"Latest Update on Statins for Diabetes".

Module 1

Introduction to Type 2 Diabetes and Cardiovascular Risk

CONTENT

Introduction

Diabetes mellitus (DM) is a chronic condition that occurs when the body cannot produce enough or effectively use of insulin, and are induced by a genetic predisposition coupled with environmental factors[1]. Three hundred sixty six million people have DM in 2011; half of these (183 million people) are undiagnosed[2]. The number of people with DM worldwide is increasing and by 2030 this will have risen to 552 million[2]. DM is a well-established risk factor for cardiovascular disease (CVD). People with type 2 diabetes mellitus (T2DM) have a higher cardiovascular morbidity and mortality, and are disproportionately affected by CVD compared with non-diabetic subjects[3]. Diabetic vascular disease is responsible for two-four-fold rise in the occurrence of coronary artery disease (CAD) and stroke, and two-eight-fold improve in the risk of heart failure[4]. It has been described that patients with T2DM and no previous history of CAD have the similar risk for cardiac events as subjects with a prior myocardial infarction[5]. However, subsequent studies have revealed variable results[6], which more indication that diabetes status may not be a CVD equivalent in all conditions, thus highlighting the necessity for multivariate approach as an suitable basis for risk stratification for CVD prevention in persons with diabetes[7]. The CVD risk follows a gradient, and taking this gradient depends on the combination of numerous risk factors[7]. Most of this excess risk is it associated with an improved prevalence of well-known risk factors such as hypertension, dyslipidaemia and obesity in these subjects. During the recent decade, conclusive evidence has been gathered that treatment of traditional risk factors is of immense importance for patients with T2DM in the reduction of CVD risk[8,9]. The poor control of the majority of cardiovascular risk factors observed in the diabetic population[10] supports the need for more aggressive arrangement of modifiable cardiovascular risk factors, especially in patients with previous CVD. However the improved cardiovascular disease in T2DM patients cannot be attributed solely to the higher prevalence of traditional risk factors. Therefore other non-traditional risk factors may be important in people with T2DM[11] (Table 1). Very few studies have shown prospectively the association of non-traditional risk factors in T2DM, independent of traditional risk factors[12]. Moreover therapies that are currently used in the management of T2DM such insulin-sensitizers and statins have a variety of effects on many of these non-traditional risk factors[13,14]. The relative magnitude of these risk factors has been widely reviewed in the literature[15]. Several studies have aided elucidate the mechanisms underlying the vascular dysfunction that leads to cardiovascular outcomes in DM. This vascular dysfunction is related with visceral adiposity, insulin resistance (IR) and changes in the levels of a diversity of circulating factors[16]. The atherogenesis begins as an endothelial cell dysfunction when various noxious insults as dyslipidaemia, hypertension, diabetes, smoking, etc. induce deficits of nitric oxide (NO) and prostacyclin. Next, mononuclear cells such as monocytes and T lymphocytes binding to the endothelium; this process is mediated by adhesion molecules present on the endothelial surface, such as vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM) and E-selectin. Monocyte migrates into the sub endothelial space, matures into a resident macrophage and takes up lipid through certain scavenger receptors such as SR-A and CD-36, becomes a foam cell. Later, smooth muscle cells migrate to the surface and form the fibrous cap of the lesion, and lastly lipid-laden macrophages release matrix metalloproteinase' s causing plaque rupture and acute coronary syndromes such as myocardial infarction and unstable angina.

Oxidative stress (OE) play an important role in atherogenesis, especially in DM[17,18], by proatherogenic role of oxidized low-density lipoprotein and its "in vivo" existence[19,20]. Elements that may promote increased OE in DM comprise antioxidant deficiencies, increased production of reactive oxygen species and the process of glycation and glycooxilation[20]. Increased plasma levels of nitrotyrosine, a marker of protein oxidation[21,22], elevated both plasma and urine levels of F2-isoprostane, a marker of OE[21-23] also the evidence of oxidative damage to DNA[24], was observed in patients with T2DM. In summary, CVD is elevated in T2DM due to a complex combination of various traditional and nontraditional risk factors, that have an important role to play in the beginning and the evolution of atherosclerosis over its long natural history from endothelial function to clinical events[25]. The clustering of vascular risk observed in association with IR has led to the view that cardiovascular risk appears early, before the development of T2DM, whereas the solid interactions between hyperglycaemia and microvascular disease suggests that this risk is not appear until frank hyperglycaemia appears. These notions highlight the progressive nature of both T2DM and related cardiovascular risk which propose specific challenges at diverse stages of the life of a subject with DM[26]; but do diabetic patients have specific risk factors which could explain the observed increase in CVD, or have all cardiovascular risk factors, traditional and nontraditional, the same strength? The objective of this review is to highlight the weight of traditional and non-traditional risk factors for CVD in the setting of T2DM and debate their position in the pathogenesis of the excess CVD mortality and morbidity in these patients. It is essential to know that these risk factors do not act in isolation. Risk factors occur simultaneously[27], compounding the risk for a cardiovascular event, although such interactions are difficult to quantify (Figure 1). Many of these risk factors may be common history for both DM and CVD, reinforcing the postulate that both disorders come independently from "common soil"[28].

Table 1 Cardiovascular risk factors in diabetes mellitus

Traditional	Nontraditional
Dyslipidaemia	Insulin resistance and Hyperinsulinemia
Hypertension	Postprandial Hyperglycaemia
Obesity	Glucose variability
Abdominal obesity	Microalbuminuria
Physical exercise	Haematological factors
Cigarette smoking	Thrombogenic factors
	Inflammation C-reactive protein
	Homocysteine and vitamins
	Erectile dysfunction
	Genetics and Epigenetics

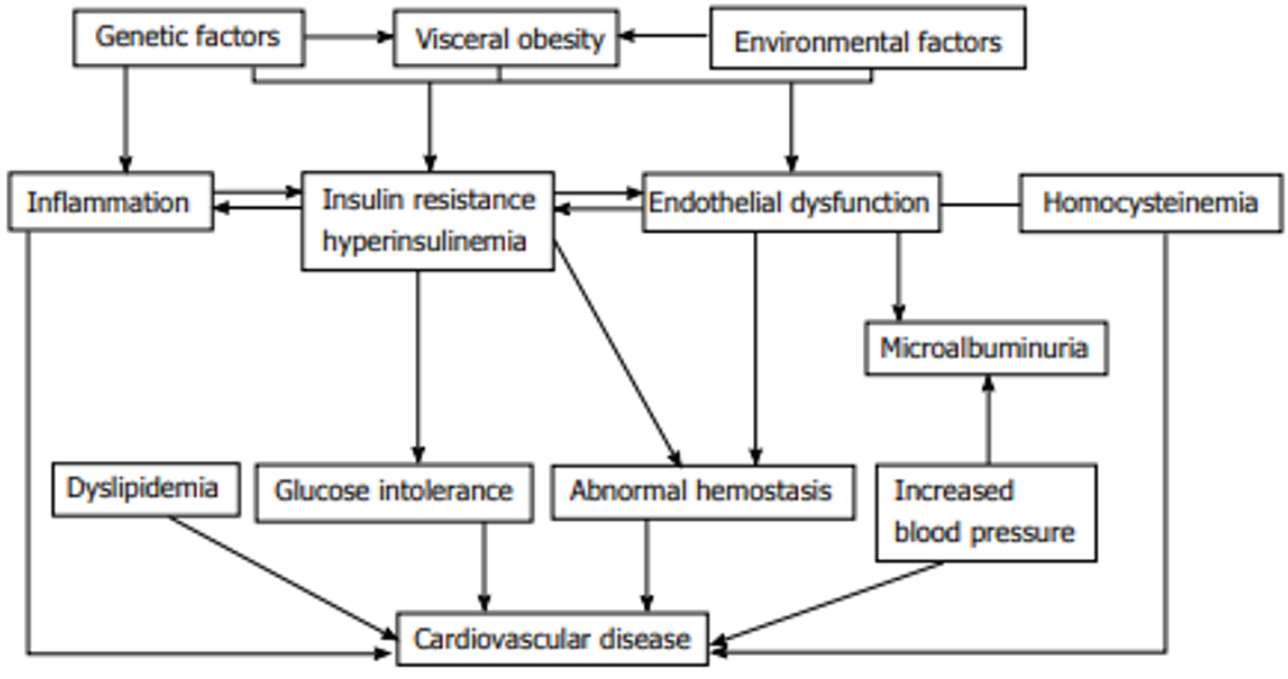

Figure 1 Interactions of traditional and non-traditional risk factors in diabetes mellitus.

Traditional Risk Factors

Dyslipidaemia

In T2DM, IR increases the mobilization of free fatty acids from adipose tissue. There are three mechanisms across which there is increased very low-density lipoproteins hepatic production: an increased lipogenesis, an exacerbation of substrate availability, and decreased apolipoprotein B-100 (ApoB) degradation. These changes carry to a lipid profile marked by low high-density lipoprotein cholesterol (HDL-C), high triglycerides (TGs), increased ApoB synthesis and small dense LDL particles[29]. This LDL subtype is more inclined to oxidation, playing an important role in atherogenesis. Stronger than LDL cholesterol, a low HDL-C or lonely elevated TGs, atherogenic dyslipidaemia (Low HDL-C and ApoA, Elevation of both fasting and post-prandial TGs, Elevation of small dense LDL particles, Elevation of ApoB) is in T2DM patients a self-determining predictor of cardiovascular risk. The protective function of HDL may be lost in type 2 diabetics owing to alterations of the protein, resulting in a pro-oxidant, inflammatory phenotype[30].

Association between dyslipidaemia and cardiovascular risk in T2DM:

A causal association exists between elevation of TGs-rich particles and their remnants, low HDL-C and cardiovascular risk[31,32] as is shown in large data from case-control, genetic, and large observational studies. Still in patients with a normal LDL-C levels, results from statin trials confirm the place of low HDL as an independent cardiovascular risk marker[33,34]. Cardiovascular event rates were significantly greater in those with dyslipidaemia: LDL-C > 2.6 mmol/L, HDL-C ≤ 0.88 mmol/L and TGs ≥ 2.3 mmol/L[35,36], as is proved in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. The FIELD study[37] defined the following variables as best predictors of cardiovascular events during a five year monitoring: lipid ratios non-HDL/HDL-C and total/ HDL-C. Ratio of ApoB/ApoA is also associated to CVD outcomes, but this ratio wasn't superior to conventional lipid ratios. Data from the Emerging Risk Factor Collaboration (ERFC) study[38] with 302430 persons with no history of cardiovascular disease, demonstrated that Apo B and non-HDL-C each had very similar association with coronary heart disease (CHD) regardless of the existence of diabetes. The ERFC study showed that an increase of 0.38 mmol/L or 15 mg/dL in HDL-C was associated with a 22% reduction in risk of CHD. Non-HDL-C was the best tool to define the risk linked with TGs rise in clinical practice[38].

Management of dyslipidaemia, significance in the prevention of CVD in T2DM:

As the development of atherogenic dyslipidaemia precedes the onset of overt glycaemia and the clinical diagnosis of diabetes, early effective intervention is recommended to reduce the risk of premature CVD. In T2DM large data exists on action mechanism and efficacy of statins in the prevention of CVD events[39]. The Collaborative Atorvastatin Diabetes Study assessed the benefits of a statin in T2DM patients and at least one of the following risk factors: albuminuria, retinopathy, hypertension or current smoking[40]. In this study, 2838 type 2 diabetics were randomized to placebo or atorvastatin 10 mg/d.

The study was finished ahead of time, because to a 37% reduction (P = 0.0001) in the primary endpoint (first acute CHD event).

Residual risk in people on LDL-lowering therapy:

Patients with T2DM at the LDL-C target are still at a significant risk of CVD events[31]. This residual risk is associated to several factors as increased on TGs-rich proteins, decreased HDL-C and small, dense LDL particles. Data of FIELD study demonstrated that fenofibrate therapy did not decrease the primary endpoint (nonfatal myocardial infarction and CAD-related death), but total CVD events were decreased from 14% to 12.5% (P = 0.035)[35,43]. However, a subgroup analysis of dyslipidaemic people (TGs > 2.3 mmol/L and HDL-C ≤ 0.9 mmol/L) in this study showed a 27% reduction in CVD risk[35]. In the ACCORD trial, 5518 patients were allocated to fenofibrate plus simvastatin (20-40 mg daily) or placebo without any additional effect on the primary endpoint. In a pre-specified subgroup analysis of people with TGs > 204 mg/dL and HDL-C < 34 mg/dL, cardiovascular risk was decreased in 31% in the fenofibrateplus-simvastatin group[44]. The effects seem to be appeared to an improvement in TGs[45]. Blood pressure Arterial hypertension is present in more than 60% of T2DM patients[46]. This is directly linked to: (1) increased renin-angiotensin-aldosterone system activity; (2) hyperinsulinemia associated to increased renal reabsorption of sodium; and (3) increased sympathetic tone[47]. Aging, obesity, and the onset of renal disease also promote an increase in the prevalence of hypertension. Hypertension and DM are additive risk factors for CVD. While the diagnosis of diabetes doubles the cardiovascular risk in men and more than triples the risk in women, hypertension quadruple cardiovascular risk in diabetic patients[5,48].

Treatment targets:

Lowering blood pressure (BP) under 140 mmHg systolic and 85 mmHg diastolic (Table 2) have shown positive effects on cardiovascular outcomes in randomized controlled trials[49-52]. The United Kingdom Diabetes Prospective Study (UKPDS) showed that strict (mean 144/82 mmHg), compared with less strict (mean 154/87 mmHg) control decreased macrovascular events by 24%. DM-related mortality decreased 15% with each 10 mmHg drop, down to a systolic BP (SBP) of 120 mmHg, with no indication of further decrease, as it was shown in a post-hoc observational analysis of the UKPDS trial[53]. Later, the ACCORD trial doesn't support a decrease of SBP below 130 mmHg[50]. Recent evidence suggests visit-to-visit variability in SBP and masked hypertension are predictors of cardiovascular disease in T2DM.

Effects of visit-to-visit variability in SBP on CVD in T2DM patients[54]:

Using the data from ambulatory BP monitoring, previous studies reported that short-term or circadian variability of BP was an important prognostic factor of cardiovascular outcomes[55-58]. Similarly, a number of observational studies have investigates the impact of long-term or visit-to-visit BP variability on the risks of cardiovascular outcomes[59-63] other new and important finding of this analysis was that visit-to-visit variability of SBP clearly predicted the future development of major microvascular complications among patients with T2DM[54].

Risk associated with masked hypertension in T2DM patients[64]: Masked hypertension (MH) is defined as an ambulatory hypertension with a normal conventional BP (CBP). The International Database on Ambulatory BP (ABP) in relation to Cardiovascular Outcomes[65], which contain a great number of diabetic patients, many of whom have MH, detected a higher prevalence of MH in DM than in non DM, and this finding was even more remarkable in treated vs non treated diabetics. Currently is not known the mechanism by which antihypertensive treatment is linked with a higher prevalence of MH. Cardiovascular risk in diabetic patients who are not receiving antihypertensive treatment and presenting with MH was significantly higher than in their normotensive comparator group. In contrast, antihypertensive-treated diabetics with MH had cardiovascular risk that was identical to treated stage 1 and stage 2 hypertensive subjects. This suggests that a significant percentage of these subjects had real hypertension that simulated MH in the presence of elevated ABP and normalized CBP[65]. Nevertheless, currently, there aren't credible studies in diabetics with MH to evidence the benefit of antihypertensive therapy or to indicate how low to go with the reduction in ABP to achieve optimal reduction in cardiovascular risk. We may have to balance the potential advantage of further reduction in systolic ABP and CBP values with the increased cardiovascular risk of lower diastolic ABP and CBP.

Obesity and abdominal obesity:

Generalised obesity assessed by the body mass index (BMI), and abdominal obesity determined by the waist circumference (WC), are related with a variety of CVD risk factors. Clinical guidelines do not indicate whether BMI or the WC measurements have identical utility in predicting cardiovascular risk in individuals with T2DM compared to non-diabetic patients[66,67]. The impact of obesity on both atherogenesis and in novel procoagulant and prothrombotic cardiovascular risk factors is of particular interest in cases of T2DM, as they contribute to increased CVD mortality in these individuals[68-72]. In diabetic patients the coexistence of multiple variables such as diabetic duration, glycaemic control and the drugs used for achieving it, lipid profile, BP or the existence of risk behaviours such as smoking or alcohol use may confound the impact of obesity on the risk of CVD[73]. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study[73] was designed to establish the association between indexes of obesity and atherothrombotic risk factors in patients with T2DM and document CVD. By only taking into account this study's baseline it was possible to evaluate among this group of patients if a higher BMI or higher WC was associated with specific cardiovascular risk factors, and whether a higher WC was related with cardiovascular risk factors independent of diabetic patient's BMI. The review of the study baseline results showed, on the one hand, that patients with BMI ≥ 40 experienced more cases of heart failure. However, a history of myocardial infarction was less common in patients with BMI ≥ 35 (26%-30%) than in those with BMI ≤ 29.9 (34%-36%), possibly because patients with BMI ≥ 35 reported fewer years smoking than those with BMI of ≤ 29.9. Smoking was proportionally, inversely related to BMI. Furthermore the BMI, independent of the WC, had a strong association with SBP, the plasminogen activation inhibitor type 1 (PAI-1), the C-reactive protein (CRP) and fibrinogen, whereas WC had robust associations with the HDL-C and TGs levels. It is well known that CVD is among the most frequent causes of mortality for diabetics and obese individuals. Studies have established the mortality risk in obese T2DM subjects taking the age into account. The data obtained from a study conducted in Verona with 3398 T2DM patients who were followed up for 10 years showed that in patients > 65 years a moderate excess weight predicted longer survival, whereas obesity was a negative prognostic factor in patients < 65 years[74].

Physical exercise Regularly practicing physical exercise is correlated with a lower risk of cardiovascular morbidity and mortality, both in primary and in secondary prevention. However it should be taken into account that this type of evidence is often subject to other lifestyle changes that take place together with exercise (for example stopping smoking, a balanced diet, etc.) [76,77]. leisure time was linked with a decrease in cardiovascular mortality and total mortality[79]. It is important to note that patients with T2DM have a reduced capacity for exercise due to age, the high BMI and the frequent presence of left ventricular dysfunction[80]. Exercise improves insulin sensitivity in diabetic patients in the same way as it does in non-diabetic patients[81-83]. Patients with diabetes have greater IR which can be mediated by different defects in the glucose metabolism, and some of which would improve with physical exercise. These defects include not only a decreased number of insulin receptors and glucose transporters, but also a reduction in the intracellular enzymes activity (pyruvate dehydrogenase and glycogen synthase) and reduced oxygenation during exercise. Increased physical activity achieves higher mitochondrial enzyme activity and increases insulin sensitivity; however the number of muscle capillaries in diabetic patients with microvascular complications does not increase or is practically negligible[84-86]. Multiple studies have shown physical exercise to improve cardiovascular risk factors (dyslipidaemia, hypertension and body composition) in patients with T2DM[87]. Although it is not all kinds of physical activity exert the same influence on this risk. Aerobic exercise only or combined with resistance exercise improves glycaemic control, BP, the amount of TGs and WC. But resistance exercise alone does not have a clear impact on cardiovascular risk factors. In prospective cohort studies, exercise was associated with improved CVD and reduced cardiovascular mortality and total mortality in patients with T2DM[88]. This risk improvement remained after adjustments for smoking, BMI, and another cardiovascular risk factors.

Smoking:

Smoking is linked with deterioration in metabolic control in diabetic patients[90,91], which is associated with an increased risk for development of macrovascular and microvascular complications and mortality in DM[92,93]. The suggested mechanisms for the influence of smoking on risk of T2DM are summarized in Table 3. Administration of nicotine rise the circulating levels of insulin-antagonistic hormones (growth hormone, catecholamines and cortisol)[94-97], and also has been proved to affect the autonomic nervous system[98,99]. Nicotine, via these and possibly also other mechanisms, decreases insulin sensitivity, directly or indirectly. Also smoking increases circulating free fatty acid levels[95], and this is an additional negative factor for the insulin-mediated glucose uptake[100]. Smoking and macrovascular complications in T2DM: CVD is responsible for the main proportion of mortality associated with T2DM. There is evidence that smoking improves the risk of CAD in T2DM. Based on data from 4540 patients with T2DM followed in the UKPDS, smoking was shown to rise the risk of CHD[101] in males and females with T2DM. The expected RR incidence of a fatal or non-fatal myocardial infarction or sudden death attributable to smoking was 1.350 (95%CI: 1.11-1.59). This study reveals that smoking is an independent and significant risk factor for stroke[102] and peripheral vascular disease[15]. However, it was proved that smoking is significantly related with an augmented risk for CHD, but not for stroke, in T1 and T2DM patients in the London cohort of the prospective (8-year follow-up) World Health Organization Multinational Study of Vascular Disease in Diabetics[93]. In a prospective cohort of female nurses with T2DM[103], cigarette smoking was found to be robustly associated with the risk of CHD, and this risk improved with the number of cigarettes smoked per day.

Compared with the nurses who had never smoked, the RR for CHD was 1.21 (95%CI: 0.97-1.51) for past smokers; 1.66 (95%CI: 1.10-2.52) for current smokers of up to 14 cigarettes per day; and 2.68 (95%CI: 2.07-3.48) for current smokers of 15 cigarettes per day or more. A relatively large prospective study examined the effects of smoking cessation on cardiovascular risk in diabetic patients[104]. Diabetic patients who are current smokers should be proposed a planned smoking cessation program that includes pharmacological treatment if is necessary. Detailed instruction should be provided according to the five A principles (Table 4) as is developed in the 2012 Joint European Prevention Guidelines[105].

Non-Traditional Risk Factors

Insulin resistance and hyperinsulinemia IR is a principal characteristic of T2DM and it develops in multiple organs involving the skeletal muscle, liver, adipose tissue and the heart. The onset of hyperglycaemia and diabetes is often preceded by several years of IR. Obesity plays a major role in this phenomenon and provides an important link between T2DM and the accumulation of fat[106]. A significant section of the population with T2DM is obese[107]. The hyperinsulinemia, as a result of IR, occurs even before the onset of DM, and could be, by chance, related to vascular disease[108-111]. The IR, measured by the hyperinsulinaemic-euglycemic clamp, or surrogate methods such as the HOMA index, the frequently-sampled intravenous glucose tolerance test or the insulin suppression test, appears in more than 76% of subjects, and is accompanied by compensatory hyperinsulinemia[112]. Although molecular mechanisms of IR are not yet entirely understood, abnormalities in insulin signalling have been explained[113]. Under normal conditions, insulin starts its action by binding to its specific cell surface receptor in peripheral tissues such as liver and skeletal muscle. The conformational changes of the insulin receptor induced by insulin binding to the extracellular alpha-subunit of the insulin receptor, causes the dimerization of neighboring receptors and the activation of the tyrosine kinase domain of the intracellular beta-subunit. Autophosphorylation of the beta-subunit itself, promoted by the onset of tyrosine kinase activity of insulin receptor, and the rapid phosphorylation of docking proteins, such as insulin receptor substrates -1, -2, -3 and -4, and some other proteins, comprising collagen homology proteins (shc) and SRC homology 2 (SH2), activates consecutively multiple intracellular signalling intermediates. In their phosphorylated forms, these proteins develop points of anchoring for intracellular proteins containing complementary SH2 domains, playing an important regulatory function in the insulinsignalling cascade. Specifically, the activation of Akt or protein kinase B, which plays an essential role in the mechanism of insulin action on GLUT-4 translocation, glucose transport, and the activation of NO synthase ("metabolic signalling pathway"), is determined by the interaction between insulin receptor substrate-1 proteins and phosphatidylinositol (PI) 3-kinase. On the contrary, the activation of Ras (predominantly through shc and, to a lesser degree, insulin receptor proteins), Raf, and mitogen-activated protein kinases (MAPK) ("growth signalling pathway") are implicated in the mitogenic, nonmetabolic, pro-inflammatory and proliferative effects of insulin[114]. A decreased activation of insulin signalling via the insulin receptor substrate-1/PI3-kinase (PI3K), can be showed in insulin-resistant animals and in vitro models. This reduction leads to a decreased glucose uptake, diminished NO synthesis, and reduced glucose utilisation in insulin target tissues pathway. Similar decrease in glucose transport is detected in the pancreatic beta cells, which induces a compensatory rise in insulin secretion. In spite of this, the MAPK-mediated insulin pathway persists unaffected. Under these conditions of hyperinsulinemia, this selective imbalance of the two signal transduction pathways can lead to a disproportionate proliferative/growth-promoting signal, while the normal transport of glucose and glucose homeostasis is conserved. Compensatory hyperinsulinemia stimulates in vascular smooth muscle and endothelial cells, an increased production of endothelin, PAI-1, proinflammatory cytokines and an augmented surface expression of adhesion molecules[115-118].

Homeostasis of blood vessels is conserved through the activation of endothelium-derived NO, stimulated by insulin. By rapid posttranslational mechanisms, which are mediated through PI3K/Akt signaling pathway, insulin augments the endothelial NO production by activating endothelial NO synthase (endothelial NOS)[119]. In IR states, the selective inhibition of the PI3K/Akt pathway detected in skeletal muscle from obese people and subjects with T2DM[120], and in the vasculature and the myocardium of obese Zucker rats, leads to endothelial dysfunction, with a consequent rise in the interaction between endothelial cells and leukocytes, an increase in vascular tone and BP, and a prothrombotic state. In this selective state, largely due to the ability of insulin to increase NO production, its physiological anti-atherogenic effects become proatherogenic[121].

Postprandial hyperglycaemia and glucose variability

Postprandial hyperglycaemia has been appeared to be related with an augmented risk of cardiovascular events in patients with and without T2DM[122-125]. Postprandial glucose excursions, especially when accompanied by increased postprandial TGs levels, are pathophysiologically related to augmented OE, systemic inflammation and endothelial dysfunction, all of which are associated to increases in atherosclerosis and cardiovascular events[126,127]. Postmeal hyperglycaemia is also linked to retinopathy, cognitive dysfunction in old people and specific cancers[128]. Relevantly, even in the setting of controlled fasting glucose levels, postprandial spikes in glucose powerfully improve both atherogenesis and cardiovascular events[122-125,129]. Two studies have examined the predictive strength of postprandial glycemia on cardiovascular events. It has been shown that intensive control of hyperglycemia prevents macrovascular events and all-cause mortality in individuals with T2DM. A meta-analysis of 5 randomized controlled trials showed that, in T2DM subjects, intensive glycaemic control considerably decreases coronary events without an increased risk of death [131]. However, the specific effect of postprandial blood glucose control on cardiovascular events and mortality, is less clear. The following evidence is available: (1) Intervention with acarbose, a drug that diminish postprandial blood glucose excursions by delaying carbohydrate digestion in the small intestine, can prevent myocardial infarction and CVD in T2DM patients[132]. Moreover, in patients with impaired glucose tolerance, in Study to Prevent Non Insulin Dependent Diabetes Mel litus, acarbose was associated with a 49% relative risk reduction in the development of cardiovascular events[133]; (2) Nateglinide, a drug that lowers postprandial blood glucose by stimulating insulin secretion from the pancreas, was incapable in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial[134] to diminish cardiovascular events among persons with impaired glucose tolerance and established CVD; however, patients on Nateglinide presented an increase of 2-h postchallenge blood glucose[134]; and (3) The Hyperglycemia and its Effect after Acute myocaRdial infarcTion on cardiovascular outcomes in patients with T2DM trial, planned to compare the effects of prandial vs fasting glycemic control on risk for cardiovascular outcomes in subjects with T2DM after acute myocardial infarction, revealed that treating diabetic survivors of acute myocardial infarction with two distinct insulin regimens (prandial vs basal) achieved differences in fasting blood glucose, less-than-expected differences in postprandial blood glucose, and no difference in risk for future cardiovascular event rates[135]. Therefore, the role of postprandial glycemia as a predictor of cardiovascular events, and its importance as a treatment target, are issues to discuss. These assessments had led to the concept of glucose variability. Recently, it has been suggested that blood glucose variability may contribute, even more than HbA1c, to the development of diabetes complications.

However, the lack of consensus on the best approach to define the glucose variability, and difficulty of measuring it, are still unsolved problems. The relationship between glucose variability and OE, is an important physiopathological element for the development of the cardiovascular complications of diabetes. Glucose variability, thus, looks set to become the main target for future treatments for diabetes, aimed to reaching better efficacy in the metabolic control of diabetes and the prevention of complications related to it[136].

Microalbuminuria

The term microalbuminuria (MA), a urinary albumin excretion between 30 and 300 mg/24 h, has been introduced to identify subjects at increased risk of early cardiovascular death and progressive renal disease. In individuals with T2DM, MA is a prematurely clinical sign suggestive of vascular damage to the glomerulus. MA has also been currently reported as an important risk factor for CVD and remains the main and most widely used marker of diabetic renal damage in clinical practice. It is also a marker of organ dysfunction, and has been appeared to be associated with an increased risk of cardiovascular morbidity and mortality in T2DM patients[137]. At present, an increased albumin excretion is considered to be a renal symptom of generalized endothelial dysfunction[138]. According to different studies, the prevalence of MA is up to 19% in T2DM[139-142]. The epidemiology of MA shows a close association with systemic and glomerular endothelial dysfunction and with vascular disease. Damage to glycocalyx, a protein rich surface layer on the glomerular endothelium, probably represents the initial step in the development of diabetic MA[143]. MA is a marker for diabetic nephropathy. It also signifies CVD as well as nephropathy in T2DM. MA may precede T2DM, and forms one of the components of the IR/metabolic syndrome which confer a particularly high risk of cardiovascular deaths. Therefore, MA accounts for the increased risk of vascular disease in subjects with metabolic syndrome[144]. Other indicators of cardiovascular risk, such as markers of inflammation, are related with MA in population of patients with and without diabetes[145]. The existence of MA in people with T2DM is the most important early sign that we alert us to the onset of a systemic vascular disease, and associated target organ damage to the heart, the brain and the kidney. Their presence serves to recognize patients at risk of early cardiovascular death and advancement of kidney disease[146]. Patients with MA are at very high vascular risk and should share identical objectives of a vascular risk factor control as patients with overt CVD[147]. MA in patients with T2DM positively correlates with the severity of coronary atherosclerosis[148]. Reinhard et al[149] showed that half of asymptomatic patients with T2DM and MA, which received an intensive multifactorial treatment for cardiovascular risk diminution, had significant atherosclerosis in at least one vascular territory. They observed a higher prevalence of coronary atherosclerosis than carotid disease[149]. On the other hand, MA was higher in T2DM patients with silent myocardial ischemia[150]. The presence of MA also indicates that a low-level inflammatory process is ongoing. In hypertensive individuals, with or without diabetes, increasing MA is related with augmented levels of inflammatory markers, endothelial dysfunction and platelet activation[151]. Elevated plasma osteoprotegerin, a cytokine receptor, is an independent predictor of the presence of CVD in asymptomatic T2DM patients with MA[152], and CRP, a marker of inflammation, was an independent risk factor for development of nephropathy in T2DM patients[153]. Finally, D-dimer, a fibrin degradation product, is associated with MA in T2DM patients; this suggests that glomerular dysfunction is in part mediated by hypercoagulability[154].

Duration of diabetes[139], diabetes severity[139], uncontrolled hypertension[139,141,153,155-157], baseline levels of urinary albumin excretion > 12 mg/24 h[153], BMI[139,157], central obesity[139,140,155], high HbA1c[139,141,157], smoking habits[140,155,157], age of the patients[156], creatinine[141], CRP > 3 mg/L[153], as well as TGs and HDL-C[136,156] were independent risk factors for the development of MA in T2DM patients. These risk factors were independently associated with established MA. Population of normotensive subjects with T2DM and MA, female sex, was related with elevated risk of fatal and nonfatal CVD, independent of the traditional cardiovascular risk factors, the severity of nephropathy or existence of retinopathy, or health care utilization[158]; and a decreased estimated glomerular filtration rate and the occurrence of MA were each related with a near doubling of the prevalence of CVD, independently of classical cardiovascular risk factors and glycaemia control in subjects with T2DM[159]. Carotid stiffness, quantified by quantitative carotid stiffness, a local functional measurement of the arterial wall, is augmented in T2DM patients with MA[160]. MA is also independently linked with arterial stiffness and vascular inflammation in individuals with newly diagnosed T2DM[161], but not with carotid intima-media thickness[161,162], with emphasizes the significance of proactive clinical investigations for atherosclerotic complications in subjects with MA in newly diagnosed DM. On the other hand, patients with MA have more severe angiographically detected CAD than those without MA[163]. Thus relative is independent of other risk factors and is particularly evident in patients with T2DM[164]. In conclusion, MA is a marker for diabetic nephropathy. It also signifies CVD in T2DM. MA is predictive, independent of classical risk factors and all causes of mortality in T2DM individuals. Determination of MA has been shown to be helpful to recognize patients with T2DM at high risk of renal and CVD. MA is correlated with higher cardiovascular mortality, especially in diabetics, but the direct relationship between MA and vascular wall properties is still not clear. Haematological and thrombogenic factors Atherothrombosis, defined as the formation of a thrombus on a pre-existing atherosclerotic plaque, is the leading cause of mortality in the Western world. Diabetes has been recognised as an independent risk factor and atherothrombosis accounts for the 80% of deaths in these patients[165,166]. It is the result of the progression of atherosclerosis, and its major manifestations are sudden cardiac death, myocardial infarction, stroke and peripheral arterial ischemia[167]. Diabetes is related with a hypercoagulable state, which is more pronounced during the postprandial period. Hyperactivated platelets at injured endothelial interfaces act, together with an improved availability of thrombotic precursors, decreased coagulation inhibitors and diminished fibrinolysis[168]. The UKPDS clearly showed that macrovascular events in patients with T2DM accounted for more than 50% of total mortality[169]. Atherosclerosis develops more quickly and aggressively in diabetes, and leads more frequently to thrombotic events due to the interaction between the vascular wall and hypercoagulability[170,171]. In DM, the activation of the intrinsic coagulation pathway occurs more easily and fibrinolysis diminishes[172]. The increased platelet activity signifies increased adhesion and aggregation in diabetic patients (Figure 2). Individuals with various stages of diabetes were showed to have increased numbers of CD62P-positive and CD63-positive platelets (activated platelets) compared to healthy subjects. This increase in circulating activated platelets is not associated with glycaemic control improvement thereby intensifying insulin therapy. Surprisingly this increase in CD62P-positive platelets can also be found in healthy, first-degree relatives of patients with T1DM. Additionally, significant increments in basal thromboxane B[164] are seen in the platelets of both type T1 and T2DM, both in patients with an absence of vascular complications, as well as those with good diabetic control. Flow cytometry has revealed that a large, hyperactive platelet subpopulation circulates in patients with DM, at a similar level to patients who have experienced a myocardial infarction.

This suggests that the increased aggregation potential of these platelets lowers their activation threshold, thus contributing to the augmented incidence of acute cardiovascular events in DM[173]. Apart from platelet hyperactivity, DM also predisposes the coagulation system to other disorders[174]. Fibrinolysis is a natural defence system against thrombosis. Under physiological conditions, there is a balance between plasminogen activators and inhibitors; however, an imbalance can be caused by a reduction in the tissue plasminogen activator levels or an increase in the PAI-1 levels. This prethrombotic state in diabetic patients has been explained by multiple hypotheses. One such hypothesis is based on various studies showing the high levels of PAI-1 found in diabetic patients[175,176]. High concentrations of PAI-1 have been implicated with an increase in cardiovascular morbidity and mortality with age. A search was made for the relation of PAI-1 with various factors such as age, gender and ethnicity in subjects with T2DM and stable CAD enrolled in the BARI 2D study. The results of this study concluded that in subjects with T2DM and stable CAD, the levels of PAI-1 antigen and its activity were paradoxically lesser with advancing age; and in contrast, D-dimer ($P < 0.0001$) was increased, revealing elevated fibrinolysis. These results may indicate a protective phenomenon resulting in an improved survival in some older people with DM that endowed them with longevity enough to permit them to participate in the BARI 2D study[177]. Another hypothesis in this prethrombotic state is that hyperglycaemia permits the protein glycosylation process, such as the fibrinogen, which affects the clot's physiological structure, and thus it is more resistant to plasmin degradation. DM is also associated with increased plasma fibrinogen, which is considered as another cardiovascular risk factor[12,178]. This increase in fibrinogen is also associated with other vascular risk factors such as old age, increased BMI, smoking, total cholesterol and TGs. Fibrinogen has been extensively studied by many researchers, and a connection between the amount of fibrinogen and fibrin present in the vascular wall, the fibrinogen plasma concentration and the severity of atherosclerosis has been established. This association has been shown to be more evident in patients with diabetes[179,180]. Furthermore, an elevated concentration of fibrinogen has been found in diabetic patients with albuminuria. Some authors believe that the increased levels of fibrinogen, factor and von Willebrand factor which have been found in DM patients serve as predictors of coronary atherosclerosis and cardiovascular risk factors[181]. This association supports the fact that diabetic patients develop cardiovascular complications more frequently than the healthy population. Inflammation: C-reactive protein Atherosclerotic CHD and other forms of CVD are the main cause of mortality in T2DM, as well a major contributor to morbidity and lifetime costs. When diabetes occurs in subjects with established CAD, absolute risk for future events is very high. Inflammation has been involved in the pathogenesis of CVD, T2DM, and cancer. Different biochemical parameters may be utilised for the evaluation of CVD risk in T2DM patients of different age[182]. CRP is an acute-phase protein produces in the liver; its release is stimulated by cytokines (interleukin 6 and tumour necrosis factor alpha). Increased levels of it are related with the presence and severity of CAD and renal impairment in individuals with T2DM[183]. Although the determination of high-sensitivity CRP (hs-CRP) level represents an interest in the screening of CVD in T2DM patients[184]. Increased concentrations of hs-CRP are associated with IR, T2DM and the development of CVD. In particular, inflammation strongly linked with endothelial dysfunction is accepted as one of the cardiovascular risk factors clustering in the IR syndrome or metabolic syndrome. Moreover, low-grade inflammation might play an important role in the pathobiology of the metabolic syndrome[185,186]. The exact mechanism linking IR and inflammation remain unclear. Several studies have drawn attention to the finding of increased levels of hsCRP in T2DM patients with features of the metabolic syndrome[187-190].

The elevation of hs-CRP was strongly correlated with BMI, serum lipids, fasting glucose and WC[191-197], features of the metabolic syndrome, indicating potential roles of obesity and abdominal obesity in the development of inflammation associated with the metabolic syndrome in T2DM patients. The strong association between IR and inflammation in atherogenesis insinuates that therapies that address both parameters, such thiazolidinediones may have benefits in decreasing diabetesrelated macrovascular complications[198]. Serum concentration of hs-CRP is a good biomarker of chronic low-grade inflammation and is an established prognostic marker in acute coronary syndrome. In subjects with DM, the presence of high plasma levels of hsCRP are predictive for fatal and non-fatal CHD[199,200]. Although suffering from an acute CAD, patients with T2DM have a poor outcome compared with non-diabetic patients, in part explained by a persistent endotheliumdependent dysfunction and inflammatory activity in these patients after acute myocardial infarction[201]. Finally, hsCRP was related with silent myocardial ischemia, and might help to detect silent myocardial ischemia in diabetic patients[202]. On the other hand, in T2DM patients hs-CRP was an independent risk factor for CHD deaths[203]. In a case control study including 60 T2DM subjects with normal lipid profile and 60 age and sex-matched healthy controls, hs-CRP was an independent cardiac risk predictor even with normal lipid profile and can help measure additional risk[204]. Moreover the Diabetes Heart Study (DHS) documents the utility of hs-CRP in predicting risk for allcause mortality in 846 European Americans with T2DM, and supports its use as a screening tool in risk prediction models[205]. However, in acute coronary syndrome few studies found no significant differences in hs-CRP between patients with and without diabetes[206]. Khatana et al[207] have found that hs-CRP may not be suitable to predict changes in cardiovascular risk among diabetic patients, and should not be a surrogate for achieving evidence based goals in traditional cardiovascular risk factors; in the Prospective Evaluation of Diabetic Ischaemia Heart Disease by Coronary Tomography Study, there was a negative association between coronary artery calcification score, obtained by electron beam tomography, and CRP in T2DM patients[208]; and the Irbesartan Diabetic Nephropathy Trial with baseline data obtained from 722 diabetic nephropathy patients showed a lack of association between hs-CRP and specific established or emerging cardiovascular risk factors[209]. Diabetic patients with MA and hypertension had more frequent association with increased marker of inflammation such hs-CRP[210]. The correlation found between hsCRP levels and albuminuria in T2DM patients[211] suggest that the inflammatory process plays a role in diabetic nephropathy patients. However, in these patients CRP does not add predictive information above and beyond that offered by traditional established risk factors[212]. Several large prospective studies have proved that baseline levels of hs-CRP are an independent predictor of cardiovascular events among apparently healthy individuals. However, prospective data on whether hsCRP predicts cardiovascular events in diabetic patients are limited so far. The Prevention of Renal and Vascular End stage Disease study, a prospective population-based cohort study in the Nederland's, including 8592 participants[213] show that elevated hs-CRP, has added value to the present metabolic syndrome defining variables in predicting new onset CVD. In a prospective cohort study, baseline hs-CRP level is associated with increased first cardio-cerebral vascular event in the population with DM[214]. In the Casale Monferrato Study[215], hs-CRP measurement is independently related with short-term mortality risk in T2DM patients, even in normoalbuminuric individuals, and in those without a prior diagnosis of CVD; and in the Chennai Urban Rural Epidemiology Study (CURES)[216], an ongoing population-based study conducted on 150 subjects selected from the CURES, hs-CRP demonstrated a solid association with CAD and diabetes even after adjusting for age and gender. Finally, in a prospective study a cohort of 746 American men aged 46-81 years who were free of CVD at the time of blood collection in 1993-1994 were followed[217].

In this study elevated plasma levels of hs-CRP were related with an improved risk of incident cardiovascular events among diabetic men, independent of currently established lifestyle risk factors, blood lipids and glycaemic control. On the other hand, in the recent ADVANCE study[218], the authors deduce that interleukin-6 levels but not CRP or fibrinogen levels, add significantly to the prediction of macrovascular events and mortality in patients with T2DM who have baseline CVD or risk factors. In conclusion, the serum levels of hs-CRP, which is a marker of systemic inflammation and a mediator of atherosclerotic disease, have been correlated with the risk of CVD in T2DM patients. The determination of it is very important as screening of CVD in T2DM patients. Homocysteine and vitamins Homocysteine (HC) is a sulphur-containing essential amino acid derived from methionine. Vitamins B6, B12 and folic acid act as coenzymes in the metabolism of methionine and HC, and individual deficiency may cause hyperhomocysteinemia (HHC)[219]. Therefore, a negative correlation exists between HC plasma levels and vitamins B6, B12 and folic acid levels[220]. The HC plasma levels are higher in men, in women they increase after the menopause, and in both sexes they rise with aging[219]. An increase in HC levels has also been described in chronic kidney disease through a mechanism that is still not entirely understood, although it has been related to decreased renal clearance and metabolism and/or a descent in the extrarenal metabolism resulting from retained inhibitory substances[221]. In T2DM subjects, elevated HC levels have been related with a rise in the risk of suffering from cardiovascular events, independent of other risk factors[222,223], such as age and renal function[223]. The close relation between HC and CVD confirms the atherosclerotic role in the same[224]. For some authors, higher HC levels are consistent not only with aging and the male gender, but also in line with the development of DM[225]. HC levels do not appear to be related with anthropometric indices such as weight, BMI, percentage of fat mass and triceps skin fold[226]. On the other hand, the HC could play an etiologic role in the pathogenesis of T2DM, promoting OE, systemic inflammation and endothelial dysfunction[227]. HC seems to be the cause of increased mortality in T2DM subjects[223], and some authors consider it as a predictor of mortality[228]. The highest HC levels have been found in diabetic patients who have suffered several cardiovascular events[222]. The role of HC as a cardiovascular risk factor in DM is unclear. The poor metabolic control of the T2DM patients appears to have a predominant role. There exists a positive correlation between the HC levels and those of HbA1c, and a negative correlation with those of insulin[229]. On the other hand, a decline in HC levels has been observed in diabetic patients with a high cardiovascular risk and an elevated intake of foods high in folate, and vitamins B6 and B12[230]. Furthermore, an important predictor of cardiovascular risk in T2DM is arterial compliance which may not only be associated with age, but also with HC levels and renal function parameters[231]. The HHC as a cardiovascular risk factor includes CHD, both in the general population and in the diabetic population, although the role it plays on T2DM is unknown. However, the HHC in plasma is closely related to the development of CAD[232]. Thus, elevated HC levels have been found in patients with CHD, closely correlated with the occurrence of the same in the presence of decreased levels of folic acid and HDL-C[233]. Silent myocardial ischemia is one of the most frequent causes of mortality in the United States and it not only affects the diabetic population. Traditional risk factors have been identified such as T2DM itself, hypertension, dyslipidaemia and smoking, but there are also a series of novel factors such as lipoprotein (a), CRP and HC that can help improve the evaluation of patients with this disease[233]. In patients with T2DM, silent myocardial infarctions have been associated with these novel cardiovascular risk factors such as increased HC[234]. The HHC is related with increased mortality in T2DM patients suffering from CAD, without, however, being a predictor factor of cardiovascular mortality[235]. MA is a predictor of CVD and shows a close relationship with HC.

The reason for this association is unknown; however it could be in the origin of MA. There are studies that show a relationship between HC and MA, irrespective of T2DM and hypertension[236]. In T2DM subjects with a high prevalence of peripheral arterial disease and nephropathy, there exists a relationship between the levels of HC and those of MA[226]. Finally, HHC is considered as a risk factor for the development of peripheral arterial disease in T2DM individuals over 65 years of age[237]. HHC is linked with the risk of developing peripheral and autonomic neuropathy. In T2DM, HC is associated with neuropathy developing through an ischemia. The rise of HC appears to be independently associated with autonomic neuropathy, showing no association with peripheral diabetic neuropathy. Small HC elevations in patients with diabetic retinopathy have been associated with capillary and endothelial dysregulation, in which the HHC could be an important risk factor for the development of a macular oedema[240]. An increase in HC levels has been described together with a decrease in levels of folic acid and vitamin B12[241]. However, taking folic acid, and vitamins B12 and B6 supplements with the aim of reducing HC levels does not decrease the risk of developing CVD[237]. Vitamin B12 deficiency together with an elevation of HC will predispose towards an augmented risk of cardiovascular morbidity and mortality in T2DM subjects. Vitamin B12 supplementation in these patients will not reduce the cardiovascular risk[242]. As regards vitamin A, it is capable of affecting the inflammatory mechanisms and the immune function and therefore be associated to CVD. However, there does not appear to be a relation to the cardiovascular risk, as variations of the same are not found in T2DM[243,244]. Neither has an association been found between the zinc levels and cardiovascular risk with the HbA1c levels in T2DM patients[244]. The actions of vitamin D are mediated by binding to a specific nuclear vitamin D receptor (VDR)[247]. Allelic variations of the VDR gene are related with improved risk of CAD in T2DM patients[245]. The hypothesis that vitamin D might protect against vascular disease, comprising atherosclerosis and endothelial dysfunction, is postulated since it has been observed that the VDR is also expressed in the vasculature[246]. An increased production of NO, the inhibition of macrophage to foam cell formation, or a decreased expression of adhesion molecules in endothelial cells, might mediate the vascular protective actions of vitamin D[247-249]. Both endothelial dysfunction and increased arterial stiffness[246,250], and more recently cardiovascular risk factors including T2DM[251], and an elevated risk of CVD[252] are related with low vitamin D levels. Of published observational studies, most have shown that lower levels of vitamin D are related with a high incidence of cardiovascular events and mortality[253-257]. Even asymptomatic CAD was associated with lower vitamin D levels in high risk T2DM patients, as observed in a recent observational study[258]. On the other hand, in T2DM patients, severe vitamin D deficiency predicts improved risk of all-cause and cardiovascular mortality, independent of urinary albumin excretion rate and conventional cardiovascular risk factors[259], and vitamin D deficiency appears to be a significant risk factor for T2DM severity and associated cardio-metabolic risk[260].Thus, we can conclude that in T2DM vitamin D deficiency is an independent cardiovascular risk factor, but whether vitamin D supplementation can significantly improve cardiovascular outcomes is yet largely unknown. However, early intervention may be considered to improve prevention of T2DM related cardiovascular complications. It has been believed for years that caffeine, one of the substances most used worldwide and included in coffee, tea, energy drinks and chocolate, increases coronary risk, hypertension and HC concentrations. However their high consumption could modulate insulin sensitivity and blood glucose levels, and in the long term it may reduce the incidence of T2DM[263]. Therefore caffeine would not have any adverse cardiovascular effects, as it demonstrates an antioxidant capacity, and presents an inverse risk association with regard to T2DM[264]. Chronic alcoholism may produce an HC plasma increase due to nutritional deficiencies associated with the said habit[265,266].

AAn association between alcohol and the development of atherosclerosis has been observed in patients with T2DM. lcohol consumption and HHC together could explain the occurrence of atherosclerosis in diabetic subjects[267]. Finally, regarding treatments for T2DM, metformin appears to reduce folic acid levels in the blood, which in the long-term would raise HC levels. Folate management in these patients would reduce the levels of the same[268].

Summary Points

Cardiovascular benefits are obtained if the control of traditional cardiovascular risk factors begins early in subjects with short duration of DM and low cardiovascular risk.

Currently there is no evidence that routine monitoring of these risk factors in diabetic patients leads to better diagnostic and therapeutic results.

Targeting multiple markers of CVD risk hopefully offers the best chance of improving CVD outcomes.

Figures

Table 3 Suggested mechanisms for the influence of smoking on risk of type 2 diabetes

Direct effects due to inhalation of smoke from tobacco products
Impaired insulin sensitivity based on influence of haemodynamic dysregulation in capillary vascular bed
Impaired insulin sensitivity due to increase in inflammatory markers secondary to bronchitis and pulmonary infections caused by smoking
Impaired beta-cell function due to toxic effects of tobacco smoke
Lipotoxicity due to influence of increased triglyceride levels
Hypercortisolaemia and increase in abdominal fat tissue
Elevated sympathetic nervous activation
Indirect effects on glucose metabolism
Unhealthy lifestyle in smokers (poor diet, lack of physical activity)
Increased alcohol consumption (toxic effects on beta cells)
Psychosocial stress and impaired sleep associated with smoking
Impaired fetal growth in smoking pregnant women, associated with increased diabetes risk in offspring in adult life

Table 4 The strategic "five As" for smoking cessation

A-ASK:	Systematically inquire about smoking status at every opportunity
A-ADVISE:	Unequivocally urge all smokers to quit
A-ASSESS:	Determine the person's degree of addiction and readiness to quit
A-ASSIST	Agree on a smoking cessation strategy, including setting a quit date, behavioral counseling, and pharmacological support
A-ARRANGE	Arrange a schedule for follow-up

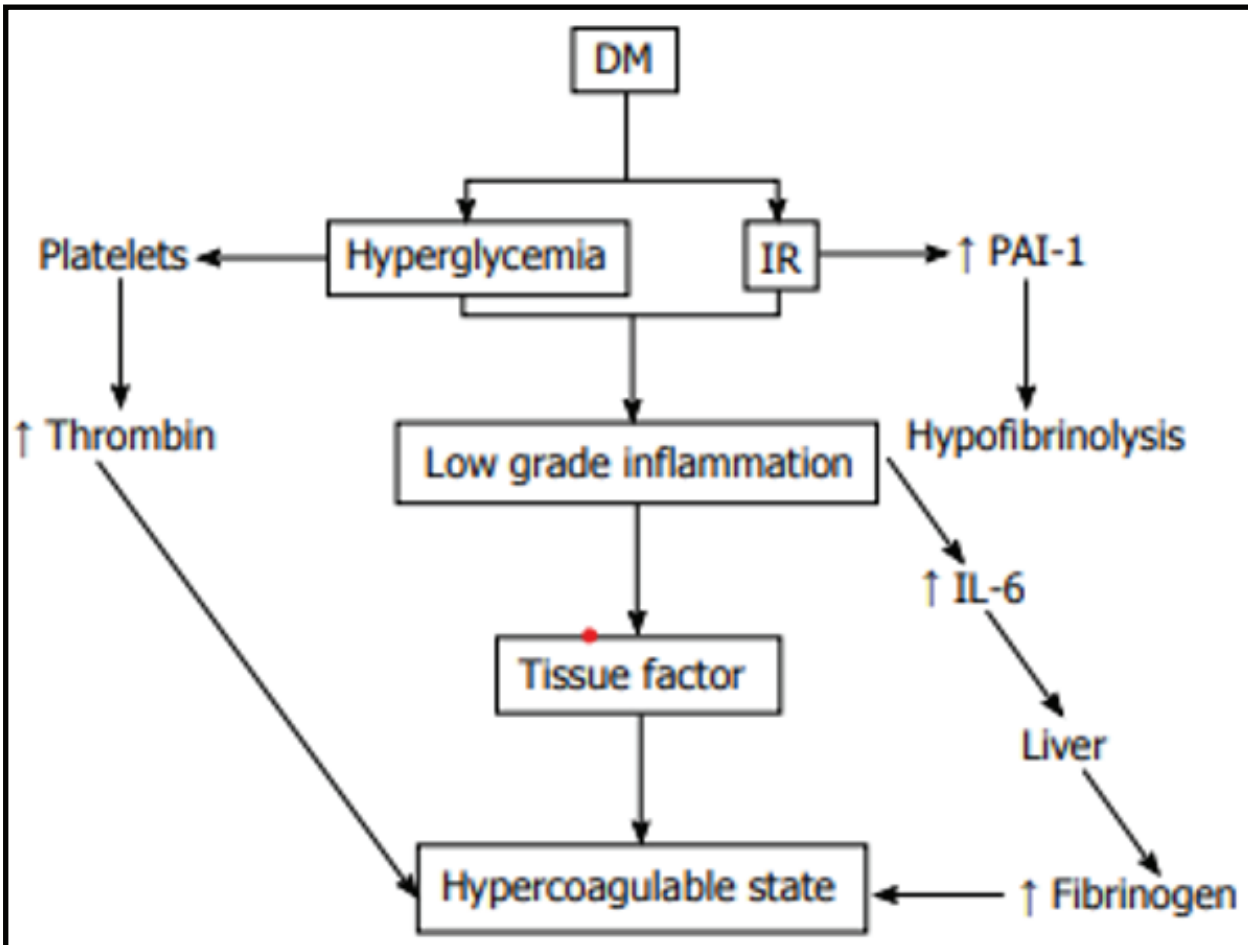

Figure 2 Prothrombotic mechanisms in diabetes mellitus. The hypercoagulable state related with diabetes mellitus is consequent to improved thrombin generation by platelets, impaired fibrinolysis due to increased levels of plasminogen activator inhibitor type 1 (PAI-1), and low-grade inflammation, that rise circulating levels of interleukin-6 (IL-6), fibrinogen, and tissue factor expression in vascular cells. DM: Diabetes mellitus; IR: Insulin resistance.

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Office No:- 99, 9th Floor, Kalpataru Avenue, Opp. ESIC Hospital,
Kandivali (East), Mumbai - 400101. M: 9322615653 | W: www.wmefi.co.in