed to be intimately involved with organ damage. Diabetes is among the leading causes of kidney failure and 10-20% of diabetics die from this. Diabetic neuropathy occurs as a result of damage to the nerves and results in tingling, pain, numbness and weakness in the extremities, which left untreated can lead to infection, ulceration and possibly amputation. Macrovascular complication refer to diseases affecting large blood vessels in the heart, brain and peripheral circulation leading to cardiovascular diseases such as atherosclerosis, heart attack and stroke, which are responsible for 50% of deaths of diabetics.

It is hypothesized that there are four main mechanisms by which hyperglycemia induces microvascular and macrovascular complications;

1. Increased polyol pathway
2. Increased glycation end-product formation
3. Activation of Protein kinase C
4. Increased hexosamine pathway flux

A common effect of each is that they increase the production of superoxide by the mitochondrial electron-transport chain. Superoxide is a reactive oxygen species that leads to oxidative stress and can subsequently cause the tissue damage that is observed in diabetes. This suggests that antioxidants, as free radical scavengers, may be used therapeutically in the future to prevent the complications associated with diabetes.

**Diabetic Nephropathy**

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) and there is a need for kidney dialysis and transplantation in the Western World (Milner. 2003). DN is a progressive microvascular end-organ complication that affects approximately 20-40% of patients with type 1 and type 2 diabetes (American diabetes A. 2009). The modifiable risk factors for DN
include glycemic control, blood pressure, dyslipidemia, diet and smoking. Unmodifiable risk factors include male sex, duration of diabetes and familial, genetic and ethnic factors. DN is defined by both functional and structural criteria, with the structural criteria being predominantly used in experimental studies, while the functional criteria are generally used in clinical practice.

Diabetic Nephropathy (DN) is the major single cause of End Stage Renal Disease (ESRD) in developing countries and extrapolations suggest that this number will multiply in the future. End stage renal disease require dialysis and is becoming a staggering challenge to public health care systems due to the prohibitive costs of renal replacement therapy that could become unaffordable even for developed countries. Advance diabetic nephropathy is also the leading cause of glomerulosclerosis and endstage renal disease worldwide.

DN manifests as a clinical syndrome that is composed of albuminuria, progressively declining GFR, and increased risk for cardiovascular disease. And it is a late complication of diabetes, occurring progressively in susceptible people only after 15 to 25 year of diabetes (Kumar et al., 2011).