Literature Review
METABOLIC SYNDROME

The metabolic syndrome is conceptualized as a constellation of metabolic and anthropometric abnormalities (Meigs, 2002), which include hyperglycemia, hypertension, dyslipidemia, central obesity, and excess body weight. Measures of insulin resistance, inflammation, thrombosis, hyperuricemia, and renal function have also been considered for inclusion. The triad of hyperglycemia, hypertension, and hyperuricemia was described as early as 1923 (Kylin, 1923). A major milestone in the history of this syndrome occurred in 1988, when Reaven proposed the concept of syndrome X, which he described as the co-occurrence of resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased very low-density lipoprotein triglyceride, decreased high-density lipoprotein (HDL) cholesterol, and hypertension (Reaven, 1988). This study stimulated renewed interest in the syndrome.

In 1998, the World Health Organization (WHO) proposed a formal definition of the metabolic syndrome (Alberti and Zimmet, 1998). Three years later, the National Cholesterol Education Programme Adult Treatment Panel III (NCEP/ATP III) proposed its definition of the metabolic syndrome (National Institutes of Health, 2001). The European Group for the study of Insulin Resistance (EGIR) also developed a definition (Balkau et al., 2002). The attention that the NCEP/ATP III report brought to the metabolic syndrome has ignited an intense interest, as evidenced by the numerous publications and meetings concerning the metabolic syndrome. Efforts by WHO, NCEP/ATP III, and EGIR to develop standard definitions have been critical in trying to determine the prevalence of this syndrome. Although they share similarities, they also differ considerably.

To meet the WHO definition, a person must have glucose intolerance or insulin resistance plus two of the following four criteria: central obesity, hypertension, dyslipidemia, and albuminuria. In 1999, a modification to the WHO definition was proposed: the blood pressure threshold was lowered from
160/90 mm Hg to 140/90 mm Hg, and the albumin: creatinine ratio threshold was raised from 20 mg/g to 30 mg/g (World Health Organization, 1999). To meet the NCEP/ATP III definition, a person must have three of the following five abnormalities: abdominal adiposity, hypertension, hypertriglyceridemia, low HDL, or hyperglycemia. Of note is that WHO and NCEP/ATP III included diabetes in their definitions, but there has been extensive debate about the appropriateness of including persons with diabetes in prevalence estimates of metabolic syndrome. The EGIR definition specifically excludes diabetes and to meet the definition, a person must have two of the following four criteria: abdominal obesity, hypertriglyceridemia, hypertension, and insulin resistance. Although all three definitions include a measure of abdominal obesity, elevated blood pressure, dyslipidemia, and hyperglycemia, the exact measures and cut points used to define elevations differ among the three definitions as represented in the Table I (TI).

RISK FACTORS FOR METABOLIC SYNDROME
The metabolic syndrome is comprised of a clustering of metabolic risk factors in one individual. The syndrome has been identified as a multidimensional risk factor for cardiovascular diseases (CVD). It is also associated with an increased risk for type 2 diabetes, which in turn is a major risk factor for CVD. The metabolic risk factors for CVD that make up the metabolic syndrome do not directly cause type 2 diabetes but are frequently associated with it. Specifically, following five criteria are listed as the major metabolic risk factors for metabolic syndrome: Atherogenic dyslipidemia (that comprises of elevated apolipoprotein B (apo-B), including elevated serum triglycerides (TGs) plus small low density lipoprotein (LDL) particles and low levels of HDL), elevated blood pressure, elevated plasma glucose, prothrombic state, and finally the proinflammatory state.
<table>
<thead>
<tr>
<th>Criteria</th>
<th>NCEP/ATP III</th>
<th>World Health organization</th>
<th>European Group for the study of Insulin Resistance</th>
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<td></td>
<td>≥ Three of the following five criteria:</td>
<td>Presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance plus ≥ two of the following four criteria:</td>
<td>No diabetes plus ≥ two of the following four criteria:</td>
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<td>Central Obesity</td>
<td>1. Waist circumference &gt;102 cm in men and &gt;88 cm in women</td>
<td>1. Waist to hip ratio of &gt;0.9 in men or &gt;0.85 in women and/or body mass index &gt;30 kg/m²</td>
<td>1. Waist circumference ≥ 94 cm for men, ≥ 80 cm for women</td>
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<td>Dyslipidemia</td>
<td>2. Triglycerides ≥150 mg/dl (1.695 mmol/l)</td>
<td>2. Triglycerides ≥150 mg/dl (1.695 mmol/l) and/or high density lipoprotein cholesterol &lt;35 mg/dl (0.9 mmol/l) in men and &lt;39 mg/dl (1 mmol/l) in women</td>
<td>2. Triglycerides ≥190 mg/dl (2mmol/l) or high density lipoprotein cholesterol concentration &lt;40 mg/dl (1 mmol/l) or treatment</td>
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<td>3. Low high density lipoprotein cholesterol: &lt; 40 mg/dl (1.036 mmol/l) in men and &lt;50 mg/dl (1.295 mmol/l) in women</td>
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<td>High blood pressure</td>
<td>4. Blood pressure ≥130/85 mm Hg.</td>
<td>3. Blood pressure ≥160/90 mm Hg</td>
<td>3. Blood pressure: systolic blood pressure ≥140 or diastolic blood pressure ≥90 or treatment for hypertension</td>
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<td>High glucose</td>
<td>5. Fasting glucose: ≥110mg/dl (≥6.1 mmol/l)</td>
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<td>Other</td>
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<td>4. Microalbuminuria: urinary albumin excretion rate ≥20 mg/min or albumin /creatinine ratio ≥20 mg/g⁴</td>
<td>4. Insulin resistance or fasting insulin concentration above the upper quartile for non-diabetic subjects</td>
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⁴ In 1999, revised WHO criteria were published. Elevated blood pressure was defined as ≥140/90 mm Hg and the albumin: creatinine ratio was increased to 30 mg/g.

**TI: Definitions of the metabolic syndrome**
**Atherogenic dyslipidemia**

This lipid disorder consists of elevations of serum TGs, apo-B and small (LDL) particles, and low levels of HDL. It can be differentiated from elevated LDL cholesterol, which is the major risk factor for CVD. Many controlled clinical trials show that LDL-lowering therapy reduces risk for CVD (National Cholesterol Education Program, 2002). The connection between atherogenic dyslipidemia and CVD risk is more complicated than for LDL cholesterol; the multiple lipid abnormalities of atherogenic dyslipidemia make it difficult to dissect the contributions of each abnormality to CVD. These multiple abnormalities almost certainly promote the development of atherosclerosis. An important point to make, however, is that elevated total apo-B overlaps with LDL cholesterol. In normal persons, apo-B is mainly carried in LDL, whereas only small amounts are present in very low density lipoproteins (VLDL). When triglycerides are elevated, however, a somewhat greater portion of apo-B is found in VLDL. With atherogenic dyslipidemia, the LDL cholesterol level in the LDL fraction underestimates the number of LDL particles present, because these particles are partially depleted of cholesterol. In atherogenic dyslipidemia, the total apo-B level frequently is abnormally elevated. There is growing evidence that all apo-B-containing lipoproteins are atherogenic. Whether the different types of lipoproteins that carry apo-B (such as VLDL, large LDL, and small LDL) have the same or different atherogenic potential is uncertain. Suggestive evidence points to small LDL particles being particularly atherogenic, but the evidence is not unequivocal. Some of the apparently higher atherogenicity of small LDL may be related to an increased number of LDL particles in the LDL fraction.

Another important component of atherogenic dyslipidemia is a low level of HDL cholesterol. This reduced level may raise the risk for CVD. At least three possibilities exist (Vega and Grundy, 1996). First, HDL may protect directly against the development of atherosclerosis. Second, a low HDL level may indicate the increase in atherogenic apo-B-containing
lipoproteins. Third, low HDL is commonly associated with the nonlipid risk factors of metabolic syndrome and hence is a powerful marker for risk (National Cholesterol Education Program, 2002). A low HDL may also be directly atherogenic because of a deficit in the protective effect of HDL.

**Elevated blood pressure**

An elevation of blood pressure is one of the components of metabolic syndrome (Grundy et al., 2004). How aberrations in metabolism produce higher blood pressure is uncertain. Conversely, it is certain that a higher blood pressure commonly accompanies other metabolic risk factors (Shen et al., 2003). Blood pressure often is only moderately elevated in persons with the metabolic syndrome. Because blood pressure regulation is a complex process, it is not surprising that the metabolic connections between the various risk factors and blood pressure regulation are difficult to dissect. The frequency of association between blood pressure and those other risk factors justifies lumping them together as a multidimensional risk factor, however (Shen et al., 2003).

In the context of metabolic syndrome, it is necessary to return to the relationship between insulin resistance, blood pressure, and risk of CVD, specifically to emphasize that no more than 50% of patients with essential hypertension are insulin resistant but that this subset of patients is at greatest risk of CVD (Zavaroni et al., 1992). For example, patients with essential hypertension with electrocardiographic evidence of ischemic changes are somewhat glucose intolerant and hyperinsulinemic as compared with either a normotensive control group or patients with essential hypertension whose electrocardiograms are entirely normal (Jeppesen et al., 2000).

Changes in endothelial function those are likely to contribute further to increased risk of CVD also vary as a function of differences in insulin-mediated glucose disposal in patients with essential hypertension. For
example, the first step in the process of atherogenesis is the binding of mononuclear cells to the endothelium (Ross, 1986), and there is evidence of increased adherence of the cells isolated from patients with hypertension to the cultured endothelial cells (Chen et al., 1999). The relationship between insulin resistance and binding of isolated mononuclear cells to endothelium was similar in normotensive and hypertensive volunteers, because the more insulin resistant an individual, regardless of blood pressure status, the greater is the adherence of their isolated mononuclear cells to endothelium. The abnormality in the binding of isolated mononuclear cells to endothelium was seen only in the subset of patients with essential hypertension who were also insulin resistant.

**Elevated plasma glucose**
An increase in plasma glucose to above normal levels typically develops late in the course of the metabolic syndrome. Glucose elevation comes in several forms. The mildest form is called impaired glucose tolerance. This abnormality is detected by an oral glucose tolerance test, which is performed in persons with normal plasma glucose (<100mg/dl). Impaired glucose tolerance is defined as a plasma glucose level of 140 to 199 mg/dl two hours after a 75-g oral glucose load. A second level of abnormality is impaired fasting glucose, which is defined as a fasting glucose of 100 to 125 mg/dl. It has been called pre-diabetes by the American Diabetes Association (Genuth et al., 2003). The third level is categorical hyperglycemia, which is designated as diabetes. Diagnosis of diabetes can be made with a fasting glucose level of 126 mg/dl or higher or a 2-hour glucose level of 200 mg/dl or higher (Genuth et al., 2003). Lesser increase in plasma glucose (impaired glucose tolerance/impaired fasting glucose) may not directly cause CVD, although they are associated with increased risk for CVD (Qiao et al., 2003). They also are strong risk factors for development of categorical diabetes (Unwin et al., 2002). All levels of increase-impaired glucose tolerance, impaired fasting
glucose, and diabetes-commonly are associated with other metabolic risk factors and must be considered as components of the metabolic syndrome (Alberti and Zimmet, 1998).

Although most insulin-resistant/hyperinsulinemic individuals do not become frankly hyperglycemic, they are at increased risk of developing type 2 diabetes. The role of insulin resistance as an important contributor to the development of human disease began with the evidence that resistance to insulin-mediated glucose disposal was a characteristic defect in patients with type 2 diabetes (Ginsberg et al., 1975). These initial observations have been confirmed on many occasions, and it has been shown that insulin resistance (or hyperinsulinemia as a surrogate measure of insulin resistance) is a powerful and independent predictor of the development of type 2 diabetes (Lillioja et al., 1993). Most insulin-resistant individuals maintain normal or near-normal glucose tolerance by secreting the large amounts of insulin needed to prevent the increase in plasma glucose and free fatty acid concentrations seen in patients with type 2 diabetes mellitus (Reaven, 1995). Type 2 diabetes only occurs when insulin-resistant individuals are no longer able to maintain the degree of compensatory hyperinsulinemia needed to maintain normal glucose homeostasis. Once hyperglycemia ensues, insulin-resistant individuals are at increased risk of developing the specific microangiopathic changes seen in patients with type 2 diabetes. Diabetic retinopathy, nephropathy, and neuropathy are the consequences of hyperglycemia, per se, not insulin resistance.

**Prothrombic state**
Several defects in the coagulation and fibrinolytic systems commonly are associated with other metabolic risk factors (Miller, 1994). These defects in aggregate can be called a prothrombic state. Examples of prothrombic defects include plasminogen activator inhibitor-1 (PAI-1), fibrinogen, and factor VII and platelet abnormalities. Theoretically, a prothrombic state could be
associated with CVD in several ways. Some of the prothrombic factors may be involved in the atherogenic process itself (Selwyn, 2003); these and others are likely to enhance the thrombotic response to acute plaque ruptures or plaque erosions (Libby, 2002). The pathogenesis of the prothrombic state varies, but because several aberrations in coagulation and fibrinolysis are common in persons who have the other metabolic risk factors, there is a growing view that these aberrations should be added to the list of metabolic risk factors.

Elevated PAI-1 levels, the principal inhibitor of fibrinolysis, are reported in many clinical and population studies of obese subjects, and they correlate with an abnormal pattern of obesity in men and women (Sakkinen et al., 2000) and other components of the metabolic syndrome inclusive of hyperinsulinemia, hypertension, high triglycerides, low HDL, and small LDL particles (Festa et al., 1999). In patients with type 2 diabetes, PAI-1 antigen localizes in endothelial and smooth muscle cells of the intima and medial layers of the arterial wall (Pandolfi et al., 2001). The accumulation of PAI-1 in arterial segments is accompanied by reduced plasma fibrinolysis. These findings provide insights into the higher clinical occurrence of thrombosis on ruptured plaques of patients with type 2 diabetes (Silva et al., 1995).

High levels of factor VII, a key component of the extrinsic coagulation cascade, may also contribute to a pro-thrombotic state, providing a potential mechanism for increased cardiovascular risk. This hypothesis was supported to some extent by the results of the Northwick Park Heart Study (NPHS; Meade et al., 1986). Similarly, the elevated levels of fibrinogen have been shown to be a strong and independent cardiovascular risk factor in prospective epidemiological studies (Ernst and Resch, 1993; Koenig, 2003). In addition, several in vivo studies have provided evidence that the loss of insulin's regulating action over platelet aggregation and activation in insulin resistance could contribute to the enhanced atherothrombotic risk associated with the metabolic syndrome (Lowe et al., 1980; Zahavi et al., 1981). Thus, it may be postulated that the metabolic syndrome has a permissive role on
thrombus formation, propagation and clot stability, and thereby increases the severity of the resultant ischemic event following plaque disruption and erosion.

**Proinflammatory state**
A final component of the metabolic syndrome is a proinflammatory state. In reference to CVD risk, this term is commonly used to indicate that atherogenesis is an inflammatory process. All of the steps in the development of atherosclerosis in one way or another are inflammatory. In classic terms, an inflammatory process has two major components: tissue injury and response to injury. Most of the metabolic risk factors such as lipid abnormalities, hypertension, hyperglycemia, and thrombotic factors potentially inflict direct injury on the arterial wall. Responses to arterial injury include infiltration of phagocytes and uptake of lipids, release of bioactive molecules by macrophages, and proliferation and collagen deposition by smooth muscle cells (Verma et al., 2003). These responses apparently elicit secondary inflammatory responses that include increased synthesis of acute phase reactants by the liver. One of these secondary products, C-reactive protein (CRP), provides a marker for the activity of the inflammatory process. Evidence is growing that persons with metabolic syndrome have high levels of CRP (Ridker et al., 2003).

The pro-inflammatory response includes an increased secretion of Interleukin-1β (IL-1β) and Tumor-necrosis factor-α (TNF-α), which then result in the release of the messenger cytokine, IL-6, especially from macrophages. IL-6, after engagement of its receptor on the liver, helps in the secretion and release of CRP and serum amyloid A (SAA). Recent evidence points to the role of vascular cells, such as smooth muscle cells, in the production of CRP. CRP mRNA and protein have been shown to be expressed in the cells of the lesion of magnitude more than that observed in plasma (Calabro et al., 2003; Kobayashi et al., 2003).
Cytokines, particularly IL-1, TNF-α, and IL-6, are the main inducers of the acute phase response (Baumann and Goldie, 1994). TNF-α is pro-inflammatory cytokine secreted by monocytes-macrophages, endothelial cells, and, to a large extent, by adipocytes. Several studies have shown that levels of TNF-α are important regulator of insulin sensitivity (Hotamisligil, 1993) and that neutralization of TNF-α improves insulin sensitivity in fa/fa rats but not in obese humans with diabetes (Arner, 2003). In human subjects, TNF-mRNA and protein correlate positively with body adiposity and decrease in obese subjects with weight loss. Insulin sensitivity was not studied, however (Dandona et al., 1998). Obesity is one of the major features of the metabolic syndrome. TNF-α levels also correlate strongly with BMI (Nieman, 1997). TNF-α is overexpressed in adipose and muscle tissue of obese individuals compared with tissues from lean individuals (Fernandez-Real and Ricart, 1999).

TNF-α and IL-6 decrease the activity of lipoprotein lipase in mice and cultured mouse adipocytes (Arner, 2003). TNF-α also promotes insulin resistance via decrease in insulin receptor tyrosine kinase activity, insulin receptor substrate-1 (IRS-1) phosphorylation, and GLUT4 synthesis/translocation (Hotamisligil et al., 1996). In contrast to IL-6, however, increased TNF-α secretion from adipose tissue has been shown only in rodents but not in humans.

HIGH-DENSITY LIPOPROTEIN IN METABOLIC SYNDROME
By definition, many subjects with the metabolic syndrome have low levels of HDL. Each of the features of the metabolic syndrome, including central adiposity, elevated plasma triglyceride, hypertension, and insulin resistance, is associated with a low concentration of HDL. Whether this reflects a causal relationship between these features and the concentration of HDL is not known. It is possible that a low level of HDL is just one of the several manifestations of same underlying condition, the metabolic basis of which
remains obscure. HDLs in subjects with the metabolic syndrome tend to be smaller and denser than normal (Chang et al., 1985). Whether this is a consequence of having the metabolic syndrome or a simple consequence of the low HDL level is not known. It is known, however, that the particle size of HDL correlates inversely with the concentration of plasma triglyceride. Subjects with plasma triglyceride concentrations more than 150 mg/dl tend to have predominantly smaller HDL (Yu and Mamo, 2000). When the triglyceride level falls below this value, there seems to be a quantum shift into a larger HDL size. Whether the elevated triglyceride in the metabolic syndrome accounts for the associated small size of the HDL particles is not known.

Several potentially pro-atherogenic forces operate in people with the metabolic syndrome. An increase in concentration of the remnants of triglyceride-rich lipoproteins has the capacity to deposit cholesterol in macrophages, converting them into foam cells (Goulinet and Chapman, 1997). There is also an increase in the concentration of small, dense LDLs, particles that are especially susceptible to oxidation (Lemieux et al., 2001) and subject to an enhanced uptake by macrophages. Subjects with the metabolic syndrome frequently manifest a pro-inflammatory state (Fielding and Fielding, 1995). Under normal conditions, pro-atherogenic forces such as these are opposed by HDLs. Not only do HDLs promote the efflux of cholesterol from cells, including macrophages (Mackness et al., 1993) but they also have antioxidant (Calabresi et al., 2002), anti-inflammatory (Rosenson and Lowe, 1998), and anti-thrombotic (Yuhanna et al., 2001) properties. They also stimulate endothelial nitric oxide production (Laws et al., 1997). In the metabolic syndrome, however, the HDL concentration is low and there is a reduced capacity to counter the cholesterol accumulation in macrophages and a decreased ability to prevent the oxidation of small dense LDL. This loss of the protection normally provided by HDL has the capacity
to amplify the already powerful pro-atherogenic forces that exist in the metabolic syndrome.

**TRIGLYCERIDE AND LOW-DENSITY LIPOPROTEIN METABOLISM IN METABOLIC SYNDROME**

*Triglyceride-rich lipoprotein*

Multiple factors contribute to altered metabolism of triglyceride and triglyceride-rich lipoproteins in the metabolic syndrome. Excess adiposity and insulin resistance foster increased hepatic production of VLDL and reduced intravascular catabolism and plasma clearance of VLDL and intestinally derived chylomicron particles. A major determinant of increased VLDL secretion in the metabolic syndrome is higher hepatic triglyceride content, derived in part from increased free fatty acid delivery from adipose tissue (Hotamisligil et al., 1995) and return of triglyceride-rich lipoprotein remnants to the liver. Changes in adipose tissue cytokines, including higher TNF-α (Yamauchi et al., 2001) and reduced adiponectin (Fisher and Ginsberg, 2002), also may increase hepatic VLDL production and impair peripheral clearance. Finally, insulin resistance and compensatory hyperinsulinemia can promote directly the increased hepatic secretion of VLDL particles (Ginsberg, 2002).

Intravascular catabolism and plasma clearance of triglyceride-rich lipoprotein involve complex interactions among lipases, apolipoproteins, lipid transfer proteins, and receptors (Krauss and Burke, 1982). Insulin resistance results in reduced activity of endothelial-bound lipoprotein lipase (LPL), which contributes to impaired triglyceride hydrolysis and uptake of chylomicron and VLDL lipids by muscle and adipose tissue. Insulin-resistant states also result in increased levels of apo-CIII, an inhibitor of LPL, and impaired apo-E-mediated receptor uptake of triglyceride-rich lipoproteins and their lipolytic remnants. Delayed postprandial clearance of diet-derived lipids in individuals with the metabolic syndrome can result from reduced intravascular catabolism of chylomicrons and competition with VLDL for
LPL activity. The net effect of changes in triglyceride-rich lipoprotein metabolism in the metabolic syndrome is an increase in plasma transport and prolonged plasma residence of these lipoproteins and their potentially atherogenic catabolic products. This in turn leads to increased levels of intermediate-density lipoproteins (IDL), the immediate metabolic precursors of LDL.

**Low-density lipoprotein**

At least seven subspecies of LDL can be distinguished on the basis of size and density. The subspecies, in turn, have been grouped into four subclasses that range from the largest, most buoyant (LDL-I) to the smallest and densest (LDL-IV) (Alaupovic, 2003). The differing subspecies of LDL have been shown to vary in lipid and carbohydrate composition and in conformation of apoB (Berneis and Krauss, 2002).

Multiple factors contribute to LDL heterogeneity, including differences in properties of their VLDL and IDL precursors and differences in intravascular transformation and catabolism. Evidence to date suggests that larger, more buoyant species arise from LPL-mediated lipolysis of smaller, relatively cholesterol-rich and triglyceride poor VLDL and IDL and by direct hepatic secretion (Karpe et al., 1993). In contrast, smaller, denser LDL species can derive from VLDL of progressively increasing size and triglyceride content by a process that involves LPL and hepatic lipase (HL) activities (Deckelbaum et al., 1984). Small, dense LDL also can arise by HL-mediated lipolysis of larger LDL and IDL after triglyceride enrichment of these particles through the action of cholesteryl ester transfer protein (Sakai et al., 1991). Cholesteryl ester transfer protein is not necessary for the production of small, dense LDL, however, as demonstrated by the presence of small triglyceride-enriched LDL particles in patients with genetic deficiency of cholesteryl ester transfer protein (Ehnholm et al., 1984). ApoE is also
believed to play a role in the conversion of VLDL to its smaller metabolic products, and loss of the protein is characteristic of most of the particles.

Several studies have shown a significant univariate relationship of reduced LDL peak particle size with increased risk of CVD. In most of these studies, however, the strength of this relationship was reduced substantially after adjustment for other risk factors [triglyceride (Stampfer et al., 1996) and total/HDL-C (Gardner et al., 1996)]. Evidence supports the selective benefit of lowering small, dense LDL particle concentrations on the risk of CVD (Miller et al., 1996). In vitro studies have suggested that small, dense LDL particles confer increased atherosclerotic risk through various mechanisms, including reduced LDL receptor affinity (Campos et al., 1996) and slower plasma clearance, increased transport into the sub endothelial space (Bjornheden et al., 1996), increased binding to heparan sulfate proteoglycans in the arterial wall, and increased susceptibility to oxidation (Chait et al., 1993).

**HYPERTENSION AND METABOLIC SYNDROME**

Within the metabolic syndrome cluster, there are several mechanisms through which one abnormality could favor the development of another. High blood pressure may modify peripheral tissue (skeletal muscle and fat) perfusion, either by microvascular rarefaction or through more functional subtle disturbances, thereby limiting vascular-to-tissue hormone and substrate exchange. Although attractive and supported by some experimental (Clark et al., 1995) and clinical (Baron et al., 1994) evidence, the vascular hypothesis for the development of insulin resistance has been challenged seriously by studies showing that in humans, physiologic hyperinsulinemia affects tissue perfusion only modestly (Utriainen et al., 1995) and that experimental improvement of tissue perfusion does not result in attenuation of skeletal muscle insulin resistance in patients with essential hypertension (Natali et al., 2000).
Alternatively, insulin resistance could raise blood pressure either by preventing the vasodilatory effects of the hormone or, via the attendant hyperinsulinemia, by upregulating the sympathetic and the antinatriuretic tone. The vascular effects of insulin are complex because they involve at least three mechanisms: hyperpolarization, nitric oxide-cyclic GMP, and β-adrenergic stimulation-cyclic AMP. This pleomorphic effect of insulin has been confirmed in vitro: in smooth muscle cells, insulin induces an increase in cAMP and cGMP that is receptor mediated and, for cGMP only, partly nitric oxide dependent (Trovati et al., 1995). At pharmacologic concentrations, insulin stimulates nitric oxide synthesis in human endothelial cells; this effect depends on the number of insulin receptors, their tyrosine kinase activity, and, downstream to the receptor, P13-kinase and Akt signaling (Zeng et al., 2000). Insulin's effect on the endothelium is not limited to the stimulation of nitric oxide synthesis. In rat mesenteric arteries, insulin vasodilatation is a transient phenomenon caused by a parallel slow-onset stimulation of endothelin synthesis (Misurski et al., 2001). The vascular net effect of insulin results from the combination of the two opposite vasoactive stimuli. Elegant experiments in vitro and in humans have shown recently that concurrent endothelin production masks the vasodilatory effect of low physiologic hyperinsulinemia (Verma et al., 2001). This could be the mechanism underlying the reduced vascular effect of insulin in insulin-resistant rats (Miller et al., 2002), which has an increased responsiveness to endothelin (Juul et al., 1996). The two effects have not only different time course but also different dose-response characteristics and may be differentially active depending on the associated conditions.

At physiologic concentrations, insulin enhances peripheral sympathetic outflow and directly desensitizes the sino-atrial node to the baroreflex control of heart rate (Muscelli et al., 1998). Mounting evidence also indicates that insulin, by trespassing (by transcytosis) the blood-brain barrier in the periventricular area, binds to neurons in the arcuate and paraventricular
nuclei, which then send inhibitory impulses to the vagus and excitatory impulses to the sympathetic nuclei (Davis et al., 1995). Overall, even in the absence of hypoglycemia, the cardiovascular system responds to acute insulin administration with a moderate, specific stress reaction. Of note is that the pattern of hemodynamic responses to euglycaemic hyperinsulinemia is maintained in obesity, an insulin-resistant state with a high-output, low-resistance hemodynamic pattern (Ferrannini, 1992). Similarly, physiologic hyperinsulinemia directly restrains renal sodium excretion by acting on the distal portions of the nephron (deFronzo et al., 1975). This action is preserved in individuals with insulin resistance of glucose metabolism (Muscelli et al., 1996) in whom chronic hyperinsulinemia might cause a rightward shift of the pressure-natriuresis curve (as documented in experimental animals (Fujiwara et al., 1999) and obese subjects (Rocchini et al., 1989).

MEDICAL TREATMENTS IN METABOLIC SYNDROME

There remains a need for medical intervention because about 50 percent of people with the metabolic syndrome do not reach targets without drugs. Furthermore, many people do not want to change their lifestyle or are unable to exercise. Therefore, drugs should be analyzed for their safety as well as effectiveness for prevention of the metabolic syndrome and associated cardiovascular diseases.

Medical treatment of diabetes in patients with the metabolic syndrome

So far drug intervention studies in pre-diabetes have been performed only in people with impaired glucose tolerance (IGT). No data from controlled prospective studies are available for subjects with impaired fasting plasma glucose (IFG). In subjects with IGT about one-third are suffering from the metabolic syndrome. In the US Diabetes Prevention Program (DPP) metformin (1-(diaminomethylidene)-3, 3-dimethyl-guanidine) was compared
with placebo and lifestyle modification. It is remarkable that metformin also reduced body weight by $\sim 1$Kg and had a beneficial effect on blood lipids but not on the blood pressure (deFronzo and Goodman, 1995).

Acarbose, an inhibitor of $\alpha$-glucosidases of small intestine, delays the release of glucose from complex carbohydrates and thus reduces postprandial glucose excursion. The efficacy of treatment of postprandial hyperglycemia with acarbose in subjects with IGT was tested in a multi-national study. Such a treatment not only reduced conversion to diabetes by 36 percent but also reduced the incidence of newly diagnosed hypertension by 34 percent (Chiasson et al., 2003). Furthermore, a significant reduction in the triglycerides and excess weight was also observed. Interestingly, the therapeutic effect of acarbose on IGT and traits of the metabolic syndrome were associated with a significantly lower incidence of major cardiovascular events. Thus, both hypoglycemic drugs (acarbose and metformin) had beneficial effects in people with IGT and the metabolic syndrome.

The beneficial effects of metformin on parameters of the metabolic syndrome in clinical diabetes were confirmed by the UK Prospective Study Group (1998a). Metformin was the only drug in this mega-trial that significantly reduced cardiovascular events. It is still an open question why metformin, despite the fact that it achieved no stronger reduction in Hba1c than glibenclamide and insulin in the other arms of the group, was superior with respect to CVD. One explanation could be that it had therapeutic effects on overweight whereas the patients in the sulphonylurea and insulin groups gained weight.

Analysis of studies in type 2 diabetes with at-least one-year duration revealed, that acarbose improved several components of the metabolic syndrome: overweight, hypertension and hypertriglyceridemia. This was associated with a reduction of the incidence of myocardial infarction by 65 percent (Hanefeld et al., 2004).
The glitazones (pioglitazone, rosiglitazone) are insulin sensitizers that have additional beneficial effects on dyslipidemia and hypertension (Campbell, 2000; Raji et al., 2003). This is mainly due to a reduction of free fatty acids derived from intra-abdominal adipose tissue (Carey et al., 2002). Via activation of the nuclear receptor family PPARγ (peroxisome proliferator-activated receptors-γ), they are involved in glucose and lipid metabolism. Thus, they act on two major pathogenetic factors of the metabolic syndrome: insulin resistance and intra-abdominal obesity. Pioglitazone also activates PPARα. Their strong effect on insulin resistance has stirred great interest in their potential benefit in prevention of the metabolic syndrome and CVD. For pioglitazone, and less pronounced for rosiglitazone, a decrease in triglycerides, an increase in HDL-cholesterol and a reduction in the small dense LDL subfraction have been described. However, a minor increase in LDL-cholesterol occurs in patients with type 2 diabetes if glitazones treatment is introduced (Campbell, 2000). This is due to the increase in large buoyant LDL particles, which are considered to be less atherogenic (Freed et al., 2002). Furthermore, a reduction of blood pressure in patients with type 2 diabetes and hypertension has been described (Grossman, 2003).

A major effect of glitazones is on the free fatty acid (FFA) release from intra-abdominal fat. The FFA flux from intra-abdominal fat depots is an important determinant of hepatic insulin resistance and contributes to the development of non-alcoholic fatty liver disease (NFLD). Earlier clinical trials have shown that glitazones reduce steatosis hepatis (Promrat et al., 2004).

A reduction of the newly diagnosed diabetes was observed in some studies with ACE inhibitors and angiotensin-II-receptor antagonists (ARA) (Yusuf et al., 2001; Lindholm et al., 2002) and in a study with the statin pravastatin (Freeman et al., 2001). New studies are under way to test the potentials of combination therapy (rosiglitazone/ramipril and nateglinide/valsartan) in subjects with IGT and IFG in the prevention of diabetes and cardiovascular complications. The surrogate markers so far available suggest
that glitazones should be effective in preventing CVD in clinical diabetes (Haffner et al., 2002).

In conclusion, oral hypoglycemics such as metformin, acarbose and insulin sensitizers are the drugs of first choice in subjects with pre-diabetes and type 2 diabetes that suffer from the metabolic syndrome. Furthermore, compounds used to treat conventional cardiovascular risk factors that improve insulin sensitivity and/or inhibit low-grade inflammation may be effective treatments for the metabolic syndrome.

**Medical treatment of hypertension in patients with the metabolic syndrome**

Recently four classes of antihypertensive drugs are commonly used as monotherapy or – in the majority of cases – in combination: angiotensin converting enzyme (ACE) inhibitors/angiotensin-II-receptor antagonists (ARA), beta-blockers, calcium channel blockers and diuretics. Besides the lowering of blood pressure, certain antihypertensives may have different pleiotropic effects on the pathophysiology of the metabolic syndrome:

ACE inhibitors such as Ramipril and ARAs like Losartan potassium have been shown to improve insulin resistance in many but not all studies. Accordingly, a reduction of newly diagnosed diabetes was reported in large prospective trials, with prevention of coronary heart disease as a primary outcome (Lindholm et al., 2002; Mann et al., 2003). Furthermore, ACE inhibitors/ARA reduces albumin excretion in diabetic patients with microalbuminuria (Sica and Bakris, 2002; Mann et al., 2003). They have only marginal effects on lipids.

Beta-blockers, even the β₁-selective drugs, increase triglycerides, lower HDL-cholesterol and worsen insulin sensitivity. There are consistent data from prospective studies showing that they precipitate the onset of diabetes (Jacob et al., 1998). The use of atenolol, a β₁-selective beta-blocker, by the UK Prospective Diabetes Group (1998b) was associated with significantly higher
levels of Hba1c and weight gain, respectively, compared with the ACE inhibitor captopril.

Calcium channel blockers obviously have no significant effect on the diseases and pathophysiology of the metabolic syndrome. Diuretics such as hydrochlorothiazide and torasemide increase triglycerides and decrease HDL-cholesterol (Ferrari et al., 1991).

In patients with the metabolic syndrome without CVD, ACE inhibitors/ARA should therefore be the drugs of first choice, followed by calcium channel blockers. This is particularly relevant for young obese people with dyslipidaemia and/or pre-diabetes. In the majority of cases treated with ACE inhibitors/ARA, low doses of diuretics will be needed in the long term to achieve near-normal blood pressure levels. However, for patients with CVD and the metabolic syndrome the introduction of selective beta-blockers is of benefit, as shown by evidence-based prospective studies.

OXIDATIVE STRESS

Oxidative stress is the term used to describe the condition of oxidative damage resulting when the critical balance between free radical generation and antioxidant defenses is unfavorable (Sies, 1991). Free radicals are reactive chemical species that contain one or more unpaired electrons. *In vivo* examples are hydrogen peroxide (H₂O₂), hypochlorous acid (HOCl), superoxide radical (‘O₂⁻), hydroxyl radical (‘OH), nitric oxide (‘NO) and nitrogen dioxide (‘NO₂⁻); collectively described as reactive oxygen species (ROS). If not quenched by an antioxidant, these compounds will react with the nearest fat, protein, carbohydrate, RNA, or DNA molecule, altering its structure and function. Such interactions may also generate additional free radical centers, especially in polyunsaturated fatty acids. The nuclear DNA in every human cell receives an estimated 10,000 oxidative “hits” per day (Ames et al., 1993), indicating that cells are under constant bombardment from ROS. The antioxidant defense system includes enzymes such as
superoxide dismutase, glutathione peroxidase, and catalase; iron- and copper-binding extracellular proteins (such as albumin, transferrin, lactoferrin, hepatoglobin, and ceruloplasmin); antioxidants, such as vitamin C, vitamin E, quinones, glutathione, uric acid, bilirubin, and the carotenoids (Krinsky, 1992); and endogenous and exogenous polyphenolic compounds such as the flavonoids and lignans contained in fruits, vegetables, and legumes (Ratty and Das, 1988). Short term oxidative stress may occur in tissues injured by trauma, infection, heat radiation, hyperoxia, toxins, and excessive exercise (Halliwell et al., 1992). Alternatively, long term oxidative stress has been linked to CVD because oxidized low-density lipoproteins (LDLs) appear to be a prerequisite for foam cell formation and atherogenesis (Abby et al., 1993).

Of the five criteria of metabolic syndrome defined in NCEP/ATP III (Alexander et al., 2003), four (and notably hypertriglyceridemia, hypertension, hyperglycemia, and abdominal obesity) are independently characterized by elevated systemic oxidative stress (Bae et al., 2001; Redon et al., 2003; Oberley, 1988; Keaney et al., 2003). Furthermore, hypertriglyceridemia, hypertension, and obesity are each associated with increased production of superoxide anion via the nicotinamide adenosine diphosphate oxidase pathway (Hiramatsu and Arimori, 1988; Zalba et al., 2001; Brasier et al., 2002). In addition, hyperglycemia leads to increased formation of oxygen free radicals as a consequence of protein glycation and glucose autoxidation (Mezzetti et al., 2000). Initially, insulin resistance is compensated by hyperinsulinemia, through which a normal glucose tolerance is preserved.
FI: Oxidative Stress: Mediator of Metabolic Syndrome.
Deterioration to impaired glucose tolerance occur when insulin resistance increases further and/or the compensatory insulin secretory response decreases. An increase in insulin, free fatty acid (FFA) and/or glucose levels can raise ROS production and oxidative stress, as well as activate stress-sensitive pathways (Evans et al., 2003). This, in turn, can worsen both insulin action and secretion, thereby accelerating the progression to overt type 2 diabetes. Impaired glucose tolerance, i.e. postprandial hyperglycemia with fasting glucose in the normal range, is a risk factor for increased cardiovascular mortality (Ceriello, 2003a) and many studies show that postprandial hyperglycemia is associated with oxidative stress generation (Ceriello, 2003a). Repeated exposure to hyperglycemia and increased levels of FFA can lead to β-cell dysfunction that may become irreversible over time (Poitout and Robertson, 2002). In its initial stages, this damage is characterized by reversible defective insulin gene expression (Bruce et al., 2003). Glucose and lipid toxicity induce the gradual, time-dependent establishment of irreversible damage to cellular components of insulin production and therefore to insulin content and secretion (Prato, 2003). Oxidative stress is convincingly the mediator of such damage (Evans et al., 2003) as represented in Fig I (Fl).

ANTIOXIDANTS AND METABOLIC SYNDROME

An antioxidant has been defined as “any substance that, when present at low concentrations compared to those of an oxidizable substrate (such as proteins, lipids, carbohydrates and nucleic acids), significantly delays or prevents oxidation of that substrate” (Halliwell, 1996). The definition proposed by the Panel on Dietary Antioxidants and Related Compounds of the Food and Nutrition Board is that “a dietary antioxidant is a substance in foods that significantly decreases the adverse effects of reactive oxygen species, reactive nitrogen species, or both on normal physiological function in humans” (Food and Nutrition Board, 1989).
When he proposed syndrome X, Reaven (Reaven, 1988) placed insulin resistance squarely at the heart of the syndrome, and considerable evidence exists to suggest that oxidative stress can contribute to insulin resistance (Evans et al., 2005). Thus, it may be instructive to examine some of the evidences about the possible benefits of antioxidants on insulin sensitivity. In a study of 1665 adults in the United States, serum concentrations of insulin were inversely associated with alpha-carotene, beta-carotene, lycopene, beta-cryptoxanthin, and lutein/zeaxanthin (Ford et al., 1999). In a study of 36 participants, those who were insulin resistant, determined with an insulin suppression test, had lower concentrations of alphacarotene, beta-carotene, lutein, alpha-tocopherol, and delta-tocopherol, but not beta-cryptoxanthin, zeaxanthin, lycopene, and gamma tocopherol, than patients without insulin resistance (Facchini et al., 2000). Among 182 participants of the Botnia study (Ylonen et al., 2003), plasma concentrations of beta-carotene were inversely associated with insulin resistance in men.

Unfortunately, little is known about how intakes of specific antioxidants may differ between people with and without metabolic syndrome. Among 8808 participants of the Third National Health and Nutrition Examination Survey (1988–1994) (Ford et al., 2003) in the United States, the use of vitamin or mineral supplements was not significantly different between participants with or without metabolic syndrome. Compared with participants who did not have metabolic syndrome, the intake of vitamin A was significantly lower among participants with the metabolic syndrome whereas the intake of vitamin C and E and carotenes was similar. In addition, participants with metabolic syndrome consumed fruits and vegetables less frequently than participants without this syndrome.

Several small studies suggested that vitamin E supplementation affects insulin action but not secretion (Paolisso et al., 1993; Paolisso et al., 1994). In 11 patients with type 2 diabetes mellitus, the use of 600 mg/day of
vitamin E for 3 months resulted in a reduction in the number of insulin receptors (Skrha et al., 1999). In a study of 80 overweight participants, vitamin E supplementation (800 IU/day for 3 months followed by 1200 IU/day for 3 months) improved insulin sensitivity during the first 3 months (Manning et al., 2004). Finally, in a randomized clinical trial, insulin sensitivity among 28 offspring of people with type 2 diabetes mellitus did not improve from using 800 IU/day of vitamin E for 12 weeks (McSorley et al., 2005). The effect of vitamin C supplementation on insulin parameters has also been studied. In a clinical trial in which participants were given 2 gm/day of vitamin C, insulin concentrations were decreased at 0.5 per hour but elevated at 2 hours during an oral glucose tolerance test (Johnston and Yen, 1994). In another trial of 40 patients with type 2 diabetes mellitus, the use of 0.5 gm/day of vitamin C resulted in decreased concentrations of insulin (Paolisso et al., 1995). In a study of 109 Japanese patients with type 2 diabetes mellitus, vitamin C supplementation (800 mg/d for 4 weeks) did not improve insulin resistance (Chen et al., 2006).

A number of cross-sectional studies have examined the associations between dietary patterns and metabolic syndrome or its components. Particularly germane to this work are studies that have examined the associations between dietary patterns characterized by increased antioxidant intake such as in a Mediterranean-style diet. This diet, in addition to "regular physical activity," emphasizes "abundant plant foods, fresh fruit as the typical daily dessert, olive oil as the principal source of fat, dairy products (principally cheese and yoghurt), and fish and poultry consumed in low to moderate amounts, zero to four eggs consumed weekly, red meat consumed in low amounts, and wine consumed in low to moderate amounts". Total fat in this diet is 25% to 35% of calories, with saturated fat at 8% or less of calories (Willett et al., 1995). The diet is often cited as beneficial for being low in saturated fat and high in monounsaturated fat and dietary fiber.
In a cross-sectional study of 2282 Greek men and women, participants who adopted a Mediterranean-style diet were less likely to have the metabolic syndrome than participants who did not (Panagiotakos et al., 2004). A few studies have suggested that a Mediterranean-style diet might favorably influence outcomes or physiologic abnormalities. Among Greek patients with an acute coronary syndrome who had metabolic syndrome, the adoption of a Mediterranean-style diet was associated with a 23% reduction in coronary risk (Pitsavos et al., 2003). In a randomized clinical trial of 180 Italian patients with metabolic syndrome, those who received the intervention that included the adoption of a Mediterranean-style diet showed favorable improvements in endothelial dysfunction and inflammatory markers (Esposito et al., 2004).

Several studies have suggested that the prevalence of metabolic syndrome differs by level of alcohol intake. Beverages such as wine are known to contain various antioxidants such as flavonoids. The studies examining dietary patterns or alcohol consumption were unable or did not isolate any possible effect of specific antioxidant intake on the study outcomes. However, Very few data are available about the associations between physiologic measurements of antioxidants, such as circulating concentrations, and metabolic syndrome from either cross-sectional studies or prospective studies. In addition, no studies have reported on the prospective associations between physiologic measurements of antioxidants and complications attributable to metabolic syndrome. No randomized clinical trials have been conducted among people with metabolic syndrome to test the effects of antioxidant supplementation on oxidative stress, antioxidant status, or other health outcomes.

VITAMIN C AS AN ANTIOXIDANT
Vitamin C is an important water-soluble antioxidant in biological fluids (Frei et al., 1990). Vitamin C readily scavenges reactive oxygen and nitrogen
species, such as superoxide, and hydroperoxyl radicals, aqueous peroxyl radicals, singlet oxygen, ozone, peroxynitrite, nitrogen dioxide, nitroxide radicals, and hypochlorous acid (Halliwell, 1996), thereby effectively protecting other substrates from oxidative damage. Although vitamin C also reacts rapidly with hydroxyl radicals, it is nevertheless unable to preferentially scavenge this radical over other substrates (Niki and Noguchi, 1997). The reason for this is that hydroxyl radicals are extremely reactive and will combine indiscriminately with any substrate in their immediate environment at a diffusion-limited rate.

Two major properties of vitamin C make it an ideal antioxidant. First is the low one-electron reduction potentials of both ascorbate (282 mV) and its one-electron oxidation product, the ascorbyl radical (2174 mV), which is derived from the ene-diol functional group in the molecule (Halliwell, 1996). These low reduction potentials enable ascorbate and the ascorbyl radical to react with and reduce basically all physiologically relevant radicals and oxidants. For this reason, vitamin C has been said to be "at the bottom of the pecking order" and "to act as the terminal water-soluble small molecule antioxidant" in biological systems (Buettner, 1993). The second major property that makes vitamin C such an effective antioxidant is the stability and low reactivity of the ascorbyl radical formed when ascorbate scavenges a reactive oxygen or nitrogen species (Equation1). The ascorbyl radical readily dismutates to form ascorbate and dehydroascorbic acid (Equation 1 and 2), or is reduced back to ascorbate by an NADH-dependent semidehydroascorbate reductase (Wells and Jung, 1997). The 2-electron oxidation product of ascorbate, dehydroascorbic acid, can itself be reduced back to ascorbate by the glutathione-dependent enzyme, glutathione dehydroascorbate oxidoreductase [glutathione dehydrogenase (ascorbate), or glutaredoxin], or the NADPH-dependent selenoenzyme thioredoxin reductase (Wells and Jung, 1997). Alternatively, dehydroascorbic acid is rapidly and irreversibly hydrolyzed to 2, 3- diketogulonic acid (DKG) (Equation 3) (Halliwell, 1996).
Equation 1 shows the reversible 1- and 2-electron oxidation of ascorbate (AH) to the ascorbyl radical (A·) and dehydroascorbic acid (A), whereas equation 2 shows the dismutation of the ascorbyl radical to form ascorbate and dehydroascorbic acid. Equation 3 represents the hydrolysis of dehydroascorbic acid to DKG, which then decomposes to oxalate, threonate, and many other products. Vitamin C has been recognized and accepted by the US Food and Drug Administration (FDA) as one of 4 dietary antioxidants, the other 3 being vitamin E, the vitamin A precursor b-carotene, and selenium, an essential component of the antioxidant enzymes glutathione peroxidase and thioredoxin reductase.

VITAMIN E AS AN ANTIOXIDANT

Vitamin E is the generic term used to describe a group of at least eight compounds that exhibit the biological activity of α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol. α-Tocopherol is the most active form of vitamin E, according to results from early animal growth assays (Food and Nutrition Board, 1989). In terms of antioxidant activity, results from more recent in vitro comparisons indicate that α-tocopherol is superior to γ-tocopherol as it usually exhibits less than 30% of the antioxidant activity of the α-tocopherol (Sies et al., 1993).

In plasma, vitamin E circulates in association with lipoproteins, mostly found in the LDL fraction under steady state conditions (Traber et al., 1993). In fact, α-tocopherol is the predominant antioxidant found in association with LDL; it is reported to be present at a molar ratio 6:1 (α-tocopherol to LDL) in well-nourished persons (Esterbauer et al., 1991). Recent epidemiologic
studies indicate that supplemental vitamin E consumption is inversely associated with the development of coronary artery disease in both men (Rimm et al., 1993) and women (Stampfer et al., 1993). Since oxidized LDL is implicated in the development and progression of atherosclerosis (Witztum and Steinberg, 1991) and α-tocopherol is known to limit LDL oxidation (Dieber-Rotheneder et al., 1991), it is attractive to speculate that the beneficial effects of α-tocopherol on coronary artery disease result from antioxidant protection of LDL. However, the effects of α-tocopherol on animal models of atherosclerosis are inconsistent (Verlangieri and Bush, 1992) despite continued protection of LDL against oxidation ex vivo (Keaney et al., 1994). Clearly then, the beneficial effects of α-tocopherol are not explained completely by its antioxidant protection of the LDL particle alone. α-tocopherol is incorporated into vascular tissue (Keaney et al., 1993) and may have important physiologic effects that are not directly related to the protection of LDL against oxidation in vivo. For example, α-tocopherol has been shown to influence leukocyte adhesion to endothelial cells (Faruqi et al., 1994), monocytes transmigration (Navab et al., 1991), and oxidant-mediated cytotoxicity (Hennig et al., 1987). Moreover, α-tocopherol is known to inhibit protein kinase C in vascular smooth muscle cells (Boscoboinik et al., 1991) and protein kinase C activation has been implicated in vascular disease due to diabetes (Tesfamariam et al., 1991) as well as oxidized-LDL (Ohgushi et al., 1993). Thus, these alternative effects of α-tocopherol have the potential to influence processes that are known to impair endothelium-dependent arterial relaxation.

Diabetic subjects and experimental animal models exhibit high oxidative stress due to persistent and chronic hyperglycemia, thereby depleting the activity of the antioxidant defense system and promoting the generation of free radicals (Hong et al., 2004). Vitamin E has been shown to decrease lipid peroxidation, inhibit platelet adhesion, aggregation, and smooth muscle cell proliferation, to exert its anti-inflammatory effect on
monocytes and to improve endothelial function (Harris et al., 2002). Animal studies have shown that vitamin E protects development of cholesterol-induced atherosclerosis by inhibiting protein kinase C activity in smooth muscle cells in vivo (Kartal et al., 2003). However, in spite of these evidences, the effect of α-tocopherol on blood pressure is controversial (Newaz and Nawal, 1998). Manifestations of vitamin E deficiency are exacerbated by deficiency of selenium (a necessary cofactor for glutathione peroxidase). This may be prevented by feeding other antioxidants (Farrell and Roberts, 1994). In cells, most of the vitamin E is situated in the membranes, adjacent to unsaturated fatty acids that are vulnerable to free-radical attack. Vitamin E is a potent chain-breaking antioxidant, scavenging oxygen radicals and terminating free-radical chain reactions (Burton and Traber, 1990). A number of studies have also suggested its role in prevention of cardiovascular diseases, cancer and Parkinson's disease as well (Hodis et al., 1995; Knekt, 1993; Stampfer et al., 1993).