CHAPTER 1

INTRODUCTION

Diabetes mellitus (DM) represents a range of metabolic disorders characterized by hyperglycemia resulting from insulin deficiency or insulin resistance or both. However, it is well known established fact that in diabetes, long-term complications ensue from abnormal regulation of glucose metabolism. In fact, all manifestations of cardiovascular disease, coronary heart disease (CHD), stroke and peripheral vascular disease are substantially more common in patients with type 2 diabetes than in non-diabetic individuals (Laakso & Lehto, 1997; Haffner, et al., 1998). Patients with type 2 diabetes (T2DM) have a two- to fourfold increased risk of fatal and non-fatal coronary events (Pyorala, et al., 1987). Hyperglycemia, the primary clinical manifestation of diabetes, is strongly associated with development of the diabetic complications. Diabetes can lead to cardiovascular damage through a number of mechanisms, each of which in turn may accelerate or worsen the others. Potential mechanisms of how hyperglycemia may induce vascular injury include an increased production of advanced glycation end products and excessive oxidative stress (Creager, et al., 2003).

Glycation is the term adopted by the International Union of Biochemistry and is given to any reaction that links a carbohydrate to free amino groups of the proteins (Newsletter, 1984). The products of the reaction that cause many of the pathological effects of non-enzymatic glycation are the advanced glycation end products (AGEs). The term 'AGEs' is now used for a broad range of the Maillard reaction products such as \( \text{N}^\varepsilon-(\text{carboxynethyl})\text{lysine} \) (CML). Hyperglycemia and hyperlipidemia which are
associated with diabetes can lead to irreversible nonenzymatic glycation of proteins and lipids and formation of AGEs (Ruderman, et al., 1992; Brownlee, et al., 1988). It has been reported that the process of AGEs formation is accelerated by hyperglycemia (Dyer, et al., 1993; Price, et al., 2001). When accelerated by hyperglycemia, AGEs accumulation is believed to contribute to the gradual development of diabetic complications. It has been reported that AGEs levels are increased in type 2 diabetic patients with coronary artery disease (Kiuchi, et al., 2001) and microvascular complications (Sampathkumar, et al., 2005).

Accumulation of AGEs with structural alterations result in altered tissue properties that contribute to the reduced susceptibility to catabolism (Wautier & Guillausseau, 2001; Monnier, et al., 1984). Several interrelations have been shown between oxidative stress and AGEs. Reactive oxygen species generated in oxidative stress can in turn accelerate AGEs formation. Yan, et al. (1994) showed that interaction of AGEs with endothelial cells leads to oxidative stress by a receptor-mediated process. Therefore, glyoxidation as a new definition arose, as proposed by Baynes (1991), which refers to AGEs formation through an oxidative pathway. CML modification of proteins is one of the major glyoxidation products formed in vitro by the reaction between glucose and protein (Reddy, et al., 1995). Mykkanen, et al. (1993) have shown that a dyslipidemic lipoprotein profile characteristic of T2DM precedes the onset of diabetes. Lipoprotein particles are also modified by glycation in the presence of hyperglycemia (American Diabetes Association, 1993). The clearance of glycated LDL particles is prolonged, and they might be more readily oxidized, leading to their increased uptake by macrophages (American Diabetes Association, 1993; Bowie, et al., 1993). Thus, disturbance of lipid and lipoprotein metabolism can commonly occur in diabetes and almost certainly contributes to the pathogenesis of vascular complications.
It is established that oxidation plays an important role in CML formation (Nagai, et al., 1997). CML is known to be a product of both lipoxidation and glycoxidation (Fu, et al., 1996). Since CML is a major product of oxidative modification of glycated proteins, it has been suggested to represent a general marker of oxidative stress and long-term damage of proteins in aging, atherosclerosis, and diabetes (Ledl & Schleicher, 1999). Serum CML levels have been found to be elevated in type 1 diabetes mellitus (Berg, et al., 1997) and may play a role in the initiation of diabetic retinopathy (Miura, et al., 2003). Moreover, CML has been identified in glucose-modified LDL and in macrophage-induced foam cells of atherosclerotic plaques (Imanaga, et al., 2000; Sakata, et al., 2001).

This study focuses on non-enzymatic modifications of LDL including oxidation and glycation and most importantly glycoxidation and carboxymethylation. It has been postulated that the uptake of glyoxidized LDL and CML-LDL by LDL receptors is impaired, thereby decreasing its clearance from the blood circulation and increasing serum LDL levels. Alternatively, the uptake of these modified LDL particles by scavenger receptors on macrophages and vascular smooth muscle cells and by AGE receptors (RAGE) on endothelial cells, vascular smooth muscle cells and monocytes is enhanced and this, in turn, is centrally positioned to contribute to the pathogenesis of diabetic vascular complication especially coronary artery disease.